Risk of disease following occupational exposure to Polychlorinated Biphenyls

Ellen Bøtker Pedersen, Peter Jacobsen, Allan Astrup Jensen, Charlotte Brauer, Lars Gunnarsen, Harald W. Meyer, Niels E. Ebbehøj, Jens Peter Bonde

Table of content

Affiliations of the authors:

Allan Astrup Jensen: Nordic Institute of Product Sustainability, Environmental Chemistry and Toxicology, Copenhagen, Denmark

Harald W. Meyer: Rockwool International A/S, Hedehusene, Denmark

Lars Gunnarsen: The Danish Building Research Institute, Aalborg University, Denmark

Charlotte Brauer, Ellen Bøtker Pedersen, Jens Peter Bonde, Niels E. Ebbehøj and Peter Jacobsen: Department of Occupational and Environmental Medicine, Bispebjerg University Hospital, Copenhagen Denmark

1. Preface

This report on human disease caused by occupational exposure to polychlorinated biphenyls (PCBs) was commissioned by the Danish Occupational Health Research Fund following a public call in September 2011.

The toxicity of polychlorinated biphenyls is complex because this group of chemicals encompass more than 200 single compounds with different physical and chemical properties, toxic potency, rate of metabolism and because they occur in different combinations and often together with other lipophilic persistent organochlorines as dioxins, dibenzofurans and chlorinated pesticides. In addition the spectrum of documented and suspected toxic effects of PCBs is broad.

The focus of this report is on health effects in humans following occupational exposure – either direct exposure by occupational handling of PCB containing products or indirect exposure by working in contaminated buildings. The background is increasing awareness for the past few years that people may be exposed, not only through food (the main route of exposure of the general population) but also in indoor air in office buildings and among construction workers handling PCB-containing building materials. While research on PCB related health effects during the past decades mostly involve environmental studies of the general population, knowledge on health effects following occupational exposure is mainly based on earlier studies in industrial workers handling PCBs. A small number of recent studies have addressed health effects and level of PCB exposure among people exposed from building materials.

Due to the heterogeneity of information we first in an introductory chapter provide brief background information on chemical, physical and toxicological properties of PCBs. In subsequent chapters we provide background information on toxicity and health effects in humans attributable to environmental exposure. Hereinafter we examine in detail health effects observed in occupational and indoor studies based on a systematic literature search of available primary reports. Finally we evaluate health risks in current Danish indoor and occupational exposure settings also taking into account the large body of experimental and environmental evidence provided in the introductory chapters 3-4 and the important differences in PCB exposure profiles in various settings.

2. Summary

There is increasing awareness that the indoor environment and handling of construction materials, products and waste may confer an occupational exposure to PCBs on top of the background exposure. In parallel, an increasing number of scientific papers report a broad spectrum of health effects related to PCB concentrations close to environmental levels. On this background the Danish Occupational Health Research Fund commissioned a narrative review of current evidence on health effects in humans following occupational exposure.

We performed a systematic literature search in the National Library of Medicine (PubMed) from 1966 through April 2012 to identify all peer reviewed primary papers in English addressing human health effects following occupational exposure to PCBs. We retrieved and reviewed 13 papers reporting occupational cohort studies of cancer mortality and 33 papers on non-malignant health effects.

The cancer mortality studies include workers exposed in three US and two European plants up to the ban of PCBs in the late 1970'es. The airborne exposure levels to PCB exceed current occupational threshold limits values by several orders of magnitude. These studies report consistently overall cancer mortality rates below national averages. Although there is no strong evidence of an increased overall cancer risk, the power to detect increased risk of rare cancers is limited. It is remarkable that an increased risk of primary liver and biliary tract cancer was found in one cohort because this specific cancer is predicted by animal studies. A few case series with follow-up and some cross-sectional studies of high-level exposed workers provide together with more recent studies of people exposed to PCBs from building materials and indoor air limited evidence of non-malignant effects on thyroid function, liver function and the immune system. Recent data suggest effects of PCBs on neurodegenerative disease in women.

In conclusion, findings related to occupationally high-level exposed groups are reassuring, but a large body of experimental and mechanistic research data on carcinogenic as well as other health effects calls for precautionary measures that eliminate any unnecessary occupational exposure relating to handling of PCBs. So far, there is no evidence that the indoor environment, which primarily confers exposure to lower chlorinated non-dioxin-like PCBs, increases the risk of disease.

3. Dansk resumé

Der har i de senere år været stigende bevågenhed omkring de mulige helbredsmæssige konsekvenser af PCB-udsættelse i indeklimaet og ved bygningsrenovering og affaldshåndtering. Parallelt hermed er der i videnskabelige undersøgelser rejst mistanke om, at forskellige helbredseffekter har kunnet sættes i forbindelse med PCB-niveauer, som ligger tæt på baggrundsbefolkningens. På den baggrund har Arbejdsmiljøforskningsfonden efterspurgt en udredning til belysning af de mulige sammenhænge mellem erhvervsmæssig PCB-eksponering og risiko for udvikling af sygdom.

Vi har foretaget litteratursøgning i National Library of Medicine (PubMed) for perioden 1966- april 2012. Formålet var at finde alle fagfællebedømte engelsksprogede artikler, som beskriver helbredseffekter som følge af arbejdsmæssig udsættelse for PCB. Vi fandt i alt 46 artikler, 13 erhvervskohortestudier der belyser cancerdødelighed, og 33 artikler der belyser ikke-maligne helbredseffekter.

Undersøgelserne af kræftforekomst omfatter erhvervskohorter fra tre amerikanske og to europæiske kondensatorfabrikker, hvor den luftbårne PCB-eksponering langt overskred vore dages grænseværdier. I disse erhvervskohorter er det et gennemgående træk at den samlede kræftdødelighed er lavere end baggrundsbefolkningens. Mortalitetsstudier har en række begrænsninger når, det drejer sig om at påvise øget risiko for sjældne cancerformer. Derfor er det bemærkelsesværdigt, at man i ét studie fandt en øget risiko for kræft i lever og galdeveje, idet netop denne type kræft også er observeret i dyreeksperimentelle studier. En række mindre tværsnits- og case-studier af højteksponerede arbejdere og enkelte nyere undersøgelser af bygningsarbejdere og indeklimaeksponerede giver beskeden evidens for påvirkning af leverenzymer, immunfunktion og skjoldbruskkirtlen. Nyere undersøgelser antyder en mulig sammenhæng mellem PCB-udsættelse og udvikling af neurodegenerativ lidelse hos kvinder.

Mens det samlede resultat af litteraturgennemgangen af helbredsrisiko ved erhvervsmæssig udsættelse således er beroligende, må man på basis af eksperimentelle forskningsresultater anbefale at unødig udsættelse for PCB undgås i forbindelse med håndtering af PCB-holdigt materiale. Indtil videre er der ingen evidens for, at PCB-udsættelse i indeklimaet medfører øget sygdomsrisiko.

4. Objectives

Against the background of ongoing discussions regarding occupational diseases, the National Board of Industrial Injuries and the Danish Occupational Health Research Fund requested a scientific reference document addressing health risk related to occupational exposure to PCBs.

The objectives of this report are:

1. to provide introductory background information on chemical, physical and toxicological properties of PCBs as well as data on use, occurrence, exposure levels and regulation

2. to perform a systematic search of the scientific literature in order to identify epidemiological research reports on health effects related to indoor air and occupational exposure to PCBs

3. to summarize recent systematic reviews on human health effects attributable to environmental PCB exposure as supporting evidence regarding occupational and indoor air health risks

4. to describe, summarize and evaluate current knowledge regarding risk of disease related to indoor and occupational exposure to PCB

5. to synthesize the information and perform an assessment of evidence on human disease risk related to indoor and occupational exposure

5. Introduction

In this chapter we provide a brief overview of basic aspects of PCBs for the convenience of readers not familiar with PCB chemistry and toxicology. Information has largely been extracted from earlier comprehensive reviews (1-3). The aim is not to provide a critical, systematic and exhaustive review of the toxicological profile of PCBs but only to summarise background information that is relevant for the discussion and interpretation of epidemiological studies addressing health effects following occupational and indoor exposure to PCBs.

PCB congeners

Polychlorinated biphenyls (PCBs) are man-made chemicals in which 1-10 hydrogen atoms in two connected benzene rings (biphenyls) are replaced by chlorine (2,4).
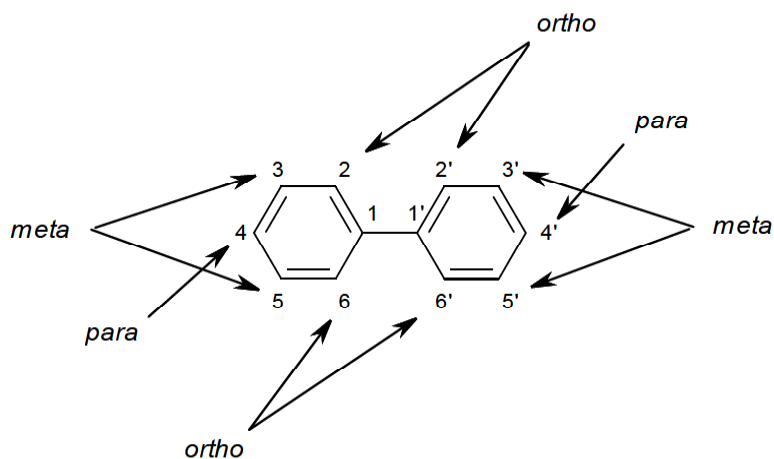
Figure 1: General structure of PCB reproduced after Lindell et al 2012. One or more hydrogen atoms attached to carbon atoms 2-6 and/or 2'-6' are substituted by chlorine atoms in PCBs.

There are in theory 209 different PCB congeners that are divided into 10 homologue groups based upon the number of chlorine atoms (from 1 to 10). Within each group of homologues, the number of isomers is ranging from 1 (decachlorobiphenyl) to 46 (pentachlorobiphenyls). The 209 PCB-congeners were *numbered* by Ballschmiter and Zell (BZ) in 1980 based upon the number and the positions of the chlorine atoms (PCB 1 to PCB 209) (5). This widely used classification has later been updated by the International Union of Pure and Applied Chemistry (IUPAC), for details see (6). Tables providing BZ numbering with later updates and the relation between PCB congener numbers and Chemical Abstract Service (CAS) numbers is provided in Appendix 4. In this report we use the updated PCB numbering system unless otherwise specified.

PCB mixtures

PCBs have been synthesized as technical mixtures of PCB congeners since 1929 under trade names as Aroclor (US), Kanechlor (Japan), Clophen (Germany) and many others (for a list of trade names, cf Table 7, p8 in (2). Around 130 of the in theory 209 possible PCB congeners have been identified in technical mixtures, which typically contain 70-100 PCB congeners with non-*ortho* and mono-*ortho* substituted congeners as minor or trace constituents (2). Depending on conditions during synthesis the proportion of chlorine in the technical products varies between 21 and 68 weight %. Although the chlorine content may be the same, the exact congener composition of commercial formulations varied from producer to producer and even from batch to batch from the same manufacturer (4). The commercial PCB-mixtures contained impurities of polychlorinated dibenzofurans (PCDFs), polychlorinated naphthalenes (PCN), polychlorinated terphenyls (PCT) and polychlorinated quaterphenyls (PCQ) (4).

The main PCB manufacturer from 1930 to 1977 was the Monsanto Company with factories in the US and United Kingdom. The PCB production of this company peaked in 1970 with about 33 000 tonnes a year (4). The cumulative global production of PCBs has been estimated to be in the order of 1.3 – 1.5 million tonnes. The Monsanto Company has been responsible for almost 50% of the production of PCBs (trade name Aroclor) (7). Other companies as Bayer from West Germany, Prodelec from France and Orgsteklo from Russia have each contributed with more than 10% of the historical global production. The Monsanto Company stopped its production in both UK and US in 1977. The Asian PCB-production ended during the 1970s, the European companies stopped their PCB-production in 1983-84 (West Germany, Spain, Italy, Czechoslovakia), while the Soviet Union/Russia continued its production until 1990-93 (7).

Physical and chemical characteristics

The pure PCB congeners are often solids while the commercial PCB-mixtures usually are liquids. At low temperatures the mixtures do not crystallize, but turn into solid resins. The PCB mixtures are chemically very stable, electrically insulating, good heat conductors and fire resistant with high flash points. PCB congeners and mixtures are lipophilic, rather insoluble in water but dissolve readily in fat and non-polar organic solvents. Vapour pressures and volatility are in general very low, but lower-chlorinated PCB congeners are more volatile than higher-chlorinated congeners and for this reason lower-chlorinated PCB congeners predominate in ambient air (3). PCBs are

combustible at high temperatures and combustion by-products include PCDFs. Pyrolysis of dielectric fluids containing technical PCB mixtures and chlorobenzenes may also result in formation of PCDDs.

Planarity. The two planar benzene rings in the PCB molecule can rotate around the connecting bond (see Figure 1). The coplanar configuration, where both benzene rings are configured in same plane, is not possible if chlorine atoms (relatively large compared to hydrogen atoms) are replacing hydrogen atoms at the ortho-positions (2, 2', 6, 6', cg figure 1). Thus non-ortho- and mono-ortho-substituted PCBs are coplanar congeners. Among the 68 coplanar PCB congeners, twelve congeners are referred to as dioxin-like PCB congeners (DL-PCB) because they like dioxins exhibit Aryl hydrocarbon Receptor (AhR) agonistic activity in cells. The twelve dioxin-like congeners are 4 non-*ortho* and 8 mono-*ortho* PCBs chlorinated in both *para-* and at least two *meta*-positions. The twelve dioxin-like PCBs are listed in Table1 (2).

Table 1. The WHO 2005 Toxic Equivalency Factors for DL-PCBs.

Compound	WHO 2005 TEF
2,3,7,8-TCDD	1
Non-ortho substituted PCBs	
PCB 77: 3,3',4,4'- tetrachlorobiphenyl	0.0001
PCB 81: 3,4,4',5 - pentachlorobiphenyl	0.0003
PCB 126: 3,3',4,4',5 - pentachlorobiphenyl	0.1
PCB 169: 3,3',4,4',5,5' - hexachlorobiphenyl	0.03
Mono-ortho substituted PCBs	
PCB 105: 2,3,3',4,44'-pentachlorobiphenyl	0.00003
PCB 114: 2,3,4,4',5 -pentachlorobiphenyl	0.00003
PCB 118: 2,3,3',4,4',5 -hexachlorobiphenyl	0.00003
PCB 123: 2',3,4,4',5 - pentachlorobiphenyl	0.00003
PCB 156: 2,3,3',4,4',5 - hexachlorobiphenyl	0.00003
PCB 157: 2',3,3',4,4',5 - hexachlorobiphenyl	0.00003
PCB 167: 2',3,4,4',5,5'- hexachlorobiphenyl	0.00003
PCB 189: 2,3,3',4,4',5,5'-heptachlorobiphenyl	0.00003

The toxic potency of the DL - PCBs is – like polychlorinated dibenzofurans (PCDFs) and polychlorinated dioxins (PCDDs) – expressed in Toxic Equivalent Factors (TEFs) relative to the most toxic of PCDDs, TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) with a TEF value of 1.0. The 2005 WHO Toxic Equivalency Factors for dioxin-like PCBs are shown in Table 1 (8).

To express the DL-PCB toxicity of a technical mixture of PCB congeners, Toxic Equivalents (TEQs) are calculated by multiplying the concentration of each DL-PCB congener with its TEF-value. The TEQs are added and express the sum of TEQs for the mixture (2).

Chirality. Nineteen PCB-congeners including PCB 91, PCB 95, PCB 149 and PCB 174 and PCB 183 are chiral compounds, that exist as pairs of nonsuperimposable mirror-images (as the right and left hands) called enantiomers (9). The PCB enantiomers have identical chemical and physical properties such as vapour pressure and lipophilicity, but may elicit different toxic effects – for instance induction of the cytochrome P450 enzyme system (10).

Analytical methods
Conventional analysis for PCBs in different materials involves extraction of the PCBs with a solvent, removal of unwanted extracted materials followed by identification and quantification. The analyses have been performed by the use of gas chromatography techniques (11).
In the early days quantification of PCBs were done by comparing one or two of the largest peaks in the sample chromatogram with the peaks of a standard technical mixture. Nowadays PCB trace analysis is congener-specific with labelled standards and identification of from 6 to more than 20 congeners with HRGC/HRMS (high resolution gas chromatography/high resolution mass spectrometer) (11).

A common way of analyzing the PCB content in building materials or in environmental samples is by the quantification of 6 non-dioxin-like indicator congeners expressed as PCB_6: PCB 28, PCB 52, PCB 101, PCB 138, PCB 153 and PCB 180 (also called DIN congeners), or with the DL PCB 118 added, expressed as PCB_7. The total PCB content in a sample is obtained by adding the amount of each of the single congeners and then multiplying the sum with a correction factor of 2 to 8, depending on sample type. For PCB_6 the average correction factor is 5. This value is the default correction factor for both PCB_6 and PCB_7 in standard methods and regulations (12).

Toxicokinetics

PCB congeners are readily absorbed from the gastrointestinal tract but in indoor and occupational settings uptake through airways and skin are the main routes of exposure. In general lower-chlorinated congeners are much better absorbed through intestines, airways and skin than higher-chlorinated compounds (2). For example, studies in rat demonstrate that 85% of a skin dose of PCB 15 was absorbed into tissues after 24 hours while the corresponding figure for PCB 155 was only 10% (Garner CE 2006 cited from (2)). In the ATSDR report from 2000 it is stated, that a maximum of 80% of the PCBs commonly seen in the adipose tissue of exposed capacitor workers may have been absorbed by the inhalation, while a maximum of 20% would have been derived from dermal or oral exposure (based on data from Wolff 1985) (13).

After systemic absorption PCBs are cleared from the blood and rapidly distributed to liver and muscles followed by slower redistribution to adipose tissue, where PCB compounds accumulate. Higher-chlorinated compounds tend to accumulate more than lower-chlorinated congeners, but accumulation also depends on positions of chlorine atom replacements (2). PCBs in the fat compartment of breast milk reflect the PCB concentrations and congener composition in adipose tissue. PCBs readily pass the placenta and the lipid adjusted PCB concentrations in cord blood is similar to maternal lipid adjusted blood concentrations. Lactation represents an efficient way of eliminating PCBs in women, is an important source of exposure in new-borns and explains the average lower PCB concentration in women relative to men (14).

As all highly lipophilic compounds, PCBs need to be transformed to more polar and water-soluble compounds in order to be excreted by urine or faeces. Higher-chlorinated PCB congeners are much more resistant to metabolic degradation than lower-chlorinated compounds which explain that higher-chlorinated compounds have longer biological half-lives and higher accumulation rates in tissues. One of the most abundant PCB congeners in the general population (2,2',4,4',5,5'-hexachlorobiphenyls PCB 153) is metabolized very slowly and primarily excreted via the bile. The half-times of low chlorinated congeners range from a few days to 6 years, while the half-times for congeners with more than 4 chlorines can be 8-24 years (15).

PCB-congeners are metabolized to more polar compounds through several steps and complementary pathways. First, higher chlorinated PCB congeners (4-10 chlorine replacements)

may be dechlorinated to lower-chlorinated congeners (and thus further obscuring relations between PCB-congener profiles in source media and biological tissues). Second, PCBs are oxidized by hepatic CYP enzymes to phenolic compounds, which are further oxidized to dihydroxy-metabolites. Third, hydroxyl-metabolites are either excreted unconjugated or as sulphate or glucoronide conjugates. Some metabolic intermediates are involved in DNA adduction. The five most important hydroxyl-PCB congeners in blood are present in concentrations 5-10 fold less than the most persistent PCB congeners (cited from (2), p 28).

For higher chlorinated congeners the predominant excretion route is via the faeces, mainly as metabolites, although small amounts of the parent PCB compound may occur in the faeces (13). Lower-chlorinated PCB congeners are mainly excreted through urine.

Mechanisms of toxicity

Toxicological mechanisms of PCBs vary with the chlorine content and substitution pattern and are grouped into congeners with toxic actions similar to dioxins (dioxin-like PCBs) and congeners without dioxin-like activity (non-dioxin like congeners).

The toxicity of the twelve non-ortho or mono-ortho substituted coplanar dioxin-like PCB-congeners is mediated through binding to a specific cytoplasmatic receptor - the aryl hydrocarbon receptor (AhR). The physiological function of the AhR is still not fully known, but studies using AhR receptor deficient mice indicate that the receptor is involved in growth, development, reproductive function, endocrine function, immune function, and nervous tissue function [cited from (16)]. In the liver the interaction between dioxin-like PCBs and the AhR receptor induces specifically cytochrom P450 enzymes belonging to the CYP1 A family. The induction of P450 enzymes, an early and highly sensitive biochemical indicator of exposure to dioxin-like compounds, is detectable by measurements of several biomarkers including the so-called EROD enzyme and results in a cascade of biochemical reactions in the liver that at higher dose levels is causing elevated serum concentrations of several liver enzymes, disruption of vitamin-A metabolism, and hem synthesis (associated with protoporphyrinuria) and at even higher doses histological changes, fat accumulation, liver enlargement and benign and malignant tumors (13,17,18).

The non-dioxin like PCB congeners do not interact with the AhR and do not induce the CYP1 A but have at higher doses toxic effects mediated by multiple pathways including induction of cytochrom P450 enzymes not belonging to the CYP1 A family (13). Some lower chlorinated non-dioxin-like PCBs as PCB 28 and PCB 52 potentiate the human $GABA_A$ receptor, which may be related to neurotoxicity (19). Some hydroxylated metabolites of lower chlorinated non-dioxin like PCB congeners have anti-estrogenic and/or anti-androgenic activity (20).

None of the PCB congeners are genotoxic, but commercial PCB mixtures are acknowledged experimental carcinogens (13). This carcinogenic effect is ascribed to the content of dioxin-like PCB congeners (and possible impurities of dioxins and dibenzofurans), which act by promoting the development of malignant tumors rather than initiating cancer in experimental animals. Therefore a no-effect level below which there is no increased risk of cancer is meaningful.

Some species differences in the sensitivity to PCB toxicity have been identified. Monkeys, guinea pigs and minks appear to be more sensitive than mice and rats.

Lowest observed adverse effect levels in experimental studies
The acute lethal toxicity of technical mixtures of PCB is low with rat oral LD_{50} ranging from 1-11 g/kg body weight and rabbit dermal LD_{50} ranging from 0.8-3.2 g/kg bodyweight (1). Accordingly acute and subacute effects of commercial PCB mixtures are unlikely in occupational settings. In contrast pure dioxin-like PCB 77 and PCB 169 are more than 1000 times as potent as technical grade PCB mixtures with oral guinea pig LD_{50} less than 1 mg/kg bodyweight (1).

Short-term toxicity studies in animals are less relevant for evaluation of findings in epidemiological studies because toxic effects primarily are related to accumulation of PCB compounds following repeated exposure for extended periods of time (months to years). Long-term oral feeding of rodents with technical PCB-mixtures in sublethal doses causes a wasting syndrome with progressive weight loss, liver toxicity (mentioned above under mechanisms), effects on eyes and skin and effects on the nervous, immune, reproductive and endocrine systems. Neurobehavioral and reproductive effects in the offspring following pre- and perinatal exposure have been demonstrated at dose-levels lower than those needed to induce effects in mature animals (17,20-22). Critical effects and NOAELs observed in long-term technical PCB feeding studies are provided in Table 2.

The presented data based upon individual studies have not been replicated and therefore cautious interpretation is warranted.

Table 2: Critical effects and LOAEL in the most sensitive tested experimental animal in long-term Aroclor feeding studies according to studies retrieved from ATSDR 2000. *Effects most likely entirely attributable to dioxin-like PCBs or impurities of dioxins and dibenzofurans.

Organ	Species	Critical effect	Lowest adverse effect level, dose/kg body weight/day
Liver	Rhesus Monkey	Liver enlargement	0,080 mg (23,24)
	Rat	Enzyme induction (EROD)	0,030 mg* (25)
Thyroid	Rat	Reduced serum T4 concentration	0,090 mg (26)
Eyes and skin	Monkeys	Nail deformities	0,005 mg* (24,27,28)
Immune system	Rhesus Monkeys	Suppression of IgG and IgM response	0,005 mg (29,30)
Nervous system	Monkeys	Reduced level of neurotransmitters (dopamine)	0,800 mg (31)
Malignant tumours	Rat	Liver and thyroid in female animals	1,000 mg* (32)
Reproduction	Rhesus monkey	Reduced fertility, resorptions, still birth	0,020 mg (24)

The toxicity of individual PCB congeners is less studied. LOAELs (Lowest Adverse Effect Level) for non-dioxin-like PCB congeners are generally higher than for non-dioxin-like congeners.

Examples are provided in Table 3. Comparing Table 2 and Table 3 it is seen that only the LOAEL for the dioxin-like PCB 126 is lower than the LOAELs for technical PCB mixtures.

Table 3: LOAEL for induction of liver enzymes and changed thyroid function following long-term oral feeding studies of selected specific PCB congeners (1) *Dioxin-like PCB

PCB congener	LOAEL value mg PCB/kg bw/day
2,4,4'- trichlorobiphenyl (PCB 28)	0.36
2,2',3,3',4,4'- hexachlorobiphenyl (PCB 128)	0.42
2,2',4,4',5,5' - hexachlorobiphenyl (PCB 153)	0.34
3,3',4,4' - tetrachlorobiphenyl (PCB 77*)	0.087
2,3,3',4,4' - pentachlorobiphenyl (PCB 105*)	0.039
2,3',4,4',5 - pentachlorobiphenyl (PCB 118*)	0.17
3,3',4,4',5 - pentachlorobiphenyl (PCB 126*)	0.0008

6. Health effects attributable to environmental PCB exposure

In this chapter we provide an overview summarizing current knowledge on health effects attributable to PCB exposure of the general population. Although the objective of this report is exclusively to review health effects following occupational and indoor exposure we have chosen to provide information on health effects in the general population according to environmental exposure since only few and/or old studies are addressing health effects in the occupational and indoor setting. Since it is far beyond possibilities to perform a systematic and critical review of the large knowledge base on environmental exposures we rely entirely on earlier comprehensive risk assessments (1,16,32) and systematic reviews published in peer-reviewed journals 2003-2012. These reviews were identified by a PubMed search in April 2012 with the following search criteria: [(PCB [TI] OR polychlorinated biphenyls [TI]) AND Toxicity AND (Review OR meta-analysis) AND past 10 years]. We got 33 hits and from abstracts we selected those nine reviews that explicitly addressed the epidemiological evidence on causal links between environmental exposure to PCBs and one ore more health outcomes (21,33-40). In addition to these reviews we included primary papers on health effects of PCB published in 2007-2012 to obtain up-to-date information (38,41-47). Finally, in this chapter we only include epidemiological studies and do not account for the fast increasing number of experimental studies.

The Yusho and YuCheng mass poisonings

Accidental contamination of rice oil used for food by technical PCB through leaks in a heat exchange system in the oil manufacture caused mass intoxication in Fukuoka, Japan, in 1968 and in Taiwan in 1979. The first accident, the *Yusho accident* (Yusho is 'rice oil disease' in Japanese) involved at least 1788 clinical intoxications due to leak of Kanechlor 400, a 48% chlorinated technical PCB. The second accident, the *YuCheng accident* (YuCheng is 'oil disease' in Chinese) involved more than 2000 clinical cases of intoxication by heat-degraded technical PCB mixtures. Symptoms, clinical signs and disease patterns have been described in numerous publications summarized in (3,48). Symptoms developed after few months and included acne-like skin eruptions, skin and nail pigmentation, eyelid swelling and discharge besides general symptoms as fatigue, headache, nausea and weight loss. Yusho patients also suffered from long-lasting airway disorder like chronic bronchitis (cough, expectoration, dyspnoea) and neurological disease (peripheral neuropathy with reduced sensory and motor nerve conduction) is described in YuCheng

victims. Laboratory tests revealed reduced erythrocyte counts and concentration of haemoglobin (anemia), changes in serum concentrations of liver enzymes and lipids, decreased serum levels of immunoglobulins (IgA and IgM) and increase in uroporphyrins. Long-term follow-up studies have shown increased cancer mortality in men but not in women (48,49). Cognitive deficits and growth retardation has been observed in children with prenatal exposure (50).

The main clinical and subclinical manifestations of the Yusho and YuCheng cannot be ascribed solely to PCB congeners because the heat-degraded technical PCB in both accidents contained substantial amounts of toxic tetrachloro-, pentachloro- and hexachloro-dibenzofuran congeners. Thus these accidents are not informative regarding health effects of PCBs as such.

Dermal effects

Chloracne is a universally recognised effect of short or long-term high exposure to PCBs and other polychlorinated organochlorines (13). It occurs in individuals with serum PCB levels 10-20 times higher than those of the general population with great variation among individuals. Chloracne eruptions usually first appear on the face, but may in severe case cover the entire body [(13) page 136-141].

Immunotoxicity

Numerous studies in experimental animals consistently indicate that PCBs have effects on the immune systems causing atrophy of thymus and suppression of both cell-mediated and humoral immunity (35). In human populations environmental PCB exposure has been associated with lower serum concentrations of circulating immunoglobulins and increased frequency of respiratory infections. Of particular interest is a series of studies first published in the Netherlands some 10 years ago showing that babies with higher prenatal PCB exposures have reduced immunological response after vaccination to measles, mumps, rubella, tetanus and diphtheria (35). PCB exposure has also in some studies been related to autoimmune diseases and to atopy and asthma. A recent prospective study from the high-level PCB-polluted Michalovce region in Slovakia indicates that in-utero and neonatal concentrations of PCBs might predict thymus volume in infants (41). Overall, these studies indicate an immunotoxic effect in human populations, which is in accordance with experimental animal evidence. However, data are limited and causal effects remain to be corroborated and characterized more precisely.

Endocrine effects

In-vitro experiments and animal studies show that PCB congeners as well as hydroxy-metabolites may interfere with the endocrine homeostasis by effects on hormone synthesis, excretion, binding to transport proteins or by interfering with hormone receptors (1,36). Experimental studies have shown decreased levels in blood of thyroid hormones and insulin and have shown disruption of the normal feed back mechanisms regulating tissue levels of androgens and estrogens. Altered levels of circulating cortisol have also been reported [cited from (16)]. A critical review addressing the evidence of PCBs on thyroid homeostasis in humans based upon 13 studies reports inconsistent findings across studies and no obvious exposure-response associations (36). It concludes that PCB exposure has not yet convincingly been shown to affect thyroid function in humans, but such associations cannot be excluded by available data. Transplacental exposure to PCBs may result in exposure of the fetus. It is a prominent hypothesis that exposure to PCBs may disrupt neurodevelopment in children through disruption of thyroid hormone homeostasis (cf below).

PCBs are diabetogenic in animal studies and a recent study in rats exposed to lipophilic persistent organic pollutants (POPs) and in-vitro studies of differentiated adipocytes provides further evidence that POPs including PCBs lead to insulin resistance and related metabolic disorders (51). A review of a large number of cross-sectional epidemiological studies and few longitudinal studies provide some evidence that PCB congeners at environmental exposure levels are associated with Type II diabetes in human populations (37,44). It remains to be established whether such associations are related to increased mobilisation of PCBs from fat deposits in patients with type II diabetes or are causal effects of PCBs on development of diabetes (52). A longitudinal study found increased risk of incident type 2 diabetes related to serum concentrations of several POPs including highly chlorinated PCBs, most pronounced among people with BMI above 30 kg/m2 (42,43). Still, the number of prospective studies are few, are based on small sample sizes and do not provide clear evidence for dose-response relationship or adequate timing of exposure relative to outcome.

Neurodevelopmental effects

Animal experimental studies have shown that prenatal exposure to PCB may result in permanent adverse effects on the nervous system of both male and female offspring in rats (cited from (16)). Neural behavioural effects include altered locomotor activity and deficits in learning and hearing as well as changes in rearing behaviour in two-generation studies. A recent review of more than nine

European and US birth cohort studies conclude that most studies identified at least one cognitive developmental effect of early life PCB exposure, but that findings are rather inconsistent and differ with respect to type of effects and with respect to their persistence (21). It is concluded that in spite of convincing findings in animals there are still uncertainty with respect to long-term neurodevelopmental risks related to early life PCB exposure in humans at current exposure levels. Another recent review addressing the same issue claims that the most consistent effects observed across studies are impaired executive functioning related to prenatal PCB exposure, but also this review points to the high degree of heterogeneity of the type of neuro-developmental changes observed in the various studies (38).

Reproductive effects

The most sensitive adverse effects seen in experimental animals following prenatal exposure to 2,3,7,8-dibenzo-p-dioxin (TCDD) are developmental, reproductive and hormonal effects in male as well as female offspring (16). Therefore the EC Scientific Committee for Food (SCF) uses these endpoints for risk assessment of TCDD (which therefore is relevant for dioxin-like PCBs). This is opposed to other assessments of human health risk from PCBs based upon carcinogenicity data in long-term rat-studies (EPA). In male offspring the most sensitive effect of TCDD is decreased sperm count occurring at 15 pg/kg body weight and in female offspring the most sensitive endpoint is endometriosis occurring at 20 pg/kg body weight (16).

Systematic reviews of the epidemiological evidence on reproductive effects of persistent organochlorines in humans are based on a large number of observational studies (34,39). One review concluded that high concentrations of persistent organochlorines including PCBs may affect semen quality, cause testicular cancer, induce menstrual cycle abnormalities and spontaneous abortions and cause delayed time to pregnancy, reduced birth weight, skewed sex ratio and altered age of sexual development (34). Such effects have in most studies been demonstrated at exposure levels higher than present days' exposures in European and North American populations. However the most recent multi-centre studies have added to the mounting evidence that PCBs in men reduce sperm motility (46) and a recent meta-analysis of more than 10 European birth cohorts with measurements of PCBs in blood indicate that even low-level exposure to PCBs may be associated with fetal growth restriction (45). Finally, there is some recent evidence that serum-concentrations

of PCBs at levels similar to the US general population through 1994-2003 is associated with failed implantation among women undergoing in-vitro fertilisation (47)

Carcinogenic effects

Already in 1987 The International Agency for Research on Cancer (IARC) classified PCBs as probably carcinogenic to humans (Group 2A) without making any distinction between dioxin-like and non-dioxin-like PCB congeners. This overall classification was based upon what was considered sufficient evidence for carcinogenicity of PCB mixtures in animals and limited evidence for human carcinogenicity – the latter mostly based upon occupational studies. Animal studies have shown that commercial PCB mixtures cause tumours mainly in the liver and to some extent in the thyroid at doses in excess of those inducing other effects.

In 2009 IARC classified the most potent dioxin-like PCB congener (PCB 126) as a human carcinogen (Group 1) based upon animal data and mechanistic information (40). This conclusion was mainly based upon a large US national toxicology programme chronic toxicity and carcinogenicity study of TCDD, PCB 126 and 2, 3, 4, 7, 8 – PCDF in order to test dose additivity of dioxin and dioxin-like compounds (16). In this study - where dose calculation was based upon the toxic equivalent factors – dose-related increases in tumours at a number of sites, including the liver and the lung, were seen. In spite of this compelling experimental evidence it is still disputed in the scientific literature, whether PCBs confer an increased risk of cancer in humans (33). A recent systematic review of the carcinogenicity of non-dioxin-like PCBs concludes from chronic carcinogenicity studies in rats that the cancer risk from PCB mixtures is related to dioxin toxic equivalence (TEFs) and not to total PCB dose, but that a weak carcinogenic potency of individual non-dioxinlike PCB congeners can still not be excluded (53). In humans there are no data to indicate whether non-dioxin-like PCBs have a carcinogenic potential.

Several case-control studies have linked PCB concentrations in mammary fat tissue with increased risk for breast cancer but other case-control studies have not corroborated these results (for a review see (33). In addition follow-up studies of women have not demonstrated associations between risk of breast cancer and PCB concentrations in blood samples taken years before the disease development. These conflicting results may be explained by secondary changes of PCB

concentration in tissue with neoplastic lesion. Thus there is no consistent epidemiological evidence that PCB increase the risk of breast cancer in women.

Concluding remarks

High accidental exposure to heat-degraded technical PCB causes dermatitis and general wasting due to toxic effects on several organ systems including the nervous system and metabolic, immune, endocrine, developmental and reproductive functions. These effects are partly explained by contamination of PCDFs. Low-level environmental exposure of the general population through contaminated food and water cannot be linked to disease in the individual case, but there is evidence mainly from animal studies that dioxin-like PCB are carcinogenic primarily causing liver and thyroid cancer. The assumed mechanism is non-genotoxic and thus a no-effect threshold is plausible. Low-level exposure at the population level may contribute to the occurrence of subtle neuro-developmental deficits in children, suppression of the immune system, growth retardation and reproductive problems and increased risk of late-onset diabetes (Type II) but the evidence is limited and partly conflicting.

7. PCB occurrence, exposure and regulation

In this chapter we provide a brief overview of the occurrence of PCBs and exposure levels in indoor and occupational settings. At the end of the chapter main regulations are summarised. As in the previous chapter the aim is to summarise relevant background information largely based on earlier comprehensive reviews (1-3).

PCB occurrence

PCBs have been used in a wide variety of industrial and consumer applications. The uses were categorized by the World Health Organization as *completely closed*, *nominally closed* and *open-ended* (3). The PCB uses included:

a) *Completely closed systems:*
   - Electrical transformers
   - Electrical capacitors (including small fluorescent lighting ballasts)
   - Electrical switches, relays and other
   - Electrical cables
   - Electric motors and magnets (very small amounts)

b) *Nominally closed systems:*
   - Hydraulic systems
   - Heat transfer systems (heaters, heat exchangers)

c) *Open-ended systems:*
   - Plasticizers in sealants and caulking material
   - Ingredient in paint and other coatings
   - Ingredient in ink and carbonless copy paper
   - Ingredient in adhesives
   - Pesticide extender
   - Plasticizer in polyvinyl chloride, neoprene and other artificial rubbers
   - Fire retardant in fabrics, carpets, polyurethane foam etc.
   - Lubricants (microscope oils, brake linings, cutting oils, other lubricants)

From the 1950s and to mid-1970s PCBs was extensively used in building materials. Examples of building materials with PCBs are listed below(54):

- Elastic (rubber) sealants and caulking material
- Sealing of dual glazing windows ("thermo windows")
- Fire retarding paints for steel structures
- Weather resistant paint for outdoor surfaces
- Floor lacquers and fillers
- Floor levelling compounds
- Plasticizer in cables

The PCB concentration in the building materials listed above varies from a few milligram/kg (ppm) to around 30 % in materials such as sealing and caulking agents.

The Danish Environmental Protection Agency has made an estimate of the amount of PCBs used in the building materials and electronic appliances in the period 1950 – 1983 (55); data are presented in Table 4. The Danish Environmental Protection Agency has no data on the current remaining amount of PCBs in Denmark.

Table 4: Estimate of total amount of PCBs used in building materials and electric appliances in Denmark in the period 1950-1983

	Total amount of PCBs used in the period in tonnes (%)	
Big capacitors and transformers	450-750	(40%)
Capacitors in light armature	175-325	(17%)
Other small capacitors	30-100	(4%)
Elastic sealants	110	(7%)
Paint	270	(18%)
Thermo windows	200	(13%)
Plastic	10	(1%)
Total	1505	(100%)

Human PCB exposure data

The human body burden of PCBs is influenced by a number of factors: Diet, age, body weight changes, breast-feeding history, occupational or other environmental exposure (4).

For the general population it has been estimated, that about 90 % of the total human PCB exposure originates from food, especially food of animal origin (56). PCBs from this source mainly consist of high-chlorinated PCB congeners accumulated in the food chain.

The major route of PCB exposure in the indoor and occupational environment is inhalation, but the relative importance of skin absorption and ingestion is not fully elucidated (2).

Occupational exposure levels of the industrial workers in the past were several orders of magnitude higher than the occupational and indoor air exposure nowadays. In order to provide an overview of the exposure levels tables from the ATSDR report (1) showing the serum PCB levels of non-occupationally and occupationally exposed populations in the period 1973-1996 are presented in appendix 5.

Occupational PCB exposure in Denmark is nowadays most likely in (54):

- Indoor environment in PCB-contaminated buildings (offices, schools and institutions etc.)
- The construction sector (maintenance, renovation and demolition)
- Waste management (collection, handling, disposal, recycling, destruction)

Exposure in indoor environment

PCB-levels in outdoor air are in the range 1-10 ng PCB/m^3 (13). Indoor air levels in buildings without PCB-containing building materials usually are lower than 30 ng PCB/m^3 (57). In a recent Danish investigation of the apartment complex Farum Midtpunkt (see below) the mean PCB$_{total}$ in apartments without PCB-containing building materials was 6.03 ng/m^3, which is equivalent with exposure levels found in other studies (58).

In buildings with PCB-containing building materials, room temperature, cleaning and ventilation influence PCB levels in the indoor air. Low chlorinated and more volatile congeners will reach higher concentrations in the air than higher chlorinated and less volatile congeners (59). PCB

molecules are adsorbed on surfaces and dust in the building and PCB molecules diffuses from the primary source to the adjacent building materials. Thus both inhalation and other routes of exposure from dust and surfaces are possible in the indoor environment (59).

The congener pattern in the indoor air depends on the PCB-source, e.g. sealants, paints, coatings and ceiling tiles because different commercial PCB mixtures have been used in various building materials. Some Aroclors contained large amounts of mono- and di- chlorinated congeners, whereas other Aroclors contained a little or none (2).

Heinzow et al. (60) found, that the distribution of PCB-congeners in the indoor air depends on the source of the PCB contamination. In rooms with PCB-containing elastic sealant PCB 28 and 52 was by far dominating. In rooms where the source was a flame retardant coating of acoustic ceiling tiles, PCB 101 was the most abundant of the 6 indicator congeners.

In a German high school with high indoor PCB levels due to evaporation from flame-retardant acoustic plates the blood levels in teachers and pupils of PCB 28 and PCB 52 were not increased but the levels of the higher chlorinated PCB 138, PCB 153 and PCB 180 were increased 3-18 times (61).

According to the review by Lindell et al (2) only a weak influence of PCB contaminated indoor air on the total PCB blood level has been found in several studies (62-64), because the blood concentration of the low chlorinated volatile PCBs (e.g. PCB 28 and PCB 52) was still low (despite an increase) compared to the mean PCB blood concentration caused by food intake, see (2) for further details.

In a Swedish study of 21 inhabitants in PCB contaminated apartments (sealants) and a control group of 15 persons living in apartments without PCB, the median PCB concentration based on the sum of 30 congeners was 434 ng PCB/g plasma lipid in the exposed individuals and 226 ng PCB/g plasma lipid in the controls (only 15 congeners could be quantified in all samples). Most of the levels of these congeners were only slightly elevated compared to the controls. The concentration of the low chlorinated PCB 28 was 30 times higher and the concentration of PCB 66 was 8 times higher than in controls (65).

In 2011 an investigation was carried out in the housing estate Farum Midtpunkt in Denmark (58,66). The indoor air concentrations of PCBs in apartments with PCB-containing elastic sealant

(n=83) were compared to the concentrations in uncontaminated reference apartments (n=21) in the same estate. Twenty-four PCB-congeners including all 12 DL-PCBs were measured in the air samples and 20 elastic sealant samples were taken. Blood analyses were carried out determining the level of the 24 congeners in plasma of 139 inhabitants from the contaminated apartments and of 134 inhabitants of the uncontaminated apartments. The mean PCB_{total} air level of 83 PCB contaminated apartments was 1030 ng/m^3 (range of 168-3843 ng/m^3) (58) mentioned above in the 21 control apartments the mean PCB_{total} was 6.03 ng/m^3. PCBs were present in all air samples from the contaminated apartments while all congeners were below the detection limit in more than half of the control apartments. In the 139 PCB-exposed individuals the mean plasma PCB_6 concentration was 3.5 µg/L (range 0.2-16 µg/L), while the mean plasma concentration of PCB_{24} was 6.8 µg/L (range 0.4-29 µg/L). In the 134 control persons the figures were 1.0 µg/L (range 0.07-4.2 µg/L) and 1.5 µg/L (range 0,2 - 11µg/L), respectively. Thus the exposed individuals had about three times higher PCB levels than the controls. There was a clear increase in PCB levels by age and women had, as expected because of elimination by lactation, lower levels than men (66).

According to the report by Lindell B (2) there is only limited data on DL-PCB in indoor air of buildings with PCB-containing building materials. In a Swiss study by Kohler et al (67) the six indicator congeners (PCB 28, 52, 101, 138, 153, 180) and all DL PCBs were measured in four public buildings and one industrial building. The source of PCBs was sealants. In the four public buildings the sum of the six indicator congeners multiplied by 5 gave a total PCB-value (in air) of 0.7-4.2µg/m^3. The most abundant of the indicator congeners were PCB 28, 52 and 101. The most common DL-congeners were PCB 118 ($\leq$ 0.010 µg/m^3) and PCB 105 ($\leq$ 0.0044 µg /m^3). The level of PCB 126 was below the detection limit in three of the public buildings and 0.000014 µg/m3 in the fourth building. In the industrial building the sum of the six indicator congeners multiplied by 5 was 13µg/m^3. The most abundant DL-congeners in the industrial building were PCB 118 (0.066µg/m^3) and PCB 105 (0.021µg/m^3) the level of PCB 126 was very low (0.000043 µg/m^3). A concentration of DL-PCBs of 1.2 pg TEQs/m^3 corresponded to a total PCB-level of 1 µg/m^3 (cited from (2)).

In a survey (60)of PCB-levels in public buildings in Germany indoor air samples were collected (n=8) in four buildings. The sum of the six indicator congeners multiplied by 5 ranged from 715 to

2250 ng/m^3. The twelve DL-PCBs were determined, PCB 118 was by far the DL-PCB occurring at the highest level, PCB 118, 126 and 156 accounted for 85-95% of the PCB-TEQs (Cited from (2)).

Occupational exposure in the building industry

Exposure to PCBs may occur during renovation and demolition of buildings. The building renovation workers are especially exposed to PCB containing dust while removing PCB-containing sealant. The congener pattern in the dust particles is similar to that of the PCB mixture used in the sealant. The workers may also be exposed to PCB vapour as in the indoor environment. This exposure is dominated by lower chlorinated congeners. This exposure can be prevented by the use of personal protection equipment (2).

In the recent Danish investigation in Farum Midtpunkt 20 elastic sealants were analyzed for PCBs, and the mean concentration of PCB$_6$ (x5) was determined to be about 25 weight-% while the measured PCB$_{24}$ mean without correction factor was 10% (max 22 %). The content of dioxin-like PCBs was about 1.3 % (66,68).

In Finland 22 renovation workers were exposed to PCBs while removing sealant from prefabricated houses. The concentrations of PCB-congeners 28, 52, 77, 101,138,153 and 180 in hygienic samples taken from the breathing zone of the workers were ranging from not detected to 3100 ng/m^3. The mean total PCB concentration (sum of 24 PCBs) in the plasma of 22 exposed workers was 3.9 µg/L, while the 21 controls had a mean PCB concentration of 1.7µg/L. The concentrations of PCB 28 and 52 in plasma were positively correlated with the concentrations in air samples taken from the breathing zone of 6 workers during the renovation period (68).

In a Swedish study it was shown 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 (280-370µg PCB/m^3) in the workplace air or 1000 times higher concentrations than the Danish action level in the indoor climate (69). The PCB-levels were determined as the sum of 19 PCB congeners. The blood levels of the exposed workers were approximately twice the level of non-exposed workers: 575 ng PCB/g lipid and 267 ng PCB/g lipid, respectively. The easy metabolized PCB 44, PCB 70 and PCB 110 congeners were associated with recent occupational exposure, while the relatively persistent PCB 56/PCB 60 and PCB 66 were good markers of long term occupational

exposure and the very persistent PCB 153 and PCB 180 were good markers for dietary exposure (70).

Exposure in waste management

The information on exposure in relation to waste management is scattered. Waste with a PCB content of 50 ppm or more is considered as hazardous waste in EU and special provisions exist for sorting, notification, classification, packaging, declaration, transporting, storing and disposal. We have not been able to find information about exposure in Danish waste management. The following summaries of studies on this topic are cited from the review made by Birgitta Lindell in 2012 (2):

In a Finnish study (71) the mean sum of 24 PCBs (including five dioxin-like congeners) in 26 workers in a hazardous waste disposal plant was 3.4 µg/L (range 1.9 – 10.9) compared to1.6 µg/L in 21 controls. Earlier the main PCB compounds found in waste incineration originated from capacitor and transformer oils, therefore nine low chlorinated congeners have traditionally been measured in workers serum (PCB 8,18,28,33,44,47,66,74,101). Nowadays construction waste and contaminated soil containing mainly high-chlorinated congeners (PCB 101,118,138,153,180) seem to be the main sources of PCB in waste incineration in Finland.

In a Swedish study (72) no difference was found in the sum of PCB_7 between 29 workers at a hazardous waste incineration plant and 60 matched controls. The mean plasma values were approximately 680 ng/g lipid for both groups. However, the mean levels of PCB 28 and PCB 52 were significantly higher in the exposed workers than in the controls; 62 ng/g lipid (range 4-724) and 2.5 ng/g lipid (range 0.5-13) for workers and 3.3 ng/g lipid (range 0.7-29) and 1.3 ng/g lipid (range 0.5-12) for controls. These results were concordant with the congener profile of the air monitoring analyses.

In a German study published in 1992 (73) no significant differences in plasma PCB levels were found between 53 workers at a municipal waste incinerator and 63 controls. The mean sum PCBs 138, 153 and 180 were 6.33 µg/L for the workers and 6.22 µg/L for controls.

In 1997 the sum of PCB_6 in blood from 14 Spanish workers at a municipal solid waste incinerator, 93 persons living near an incinerator and 91 persons living far from an incinerator was found to be 1.47, 2.11 and 1.99 µg/L, respectively (74)

Regulatory approaches

In Denmark all open applications were banned in 1976 (75). This ban was effective from 1st January 1977 and an implementation of provisions in the EU Directive 76/769/EEC. At the beginning of the 1980s there were about 50.000 transformers and 8 million small PCB-containing capacitors in use in Denmark (76).

From November 1986 all new uses of PCBs were banned in Denmark (77). However the use of larger PCB-containing capacitors and transformers was allowed until 1st January 1995 and the use of small capacitors and transformers was allowed during their remaining lifetime.

In 1998 a new Danish regulation based on a EU directive from 1996 was introduced allowing the larger equipment a lifetime until 1st January 2000 (78). According to a report from the Danish Environmental Protection Agency from the year 2000, PCB-containing appliances has been out-phased in Denmark (79).

Indoor air

In 2009 the Danish National Board of Health introduced two action levels for PCB in indoor air. At levels >3000 ng/m^3 immediate action is recommended, and exposure levels between 300 and 3000 ng/m^3 is considered a potential health risk and an action plan is recommended to bring levels down. It was later specified that levels between 2000 and 3000 ng/m^3 required action within a year and lower levels within two years (80). There is no specific action level for dioxin-like PCBs in Denmark.

Heinzow and co-workers reported a total TEQ level of 0.3-0.6 pg/m^3 per 1000 ng total PCB/m^3 in buildings with permanent elastic PCB sealants and 1.8-4.7 pg/m^3 per 1000 ng total PCB/m^3 in buildings with PCB containing acoustic ceiling tiles. The authors propose that the existing German guideline for non-dioxin-like PCBs in indoor air be supplemented with a tolerable concentration level for the integrated indoor exposure to dioxin-like PCBs, polychlorinated dibenzo-*p*-dioxins and dibenzofurans of 0.4 pg TEQ/m^3 and an action level of 4 pg TEQ/m^3(81).

Occupational exposure

The NIOSH (US National Institute for Occupational Safety and Health) has established a recommended exposure limit (REL) of 0.001mg PCB/m^3 as a TWA (Time Weighted Average) for up to a 10-hour workday. The ACGIH (American Conference of Industrial Hygienists) Threshold Limit Values/Time Weighted Average (TLV/TWA) for Aroclor 1254 contrast to this with TLV at 0.5 mg PCB/m^3 and 1.0 mg/m^3 for Aroclor 1242 for an 8 hour work day (critical effects: Upper respiratory tract irritation, eye irritation, liver damage and chloracne) (13) . The Danish TLV/TWA is 0.01mg PCB/m^3 (82).

8. Health effects in humans attributable to occupational PCB exposure: summary of a systematic review of primary reports

In this chapter our findings from the literature search on occupational PCB exposure and health effects are summarized and discussed. The systematic literature search and the criteria for selection of primary reports included in the review are given in Appendix 1, and detailed descriptions and reviews of all studies are given in Appendix 2 (cancer) and Appendix 3 (other health effects).
In this chapter we provide a summary of findings in studies addressing cancer (described in details in Appendix 2), hereinafter we provide a summary of the retrieved studies addressing other health effects (described in details in Appendix 3).

Cancer

Thirteen cancer studies were retrieved. Ten of the studies are mortality studies and three of the studies are dealing with cancer incidence.

In the mortality studies thousands of male and female capacitor workers exposed to PCBs in the production of capacitors in American and European capacitor manufacturing plants are followed for 20 to 60 years providing several hundred thousands person years of observation. Vital status was obtained for 95 - 99% of the study populations.

PCB mixtures with various compositions and trade names were used in the capacitor plants from about 1940 to the late 1970-es. During this period the chlorine content of the PCB mixtures was reduced from 54% to about 42 %. The major route of exposure was probably inhalation; other possible routes of exposure were skin absorption and ingestion by hand-mouth activities.

In some of the earliest measurements the workplace area air concentrations of PCBs were between 5.200 $\mu g/m^3$ and 6.800 $\mu g/m3$. In the 1970s the reported area air levels were ranging from about a few microgram per m3 in low exposure areas up to about 2000 $\mu g/m^3$ in high exposure areas. In the 1970s the average serum PCB levels in the worker cohorts ranged from about 100 to1500 ppb, while serum PCB levels were at average 5 – 15 ppb in the general population. Due to limitations in the early laboratory techniques, no information on specific congeners was available. In general,

exposure was expressed as measurements of total PCB or of higher and lower chlorinated PCB homologues.

Causes of death in the cancer mortality studies were retrieved from death certificates. In some cases autopsy reports, medical records or the results of histological examinations were retrieved providing more detailed diagnostic information about the workers. Excess mortality has been found I some studies for cancer in the liver, gall bladder and biliary tract, malignant melanoma, connective tissue cancer, multiple myeloma, cancer in "the digestive tract" in men and rectal, intestinal and hematopoietic cancer in women.

The 13 cancer epidemiology studies were conducted in five cohorts derived from workers at the same plants. Thus they do represent repeated analyses with increasing observation time in populations that overlap to varying degree. In general an increased mortality due to a site-specific cancer in one cohort was not corroborated in other cohorts and frequently not in subsequent studies of the same cohort. However, Prince et al (83) confirmed the excess mortality due to cancer in biliary tract, gall bladder and liver demonstrated by Brown in 1987 (84) by adding six more cases from the extended period of follow-up of a high-level exposed group of workers. In a concomitant study from the same capacitor plants also including less exposed workers no excess of hepatic or biliary cancer was demonstrated. In none of the studies there is convincing evidence that risk is related to cumulative exposure or time since first exposure to PCBs.

Three studies were addressing cancer incidence among capacitor workers. Two of these were in the same Swedish cohort of a couple of hundreds capacitor workers (85,86). In the Swedish study from 1997 the standardized incidence rate (SIR) for all malignant tumors was found to be 86 (95%; CI 51-137) and no single cancer type had significantly elevated SIR compared to the general population. However, two cases of biliary cancers were observed – SIR: 256 (CI: 31-926).
In 2009 Silver et al investigated the relation of PCB exposure and risk of developing breast cancer in a cohort of 5,752 female capacitor workers from the three previously studied US plants (87). No increased risk of breast cancer with cumulative exposure or employment duration was found, overall SIR: 81 (95%; CI 72 - 92).

In conclusion, we have reviewed thirteen historical follow-up studies of cancer mortality among capacitor workers in three US and two European plants. Airborne exposure levels to PCB mixtures have been many orders of magnitude higher than general population exposure. These studies report consistently over-all cancer-mortality rates below national average. Considering specific cancers sites, findings have only been consistent upon repeated analyses after longer follow-up in one of the five cohorts. Moreover, no consistent evidence is revealed that risk is related to cumulative exposure or time since first exposure to PCBs.

Other health effects

Endocrine and immunologic effects:

In the research on environmental PCB exposure conflicting results has been reported regarding thyroid function, diabetes and immune system function. Some of the retrieved occupational studies address these issues:

In a cross sectional study from 1998 Langer et al found that the volume of the thyroid gland estimated by ultra-sound was significantly increased in a group of heavily exposed male and female workers compared to a control group. There was no difference in the levels of TSH and thyroxin, but an increased prevalence of some thyroid antibodies in the worker population, suggested to be a result of immunotoxic effects of the PCB exposure (88).

In a Swedish study from 2008 Seldén et al compared 36 construction workers removing old plastic sealants with 33 controls. The PCB level was twice as high in the exposed group, no difference between the two groups in either thyroid function or cytokine levels was demonstrated.

In a cross sectional study of 118 postmenopausal former female capacitor workers, self-reported history of diabetes was significantly associated with the blood levels of PCBs (89).
In 2002 Langer et al showed that compared to controls heavily PCB exposed workers had an increased level of anti-GAD (an antibody to glutamic acid decarboxylase in the insulin producing pancreatic beta cells associated with development of diabetes) (90).

In 1997 Langer et al found significantly lower blood levels of beta 2- microglobuline (a cell membrane protein related several biological processes including cell mediated immunity) in highly

PCB exposed workers compared to controls. This finding was suggested to be a result of an immunotoxic effect of the PCBs (91).

Nervous system:

In 2006 Steenland et al published a retrospective mortality US study of 17,321 former male and female capacitor workers addressing mortality from neurological diseases (92). No overall excess mortality for Parkinson disease, amyotrophic lateral sclerosis or dementia was seen, but women had an excess mortality due to amyotrophic lateral sclerosis and highly exposed women had an excess mortality due to Parkinson disease and dementia. It was concluded, that these findings are suggestive of an effect of PCBs on neurodegenerative disease in women.

In 2010 Seegal et al published the results of Beta-CIT SPECT imaging of 89 former male and female capacitor workers. An inverse relationship between blood levels of PCBs and dopamine densities was shown for women. It is suggested, that these finding reflect, that PCB exposed women are at increased risk of developing Parkinson disease, and that the sex differences could be caused by difference of level in gonadal hormones, since these hormones experimentally has been shown to alter the response to dopamine neurotoxicants (93).

Reproduction:

In 1984 and 1989 Taylor et al published two studies about the influence of PCBs on birth weight and gestational age among offspring of female capacitor workers (94,95). The overall conclusion on these studies was that there was a small but significant effect of exposure to high chlorinated PCB homologues on birth weight (decrease) and an inverse association between gestational age and serum PCB level. It was concluded that the magnitude of these effects was small compared to other known determinants of gestational age and birth weight, and that the biologic importance of the effects is likely to be negligible except among already low birth weight or short gestation infants.

In 2011 Rocheleau et al found no evidence of altered sex ratio in children born to primiparous PCB exposed female capacitor workers (96).

Dermal effects:

In two studies from 1982 and 1985 Fishbein et al addressed dermal and oculodermatological findings among capacitor workers (97,98). Acneform eruptions and palpebral and conjunctival abnormalities were described. The findings did not correlate well with the blood levels of PCBs. It

was suggested, that polychlorinated dibenzofurans could be the aetiologic factor. Dermatologic findings, most frequently acneform eruptions, have also been reported in some of the studies addressing metabolic effects of PCBs.

Liver function abnormalities:

Great effort has been paid to investigate changes in liver function due to PCB exposure. A number of cross sectional studies dealing with this issue have given somewhat conflicting results. Overall data suggest that high exposure to PCBs causes subtle changes in hepatic function – most likely a result of induction of liver metabolizing liver enzymes. Most changes in liver enzymes reported are within normal range.

Accidents:

In 1985 Elo and Seppäläinen investigated the health consequences of high PCB exposure due to the explosion of several PCB containing capacitors (99,100). A few hours after the explosion the air concentration of PCBs was 8,000 - 16,000 µg/m3 (8-16 x 10^6 ng/m^3). Three days after the explosion the highest serum PCB level in the workers performing clean up was 30 µg/L (30.000 ng/l). Probably these workers were as well exposed to chlorinated dibenzofurans during the clean up, this may have attributed to the health effects. The acute symptoms in these workers were irritation of nose, eyes, skin and respiratory tract and general symptoms as nausea, headache and vertigo. Liver function test revealed a transient rise in various enzymes. Some time after the explosion, some workers experienced paresthesia in extremities. Neurophysiologic tests performed 2 and 6 months after the accident revealed that conduction velocities in sensory nerve fibers were slightly and transient reduced.

In 1986 Stark et al published a study of 52 subjects exposed to PCB spill in an office building resulting from a transformer explosion without subsequent fire. Laboratory testing including liver enzymes were unremarkable, mean serum PCB level was 7.0 µg/L (7.000 ng/l) for the exposed subjects. Dibenzofurane formation at the explosion is likely. Transient skin irritation and redness was associated with the PCB exposure (101).

Exposure in indoor air

Only two studies on health effects of indoor air exposure to PCBs were retrieved.

In a study from 2008 by Broding et al 583 subjects working in a PCB contaminated building reported more subjective complaints, answering the 24-item Giessen Subjective Complaints Score List in comparison with 205 non-exposed subjects (102). The symptoms were within the subscales exhaustion, limb complaints and cardiac complaints; the complaints were not related to current PCB plasma concentrations. In a study from 2005 by Peper et al, 30 PCB exposed teachers and employees were compared with 30 unexposed controls (103). Extensive neuropsychological testing was carried out and blood levels of PCBs were estimated. No neuropsychological effects were demonstrated by traditional testing.

9. Overall discussion

Polychlorinated biphenyls became an environmental health concern already in the late 1960's, when it became obvious that these man-made and widely used industrial chemicals are highly persistent in the environment and biomagnify and accumulate in living organisms including humans. In spite of a general worldwide ban of industrial use of these chemicals in the 1970's PCB's can still be measured in fat tissues and other organs in almost every single individual all over the globe even in remote regions. As a consequence numerous experimental and epidemiological studies of health effects of polychlorinated biphenyls and other persistent organochlorines have during the past decades been given high priority in environmental health research. This research has primarily addressed the general population.

New focus on possible exposure from building materials and studies demonstrating that people living in buildings with PCB-containing building materials and people handling these materials during or after demolition may have a substantial PCB exposure on top of the environmental exposure has fuelled new health concerns. It has become a current priority to evaluate the health risks in relation to indoor environment and in relation to worker handling of PCB contaminated material – first of all construction workers, demolition workers and workers involved in waste handling and industrial recycling. The question whether handling of PCB contaminated materials and working in PCB contaminated buildings represents a health hazard is the focus of this report.

We address this question by systematically scrutinising of the scientific literature in order to retrieve and evaluate information on health risk related to PCB exposure in the occupational setting. The evidence database is limited, and the main body of studies is comprised of earlier US and European studies on cancer mortality in industrial capacitor workers.

Risk of cancer
We identified thirteen occupational cancer mortality studies of industrial capacitor workers. The strengths of these studies are sample sizes including several thousands workers, almost complete follow-up for up to 60 years and reliable and independent outcome ascertainment. All studies provide risk estimates adjusted for age and gender but control for life style factors as smoking, alcohol intake and physical activity and for concomitant exposure to other potentially carcinogenic

chemical exposures was not possible, because these studies were based upon follow-up in registries. Potential confounding by other risk factors is hardly a major concern since cancer risk in exposed workers in general was not elevated and negative confounding seems unlikely. Misclassification of the cause of death could lead to both an under- and an over estimation of a given cancer risk but serious differential (exposure related) misclassification is hardly an issue.

Assessment of exposure intensity and duration was based on information on job title, department, work tasks, and hygiene measurement of PCB in air samples, on workplace surfaces or in blood specimens. Information about the use of personal protection equipment, room ventilation and exhaust ventilation systems is sparse as is the information on changes in work methods over the years. The inevitable risk of misclassification of exposure usually tends to blur any effect caused by the exposure and is in particular an issue in studies showing no increased risk. However, this problem is to some degree counteracted by the use of biological indicators of exposure (serum-PCB) in the majority of studies.

Results of the cancer mortality studies are remarkable consistent. They do not indicate an overall increased risk of cancer (all sites) and do not point consistently to increased risk of specific cancers (33,104). It is, however, noteworthy that two studies observed 2-3 fold increased SMR for liver and biliary cancer based on few cases when the compelling evidence for malignant liver tumors following oral ingestion of commercial PCB mixtures in several animal species is taken into account. On the other hand these studies did not control for known strong determinants of primary liver cancer as alcoholic beverages, gallstone and hepatitis. The finding of increased risk of melanoma (two studies) is not supported by animal evidence. Sun exposure is a competing risk for melanoma that was not taken into account.

How do these largely negative and reassuring findings in occupational settings with substantial and long-term PCB exposure comply with IARC and other authoritative risk assessments - a question which is reinforced by the recent IARC evaluation of the most potent dioxin-like congener PCB 126 as a group 1 carcinogen? There are several competing explanations.

First, how does occupational exposure among capacitor workers compare to animal carcinogenicity studies with respect to exposure route, exposure level and congener mixture? In workers the

exposure is predominantly via inhalation and to a lesser extent via skin uptake (Perkins and Knight 1989, cited from ATSDR p 566), while animal studies are based upon oral feeding. No inhalation studies have been performed in animals up to year 2000 (ATSDR 2000). Uptake following inhalation may be less than uptake through the gastrointestinal tract, but the 20-100 times higher levels of total PCB in blood and serum in capacitor workers compared to the general US population clearly indicate an substantial uptake of PCBs among capacitor workers (cf. Tables 6.21 and 6.26 in appendix 5). Furthermore, airborne PCB exposure levels in capacitor industries in the 1950's and 60's were extremely high exceeding present day occupational exposure limit levels (10 $\mu g/ m^3$) by a factor 100-1000 and were associated with clinical signs of intoxication in terms of dermatitis and subclinical signs of intoxication in terms of disturbed metabolism and abnormal liver function. However, the lowest dose of various commercial PCB mixtures that are associated with cancer in comprehensive rodent studies was in the range of 1-2 mg/kg bw/day through 24 months (18), which is two orders of magnitude higher than exposure conferred by an occupational exposure to 1 mg/m^3 PCB in ambient air through 8 hours a day: Assuming a pulmonary ventilation of 6 m^3 ambient air per 8 hours in a worker weighing 70 kg with moderate physical activity this exposure would result in 1mg/ m^3 * 6m^3 /70 kg = 0,01 mg/kg bw per day. Thus, the exposure levels may have been rather low relative to levels causing cancer in experimental animals.

Second, since PCBs have no inherent genotoxic effects and the dioxin-like PCBs are considered tumor promoters rather than initiators this is compatible with exposure levels below which there is no increased cancer risk.

Third, differences in the PCB conger profiles in the occupational and animal experimental context may be even more important for cancer risk. The carcinogenic effects of PCB mixtures are almost entirely attributed to the content of dioxin-like PCB congeners (cf. Kociba 1978, cited from Gunnarsen L et al, Miljøstyrelsen 2009 and the NTP study of PCB 126). Although the commercial PCB mixtures used in the comprehensive animal experiments by Mayes et al (18)is comparable to those handled by capacitor workers, the composition of airborne PCB will be different from commercial mixtures with a lower proportion of the heavier and less volatile highly chlorinated PCB congeners, which encompasses most of the dioxin-like activity of commercial PCB mixtures. Thus the actual uptake of carcinogenic dioxin-like congeners may have been relatively low in exposed workers. Unfortunately there are no studies of body burdens of dioxin-like PCB congeners

in capacitor workers which based upon TEQ values of the twelve dioxin-like PCB congeners would allow a direct comparison with the Aroclor carcinogenicity studies in rodents.

Fourth, there are methodological issues related to the epidemiological studies that should be acknowledged. Most of the reviewed studies reported a lower overall mortality in comparison with the general population reference. This so-called healthy worker effect is due to a selection process excluding unhealthy individuals from the workforce leading to a difference in health status between workers and the general population. It tends to attenuate the effect of the exposure towards the appearance of no effect. It has been suggested, that the healthy worker effect is relatively weak for malignant diseases and stronger for instance for cardiovascular and respiratory diseases. Nevertheless, the healthy worker effect could cause an underestimation of the cancer mortality in the reviewed studies; but it cannot explain the lack of consistency across the studies.

Fifth, cancer mortality studies are less sensitive to detect exposure related effects than cancer incidence studies, since a varying, but large proportion of cancer patients survives their disease. However, for cancer of the liver and biliary tract fatality is high, thus difference in ascertainment between morbidity and mortality studies would probably have minor importance.

Sixth, although years at risk in the cancer mortality studies provide sufficient power to identify overall cancer risk, it may be insufficient for studies of rare specific cancers. Increased risk of the rare cancers of the liver and biliary tract, which is germane considering findings in experimental studies, might not be identified due to limited power of the present studies. None the less elevated risk of this particular cancer type was found in one highly exposed cohort.

Considering the above issues it seems prudent to conclude that occupational long-term high-level airborne and dermal exposure to commercial PCB mixtures is probably not associated with increased overall risk for cancer, but an elevated risk of rare cancers as primary liver and biliary tract cancer may not have been detected by these studies. Extending this evaluation to current indoor exposure in buildings and intermittent exposure through handling of PCB contaminated material among construction and waste management workers, an increased risk for cancer seems unlikely since exposure levels in these settings are several order of magnitude lower compared to

earlier industrial exposure. This line of arguments is supported by the presumed non-genotoxic mechanism of carcinogenicity of PCB.

Risk of non-malignant disease

Epidemiological studies on non-malignant toxicity following occupational exposure are few and addressing different outcomes so the options for an examination of consistency across studies are limited. Other limitations are the cross sectional study design applied by most but not all studies, small sample sizes and for the earlier studies limitations in analytical methods. There is an obvious need for replication of findings in independent studies but, nevertheless, these occupational studies of high-level exposed workers provide suggestive evidence for several human health effects and some results are supported by toxicity studies in animals and mechanistic evidence. This includes skin disorders, subtle thyroid disorders and liver function anomalies, diabetes mellitus, degenerative neurological disease in women, and reduced birth weight in children with prenatal exposure.

Earlier high-level occupational exposure in comparison with current low-level exposure

While earlier industrial capacity worker exposure might reach 5 to 6.000 $\mu g/m^3$ PCB in ambient air, measurements in current construction workers and residents living in contaminated buildings show exposure levels between, respectively, 5 and 400 $\mu g/m^3$ (workers) and 1-5 $\mu g/m^3$ (indoor air) – differences spanning 2-3 orders of magnitude (13). It can be questioned, however, whether the PCB congener exposure profile is comparable across early occupational settings and current exposures including exposure in the indoor environment. Although the air-borne PCB exposure is skewed towards the lighter low chlorinated PCB congeners containing less dioxin-like compounds in both settings, some studies have revealed striking differences in air-borne PCB-congener profile depending on the source of PCBs – for instance as demonstrated for exposure related to PCB ceilings in buildings and PCBs containing flame retarding paints. In any case, the limited evidence of risk of non-malignant disease in occupational studies is inadequate for risk assessment.

Current indoor-air and occupational exposure in comparison with background exposure

Are results of the large and increasing number of population based environmental studies of thyroid disorders, immunologic disorders, diabetes and developmental and reproductive disorders informative when considering risk related to current occupational exposure? In spite of the low volatility of PCB congeners, the predominant route of exposure in the occupational setting is

inhalation of air-borne PCBs. This is contrary to the exposure of the general population, where inhalation exposure is negligible and the predominant route of exposure is through food items. If it is assumed that toxic effects of PCBs primarily are caused by the dioxin-like PCBs one needs to consider the relative contribution to the body burden of dioxin TEQs, which is conferred by the two sources of exposure. According to an estimate based upon national food consumption data performed by WHO (Joint Expert Committee on Food Additives), the monthly median dioxin TEQ contribution from PCBs in various countries is 10-50 pg/kg bw and the 90th percentile 25-130 pg/kg bw (JECFA, Geneve 2002, cited from (16)). The contribution from polychlorinated-p-dibenzodioxins and dibenzofurans is for each class of chemicals of the same order of magnitude. We have not identified published data estimating the dioxin TEQs conferred by occupational PCB exposure, but a German study reported a TEQ concentration of 0.3-0.6 pg/m^3 in buildings with permanent elastic PCB sealants and 1.8-4.7 pg/m^3 in buildings with PCB containing acoustic ceiling tiles (81). This corresponds to about 1%-20% of the average total TEQ intake (our calculation assuming inhalation of 6m^3 per day for 20 days a month, 80% pulmonary absorption and a body weight of 70kg).

Non-dioxin-like PCB congeners constitute more than 95 weight percent of PCBs in ambient air among exposed workers. An increasing body of experimental research demonstrate that these compounds elicit neurobehavioral and endocrine effects through several non-Ah-receptor mediated pathways and some hydroxylated non-dioxin-like PCB metabolites have anti-estrogenic effects and cause hypothyroidism and reduced vitamin A plasma levels. Implications for risk assessment for exposures in the occupational setting with a relatively higher content of low-chlorinated non-dioxin-like PCBs are uncertain (for a review see (20,105)).

10. Overall conclusion and recommendations

This report presents a review of the scientific literature on health effects of PCBs as it has been studied in occupational settings. Most information is derived from epidemiologic studies in cohorts of highly exposed workers handling PCBs before bans on PCBs use was enforced in the 1970's. A few case-series with follow-up and some cross-sectional studies of highly exposed workers together with more recent studies of people exposed to PCBs from building materials and indoor air have also been included. The review has been supplemented with an overview on the toxicology of PCBs in experimental animals and an update on health effects in humans based on recent reviews of studies in the general population with environmental exposure. Based on this information we conclude that:

- Occupational exposure to PCB mixtures during production of capacitors from the 1930's to the mid 1970's was more than hundred times higher than background exposure encountered by the general population during the same period of time

- Current occupational exposure to PCBs in buildings with PCB containing materials is probably significantly higher than background exposure. This exposure is likely to be skewed toward more volatile low-chlorinated PCBs, but the significance of this is unsettled.

- Occupational handling of PCB containing materials during building renovation or waste management results in exposure that only to a limited extend is characterized. It can be assumed that the exposure is similar to the handled materials in congener composition and that the quantitative exposure depends on well-known parameters as cumulated external exposure and effectiveness of protective equipment.

- Based on animal and mechanistic evidence PCB's as a group are classified as likely carcinogens (IARC-group 2A). The most potent dioxin-like PCB congener PCB 126 is classified as a human carcinogen (IARC group 1). The mechanism of carcinogenesis is probably tumour promoting rather than tumour initiating.

- Cancer caused by industrial handling of PCB has been studied in several historical cohort studies. There is no evidence of an increased cancer risk in these populations despite high-level exposure and long-term follow-up. However, uncontrolled methodological issues might obscure a small increased risk of rare cancers as liver and biliary tract tumours.

- In animal experiments PCBs have produced non-cancer effects including change in liver and immune functions, metabolism of lipids, porphyrins and vitamin-A, and the endocrine, the

reproductive and the nervous system. Similar effects have been reported in humans following accidental exposure and in some large epidemiological studies of humans with environmental exposure.

- In highly exposed occupational groups dermal abnormities including chloracne and subtle changes in hepatic function have been described in several cross-sectional studies. However the exposure is not sufficiently characterized to rule other relevant exposures out.

- Occupational exposure has also been associated with non-malignant effects on endocrine organs as the thyroid gland and pancreas, and of immune modulating effects. Some data are suggestive of an effect of PCBs on neurodegenerative disease in women. However these observations are based on few studies with limited methodological strength and the results should be replicated.

- Small decrease in birth weight and in gestational age has been associated with occupational PCB exposure in pregnancy.

- There is no evidence that human air-borne exposure at current concentration levels encountered in indoor air and in occupational setting is related to increased risk of disease or reproductive disorders, but the evidence base is limited with respect to number and quality of studies.

Recommendations

Although the observations in occupational highly exposed groups are reassuring with respect to cancer, the experimental and mechanistic data on carcinogenic and other health outcomes calls for precautious measures that eliminate any unnecessary occupational exposure to PCBs. Precautious measures include:

1. Mapping of PCB containing building materials and industrial products in Denmark enabling employees and workers to prevent exposure by appropriate action

2. Adequate protection of airways and skin when handling PCB containing material in accordance with guidelines set by the Danish Labour Inspection Service (whole body cover, filter mask and gloves)

3. Biological monitoring of relevant PCB congeners among workers performing long-lasting work tasks with potential exposure to PCBs

4. Development of biological threshold-limit values for specific congeners or groups of congeners to allow for risk-assessment and management.

5. Pregnant women should not perform work tasks associated with release of PCB congeners, but indoor air exposure in office buildings and institutions are not considered hazardous.

6. Due to PCB's status as a likely human carcinogen certain cancers like liver-biliary and thyroid cancer should be accepted for compensation as occupational disease if exposure to dioxin-like PCB congeners clearly has exceeded the exposure of the general population.

Recommendations on future research

1. Methods for quick determination of PCB content in building materials should be developed to ensure safe handling.

2. Purposeful research on exposure in indoor environment including routes and ways of exposure and congener-profiles.

3. Epidemiologic follow-up studies of with sensitive markers of metabolic, endocrine, immune, reproductive and nervous system outcomes in large groups of employees and residents with long-term exposures clearly exceeding background exposure.

4. Experimental studies on the toxic effects of non-dioxin-like PCBs relevant in relation to human exposure.

Appendix 1: Literature search

Our literature search was performed in PubMed. The search used the following terms:
(Polychlorinated Biphenyls [MesH] OR Aroclors[MesH] OR pcbs[All fields] OR polychlorinated biphenyls [All fields] OR aroclors[All fields]) AND ("Occupational exposure" [MesH] OR "Occupational diseases" [MesH] OR "Accidents, Occupational" [MesH] OR "workplace" [MesH] OR "Air Pollution, Indoor" [MesH] OR occupational [All fields] OR capacitor [All fields] OR "work place" [All fields] OR "workplace" [All fields] OR "indoor air" [All fields]). The search limits were: Only human studies; language: English, Danish, Swedish or Norwegian.

The weekly automatic PubMed search was terminated at the end of April 2012.

Only studies concerning occupational exposure were included. We included studies describing diseases, clinical and laboratory tests or other para-clinical findings as a possible consequence of occupational PCB exposure.

Studies with complex chemical exposure and studies without measurements of the PCB exposure were excluded. Studies without a control group or internal control were excluded except a few descriptive studies of capacitor accidents and some studies concerning dermal and pulmonary findings.

If there were doubts to whether a study should be included or not, it was discussed between members of the group.

With this search strategy 581 original scientific studies were identified. After reading titles, abstracts or the whole article 40 studies were selected.

Additionally six studies were retrieved from reviews, references in other studies; search on Embase, and from members in the working group.

Thirteen of the studies had cancer as end-point and the remaining 33 studies had several other diseases or health effects as focus.

Appendix 2: Findings in studies addressing cancer

Thirteen occupational cohort studies concerning cancer mortality and cancer incidence were identified; they are summarized in table 1. Each study will be described shortly below.

The American cohort studies

9 of the selected occupational cohort studies were carried out in United States in a population of workers from 3 capacitor-manufacturing plants. One plant was located upstate New York; this plant had two sites located 1 mile apart. The two other similar plants were located in Massachusetts and Indiana.

Study	Upstate new York (Plant 1)	Massachusetts (Plant 2)	Indiana (Plant 3)
Brown and Jones1981	x	x	
Brown 1987	x	x	
Nicholson 1987 *	x		
Taylor 1988*	x		
Sinks et al 1992			x
Kimbrough et al 1999	x		
Kimbrough et al 2003	x		
Ruder et al 2006			x
Prince et al May 2006	x	x	
Prince et al Oct. 2006	x	x	
Silver et al 2009	x	x	x

Distribution of studies of worker cohorts on three American capacitor plants.
* Not published in peer-reviewed journal

Brown and Jones (1981) (106)did a historical follow-up study of 2567 workers from two electrical capacitor plants (plant 1 and 2). From 1940-1976 39.018 person-years were identified among workers employed at least 3 months in areas with known high PCB exposure. In 1977 air samples were taken determining PCBs and trichloroethylene, tin, lead, zinc, aluminum, iron and toluene, but no further analyses were carried out. The authors noted that potential carcinogenic stabilizers were added to the PCBs (1 % or less) from the early 1960s mentioning diglyceride ether-disphenol-a and vinyl cyclohexene dioxide.
Vital status was determined for 98 % of the study population at end of follow-up. Cause of death was obtained from death certificates. All-cause mortality was lower than expected (163 deaths were registered vs.182.4 expected according to US mortality rates and so was all cancer mortality (39 observed vs. 43.8 expected). There was no excess mortality from cancer of the stomach, intestine, pancreas, respiratory system, and breast, hematopoietic or lymphatic systems. No observed deaths were due to malignant melanoma. A non-significant excess mortality was found for rectal cancer and liver cancer. The only statistically significant excess mortality occurred in women from the Massachusetts plant for rectal cancer, with 3 observed deaths vs. 0.50 expected, SMR 336, p < 0.05.
No association between duration of exposure and length of latency period and cancer mortality was found. The authors pointed out that their findings are only tentative, due to the relatively small numbers of deaths and the short period of observation.
In 1987 *Brown* (84) published an update on the mortality study from plant 1 and 2 presented by Brown and Jones in 1981. Seven years of observation were added, and 21 workers who met the inclusion criteria's were added to the cohort giving a total of 2,588. The number of deaths had increased from 163 to 295. As in the former study no excess mortality was found for all causes (295 observed vs. 318 expected) or for all cancers (62 observed vs.80 expected). The only new finding was a statistically significant mortality rate for cancer in the liver, gall bladder and biliary tract 5 observed deaths vs. 1.9 expected; p< .05. The SMR for rectal cancer in women in the Massachusetts plant remained elevated, but no longer statistically significant so. Brown noted that compared to the original study, the change in SMRs for most of the major death groupings is

minimal. Pathology- and hospital reports revealed that one of the 5 deaths was due to metastatic disease with unknown primary site; one was possibly of hepatic origin while the rest were cancers developed from the biliary tract system. In four of the cases duration of employment at the plant was 1.5 year or less. Brown concluded, that it "remains difficult to interpret the findings in regard to PCB exposure".

Sinks T et al (1992) conducted a historic follow-up study involving 3,588 electrical capacitor manufacturing workers from a plant in Indiana (plant 3) (107). PCB was used in this plant from 1957 to 1977. Aroclor 1242 was used from 1957 to 1970; Aroclor 1016 was used from 1971 and onward. Area air samples and personal breathing zone samples were taken in 1977. Serum PCB-levels of the workers were collected the same year. Vital status was determined in 1986. Proportional hazards modeling was performed to determine whether a dose-response relationship existed between cumulative PCB-exposure and mortality from site specific cancer.
All-cause mortality (192 deaths observed, 283.3 expected) and total cancer mortality (54 deaths observed, 63.7 expected) were lower than expected. Significantly more deaths were observed than expected for malignant melanoma – eight deaths observed vs. two expected SMR= 4.1, 95% CI 1.8-8.0. The death rate for brain and nervous system cancers was non-significantly elevated: 5 deaths observed 2.8 expected, SMR=1.8, 95% CI 0.6-4.2. The average estimated cumulative dose for the cases of brain cancer was greater than for other workers. The risk of malignant melanoma was not related to cumulative PCB exposure. The follow-up was relatively short with less than 10% of the person-years at risk were calculated with more than 19 years since date of hire. It was noted by the authors, that the healthy worker effect together with the inclusion of persons lost to follow up could be part of the explanation for the low overall mortality of the cohort. The authors concluded that the results provide some evidence of an association between employment at this plant and malignant melanoma and cancer of the brain, but that their findings could be due to chance, bias, or confounding.

In 1999 *Kimbrough* et al (108) published a mortality study involving 7,075 workers employed at a capacitor manufacturing plant up-state New York (plant 1). A total of 212,778 person-years were calculated from 1946 to1993. The employees were divided by sex and type of employment into hourly workers or salary workers. Average follow–up time was 31 years, 85% of the cohort was observed for at least 20 years. SMRs were calculated and compared to mortality rates in US general population and eight regional counties.
The total number of deaths was 1,195. Vital status was obtained from 98.7 % of the cohort.
PCB exposure consisted of Aroclor 1254 until about 1954; Aroclor 1242 until 1971 and from 1971-1977 Aroclor 1016 was used. PCB exposure was measured by area air samples from high and low exposure areas in the plant. Toluene and trichloroethylene, lead, aluminum and iron air levels were measured from selected areas of the plant, all measurements showed low air levels and exposure was assessed as limited. High and low chlorinated PCB levels were measured in serum of 290 self-selected employees.
All jobs were classified according to their levels of PCB exposure addressing both inhalation and dermal exposure. High-exposed workers were divided into three categories (worked in a high exposure job: Ever, at least 6 months or at least one year). Length of exposure was divided into categories: <1year, 1 to < 5 years, 5 to < 10 years and ≥ 10 years. Two latency categories were defined: ≤ 20 years and > 20 years.
The study showed a marked healthy worker effect with no statistically significant increases in all-cause mortality and all-cancer mortality. Among the most highly exposed workers there was no significant excess mortality, and the SMRs did not increase with length of cumulative employment and latency. Analyses for site specific cancers didn't show any significant elevations in SMR except for connective tissue cancer with two observed deaths vs. 0.2 expected, SMR 1290; 95% CI 156-4659 in salaried female workers. One of the two neoplasms was a pericytoma (a borderline malignancy). SMRs for liver cancer in the cohort were similar to those of the US-population.

In 2003 *Kimbrough* at al (109) made an up-date of the cohort study published in 1999. Five years of observation were added for the 7075 capacitor workers providing 235,984 person-years and a total of 1654 deaths. Vital status was determined in 1998. Again no significant excess mortality from all causes, all cancers or site specific cancer could be demonstrated, except for connective tissue cancer among salaried women as in the study from 1999.

In 2006 *Ruder* et al (110) published a follow up on the worker cohort from the Indiana capacitor plant (plant 3) studied by Sinks et al in 1992. 3,569 workers exposed to PCBs from 1957 to 1977 were included. Mortality was updated through 1998. Cumulative exposure assessment was based on a job–exposure matrix. Overall mortality was lower than expected (547 deaths; SMR 0.81; 95% CI, 0.7–0.9). There were 171 all-cancer deaths, SMR 0.90; 95% CI 0.80-1.0. Melanoma remained in excess (9 deaths; SMR 2.43; 95% CI, 1.1–4.6), but was not associated with estimated cumulative exposure. There were 12 brain cancer deaths (SMR 1.91; 95% CI, 1.0–3.3) 7 of the brain cancers occurred after the original study by Sinks. The brain tumors were 8 gliomas and 4 carcinomas, two of the latter may have been metastatic. Brain cancer mortality did not demonstrate a clear dose–response relationship with estimated cumulative exposure.
One of the melanomas was diagnosed prior to employment and one melanoma was located in the gall bladder. There was no information about sun exposure.

In May 2006 *Prince et al* (83) published a follow up on the cohort studied in 1981 by Brown and Jones and in 1987 by Brown. Vital status was updated through 1998 for 2,572 highly exposed workers from two electrical capacitor manufacturing plants (plant 1and 2). Standardized mortality ratios (SMRs) were calculated using national and county referent rates. Duration of employment was used as a proxy for exposure.
Overall mortality was similar to expected 798 deaths, SMR 0.99; 95% CI 0.92-1.06 and so was all cancer mortality 218 deaths, SMR 1.01 95% CI 0.88-1.15. As in the follow-up by Brown in 1987, mortality from biliary passage, liver and gall bladder cancer was significantly elevated (11 deaths, SMR 2.11, 95% CI 1.05 - 3.77), but mortality from rectal cancer was not (6 deaths, SMR 1.47, 95% CI 0.54 - 3.21). Among women, mortality from intestinal cancer (24 deaths, SMR 1.89, CI 95% 1.21 - 2.82) and from category "other diseases of the nervous system and sense organs", which include Parkinson's disease and amyotrophic lateral sclerosis were elevated, (15 deaths, SMR 2.07, CI 95% 1.16 - 3.42). In women there were four deaths from ALS, (SMR 4.35, CI 95% 1.19-11.14). No associations between mortality and duration of employment were observed for the cancers of interest. Prostate cancer was not elevated; 7 deaths, SMR 1.14 95% CI 0.46-2.35. Because of the small numbers of deaths and the lack of an exposure-response relationship with duration of employment no conclusion was drawn regarding PCB exposure and these causes of death.

In the study by *Prince et al* from October 2006 (111) an existing cohort of highly exposed workers (n=2,588) at two capacitor manufacturing plants (plant 1 and 2) was expanded to include all workers with at least 90 days of potential PCB exposure during 1939–1977 (n=14,458). Vital status of the workers was ascertained in 1998. Cumulative PCB exposure was estimated by a semi quantitative job exposure matrix using detailed job descriptions and process information. Jobs were assessed separately for potential inhalation and dermal exposures. Plant-specific air concentrations were used to assign values to the qualitative inhalation and dermal exposure ratings (high, medium, low, background). Combined inhalation and dermal exposure scores were calculated, the cumulative exposure expressed in "number of unit-days". Concomitant exposure to trichloroethylene was evaluated. Cause of death was obtained from death certificates. Standardized mortality ratios (SMRs) were calculated using national and county referent rates.
Among women, intestinal cancer mortality was elevated with 67 deaths observed, SMR 1.31; 95% CI 1.02–1.66, especially in higher cumulative exposure categories, but without a clear trend. There was a significant increase in myeloma mortality in all workers with 28 deaths observed, SMR 1.85, 95% CI 1.23-2.67, but there was no significant exposure response trend. It is stated by the authors, that the analyses only provided suggestive evidence of that PCB exposure did contributed to the observed excess myeloma mortality. Among men, stomach cancer mortality was elevated 24 deaths; SMR 1.53; 95% CI, 0.98–2.28 and increased with cumulative exposure (trend *p*-value = 0.039). Prostate cancer mortality, which was not elevated (34 deaths; SMR 1.04; 95% CI, 0.72–1.45), increased with cumulative exposure (trend *p*-value = 0.0001). Mortality was not elevated for liver cancer; 21 deaths; SMR 0.89; 95% CI, 0.55–1.36, but increased with cumulative exposure (trend *p*-value = 0.071). No excess in all-cause mortality or all cancer mortality was demonstrated. Mortality from Non-Hodgkin Lymphoma, melanoma, and rectal, breast, and brain cancers were neither in excess nor associated with cumulative exposure.

Silver et al (2009) (87) followed 5752 women employed for at least 1 year in one of three capacitor manufacturing facilities (plant 1, 2 and 3), identifying breast cancer cases from questionnaires, cancer registries, and death certificates through 1998. They collected lifestyle and reproductive information via questionnaire from participants or next of kin and used semi quantitative job-exposure matrices for inhalation and dermal exposures combined. Standardized incidence ratios (SIRs) and standardized rate ratios were generated and used Cox proportional hazards regression models to evaluate potential confounders and effect modifiers.

Overall, the breast cancer SIR was 0.81 (95% confidence interval, 0.72–0.92; *n* = 257). Regression modeling showed little effect of employment duration or cumulative exposure. For 362 non-white women statistically significant associations with employment duration and cumulative exposure were found; only smoking, birth cohort, and self- or proxy questionnaire completion had statistically significant explanatory power, when added to models with exposure metrics. It was concluded, that there was no overall elevation in breast cancer risk after occupational exposure to PCBs.

European studies

In 1982 *Bertazzi* et al (112) did a historical follow-up study of 1,310 male and female workers employed at an Italian capacitor plant located close to Milan. The workers were exposed to PCBs with the trade names Aroclor and Pyralene. During the observation period the chlorine content of the PCB mixture declined from 54% to 42%. The use of PCBs was banned in 1979 in Italy.
The study covered 25 years (1954-1978) and included workers with at least 6 months of employment, administrative workers were excluded. As a reference the mortality of the city the plant was located in was used. Vital status was ascertained for 98% of the cohort and 20,565 person-years were included.
Twenty-seven deaths were registered. For males overall mortality was lower than expected, there were 8 cancers observed vs. 3.3 expected, SMR=241; 95% CI 104-475. Mortality from neoplasms in digestive organs, peritoneum and lymphatic and hematopoietic tissue was in excess, but not significantly so.
The overall mortality among female workers was significantly increased with 15 deaths observed vs. 7.7 expected; SMR= 194; 95% CI 109-320. Six neoplasms were observed vs. 2.3 expected, this finding was not significant; the cancer sites were mainly lymphatic and hematopoietic. Five violent deaths for the female workers were observed against 2.2 expected.
The small number of deaths prevented stratification by type of exposure, duration of exposure and latency. Because of small numbers and a rather young worker population the authors stated, that any conclusion could only be tentative.

Bertazzi et al. published a historical cohort study in 1987 (113) involving 1556 workers who had worked at least one week on a the same capacitor manufactory plant described above. The PCBs used were Aroclor and Pyralene as described above. All workers in the building including workers in the administration were included in the study, because it was discovered, that surfaces all over the building was contaminated with PCBs. Measurements of PCB contamination of workplace surfaces and the workers hands were carried out. Area air samples were taken and PCBs were measured in the blood of a limited number of workers, selected as representative to the "typical" exposure conditions of the plant. It wasn't possible to make a quantitative description of the exposure of each worker. According to this study the use of PCBs was completely abandoned in 1980 in Italy.
Sixty-four deaths were reported. For the male workers (n=544) the overall mortality didn't differ from the expected, but there was a significant excess mortality for all cancers with 14 observed vs. 5.5 exp. according to national and 7.5 exp. according to local reference populations (SMR 253 and 183 respectively). Cancer in "the digestive tract" was significantly higher than expected with 6 deaths observed vs. 1.7 exp. nationally, SMR: 346 and vs. 2.2 exp. locally, SMR: 274. The cancers were: two stomach cancers, two pancreas cancers, one liver cancer and one cancer in the biliary tract. A non-significant excess mortality was found for hematologic neoplasms with 3 observed vs. 0.8 and 1.1 exp. nationally and locally.
For the 1,556 female workers there was significant excess in all-cause mortality with 34 observed deaths vs. 16.5 expected local; (SMR: 206). The excess mortality was primarily due to cancer and accidents.

Mortality due to cancer was significantly increased with 12 observed vs. 5.3 exp. local, SMR 226. Mortality due to hematologic neoplasms was significantly elevated with 4 observed deaths compared to the local mortality rate on 1.1. For the hematopoietic neoplasms the duration of exposure was 3 months in one case and 8 months in another, latency time was 3 months in one case and two years in another. The cancer sites were stomach (1), breast (2) ovary (1) lung (1) rhinopharynx (1) brain (1) and one with unknown primary site. The remaining 4 cancers were hematologic neoplasms.

There was no pattern or trend for mortality when analyses for duration of exposure or latency were carried out for both sexes. The authors concluded, that the study "did not permit a causal association to be either proved or dismissed".

According to a review by Golden R et al (114) *Tironi* et al. made a follow up on the *Bertazzi* cohort in 1996. The article was published in Italian, and therefore not part of this review. In summary Tironi et al couldn't confirm the previously reported excess mortality caused by cancer in certain sites found by Bertazzi et al. The only significant excess mortality in the study was due to accidents and trauma.

In 1986 *Gustavsson et al* (85) investigated mortality and cancer incidence in a cohort study of 142 male capacitor manufacturing workers employed for at least 6 months between 1965 and 1978. 42% chlorinated PCBs were used at the factory between 1960 and 1978. The observation period was until 1982 for mortality and from1965 to 1980 for cancer incidence. The use of PCBs was banned in Sweden in 1978.

Air samples from the working area were collected in 1973. No excess in mortality or cancer incidence was demonstrated. One person had developed a slow growing mesenchymal tumor and a malignant lymphoma. The authors considered their study to be inconclusive due to small size of the cohort and a brief follow up period.

In 1997 *Gustavsson and Hogstedt* (86) made a follow up on the cohort studied in 1986. They expanded the cohort to 242 male workers employed for at least 6 months, and followed mortality and cancer incidence from 1965 to 1991. All cohort members were classified as low- or high exposed based on their work task, length of employment and latency time. Causes of deaths were obtained from death certificates; cancer registrations were obtained from the Swedish National Cancer Registry. Some cases were supplied with the results of histological examination.

In the entire cohort, there was no significant excess in all-cause mortality or cancer mortality. There were two cases of cancer in the liver and bile duct system (one cholangiocarcinoma and one Papilla Vateri cancer), no significant increase in mortality for any tumor type. The cancer incidence was lower than expected: 18 obs. 20.81 exp., SIR=86; 95%; CI 51-137. Mortality from all causes was significantly elevated for high exposed workers with at least 10 years of latency: 21 obs., 10.86 exp., SMR=193; 95%; CI: 120-296. This was due to cancer and cardiovascular disease.

There was significant excess of cardiovascular deaths in the high exposure group employed at least 5 years with a latency of 20 years or more: 5 obs., 1,52 exp., SMR=328; 95%; CI 107-766.

There was no information about smoking, alcohol intake, medication, diet, family history etc.

Table 1a

Study /year/location	Study design	Population	Source and measure of exposure	Outcome
Brown and Jones, 1981, USA (106)	Historical cohort study Mortality/cancer Study period: 1940-1976 Exposure measurements were carried out in 1977 Vital status for 98% of the cohort	2567 workers from capacitor plant 1 and 2 M:1258 F:1309 At least 3 months of employment in plant areas with high PCB-exposure 39,018 PY Number of deaths: 163	Aroclor: 1254, 1242, 1016 TWA personal air samples (1977): Plant 1: 24 $\mu g/m^3$ – 393 $\mu g/m^3$ Plant 2: 170 $\mu g/m^3$ – 1260 $\mu g/m^3$ TWA area air samples (1977): Plant 1: 3 $\mu g/m^3$ – 476 $\mu g/m^3$ Plant 2: 50 $\mu g/m^3$ – 810 $\mu g/m^3$	All-cause mortality: 163 obs. vs. 182.4 SMR 89; 95% CI 76-104 exp.) All-cancer mortality: 39 obs. vs. 43.8 exp. SMR 89; 95% CI 63-122 Non-significant excess mortality for: rectal cancer (4 obs. vs. 1.19 exp. SMR 336; 95% CI 92-860) and liver cancer (3 obs. vs. 1.07 exp. SMR 280; 95% CI 58-820) Women from plant 2: Significant elevated mortality for rectal cancer 3 obs. vs. 0.50 expected, SMR 336, p<0.05. No dose-response relationship between SMR and duration of employment and latency.
Brown 1987, USA(84)	Follow up on the historical cohort study from 1981 described above. Study period: 1940-1982 Blood samples in 1976 and 1979 Vital status for 96% of the cohort	2588 workers from capacitor plant1 and 2 Number of deaths: 295	PCB-blood levels in plant 1: 1976 Geometric mean serum levels: Aroclor 1242: 1470 ppb Aroclor 1254: 84 ppb 1979 Geometric mean serum levels: Aroclor 1242: 277 ppb Aroclor 1254: 54 ppb (No blood levels from plant 2) Plant 1 area air sampling (1975) 260 $\mu g/m^3$ – 1160$\mu g/m^3$ 360 $\mu g/m^3$ – 2000$\mu g/m^3$ Background population geometric mean serum levels: Aroclor 1242: 6.6 ppb Aroclor 1254: 14.4 ppb	All-cause mortality: SMR 97; 295 obs. vs. 318 exp. All-cancer mortality: SMR 78; 62 obs. vs. 80 exp. Significant excess in deaths in disease category including: cancer of the liver (primary and unspecified), gall bladder and biliary tract (5 obs. vs. 1.9 exp.; p<.05). No dose-response relationship between SMR and duration of employment and latency.

Study /year/location	Study design	Population	Source and measure of exposure	Outcome
Sinks et al 1992, USA (107)	Historical cohort study Mortality/cancer Exposure period:1957-1977 Vital status for 96% of the cohort Fewer than 10% of the person-years at risk were calculated with more than 19 years since date of hire.	3588 workers from capacitor plant 3 M:2742 F: 846 Workers employed for at least 1 day	Aroclor 1242 from 1957 to 1970 Aroclor 1016 from 1971 to 1977 1977 PCB mean serum levels: 98 – 763 ng/mL 1977 PCB personal air samples mean level: 38 µg/m^3 1977 area air samples mean level: 16- 76 µg/m^3	All-cause mortality 192 deaths obs. SMR =0.7; 95% CI 0.6-0.8 All-cancer mortality 54 deaths obs. SMR = 0,8; 95% CI 0.6-1.1 Skin cancer mortality: 8 deaths obs. vs. 2 exp. SMR= 4.1, 95% CI 1.8-8.0 All 8 skin cancer deaths were due to malignant melanoma. No dose response relationship for level of PCB-exposure, duration of employment or latency. One of the malignant melanomas was diagnosed prior to employment, removing this case SMR was 3.5, 95% CI 1.4-3.7 The death rate for brain and nervous-system cancers was non-significantly elevated: 5 deaths obs. 2.8 exp. SMR=1.8, 95% CI 0.6-4.2 No excess death rates were reported for other cancers.
Kimbrough et al, 1999, USA (108)	Historical cohort study Mortality/cancer Study period 1946-1993 Vital status for 98.7% of the cohort	7075 workers from capacitor plant 1 and 2 M: 4062 F:3013 At least 3 months of employment Total number of deaths: 1,195 (M: 763, F:432) PY: 212,778 Socioeconomic information: education	Aroclor 1254,1242,1016 Area air samples, high exposure 1975: 227-1500 µg/m^3 1977: 170 -576 µg/m^3 Area air samples, low exposure 3- 50 µg/m^3 Serum levels: 6-2530 ppb (ng/mL) for lover chlorinated PCBs 1-546 ppb (ng/mL) for higher chlorinated PCBs General population average 5-7 ppb	Hourly male workers all-cancer mortality: SMR=81; 95%CI 68-97 Hourly female workers all-cancer mortality: SMR= 110; 95% CI 93-129 No significant elevation in mortality for any site-specific cause was found in the hourly workers. Salaried male workers all-cancer mortality: SMR=69; 95% CI 45-118 Salaried female workers all-cancer mortality: SMR=75;95%; CI 45-118 No significant elevations in site-specific cancer mortality were found in the salaried workers except for: connective tissue cancer: 2 obs. vs. 0.2 exp. (one pericytoma borderline malignancy) SMR=1290; 95%; CI 156-4659 in salaried female workers. No SMR increase with length of cumulative employment and latency

Study /year/location	Study design	Population	Source and measure of exposure	Outcome
Kimbrough et al, 2003, USA (109)	Follow up on the historical cohort study from 1999 described above. Study period 1946-1998 Vital status for 98% of the cohort	7075 workers from capacitor plant1 and 2 M: 4062 F:3013 Total number of deaths: 1654 (M:, F:432) PY: 235,984	As above.	Hourly male workers all-cause mortality: SMR=95; 95% CI 88-102 Hourly female workers all-cause mortality: SMR= 104; 95% CI 95-112. Hourly male workers all cancer mortality: SMR=98; 95% CI 84-112 Hourly female workers all cancer mortality: SMR=110; 95% CI 94-126. No significant elevation in mortality for any site- specific cause was found in the hourly workers. Salaried male workers all-cause mortality: SMR=59; 95% CI 51-56 Salaried female workers all-cause mortality: SMR=79; 95% CI 62-98 Salaried male workers all-cancer mortality: SMR=77; 95% CI 61-95 Salaried female workers all-cancer mortality: SMR=84; 95% CI 55-122 Connective tissue tumors among female salaried workers: SMR 956; 95% CI 115-3451. No other excess site-specific cancer death was found among salaried workers.
Ruder et al, 2006, USA (110)	Historical cohort study Mortality/cancer, follow up on the study by Sinks from 1992 Exposure assessment in 1977: blood samples, personal and area air sampling and skin smear samples. Vital status for 97% of the cohort Study period: 1960-1998 Job exposure matrix	3569 workers from capacitor plant 3 M: 2717, F:852 Number of deaths 547 Analyses were carried out for workers employed at least 3 months	Aroclor 1242 was used from 1957 to 1971, Aroclor 1016 from 1971-1977 Mean serum level in high exposure workers: 546 ng /mL Mean serum level in low exposure workers: 111 ng /mL	Mortality overall was reduced: 547 deaths; SMR= 0.81; 95% CI, 0.7–0.9. Over all cancer mortality: 171 deaths; SMR=0.90; 95% CI, 0.8-1.0. Melanoma: 9 deaths; SMR= 2.43; 95% CI, 1.1–4.6. No association with estimated cumulative exposure. One melanoma was located in the gall bladder; one melanoma was diagnosed prior to employment. No information about sun exposure. 12 deaths were caused by brain cancer, SMR=1.91; 95% CI, 1.0–3.3. Two of the brain tumors may have been metastatic. Brain cancer mortality did not demonstrate a clear dose–response relationship with estimated cumulative exposure.

Study /year/location	Study design	Population	Source and measure of exposure	Outcome
Prince et al, May 2006, USA (83)	Historical cohort study. Follow up on the cohort described in 1981 by Brown and Jones and in 1987 by Brown. Vital status for 99% of the cohort	2572 highly exposed workers from capacitor plant 1 and 2 M:1247, F1325 Number of deaths 798 PY: 93,623	Same exposure data as in the studies from 1981 and 1987 by Brown	Overall mortality: 798 deaths obs., SMR=0.99; 95% CI 0.92-1.06 All cancer mortality: 218 obs., SMR=1.01; 95% CI 0.88-1.15 Death from cancer in biliary passage, liver and gall bladder was significantly elevated: 11 obs., SMR=2.11; 95% CI 1.05-3.77 Mortality caused by intestinal cancer was significantly elevated in women: 24 obs., SMR=1.89; 95% CI 1.21-2.82. There were no association between mortality and duration of employment.
Prince et al, October 2006, USA (111)	Historical cohort study. Mortality/ cancer Follow up on the cohort described in 1981 by Brown and Jones and in 1987 by Brown. Exposure period: 1939-1977. Vital status determined in 1998 Vital status for 95% of the cohort	14458 workers from capacitor plant 1 and 2 M: 6497 F:7961 All workers with at least 90 days of employment PY: 496,123	Same exposure data as in the studies from 1981 and 1987 by Brown Job exposure matrix (JEM)	Over-all mortality 3417 obs. SMR=0.93;95% CI 0.90-0.96 All cancer mortality 1015 obs. SMR= 1.00; 95% CI 0.94-1.06 Significant elevated intestinal cancer mortality in women: 67 obs. SMR=1.31; 95% CI 1.02-1.66, especially in the higher exposure groups but with no clear trend. Significant increase in myeloma mortality in all workers: 28 deaths obs. SMR=1.85; CI 1.23 – 2.67.

Study /year/location	Study design	Population	Source and measure of exposure	Outcome
Silver et al, 2009, USA	Historical cohort study Breast cancer incidence Study period 1940-1998 Exposure period 1939-1977	5752 female workers from capacitor plant 1, 2 and 3 281 cases of breast cancer Employed for at least 1 year	PCB exposure period for the 3 plants ranged from 1939-1977 Exposure data from earlier studies of the same cohort (Brown1981and 1987 Sinks 1992) Job exposure matrix (JEM). Cumulative exposures estimated with JEM corresponded well with serum PCB levels	Overall, the breast cancer SIR was 0.81; 95%; CI 0.72–0.92; number of cases: 257, occurring in1970 or later. Regression modeling showed little effect of employment duration or cumulative exposure. For 362 women of questionnaire-identified races other than white, positive, statistically significant associations with employment duration and cumulative exposure was observed. Information from questionnaire: Family history, reproductive history, lifestyle factors and demographic parameters.
Bertazzi et al, 1982, Italy (112)	Historical cohort study Mortality/cancer Study period: 1954-1978 Vital status for 98% of the cohort. PCB measured in blood, on workplace surfaces, on workers hands, in air samples.	1310 workers M: 290 F: 1020 from a capacitor plant At least 6 months of employment at the plant. 20,565 PY Number of deaths: 27	Aroclor 1254, Pyralene 1476 Pyralene 3010, 3011 In 1954 air concentrations of Aroclor 1254 ranged between $5,200\mu g/m^3$ - $6,800\mu g/m^3$. In 1977 air concentrations of Pyralene 3010 ranged between $48\mu g/m3$ and $275\mu g/ m^3$. Blood samples from 67 workers in 1977: Mean blood level of 54% chlorinated PCB: 231 ppb Mean blood level of 42% chlorinated PCB: 114 ppb	**Male workers:** All-cause mortality: 12 obs. vs. 12.7 exp. SMR= 94. All cancers mortality: 8 obs. vs. 3.3 exp. SMR=241; 95% CI 104-475. **Female workers**: All-cause mortality: 15 obs. vs. 7.7 exp. SMR= 194; 95% CI 109-320. All cancer mortality: 6 obs. vs. 2.3 exp. SMR= 258 (not significant) (SMR reference was the mortality of the city where the plant was located)

Study /year/location	Study design	Population	Source and measure of exposure	Outcome
Bertazzi et al, 1987, Italy (113)	Historical cohort study Mortality/cancer Study period: 1946-1982 Vital status for 99% of the cohort. PCB measured in blood, on workplace surfaces, on workers hands, in air samples.	2100 workers M: 544 F: 1556 from a capacitor plant At least 1 week of employment in the plant. 41,019 PY Number of deaths: 64	Aroclor 1254, Pyralene 1476 Pyralene 3010, 3011 In 1954 air concentrations of Aroclor 1254 ranged between $5,200\mu g/m^3$ - $6,800\mu g/m^3$. In 1977 air concentrations of Pyralene 3010 ranged between $48\mu g/m3$ and $275\mu g/m^3$. Mean serum concentrations of PCB with 54% chlorine content were: In 1977: 282.8 ppb In 1982: 202.8 ppb. Mean serum concentrations of PCB with 42% chlorine content were: In 1977 142.8 ppb In 1982 42.9 ppb	**Male workers**: All-cause mortality: 30 obs. vs. 27.8 exp. SMR=108. All cancers mortality: 14 observed vs. 5.5 exp. according to national reference population SMR=253; 95% CI 144-415. Cancer in "the digestive tract": 6 obs. deaths vs. 1.7 exp. according to national reference population SMR=346; 95% CI 141-721. **Female workers**: All-cause mortality 34 obs. deaths vs. 16.5 expected according to local mortality; SMR: 206; 95% CI 145-285. All cancer mortality 12 obs. vs. 5.3 exp. according to local reference population, SMR 226, 95% CI 123-385. Hematologic neoplasms was significantly elevated with 4 obs. vs. 1.1 exp. according to local reference SMR= 377; 95% CI 115-877. For the hematopoietic neoplasms the duration of exposure was 3 months in one case and 8 months in another, latency time was 3 months in one case and two years in another.
Gustavsson et al, 1986, Sweden (85)	Historical cohort study Mortality and cancer incidence Exposure measurement was carried out in 1973 Study period 1965-1982/80 Vital status for all but 3 workers (98%)	142 male workers from a capacitor plant Employed at least 6 months Number of deaths 21	42% chlorinated PCBs was used from 1960-1978 Area air sample: 0,1 mg/ m^3	21 deaths obs., 22.12 exp. RR= 0.95; 95%; CI 0.58-1.45. 7 cancers obs., 5,39 exp. RR=1.30; 95%; CI 0.52-2.67 No excess in incidence or mortality rate of hepatic or biliary cancer.

Study /year/location	Study design	Population	Source and measure of exposure	Outcome
Gustavsson and Hogstedt 1997 Sweden (86)	Historical cohort study Mortality and cancer incidence Exposure measurement was carried out in 1973 Study period 1965-1991 Vital status for all but 1 worker (99,6%)	242 male workers from a capacitor plant Employed at least 6 months Number of deaths: 56	42% chlorinated PCBs was used from 1960-1978 Area air sample: 0,1 mg/ m^3	All-cause mortality: 56 obs. 47.92 exp., SMR=116; 95%;CI 88-151 All-cancer mortality 16 obs. 12.02 exp., SMR=133; 95%; CI 76-216 Mortality from all causes was significantly elevated for high exposed workers with at least 10 years of latency: 21 obs., 10.86 exp., SMR=193; 95%; CI: 120-296. No significant increase in mortality for any tumor type Cancer incidence of the entire cohort: 18 obs., 20.81 exp., SIR=86; 95%; CI 51-137. Significant excess of cardiovascular deaths in the high exposure group employed at least 5 years with a latency of 20 years or more: 5 obs., 1,52 exp., SMR=328; 95%; CI 107-766

M=male, F= female. Chlorine content: Aroclor 1254: 54%; Aroclor 1242: 42%; Aroclor 1016: 41%, Pyralene 1476: 54%, Pyralene 3010 and 3011: 42%, TWA Time-weighted average, PY: person-year

Appendix 3:Findings in studies addressing other health effects.

Thyroid effects

1) A cross sectional Slovakian study by Langer P et al (88) comparing 238 heavily exposed male and female workers from a factory that previously produced PCBs with 454 adolescents from the surrounding PCB polluted area and a control group consisting of 572 adults and 965 adolescents from much less polluted areas. The survey was conducted in the middle of the 1990s; the PCB production took place from 1955 to 1985.Thyroid volume was measured by ultrasound (no information on blinding), and a battery of thyroid blood tests were taken together with estimation of urinary iodine.
The volume of the thyroid gland of the employees was significantly higher (p<0.001) than in the control group with a mean volume of 18.9 ml and 13.5 ml respectively. The thyroid volume in adolescents from the polluted area was significantly higher than in controls being 9.4 ml and 8.1 ml respectively (p<0.001).
In employed women of all ages, a significantly increased prevalence of autoantibodies against thyroid peroxidase (anti-TPO) was found. There was a higher prevalence of the thyroid antibody anti-thyroglobulin in employed women aged 31-60 years and of antibodies against TSH-receptor in employed men and women compared with sex- and age-matched controls.
No difference was found between employees and controls in the levels of thyroxin and TSH. The prevalence of individuals without any defined clinical or laboratory signs of thyroid disorders among employees who had worked in the factory for 21-35 years was significantly lower than in matched controls. (Normal thyroid was defined as: negative personal history, normal clinical and ultrasound examination, normal plasma TSH and thyroid hormone concentrations, negative thyroid antibodies and a thyroid volume< 22.0 ml.)
As the iodine intake in Slovakia is considered sufficient, the authors conclude that the increased thyroid volume and prevalence of thyroid disorders in the polluted areas presumably results from long-term exposure to toxic substances rather than from a difference in life-long iodine intake. The increased prevalence of some thyroid antibodies is suggested to be a result of the known immunomodulatory effects of PCBs.

2) A cross sectional Swedish study By Selden et al (89) of 36 construction workers removing PCB containing sealants and 33 sex and age matched control construction workers were investigated in 2002. Information about medical and occupational history and lifestyle factors was obtained by a questionnaire. Blood sampling was carried out to determine thyroid function, the level of various cytokines, 19 PCB congeners and some other organochlorine compounds. Twenty-eight of the exposed workers had their blood test taken a second time after10 months additional exposure and were interviewed about their use of protection equipment during the 10 months.
The sum of 19 PCB congeners in blood plasma in the exposed group was twice the level in the controls with a geometric mean on 580 vs. 260 ng/g lipid; (p<0.001). There was no evidence of thyroid function or immune system involvement; neither thyroid function nor cytokine levels were associated with PCB exposure. No statistically significant increase in overall PCB levels was observed in the reinvestigated workers, declining levels was shown for some congeners, indicating a sufficient protection of the workers.

Diabetes

3) A cross sectional US study by Persky V et al (115) of 118 postmenopausal women previously employed at a capacitor manufacturing plant. In 1996 detailed information about medical history, previous occupational exposures and life style factors were collected. Blood samples were analyzed for PCBs, various hormones, immune function, lipids and liver enzymes lipids, liver function etc. Different exposure groups were defined based on job-score and blood levels of different types of PCBs.
Diabetes was defined as a confirmatory answer to the question:"Have you ever been diagnosed by a doctor as having diabetes mellitus or high blood sugar." Sixteen subjects (13.4%) had diabetes; about 70% of these were taking diabetes medication.
All PCB exposure groups were significantly related to self-reported history of diabetes, but not to measured insulin resistance. Diabetes was also independently and inversely associated with follicle stimulating

hormone (FSH), dehydroepiandrosterone sulfate (DHEAS) and triiodothyronine (T3) uptake. The possibility of reversed causation is mentioned e.g. diabetes resulting in a slower metabolism of the PCBs.

4) A cross sectional Slovakian study by Langer P et al (90) comparing 240 heavily exposed male and female employees with 704 control subjects. The PCB production at the factory stopped in 1985, sera were obtained in surveys in 1994 and 1998. Many of the subjects were identical with the subjects examined for auto antibodies against thyroid peroxidase (anti-TPO) in the study by Langer et al published in 1998.The frequency of glutamic acid decarboxylase antibody values (anti-GAD an antibody against glutamic acid decarboxylase in the insulin producing pancreatic β cells) that exceeded 1.20 U/ml in all employees (40.4%), was 4 times higher than in all controls (10.5%), and was 5 times higher in employees aged 51-60 years (53.2%) than in age-matched controls (10.5%). The prevalence of diabetes could not be determined in this study, but the increased prevalence of anti-GAD antibodies in the workers suggests an immunomodulatory effect of PCBs. The authors note that anti-GAD antibodies may be present decades before the development of clinical diabetes, and that only some anti-GAD antibody-positive individuals become diabetic.

Immune system

5) A cross sectional Slovakian study by Langer P et al (91) of 242 heavily exposed male and female workers employed at least 5 years at a factory that produced PCBs between 1955 and 1985. The level of beta 2-microglobulin (a cell membrane protein involved in the regulation of the immune system response, related to cell-mediated immunity) was measured in the serum from the workers and two control groups from much less polluted areas: 1,277 females from one region and 2,179 adults from another region.
The level of thymidine kinase (a bio-marker associated with various malignant and haematological disorders) was measured in the workers and the female control group.
In addition, age-matched groups of 155 women from all areas were evaluated.
In both the whole group and the age-matched group from the factory the level of beta 2-microglobulin was significantly lower than that in the respective control groups. No difference was found in the thymidine kinase level. It is suggested that the decrease of beta 2-microglobulin in the employees could be related to the immunotoxic effects of organochlorines.

Nervous system

6) A retrospective US mortality study by Steenland et al (92) of 17,321 PCB-exposed male and female capacitor workers investigating mortality from Parkinson disease, dementia, and amyotrophic lateral sclerosis. Job-exposure matrices were used to rank the intensity of exposure of the workers; causes of death were obtained from death certificates. All workers had at least 30 days of employment from the 1940s to the 1970s. PCB serum levels in workers taken in the 1970s were about 10 times the background level.
No overall excess of Parkinson disease, amyotrophic lateral sclerosis, or dementia in the PCB-exposed cohort was shown.
Sex-specific analyses revealed that women had an excess of amyotrophic lateral sclerosis with 10 deaths observed, SMR=2.26; 95% CI: 1.08-4.15. Highly exposed women had an excess of Parkinson disease with 6 deaths observed, SMR=2.95; 95% CI: 1.08-6.42 and dementia with 14 deaths observed and SMR=2.04; 95% CI: 1.12-3.43.The authors conclude, that their findings are suggestive of an effect of PCBs on neurodegenerative disease for women.

7) A cross sectional US study by Seegal et al (93) of 89 former male and female capacitor workers. Beta-CIT SPECT imaging was used to estimate basal ganglia dopamine transporter density in former capacitor workers. The study included neurological and neuropsychological assessments and different laboratory testing among these determination of circulating thyroid hormone and serum PCB concentrations. The geometric mean PCB concentrations in men and women were 1010 and 950 ng/g lipid respectively. An inverse relationship between lipid-adjusted total serum PCB concentrations and dopamine transporter densities was shown for women only; there were no differences in serum PCB levels in men and women. It is suggested that the results of the Beta-CIT-imaging may reflect that women occupationally exposed to

PBCs are at heightened risk of developing Parkinson's disease. It is also suggested that the sex differences in the findings may reflect age-related reductions in the levels of gonadal hormones since these hormones have been shown experimentally to alter response to dopamine neurotoxicants.

Reproductive effects

8) A retrospective US study by Taylor et al (94) of infants born to capacitor worker women between 1958 and 1975. Information was collected by birth certificates and information obtained from hospital and physician records.
Mothers were divided into a high exposure and a low exposure group depending on whether they had direct contact with PCBs during their work for a minimum of one year prior the birth. The PCBs used were: Aroclors 1254, 1242 and 1016. Industrial hygiene surveys had shown that the air concentrations in the high exposure areas were 10 fold greater than in the low exposure areas.
The 51children born to 39 high-exposure mothers had a mean birth weight of 153 grams less than that of 337 infants born to 280 women who had worked in low-exposure areas. The mean gestational age was 6.6 days shorter in the high-exposure infants. Adjustment for gestational age reduced the difference in birth weight, indicating that the observed reduction in birth weight in the high-exposure group was due mainly to shortening of gestational age. The data didn't contain information about tobacco use, underlying medical conditions, maternal height and pervious history of low birth weight, because of this and because of other limitations in study design, the authors considered their conclusion to be only tentative.

9) A study by Taylor et al (95) of the relation of PCBs to birth weight and gestational age among the live offspring of capacitor worker woman exposed to PCBs for at least 3 months in the period 1946 to 1975. In order to ascertain information on reproductive history and life style factors etc. interviews were conducted in 1982 with 200 women who had held jobs with direct exposure (air or air and dermal contact with PCBs) and 205 women who had never held a direct-exposure job (women working in offices or in areas where PCBs were not directly used - also termed indirect exposure). Industrial hygiene data from 1979 showed that the geometric mean serum PCB concentrations in capacitor workers with direct exposure were 269 ppb for low chlorinated PCBs, 33 ppb for high chlorinated PCBs and 302 ppb for total PCB. For workers with indirect exposure, the figures were 50 ppb, 11ppb and 61ppb respectively. In total 172 live births from the direct exposed group and 184 live births from the indirect exposure group were used in the analyses.
There was a small but significant effect of high chlorinated PCB exposure on birth weight (slope of the regression $\beta= -33$g/unit change in ln (ln=natural logarithm) estimated serum PCB). A small but significant decrease was observed for gestational age with an increase in estimated PCB level with a $\beta= -1.1$ days/unit change in ln estimated serum PCB. The authors concluded that" the magnitude of these effects was quite small compared with those of other known determinants of gestational age and birth weight, and the biologic importance of these effects is likely to be negligible except among already low birth weight or short gestation infants".

10) In this retrospective US study by Rocheleau et al (96) primipara singleton births of 2595 capacitor worker women was investigated. A cumulative estimate of the PCB exposure at the time of the infants' conception was calculated by using job exposure matrices. Detailed information on non-occupational risk factors was collected by a questionnaire.
48% of the participants were exposed to PCBs prior to conceiving their first live-born children.
In the PCB-exposed group 49.8% live born children were male, in the in the non-exposed group 49,9% of the children were male, i.e. this study provides no evidence of altered sex ratio among children born to primiparous PCB-exposed female workers.

Dermal effects

11) A cross sectional US study by Fischbein et al (97) of 326 male and female capacitor workers. Detailed information on dermatologic complaints was collected by a questionnaire. All subjects had a physical and

dermatological examination and blood test were taken to evaluate liver function and the level of PCB and various lipids in the blood.

A high prevalence (37%) of dermatological abnormalities was found: acneform eruptions (6%) and different conjunctival and palpebral abnormalities were found in 16% of the workers. An association between dermatological signs and plasma levels could only be demonstrated between male workers and higher homologues of PCB. It is noted that concomitant exposure to polychlorinated dibenzofurans could be responsible for some of the dermatological findings.

12) A cross sectional US study by Fischbein et al (98)of 326 male and female capacitor workers with long term employment examined in 1976; 195 of these were re-examined in 1979. Occupational and medical history was obtained by a questionnaire and physical and dermatologic examination and a wide range of laboratory tests were performed. The median blood values of lower homologues of PCBs were 63 ppb (in plasma) in 1976 and 49 ppb (in serum) in 1979, and of the higher homologues 18 ppb and 17.5 ppb respectively. The prevalence of ocular and dermatological findings in the eye surroundings that might be related to PCB-exposure were 9.4% and 13.3% at the two examinations. The most common findings were: Injected conjunctivae, eye discharge, swelling of the upper eyelid and enlarged Meibomian glands. No abnormal pigmentation of the conjunctivae was seen. No significant association between the clinical findings and the blood levels of PCBs could be demonstrated.

Despite a higher PCB blood levels in the capacitor workers than in Yusho and Yu-Cheng poisoning patients a lower prevalence of oculodermal findings was registered. Possible explanations for the difference are discussed, among others the importance of polychlorinated dibenzofurans as a possible aetiological factor and difference in route of exposure

Liver

13) A cross-sectional US study by Fischbein A (116)of 261 male and female capacitor workers examined in1976 and again in 1979. PCB was used in the production from late 1940s until 1977. Almost 70% of the study population had been employed for 10 years or more. For 35% of the workers the plasma LPCB (lower chlorinated PCB-congeners) level was 100 ppb or higher, 44% had plasma HPCB (higher chlorinated PCB-congeners) concentration of 25ppb or higher. Liver function tests included: γ-GTP, SGOT, SGPT, alkaline phosphatase, LDH and bilirubin.

The prevalence of abnormal liver function tests was low; mean values for all tests were within normal laboratory ranges. The author summarizes his findings in this way: "At the initial examination, weak, but statistically significant correlations were found between log LDH and plasma levels of log HPCB (higher chlorinated PCB-congeners) and log TPCB (total polychlorinated biphenyls) among the female workers, while log gamma-GTP correlated significantly only with log HPCB among the male workers. A significant increase to abnormal levels of γ-GTP was noted at the follow-up examination in both male and female workers, there was no obvious explanation for this last finding.

14) An Italian cross-sectional study by Colombi et al (117)of 67 male and female workers employed at a factory producing PCB-filled transformers and condensers. A control group of 67 subjects was established. None of the participants in the two groups had a history of liver disease, heavy drinking or heavy smoking. The workers had a mean blood PCB concentration of 386 ± 257, range 162–1319 ppb.

Urinary porphyrin excretion was estimated by determining the urinary concentration of uro-, hepta-, hexa-, penta-, and coproporphyrin homologues. No qualitative alterations of the urinary porphyrin excretion were found, but here was a definite increase in the excretion of all the porphyrinic homologues. The average concentration of total porphyrins in urine was 94.5μg/l in the exposed group versus 48.3μg/l in the control group. It is suggested, that the increase in urinary porphyrin excretion is due to the inductive properties of PCBs on liver microsomal enzymes.

Exposure to PCBs in occupational accidental spills

15) A cross sectional US study by Stark et al (101) of 52 subjects exposed to PCB spill in an office building resulting from a transformer explosion with no subsequent fire in December 1983. The incident provided 68 non-exposed individuals matched to the exposed group by sex, age, employer, and job description. One week after the spill all participants underwent an interview collecting data on past medical history, lifestyle factors other chemical exposure and various demographic characteristics. For the exposed group detailed information about their activities at the spill site was collected. Laboratory testing was preformed estimating about 25 biochemical parameters among these SGOT, SGPT, total protein, complete blood count (CBC), cholesterol, triglyceride levels, and fasting blood PCB level. Six weeks after the spill all participants were re-interviewed and laboratory tests were repeated except CBC and PCB levels.
Laboratory results were unremarkable for exposed as well as non-exposed. Mean serum PCB-level was 7.0 ppb for the exposed individuals. Some transient skin irritation and redness believed to be associated with PCB exposure was noted. For both exposed and non-exposed individuals triglyceride level was highly correlated with serum PCB level.

16) A Finnish investigation by Elo O et al (99) of 15 persons with high PCB exposure due to the explosion of several electric capacitors containing PCB. A few hours after the explosion, the air concentration of PCBs was 8.000 – 16.000µg/m3. The highest concentration of PCB in the serum was 30µg/L 3 days after the explosion, the PCB-serum levels returned to background level in 4 weeks. Blood levels of tetrachlorodibenzofurans (TCDFs) were under the detection limit. The acute symptoms were irritation of the eyes, skin and respiratory tract and general symptoms as nausea, headache and vertigo. Liver function tests revealed a rise in various enzymes, partly explained by exposure to PCBs and its derivatives.
Conduction velocities of peripheral sensory nerve fibers were slightly and transiently reduced. The total number of T-cells was lowered as was the T-helper /T-suppressor cell ratio. No statistically significant changes of the frequencies of chromosomal aberrations or sister chromatide exchanges were demonstrated.

17) A Finnish follow up study by Seppäläinen et al (100) of 15 men involved in an accident leading to high PCB-exposure, described by Elo O et al in May 1985. Neurophysiologic examination was carried out two and six months after the explosion. Thirty male workers with a similar age distribution served as referents. The two groups did not differ significantly by motor conduction velocities. Two months after the explosion sensory conduction velocity was significantly slower in the exposed men, and still slightly slower at the second examination. At the second examination, all measured conduction velocities were within normal ranges. No clear correlations between PCB-levels and the nerve conduction velocities were found. It is concluded that PCBs seem to exhibit neurotoxic properties in humans.

Indoor Air

18) A German cross sectional study by Broding et al (102) of 583 subjects who had worked for an average of 14.7 years in a PCB contaminated building in Germany, and 205 control subjects working in a non-contaminated building. The PCBs in the contaminated building came from insulation materials and elastic sealing compounds. Air and plasma concentrations of six indicator PCBs were measured (28, 52,101,138,153,180). All subjects completed a questionnaire and the 'Giessen Subjective Complaints List' (GSCL-24). The median sum of PCBs in the air in the contaminated building was 1280 ng/m3. The mean value of the sum of PCBs in plasma in exposed subjects was 2.65 µg/l. For congeners 28 and 52 the mean plasma concentrations in the control group were about 20 % of the concentration in the exposed group, indicating, airborne exposure in the contaminated building. Compared to the non-exposed subjects, the exposed subjects scored significantly higher values on all the GSCL subscales except one (stomach complaints). There was no correlation between symptoms and the concentrations of PCB congeners in plasma. The authors concluded, that subjects working in a PCB-contaminated building report more subjective complaints in comparison to non-exposed subjects, but the complaints were not related to current PCB plasma concentrations.

19) A German cross sectional study by Peper et al (103) of 30 teachers and other employees exposed to indoor air contaminated with PCBs from elastic sealants in a school building compared to 30 non-exposed controls matched for education and age, controlling for gender. 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, total concentration of PCB in air ranged from 2.870 ng/m3 to 17.460 ng/m3.

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 microg/l was identified and compared with 16 paired controls.

The mean total PCB concentration in plasma was 4.45 microg/l. The mean plasma level of PCB 28 was 0.28 microg/l and of PCB 101: 0.07 microg/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.

Respiratory system

20) A longitudinal US study by Lawton et al (118) of 194 capacitor male and female workers examined in 1976, 1979, 1981 and 1983. The survey included medical history, physical examination, spirometry, chest x-ray, ECG and blood and urine analysis. The mean serum PCB level in 1979 was 35 to 40 times the background level in humans. The study provided no evidence of PCB exposure being associated with persistent spirometric abnormalities. Observations made in 1976 demonstrated restrictive impairment in 16% of the workers, the finding was transient and believed to be artifactual due to an untrained nurse.

21) A cross sectional US study by Warshaw et al (119) of 243 capacitor male and female workers. Mean values for duration of employment was about 15 years. The respiratory studies were part of clinical field survey including past medical and occupational history and respiratory symptoms. Physical examination was performed and chest x-rays were taken.

In 34 (14%) of the workers a reduced Forced Vital Capacity (FVC <80% of the predicted value) was demonstrated. Twenty-seven of these workers showed a restrictive pattern with FEV1/FVC > 0.70, only one worker had an abnormal chest radiogram with interstitial changes. It is noted that restrictive spirometric impairment with no radiographic change is unusual in occupational exposure.

Mutagenicity and genotxicity

22) A Czechoslovakian cross-sectional study by Kalina et al (120) of 32 workers exposed to PCBs in a factory producing the PCB-products named Delor 103 and Delor 106. All study subjects answered a questionnaire about medical history and lifestyle and blood tests were taken. Mean plasma PCB levels of the exposed subjects were between 305 – 420 µg/liter

The ability of PCBs to induce chromosome aberrations and sister chromatid exchanges (SCE) in peripheral lymphocytes was compared between the exposed group and two control groups. A significant increase in the frequency of aberrant cells was found in workers exposed for more than 10 years. In workers exposed more than 15 years SCE-values were found to be significantly increased. It is noted by the authors that the plasma PCB levels of the workers didn't have any significant effect on the cytogenetic scoring.

Other cross-sectional studies

23) A cross-sectional US study by Lawton et al (121) of almost 200 male and female capacitor workers were examined in 1976 and 1979; the use of PCBs was banned in 1977. The study population included workers with long-term exposure from back in the 1950'es. The geometric mean for lower chlorinated PCBs in 1976 was 363 ppb and for higher chlorinated 30ppb. I 1979 the same figures were 68ppb and 19ppb.

Associations between serum PCB concentrations and more than 40 biochemical outcomes (such as indicators of liver function, kidney function, protein-synthesis, metabolism and hematological measures) were

analyzed. At the first examination their major findings were a depression in serum bilirubin and elevations in serum GGTP and lymphocyte levels. Only monocytes were elevated at the second examination, this may be a chance-association. In this study an association between serum levels of PCBs and lipids was demonstrated, but it was shown to be due to the so-called partitioning phenomena (the solubility of PCBs being a function of blood lipid content) rather than changes in liver function. It is suggested that PCBs may induce microsomal enzymes in the liver, which is compatible with experimental evidence.

24) A cross sectional US study by Acquavella et al (122) of 205 male and female capacitor workers examined in 1982.The survey consisted of a life style questionnaire, medical history and medical examination, 26 clinical laboratory tests and estimation of serum PCB. The geometric mean serum PCB level for the workers was 18.2 ppb, with a range of 0 to 424 ppb. The worker serum PCB levels were found to be predicted by duration of employment, cumulative occupational exposure, cumulative fish consumption, and cholesterol level. Duration of employment and cumulative occupational exposure were the strongest contributors and contributed equally to the regression model. Serum triglyceride did not predict serum PCB-level. Log serum PCB did not correlate with γ-GTP, LDH, SGOT, triglycerides, cholesterol and blood pressure. No liver or skin abnormalities attributable to PCB-exposure were found at the clinical examination.

25) A cross sectional Italian study by Maroni et al (123)of 80 male and female workers with long occupational exposure to PCBs in electrical manufacturing and testing plants. The survey included physical examination, obtaining of a detailed medical history, evaluation by a dermatologist and laboratory tests including: haematologic parameters, different liver enzymes and serum proteins. Blood PCB concentrations ranged from 41 to 1319μg/kg.
Four workers, who had been working with capacitor impregnation for many years, were diagnosed with chloracne. Their mean blood PCB-levels was 450μg/kg, range 310-495μg/kg, which wasn't significantly different from the other 5 workers performing the same job.
Sixteen male workers showed more or less pronounced hepatic involvement, consisting most often of hepatomegaly with an increase in serum GGT, AST, ALT, and OCT values. A significant positive association was found between the abnormal liver findings and blood PCB concentrations, particularly trichlorobiphenyl blood concentrations. It is concluded, that the abnormal hepatic findings may be considered as clinical signs of hepatic microsomal enzyme induction.

26) A cross-sectional US study by Emmett et al (124) comparing 55 transformer repairmen, 38 currently, and 17 previously exposed to PCBs with 56 non-exposed subjects (1980). The survey consisted of a questionnaire, a standardized medical examination including an examination by a dermatologist, delayed hypersensitivity testing; and determination of serum and adipose tissue lipid total PCB concentrations. The geometric mean serum PCB concentration for the currently exposed was 12.2 ppb vs. 5.9 ppb in the previously exposed group and 4.6 ppb in the non-exposed group. Adipose tissue PCB geometric mean for the currently exposed was 2.1 ppm, vs. 0.83 ppm in previously exposed group and 0.60 ppm in the non-exposed group.
Different neurobehavioral and irritant symptoms were significantly more prevalent in the exposed group, but not explained by serum PCB levels. None of the subjects were diagnosed with chloracne. No difference in cutaneous delayed hypersensitivity was detected.

27) A cross-sectional US study by Emmett al (125)investigating the same study population of 55 transformer repairmen described above. Measurements were made of serum liver function tests, gamma-glutamyltranspeptidase (GGT), lipid profile, thyroid function tests, and other serum biochemistry; hemoglobin; white cell count; 24-hour excretion of delta-aminolevulinic acid, porphyrins, 17-hydroxycorticosteroids and 17-ketosteroids; sperm count; spirometry; and antipyrine half-life to evaluate microsomal mixed function oxidase induction.
The only a statistically significant correlations after adjustment for confounding variables were a positive correlation between serum PCBs and GGT and a negative correlation between adipose tissue PCBs and 17-hydroxycorticosteroid excretion. According to the authors this may reflect subtle metabolic effects of PCBs.

Significant correlations between serum PCBs and serum lipids were removed by adjustment for confounding variables. Differences in FEV1 were attributable to smoking. No reproductive abnormality was attributed to PBC exposure.

28) A cross-sectional US study by Emmet (126) investigating the same study population of transformer repairmen as above. The same results and conclusions concerning the laboratory tests are reported. Individual PCB congeners were quantitated in adipose tissue, showing quantifiable levels of different congeners including microsomal enzyme inducers in all exposure groups.

29) A cross-sectional US study by Chase et al (127) of 120 male workers employed at a railroad passenger car and locomotive maintenance facility. Three groups were defined: 86 exposed subjects, 15 "nominally" exposed and 19 non-exposed subjects. The nominally exposed subjects were working on the same facility as the exposed, but with no direct contact with PCB containing fluids. The averaged plasma PCB-levels in the three groups were 33.4 ppb, 14.2 ppb and 12.0 ppb respectively. The survey included a complete work- and clinical history, physical examination and a battery of laboratory tests. Plasma PCB and fat PCB levels were determined the latter only for some of the participants.
Several cases of chloracne were observed in the exposed group.
In the exposed group after controlling for age and length of employment, significant correlations were found between plasma PCB and serum triglyceride and SGOT. No significant correlations were found between PCB levels and cholesterol, high-density lipoprotein cholesterol or other liver function test than SGTO.

30) A cross sectional US study by Ouw et al (128)comparing 34 capacitor workers with 30 unexposed workers. The survey consisted of a detailed questionnaire concerning medical and work history, physical examination and a battery of laboratory tests including hepatic function test. The mean blood Aroclor level in the exposed group was approximately 400 ppb. Different complaints in the exposed group were noted: a burning sensation of the face and hands, nausea, and a persistent body odor. One was diagnosed with chloracne, and five suffered from an eczematous rash on the extremities. All hepatic function tests were normal.

31) A cross sectional US study by Smith et al (129)describing three groups of workers occupationally exposed to PCBs by manufacturing or maintaining PCB-filled transformers. All subjects completed a questionnaire, underwent physical examination and laboratory blood and urine testing was carried out examining liver function, haematology, kidney function, serum lipids, T4, metabolic parameters etc.
Serum PCB concentrations were quantitated as lower chlorinated biphenyls (L-PCBs) and higher chlorinated biphenyls (H-PCBs). Mean serum L-PCB concentrations were 8-50 times higher in capacitor manufacturing workers than in the general population, H-PCB concentrations in the capacitor manufactory workers were and 2 to 4 times the background level.
Statistically significant positive correlations of symptoms such as coughing irritated or burning eyes, loss of appetite and tingling in the hands were noted with increasing levels of serum PCB.
At the physical examination no clinical abnormalities attributable to exposure to PCB were observed, no cases of chloracne were found; diastolic blood pressure was not associated with PBC serum level. PCB concentrations were positively and significantly correlated with SGOT, GGTP and plasma triglyceride, and inversely correlated with plasma high density lipoprotein-cholesterol. It is stated by the authors that the findings are indicative of PCBs' physiological effect on the liver, but that the long-term consequence of their finding is unknown.

32) A Japanese follow-up study by Hara et al (130)of capacitor manufacturing male and female workers exposed to polychlorinated biphenyls (PCBs) and their children. The PCBs used were Kanechlor 500 with a chlorine content of 55% and Kanechlor-300 with a chlorine content of 43%, the use of Kanechlor was banned in 1972 in Japan. Annual examinations took place from 1973 to 1979. 155 workers were examined the first year, the participation declined to 62 workers in 1979.

The PCB levels in whole blood of workers and in breast milk of the exposed lactating mothers were approximately 10 to 100 times those of non-exposed Japanese. Blood PCB levels correlated with the duration of PCB handling and breast milk PCB levels correlated well with blood PCB levels.

The workers had dermatologic complaints: black comedones and acne (40%) and irritative skin symptoms (13%), the symptoms decreased during the observation period.

The blood tests revealed no abnormalities in liver or kidney function, only in1974 serum triglyceride concentrations were found to be significantly correlated with blood PCB levels.

Complaints in children born from mothers who had handled PCBs were monitored in a questionnaire. Symptoms were reported more frequently in children born from mothers who handled PCB in the factory, especially if they were fed breast milk for a long period. The symptoms reported were: fatigue, catching a cold, fever, various digestive symptoms, coughing, wheezing, red eyes, eczema and itchy skin.

33) A cross sectional US study by baker et al (131) investigating the possible health consequences of using PCB-contaminated sewage sludge as fertilizer. Four groups were defined: Sludge users (persons exposed to sewage sludge containing PCBs used as fertilizer), subjects occupationally exposed to PCBs (most of these were capacitor workers), these workers' family and community controls. In 1977 all participants underwent a detailed interview, physical examination and had a battery of laboratory blood tests taken. Mean serum PCB levels were 17.4 ppb in 89 sludge users, 75.1 ppb in 18 workers with occupational exposure to PCB, 33.6 ppb in 19 members of those workers' families, and 24.4 ppb in the 22 community controls. No subjects had chloracne and no other clinical findings or symptoms were attributable to PCB-exposure. No significant correlations were found between PCB levels and tests of hematologic, hepatic, or renal function. Plasma triglyceride levels increased significantly with serum PCB concentrations in both alcohol drinkers and nondrinkers. It is suggested that PCBs may alter the lipid metabolism.

Appendix 4: PCB nomenclature conversion tables

Attached as pdf-file. (2 pages)

Appendix 5: Tables with serum PCB values

Attached as pdf-file. (3 pages)

Reference List

(1)   ATSDR. Toxicological Profile for Polychlorinated Biphenyls. Atlanta: ATSDR; 2000.

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

(3)   WHO. IPCS Environmental Health Criteria 140 Polychlorinated biphenyls and terphenyls (second edition. Geneva: WHO; 1993.

(4)   Kimbrough R, Jensen A. Halogenated biphenyls, terphenyls, naphthalenes, dibenzodioxins and related products. Amsterdam: Elsevier; 1989.

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

(6)   Mills SA, III, Thal DI, Barney J. A summary of the 209 PCB congener nomenclature. Chemosphere. 2007;68:1603-12.

(7)   Breivik K, Sweetman A, Pacyna JM, Jones KC. Towards a global historical emission inventory for selected PCB congeners--a mass balance approach. 1. Global production and consumption. Sci Total Environ. 2002;290:181-98.

(8)   Van den Berg M, Birnbaum L, Bosveld AT, Brunstrom B, Cook P, Feeley M, et al. Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife. Environ Health Perspect. 1998;106:775-92.

(9)   Warner NA, Norstrom RJ, Wong CS, Fisk AT. Enantiomeric fractions of chiral polychlorinated biphenyls provide insights on biotransformation capacity of arctic biota. Environ Toxicol Chem. 2005;24:2763-7.

(10) Rodman LE, Shedlofsky SI, Mannschreck A, Puttmann M, Swim AT, Robertson LW. Differential potency of atropisomers of polychlorinated biphenyls on cytochrome P450 induction and uroporphyrin accumulation in the chick embryo hepatocyte culture. Biochem Pharmacol. 1991;41:915-22.

(11) MuirD, Sverko E. Analytical methods for PCBs and organochlorine pesticides in environmental monitoring and surveillance: a critical appraisal. Anal Bioanal Chem. 2006;386:769-89.

(12) Beck H, Mathar W. Bundesgesundheitblatt 28, I. 14. 1985.
      Ref Type: Magazine Article

(13) ATSDR 2000. Toxicological profile for polychlorinated biphenyls (update). Public Health Service, Agency for Toxic substances and Disease registry, Atlanta, US: US Department of Health and Human Services; 2000.

(14) Jensen A, Slorach S. Chemical Contaminants in Human Milk. Boca Raton: CRC Press; 1991.

(15)   Wolff MS, Fischbein A, Selikoff IJ. Changes in PCB serum concentrations among capacitor manufacturing workers. Environ Res. 1992;59:202-16.

(16)   Larsen JC. Risk assessments of polychlorinated dibenzo- p-dioxins, polychlorinated dibenzofurans, and dioxin-like polychlorinated biphenyls in food. Mol Nutr Food Res. 2006;50:885-96.

(17)   Giesy JP, Kannan K. Dioxin-like and non-dioxin-like toxic effects of polychlorinated biphenyls (PCBs): implications for risk assessment. Crit Rev Toxicol. 1998;28:511-69.

(18)   Mayes BA, McConnell EE, Neal BH, Brunner MJ, Hamilton SB, Sullivan TM, et al. Comparative carcinogenicity in Sprague-Dawley rats of the polychlorinated biphenyl mixtures Aroclors 1016, 1242, 1254, and 1260. Toxicol Sci. 1998;41:62-76.

(19)   Freeman GB, Lordo RA, Singer AW, Peters AC, Neal BH, McConnell EE, et al. An assessment of neurotoxicity of aroclors 1016, 1242, 1254, and 1260 administered in diet to Sprague-Dawley rats for one year. Toxicol Sci. 2000;53:377-91.

(20)   Henry T, DeVito MJ. Non-dioxin-like PCBs: effects and consideratins in ecological risk assessment. US: Evironmental Protection Agency; 2003.

(21)   Korrick SA, Sagiv SK. Polychlorinated biphenyls, organochlorine pesticides and neurodevelopment. Curr Opin Pediatr. 2008;20:198-204.

(22)   Ross G. The public health implications of polychlorinated biphenyls (PCBs) in the environment. Ecotoxicol Environ Saf. 2004;59:275-91.

(23)   Bell FP, Iverson F, Arnold D, Vidmar TJ. Long-term effects of Aroclor 1254 (PCBs) on plasma lipid and carnitine concentrations in rhesus monkey. Toxicology. 1994;89:139-53.

(24)   Arnold DL, Nera EA, Stapley R, Bryce F, Fernie S, Tolnai G, et al. Toxicological consequences of Aroclor 1254 ingestion by female rhesus (Macaca mulatta) monkeys and their nursing infants. Part 3: post-reproduction and pathological findings. Food Chem Toxicol. 1997;35:1191-207.

(25)   Litterst CL, Farber TM, Baker AM, Van Loon EJ. Effect of polychlorinated biphenyls on hepatic microsomal enzymes in the rat. Toxicol Appl Pharmacol. 1972;23:112-22.

(26)   Byrne JJ, Carbone JP, Hanson EA. Hypothyroidism and abnormalities in the kinetics of thyroid hormone metabolism in rats treated chronically with polychlorinated biphenyl and polybrominated biphenyl. Endocrinology. 1987;121:520-7.

(27)   Arnold DL, Bryce F, Stapley R, McGuire PF, Burns D, Tanner JR, et al. Toxicological consequences of Aroclor 1254 ingestion by female rhesus (Macaca mulatta) monkeys. Part 1A. Prebreeding phase: clinical health findings. Food Chem Toxicol. 1993;31:799-810.

(28)   Arnold DL, Bryce F, Karpinski K, Mes J, Fernie S, Tryphonas H, et al. Toxicological consequences of Aroclor 1254 ingestion by female rhesus (Macaca mulatta) monkeys. Part 1B. Prebreeding phase: clinical and analytical laboratory findings. Food Chem Toxicol. 1993;31:811-24.

(29) Tryphonas H, Luster MI, Schiffman G, Dawson LL, Hodgen M, Germolec D, et al. Effect of chronic exposure of PCB (Aroclor 1254) on specific and nonspecific immune parameters in the rhesus (Macaca mulatta) monkey. Fundam Appl Toxicol. 1991;16:773-86.

(30) Tryphonas H, Karpinski K, O'Grady L, Hayward S. Quantitation of serum immunoglobulins G, M, and A in the rhesus monkey (M. mulatta) using human monospecific antisera in the enzyme-linked immunosorbent assay: developmental aspects. J Med Primatol. 1991;20:58-66.

(31) Seegal RF, Bush B, Brosch KO. Sub-chronic exposure of the adult rat to Aroclor 1254 yields regionally-specific changes in central dopaminergic function. Neurotoxicology. 1991;12:55-65.

(32) IARC Monographs on polycholorinated biphenyls and polybrominated biphenyls. Lyon: IARC; 1978.

(33) Golden R, Kimbrough R. Weight of evidence evaluation of potential human cancer risks from exposure to polychlorinated biphenyls: an update based on studies published since 2003. Crit Rev Toxicol. 2009;39:299-331.

(34) Toft G, Hagmar L, Giwercman A, Bonde JP. Epidemiological evidence on reproductive effects of persistent organochlorines in humans. Reprod Toxicol. 2004;19:5-26.

(35) Hertz-Picciotto I, Park HY, Dostal M, Kocan A, Trnovec T, Sram R. Prenatal exposures to persistent and non-persistent organic compounds and effects on immune system development. Basic Clin Pharmacol Toxicol. 2008;102:146-54.

(36) Hagmar L. Polychlorinated biphenyls and thyroid status in humans: a review. Thyroid. 2003;13:1021-8.

(37) Everett CJ, Frithsen I, Player M. Relationship of polychlorinated biphenyls with type 2 diabetes and hypertension. J Environ Monit. 2011;13:241-51.

(38) Boucher O, Muckle G, Bastien CH. Prenatal exposure to polychlorinated biphenyls: a neuropsychologic analysis. Environ Health Perspect. 2009;117:7-16.

(39) Meeker JD, Hauser R. Exposure to polychlorinated biphenyls (PCBs) and male reproduction. Syst Biol Reprod Med. 2010;56:122-31.

(40) Baan R, Straif K, Grosse Y, Secretan B, El GF, Bouvard V, et al. Carcinogenicity of some aromatic amines, organic dyes, and related exposures. Lancet Oncol. 2008;9:322-3.

(41) Jusko TA, Sonneborn D, Palkovicova L, Kocan A, Drobna B, Trnovec T, et al. Pre- and postnatal polychlorinated biphenyl concentrations and longitudinal measures of thymus volume in infants. Environ Health Perspect. 2012;120:595-600.

(42) Lee DH, Steffes MW, Sjodin 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;118:1235-42.

(43) Lee DH, Steffes MW, Sjodin A, Jones RS, Needham LL, Jacobs DR, Jr. Low dose organochlorine pesticides and polychlorinated biphenyls predict obesity, dyslipidemia, and insulin resistance among people free of diabetes. PLoS One. 2011;6:e15977.

(44) Silverstone AE, Rosenbaum PF, Weinstock RS, Bartell SM, Foushee HR, Shelton C, et al. Polychlorinated Biphenyl (PCB) Exposure and Diabetes: Results from the Anniston Community Health Survey. Environ Health Perspect. 2012;120:727-32.

(45) Govarts E, Nieuwenhuijsen M, Schoeters G, Ballester F, Bloemen K, de BM, et al. Prenatal Exposure to Polychlorinated Biphenyls (PCB) and Dichlorodiphenyldichloroethylene (DDE) and Birth Weight: A Meta-analysis within 12 European Birth Cohorts. Environ Health Perspect. 2011.

(46) Bonde JP, Toft G, Giwercman A, Rylander L, Rignell-Hydbom A, Giwercman A, et al. Fertility and Markers of Male Reproductive Function in Inuit and European Populations spanning Large Contrasts in Blood Levels of Persistent Organochlorines. Environmental Health Perspectives. 2008.

(47) Meeker JD, Maity A, Missmer SA, Williams PL, Mahalingaiah S, Ehrlich S, et al. Serum concentrations of polychlorinated biphenyls in relation to in vitro fertilization outcomes. Environ Health Perspect. 2011;119:1010-6.

(48) Schecter A. Dioxins and Health Including Other Persistent Organic Pollutants and Endocrine Disruptors. 3th ed. Hoboken New Yersey: John Wiley & Sons; 2012.

(49) Ikeda M, Kuratsune M, Nakamura Y, Hirohata T. A cohort study on mortality of yusho patients--a preliminary report. Fukuoka Igaku Zasshi. 1987;78:297-300.

(50) Chen YC, Guo YL, Hsu CC, Rogan WJ. Cognitive development of Yu-Cheng ("oil disease") children prenatally exposed to heat-degraded PCBs. JAMA. 1992;268:3213-8.

(51) Ruzzin J, Petersen R, Meugnier E, Madsen L, Lock EJ, Lillefosse H, et al. Persistent organic pollutant exposure leads to insulin resistance syndrome. Environ Health Perspect. 2010;118:465-71.

(52) Longnecker MP, Klebanoff MA, Brock JW, Zhou H. Polychlorinated biphenyl serum levels in pregnant subjects with diabetes. Diabetes Care. 2001;24:1099-101.

(53) Knerr S, Schrenk D. Carcinogenicity of "non-dioxinlike" polychlorinated biphenyls. Crit Rev Toxicol. 2006;36:663-94.

(54) Jensen AA, Schleicher O, Sebastian W, Trap N, Zeuten F. Forekomst af PCB i en- og tofamiliehuse. EBST 09/02028. 2009.

(55) Danish Environmental Protection Agency. Miljøprojekt 1084, 2006. 2006.

(56) Alexander J et al. Opinion of the scientific panel on contaminants in the food chain on a request from the Commision related to the presence of non doixin-like polychlorinated biphenyls (PCB) in feed and food. The EFSA Journal. 2005;284:1-137.

(57) McLeod KE. Sources of emissions of polychlorinated biphenyls into the ambient atmosphere and indoor air. UK: Research Triangle Park; 1979.

(58) Frederiksen M, Meyer HW, Ebbehoj NE, Gunnarsen L. Polychlorinated biphenyls (PCBs) in indoor air originating from sealants in contaminated and uncontaminated apartments within the same housing estate. Chemosphere. 2012;89:473-9.

(59) Gunnarsen L, Larsen JC, Mayer P, Sebastian W. Sundhedsmæssig vurdering af PCB-holdige bygningsfuger. The Danish Environmental Protection Agency; 2009.

(60) Heinzow B, Mohr S, Ostendorp G, Kerst M, Korner W. PCB and dioxin-like PCB in indoor air of public buildings contaminated with different PCB sources--deriving toxicity equivalent concentrations from standard PCB congeners. Chemosphere. 2007;67:1746-53.

(61) Köster D. Während einer Schulsanierung erhobene PCB-Blutwerte bei Lehren und Schülern - eine vergleichende Untersuchung. Umwelt Medizin Ges. 2001;14:301-4.

(62) Gabrio T, Piechotowski I, Wallenhorst T, Klett M, Cott L, Friebel P, et al. PCB-blood levels in teachers, working in PCB-contaminated schools. Chemosphere. 2000;40:1055-62.

(63) Schwenk M, Gabrio T, Papke O, Wallenhorst T. Human biomonitoring of polychlorinated biphenyls and polychlorinated dibenzodioxins and dibenzofuranes in teachers working in a PCB-contaminated school. Chemosphere. 2002;47:229-33.

(64) 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.

(65) Johansson N, Hanberg A, Wingfors H, Tysklind M. PCB in building sealant is influencing PCB levels in blood of residents. Organohalogen Compounds. 2003;63:381-4.

(66) Danish Health and Medicines Authority. PCB eksponering i Farum Midtpunkt - målinger i boliger og i blod. 2012.

(67) Kohler M, Zennegg M, Waeber R. Coplanar polychlorinated biphenyls (PCB) in indoor air. Environ Sci Technol. 2002;36:4735-40.

(68) Kontsas H, Pekari K, Riala R, Back B, Rantio T, Priha E. Worker exposure to polychlorinated biphenyls in elastic polysulphide sealant renovation. Ann Occup Hyg. 2004;48:51-5.

(69) Selden A, Wingfors H, Fedeli C, Johansson N. PCB belastning och effecter på sköldkörtelfunktion hos bygnadsarbetere vid sanering av PCB-hältiga fogmassor. Yrkesmedicin YM 3/5. Universitetssjukhuset Örebro; 2005.

(70) 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.

(71) Kontsas H, Pekari K. Determination of polychlorinated biphenyls in serum using gas chromatography-mass spectrometry with negative chemical ionization for exposure estimation. J Chromatogr B Analyt Technol Biomed Life Sci. 2003;791:117-25.

(72) Selden AS, Westberg HB, Hanberg A, Nygren Y. Congener specific monitoring of PCB and hexachlorobenzene in harzardous waste incineration workers. Organohaloge Compound. 1997;33:398-401.

(73) Angerer J, Heinzow B, Reimann DO, Knorz W, Lehnert G. Internal exposure to organic substances in a municipal waste incinerator. Int Arch Occup Environ Health. 1992;64:265-73.

(74) Gonzalez CA, Kogevinas M, Gadea E, Huici A, Bosch A, Bleda MJ, et al. Biomonitoring study of people living near or working at a municipal solid-waste incinerator before and after two years of operation. Arch Environ Health. 2000;55:259-67.

(75) Danish Ministry of Environment. Bekendtgørelse nr. 18 af 15. januar 1976 om begrænsninger i indførsel og anvendelse af PCB og PCT og bekendtgørelse nr. 572 af 26. november 1976 om ændring af og ikrafttræden af bekendtgørelse om begrænsninger i indførsel og anvendelse af PCB og PCT. 1976.
Ref Type: Statute

(76) Hansen EGA. PCB/PCT-forurening. En udredning om forbrug, forurening og transportveje for PCB og PCT i Danmark. København: Miljøstyrelsen; 1983.

(77) Danish Ministry of Environment. Bekendtgørelse nr. 718 af 9. oktober 1986 om begrænsninger i anvendelsen af PCB og PCT. 1986.
Ref Type: Statute

(78) Danish Ministry of Environment. Miljøministeriets bekendtgørelse nr. 925 af 13. december 1998 om PCB, PCT og erstatningsstoffer herfor. 1998.
Ref Type: Statute

(79) Maag J, Lassen C. PCB i apparater i Danmark. Arbejdsrapport fra Miljøstyrelsen 15, 2000. København: Miljøstyrelsen; 2000.

(80) Danish Health and Medicines Authority. PCB og sundhed - Sundhedsstyrelsens bidrag til et tværministerielt faktaark om PCB. www sst dk 2009

(81) Heinzow B, Mohr S, Ostendorp G, Kerst M, Korner W. PCB and dioxin-like PCB in indoor air of public buildings contaminated with different PCB sources--deriving toxicity equivalent concentrations from standard PCB congeners. Chemosphere. 2007;67:1746-53.

(82) Danish Working Environment Authority. PCB i bygninger. AT intern instruks nr. 3/2011. www.at.dk 2011

(83) Prince MM, Hein MJ, Ruder AM, Waters MA, Laber PA, Whelan EA. Update: cohort mortality study of workers highly exposed to polychlorinated biphenyls (PCBs) during the manufacture of electrical capacitors, 1940-1998. Environ Health. 2006;5:13.

(84) Brown DP. Mortality of workers exposed to polychlorinated biphenyls--an update. Arch Environ Health. 1987;42:333-9.

(85) Gustavsson P, Hogstedt C, Rappe C. Short-term mortality and cancer incidence in capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). Am J Ind Med. 1986;10:341-4.

(86) Gustavsson P, Hogstedt C. A cohort study of Swedish capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). Am J Ind Med. 1997;32:234-9.

(87) Silver SR, Whelan EA, Deddens JA, Steenland NK, Hopf NB, Waters MA, et al. Occupational exposure to polychlorinated biphenyls and risk of breast cancer. Environ Health Perspect. 2009;117:276-82.

(88) Langer P, Tajtakova M, Fodor G, Kocan A, Bohov P, Michalek J, et al. Increased thyroid volume and prevalence of thyroid disorders in an area heavily polluted by polychlorinated biphenyls. Eur J Endocrinol. 1998;139:402-9.

(89) Selden 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.

(90) Langer P, Tajtakova M, Guretzki HJ, Kocan A, Petrik J, Chovancova J, et al. High prevalence of anti-glutamic acid decarboxylase (anti-GAD) antibodies in employees at a polychlorinated biphenyl production factory. Arch Environ Health. 2002;57:412-5.

(91) Langer P, Kausitz J, Tajtakova M, Kocan A, Bohov P, Hanzen E. Decreased blood level of beta 2-microglobulin in the employees of a factory which produced polychlorinated biphenyls. Chemosphere. 1997;34:2595-600.

(92) Steenland K, Hein MJ, Cassinelli RT, Prince MM, Nilsen NB, Whelan EA, et al. Polychlorinated biphenyls and neurodegenerative disease mortality in an occupational cohort. Epidemiology. 2006;17:8-13.

(93) Seegal RF, Marek KL, Seibyl JP, Jennings DL, Molho ES, Higgins DS, et al. Occupational exposure to PCBs reduces striatal dopamine transporter densities only in women: a beta-CIT imaging study. Neurobiol Dis. 2010;38:219-25.

(94) Taylor PR, Lawrence CE, Hwang HL, Paulson AS. Polychlorinated biphenyls: influence on birthweight and gestation. Am J Public Health. 1984;74:1153-4.

(95) Taylor PR, Stelma JM, Lawrence CE. The relation of polychlorinated biphenyls to birth weight and gestational age in the offspring of occupationally exposed mothers. Am J Epidemiol. 1989;129:395-406.

(96) Rocheleau CM, Bertke SJ, Deddens JA, Ruder AM, Lawson CC, Waters MA, et al. Maternal exposure to polychlorinated biphenyls and the secondary sex ratio: an occupational cohort study. Environ Health. 2011;10:20.

(97) Fischbein A, Thornton J, Wolff MS, Bernstein J, Selifoff IJ. Dermatological findings in capacitor manufacturing workers exposed to dielectric fluids containing polychlorinated biphenyls (PCBs). Arch Environ Health. 1982;37:69-74.

(98) Fischbein A, Rizzo JN, Solomon SJ, Wolff MS. Oculodermatological findings in workers with occupational exposure to polychlorinated biphenyls (PCBs). Br J Ind Med. 1985;42:426-30.

(99) Elo O, Vuojolahti P, Janhunen H, Rantanen J. Recent PCB accidents in Finland. Environ Health Perspect. 1985;60:315-9.

(100) Seppalainen AM, Vuojolahti P, Elo O. Reversible nerve lesions after accidental polychlorinated biphenyl exposure. Scand J Work Environ Health. 1985;11:91-5.

(101) Stark AD, Costas K, Chang HG, Vallet HL. Health effects of low-level exposure to polychlorinated biphenyls. Environ Res. 1986;41:174-83.

(102) Broding HC, Schettgen T, Hillert A, Angerer J, Goen T, Drexler H. Subjective complaints in persons under chronic low-dose exposure to lower polychlorinated biphenyls (PCBs). Int J Hyg Environ Health. 2008;211:648-57.

(103) 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.

(104) Longnecker MP, Rogan WJ, Lucier G. The human health effects of DDT (dichlorodiphenyltrichloroethane) and PCBS (polychlorinated biphenyls) and an overview of organochlorines in public health. Annu Rev Public Health. 1997;18:211-44.:211-44.

(105) DeVito MJ, Thomas T, Martin E, Umbreit TH, Gallo MA. Antiestrogenic action of 2,3,7,8-tetrachlorodibenzo-p-dioxin: tissue-specific regulation of estrogen receptor in CD1 mice. Toxicol Appl Pharmacol 1992 Apr;113(2):284 92. 1992;-92.

(106) Brown DP, Jones M. Mortality and industrial hygiene study of workers exposed to polychlorinated biphenyls. Arch Environ Health. 1981;36:120-9.

(107) Sinks T, Steele G, Smith AB, Watkins K, Shults RA. Mortality among workers exposed to polychlorinated biphenyls. Am J Epidemiol. 1992;136:389-98.

(108) Kimbrough RD, Doemland ML, LeVois ME. Mortality in male and female capacitor workers exposed to polychlorinated biphenyls. J Occup Environ Med. 1999;41:161-71.

(109) Kimbrough RD, Doemland ML, Mandel JS. A mortality update of male and female capacitor workers exposed to polychlorinated biphenyls. J Occup Environ Med. 2003;45:271-82.

(110) Ruder AM, Hein MJ, Nilsen N, Waters MA, Laber P, vis-King K, et al. Mortality among workers exposed to polychlorinated biphenyls (PCBs) in an electrical capacitor manufacturing plant in Indiana: an update. Environ Health Perspect. 2006;114:18-23.

(111) Prince MM, Ruder AM, Hein MJ, Waters MA, Whelan EA, Nilsen N, et al. Mortality and exposure response among 14,458 electrical capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). Environ Health Perspect. 2006;114:1508-14.

(112) Bertazzi PA, Zocchetti C, Guercilena S, Della Foglia M, Pesatori A, Riboldi L. Prevention of Occupational Cancers - International Symposium. 1982;242-8.

(113) Bertazzi PA, Riboldi L, Pesatori A, Radice L, Zocchetti C. Cancer mortality of capacitor manufacturing workers. Am J Ind Med. 1987;11:165-76.

(114) Golden R, Doull J, Waddell W, Mandel J. Potential human cancer risks from exposure to PCBs: a tale of two evaluations. Crit Rev Toxicol. 2003;33:543-80.

(115) Persky V, Piorkowski J, Turyk M, Freels S, Chatterton R, Jr., Dimos J, et al. Associations of polychlorinated biphenyl exposure and endogenous hormones with diabetes in post-menopausal women previously employed at a capacitor manufacturing plant. Environ Res. 2011;111:817-24.

(116) Fischbein A. Liver function tests in workers with occupational exposure to polychlorinated biphenyls (PCBs): comparison with yusho and yu-cheng. Environ Health Perspect. 1985;60:145-50.

(117) Colombi A, Maroni M, Ferioli A, Foa V, Castoldi M, Ke Jun L, et al. Increase in urinary porphyrin excretion in workers exposed to polychlorinated biphenyls. J Appl Toxicol. 1982;2:117-21.

(118) Lawton RW, Ross MR, Feingold J. Spirometric findings in capacitor workers occupationally exposed to polychlorinated biphenyls (PCBs). J Occup Med. 1986;28:453-6.

(119) Warshaw R, Fischbein A, Thornton J, Miller A, Selikoff IJ. Decrease in vital capacity in PCB-exposed workers in a capacitor manufacturing facility. Ann N Y Acad Sci. 1979;320:277-83.

(120) Kalina I, Sram RJ, Konecna H, Ondrussekova A. Cytogenetic analysis of peripheral blood lymphocytes in workers occupationally exposed to polychlorinated biphenyls. Teratog Carcinog Mutagen. 1991;11:77-82.

(121) Lawton RW, Ross MR, Feingold J, Brown JF, Jr. Effects of PCB exposure on biochemical and hematological findings in capacitor workers. Environ Health Perspect. 1985;60:165-84.

(122) Acquavella JF, Hanis NM, Nicolich MJ, Phillips SC. Assessment of clinical, metabolic, dietary, and occupational correlations with serum polychlorinated biphenyl levels among employees at an electrical capacitor manufacturing plant. J Occup Med. 1986;28:1177-80.

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

(124) Emmett EA, Maroni M, Schmith JM, Levin BK, Jefferys J. Studies of transformer repair workers exposed to PCBs: I. Study design, PCB concentrations, questionnaire, and clinical examination results. Am J Ind Med. 1988;13:415-27.

(125) Emmett EA, Maroni M, Jefferys J, Schmith J, Levin BK, Alvares A. Studies of transformer repair workers exposed to PCBs: II. Results of clinical laboratory investigations. Am J Ind Med. 1988;14:47-62.

(126) Emmett EA. Polychlorinated biphenyl exposure and effects in transformer repair workers. Environ Health Perspect. 1985;60:185-92.

(127) Chase KH, Wong O, Thomas D, Berney BW, Simon RK. Clinical and metabolic abnormalities associated with occupational exposure to polychlorinated biphenyls (PCBs). J Occup Med. 1982;24:109-14.

(128) Ouw HK, Simpson GR, Siyali DS. Use and health effects of Aroclor 1242, a polychlorinated biphenyl, in an electrical industry. Arch Environ Health. 1976;31:189-94.

(129) Smith AB, Schloemer J, Lowry LK, Smallwood AW, Ligo RN, Tanaka S, et al. Metabolic and health consequences of occupational exposure to polychlorinated biphenyls. Br J Ind Med. 1982;39:361-9.

(130) Hara I. Health status and PCBs in blood of workers exposed to PCBs and of their children. Environ Health Perspect. 1985;59:85-90.

(131) Baker EL, Jr., Landrigan PJ, Glueck CJ, Zack MM, Jr., Liddle JA, Burse VW, et al. Metabolic consequences of exposure to polychlorinated biphenyls (PCB) in sewage sludge. Am J Epidemiol. 1980;112:553-63.