

Risk Assessment of Polychlorinated Biphenyls (PCBs)

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PREFACE

The present report has been developed at the Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden by:

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1 INTRODUCTION

This document was developed at the request of the Nordic Council of Ministers. The document is not intended to be a complete health criteria document. For more complete annotated bibliographies and reviews the reader is referred to the references given under the heading "Selected reviews". Two documents have served as the main review base, i.e. the WHO/IPCS Environmental Health Criteria on PCBs and PCTs (in press) and the US/EPA Drinking Water Criteria Document for Polychlorinated Biphenyls (1990). Additional articles have been reviewed and included when necessary.

The intention of the document has been to identify the critical effects of PCB mixtures and/or single congeners and, where possible, to establish quantitative relationships that can be used for human risk assessment. Consequently, only studies judged to be of importance for these purposes will be reviewed. The document is not intended to deal with the ecotoxicological aspects of PCBs. Therefore, only studies on mammalian species have been included.

A wealth of studies have been performed on the commercially-available mixtures of PCBs. Due to variability in persistence, metabolic conversion and breakdown, nature acts much like a selective filter and man will, except under occupational exposure, be exposed to a PCB mixture with a composition quite different from those that have been commercially used.

Polychlorinated biphenyls (PCBs) have been used commercially since 1929 as dielectric and heat exchange fluids and in a variety of other applications. However, the distribution of PCBs in the environment was not recognized until 1966 when Jensen identified PCBs in human and wild-life samples (Jensen 1966). Many countries and inter-governmental organizations have now banned or severely restricted the production, use, handling, transport and disposal of PCBs. In Sweden, the use of PCBs was restricted in 1972 to only allow PCBs in closed systems. No new PCB-containing products have been allowed in Sweden since 1978, in Norway since 1980, in Finland since 1985, in Denmark since 1986, and in Iceland since 1988. By 1995 all PCBs will be replaced in Sweden, Norway, Denmark and Finland. In Iceland, no final decision has yet been taken. In Norway and Sweden, PCB-containing waste should be sent to an approved hazardous waste handling site for destruction, and in Denmark, Finland, and Iceland waste containing >50 ppm PCB should be treated as hazardous waste and destroyed by combustion.

2 INLEDNING

Detta dokument har utarbetats på begäran av Nordiska ministerrådet. Dokumentet har inte för avsikt att vara ett komplett hälsokriteriadokument. För mer kompletta biografier och översikter hänvisas läsaren till de referenser som ges under rubriken "Selected reviews". Två dokument har utgjort de huvudsakliga källorna för detta dokument, dvs WHO/IPCS Environmental Health Criteria on PCBs and PCTs (under utarbetande) och US/EPA Drinking Water Criteria Document for Polychlorinated Biphenyls (1990). Ytterligare artiklar har granskats och inkluderats när så har varit nödvändigt.

Dokumentets avsikt är att identifiera kritiska effekter av PCB-blandningar och/eller enskilda kongener, samt att när så är möjligt, etablera kvantitativa förhållanden som kan utnyttjas för en riskbedömning för människa. Följaktligen har endast studier av betydelse i detta avseende inkluderats. Dokumentet har inte heller för avsikt att belysa ekotoxikologiska aspekter av PCB. Av den anledningen har endast studier på däggdjur behandlats.

En lång rad studier har utförts på de blandningar av PCB som tidigare varit kommersiellt tillgängliga. På grund av variation i persistens, metabolisk omvandling och nedbrytning, så fungerar naturen i stor utsträckning som ett selektivt filter vilket innebär att människan, med undantag av vid yrkesmässig exponering, kommer att exponeras för en PCB-blandning som har en helt annan sammansättning än de blandningar som har använts kommersiellt.

Polyklorerade bifenyler (PCB) har använts kommersiellt sedan 1929 som dielektriska och värmeväxlingsvätskor och för en lång rad andra applikationer. Att PCB förorenat miljön insågs inte förrän 1966 när Jensen identifierade PCB i prov både från människa och naturen (Jensen 1966). Många länder och internationella organisationer har nu förbjudit eller starkt begränsat produktion, användning, transport och omhändertagande av PCB. I Sverige begränsades användningen 1972 till att endast tillåta PCB i slutna system. Inga nya PCB-innehållande produkter har tillåtits i Sverige sedan 1978, i Norge sedan 1980, i Finland sedan 1985 och i Danmark sedan 1986 samt på Island sedan 1988. Efter 1995 skall all PCB ha bytts ut i Sverige, Norge, Danmark och Finland. I Norge och Sverige måste PCB-innehållande avfall skickas till godkända destruktionsanläggningar, i Danmark, Finland och Island måste avfall som innehåller mer än 50 ppm PCB behandlas som miljöfarligt avfall och förstöras genom förbränning.

3 SUMMARY

3.1 Introduction

The risk assessment from exposure to PCBs presents problems which are more complicated than are usually encountered when dealing with a group of compounds. Indeed, it is certainly much more complicated than the earlier risk assessment of dioxins (Ahlborg *et al.* 1988).

The PCBs constitute a series of 209 individual congeners, varying in the number and sites of chlorine substitution. The biological effects caused by the various congeners differ, not only in potency but also qualitatively. Our knowledge of the mechanisms of toxicity indicates that some of the PCB congeners act by the same mechanisms as the chlorinated dioxins, i.e. the toxicity is probably mediated through interaction with the Ah receptor, and they are potent inducers of certain cytochrome enzymes. Other PCB congeners presumably act by different mechanisms and are potent inducers of a different set of cytochromes. In addition, there are PCB congeners which are intermediate in this respect, i.e. they elicit a mixed spectrum of enzyme induction. Some typical toxic effects of PCBs, such as tumour promotion, are caused by PCB congeners in all of these three classes, but the underlying mechanisms involved are probably different. Our knowledge of possible interactions between the various groups of PCBs is still very limited.

Almost all animal studies with PCB mixtures have been performed using commercially-available PCBs. Due to differences between individual congeners, with regards to resistance to degradation and metabolism, the composition of a commercial mixture is different from the composition of the mixtures which humans will be exposed to, especially from food.

A further complication in the risk assessment is the fact that many PCB congeners are metabolized to yield hydroxy- and methyl sulphone metabolites. The available data on the possible biological and toxicological effects of these metabolites are, however, very limited and preclude consideration of these metabolites in the present risk assessment.

The risk assessment of PCBs has been approached in two different ways.

* **Assessing the risk from the exposure to mixtures of PCBs** utilizing data from human studies and experimental animal studies. The various end-points which can be used for such an assessment are immunotoxicity in animals, cancer in humans and animals, and developmental/behavioural effects in humans and animals.

* **Assessing the risk from exposure to individual PCB congeners.** In this case, only data from animal studies are at present available for evaluation. Furthermore, the present data-base will only allow for this exercise to be performed on congeners acting through the same mechanisms as the chlorinated dioxins.

3.2 Mixtures of PCBs

The critical endpoints for risk assessment of PCBs are identified as cancer, immunotoxic and behavioural effects.

3.2.1 Cancer

Positive, long-term bioassays in the rat have all been performed with one dose level, 100 ppm, of either of two commercial mixtures (Aroclor 1260 or Clophen A60), roughly corresponding to 5 mg/kg b.w. and day. An increased frequency of liver tumours is reported in several strains. Due to the lack of dose-response data from animal bioassays, it is presently impossible to perform any quantitative risk evaluation, including the establishment of a no observed adverse effect level (NOAEL). Discrepancies between the commercial mixtures and environmental exposures, with regards to congener composition, also imply that the predictive value of these studies is limited with respect to judgement of the risks from environmental exposure. However, intake estimates for humans indicate that non-occupational exposure in men is several orders of magnitude lower than the tested carcinogenic dose of the commercial mixtures.

A few epidemiological studies of occupationally-exposed workers have indicated an increased incidence of cancer of the liver and of the biliary tract. However, in all of these studies the exposure occurred to commercial PCB mixtures, the compositions of which clearly differ from those of PCBs in food. In addition, the PCB mixtures were contaminated to various extents with other chlorinated compounds, especially polychlorinated dibenzofurans (PCDFs), which might have contributed to the observed effects. Taken together with the lack of good exposure measurements, it is not possible to use these qualitative data for the present risk assessment.

3.2.2 Immunotoxicity

Long-term, low-level exposure to one commercial mixture (Aroclor 1254) has been shown to produce moderate, but statistically significant, effects on certain immunological parameters in Rhesus monkeys. The significance to health of these findings is difficult to evaluate since it is not known how they are related to functional impairment of the immune system.

3.2.3 Behavioural effects

Hyperactivity and impaired learning ability have been reported for Rhesus monkey infants exposed to Aroclors 1248 and 1016 *in utero* and during lactation. The congener patterns of these mixtures are quite different from those seen in most biological samples, including fish and human milk. It is thus difficult to utilize the data on these monkeys directly for the present risk assessment. However, supportive data are available from studies in rats, mice and quails.

Behavioural effects similar to those seen in monkeys have also been reported for human infants whose mothers were exposed to PCBs through the intake of contaminated fish in Michigan, U.S.A. The effects recorded in infants were slight, but should still be regarded as adverse. However, the study is not fully conclusive from an epidemiological point of view. Thus, a causal relationship between PCB and the effects is not proven due to some potentially important confounding factors. On the other hand, a causal relationship is definitely possible. Furthermore, supportive evidence comes from a similar study performed in North Carolina, U.S.A.

Although there are great uncertainties involved, a lowest observed effect level (LOEL) for slight neurotoxic effects in infants from exposed mothers can be calculated to be in the range 0.014 - 0.9 $\mu\text{g}/\text{kg}$ b.w./day. This can be compared with an estimated intake in Nordic countries of around 0.2 $\mu\text{g}/\text{kg}$ b.w./day. People with a higher than average fish intake may have considerably higher intake of PCB.

3.3 Dioxin-like PCB congeners

Several non- and mono-*ortho*-substituted PCB congeners induces effects similar to those caused by chlorinated dioxins and dibenzofurans. In common with that established for chlorinated dioxins and dibenzofurans, the toxicity of such PCB congeners can be expressed in terms of TCDD-equivalency factors (TEFs), i.e. expressed as a fraction of the toxicity of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). For the calculations performed in this document, data mainly from *in vivo* studies have been utilized. However, it should be noted that the derived TEFs are still based on acute effects at relatively high doses.

Applying such TEFs to samples of fish and human milk demonstrates that the contribution from PCBs to large total dioxin-like toxicity is very important. Thus, in fish the contribution from PCBs is at the same level as that from dioxins and dibenzofurans although, so far, only non-*ortho* congeners have been analyzed. In human milk, the total contribution from non-*ortho* and mono-*ortho* substituted congeners is higher than that from dioxins and dibenzofurans. However, not all of the mono-*ortho*-substituted PCB congeners have yet been analyzed. The total contribution from the PCBs may thus be appreciably higher if all congeners are taken into account.

3.4 Conclusions

The evaluation of the available data on PCBs has demonstrated that the present data-base does not allow a traditional risk assessment to be performed, i.e. it is not possible to recommend a tolerable daily intake of either total PCBs or of any individual congeners.

Furthermore, the evaluation of PCBs suggests that the present exposure of Nordic populations is of the same order of magnitude to that at which subtle health effects may occur in children exposed *in utero* and, also possibly through breast-feeding. Further studies are necessary to clarify whether such effects actually occur and, if so, whether they are reversible. Studies are also required to determine the mechanisms behind these effects.

In addition, certain non- and mono-*ortho*-substituted PCB congeners exhibit dioxin-like toxicity. When their concentrations are taken into account, the joint risk from the PCB congeners in human milk and certain other foods appears to be of more importance than the risks due to the polychlorinated dioxins and dibenzofurans (PCDDs/PCDFs) in the same food items. When the integrated toxicity of these dioxin-like pollutants is considered, the consumption of certain fish species from contaminated areas may lead to an intake which exceeds the tolerable daily intake (TDI) of 5 pg TCDD equivalents/kg bw (TWI 35 pg/kg b.w. and week), which has been recommended by a Nordic Expert Group. However, it should be recognized that such a TDI has been considered non-applicable when dealing with the intake of PCBs by human infants from mother's milk during a limited period (WHO/EURO 1988).

Taking into account the many well-known benefits of breast-feeding for developing infants, the expert group recommended that breast-feeding should be continued and promoted in spite of the occurrence of PCBs and other chlorinated compounds in mother's milk. However, the magnitude of the safety margin cannot be determined at present, and the information available does not exclude the possibility that no safety margin may be present. The Expert Group recognizes the seriousness of this situation and it is thus important to further explore and implement all possible measures to prevent continued PCB contamination of the environment.

3.5 Recommendations for further research

The neurobehavioural effects of the PCBs appear to be critical in the risk assessment of these environmental contaminants. However, there are a number of uncertainties in the PCB data-base related to the mechanisms of action, relative congener potency, the dose-response relationships, inter-species effect relationships and the human exposure levels, as well as in the validity of extrapolation from the two epidemiological studies. Certain immunotoxic effects are also seen at low doses of PCB-exposure. It is as yet uncertain whether these data indicate a functional impairment of the immune system which is of importance to human health. The total lack of dose-response data in the carcinogenicity studies of the PCBs is remarkable. Such data are crucial for a meaningful extrapolation to the human situation. There is an urgent need to clarify all of these issues. The Expert Group has thus recommended several new studies on the assessment of exposure and on relevant aspects of toxicology and epidemiology.

4 SAMMANFATTNING

4.1 Inledning

Riskbedömningen av PCB-exponering innebär problem som är mer komplicerade än vad man vanligen möter när man skall bedöma en grupp föreningar. Den är också mycket mer komplicerad än den tidigare genomförda riskbedömningen av dioxiner (Ahlborg *et al* 1988).

PCB utgör en serie av 209 enskilda kongener som skiljer sig genom antalet kloratomer och deras plats på molekylens. De biologiska effekter som förorsakas av de olika kongenerna skiljer sig inte bara i styrka utan också kvalitativt. Vår kunskap om mekanismerna bakom toxiciteten tyder på att vissa PCB kongener verkar via samma mekanismer som de klorerade dioxinerna, dvs att toxiciteten troligen medieras genom interaktion med Ah-receptorn, och de är starka inducerare av vissa cytokromenzym. Andra PCB kongener fungerar förmodligen via andra mekanismer och är starka inducerare av andra cytokromer. Därutöver finns det också PCB kongener som intar ett mellanläge i detta avseende, dvs de utlöser en kombinerad enzyminduktion. Vissa typiska toxiska effekter av PCB, som tumörpromotion, kan förorsakas av PCB-kongener från samtliga dessa tre klasser men de underliggande mekanismerna skiljer sig troligen åt. Vår kunskap om möjliga samverkans effekter mellan de olika PCB-grupperna är ännu mycket begränsad.

Nästan alla djurstudier med PCB-blandningar har utförts med tidigare tillgängliga kommersiella blandningar. På grund av skillnaderna mellan olika kongener när det gäller motståndskraft mot nedbrytning och omsättning så skiljer sig sammansättningarna av dessa kommersiella blandningar i stor utsträckning från den blandning som människan kommer att utsättas för, framför allt från födan.

Ytterligare en komplikation när det gäller riskbedömningen är det faktum att många PCB kongener metaboliseras under bildning av hydroxy- och metylsulfonmetaboliter. Tillgängliga data om de biologiska och toxiska effekterna av dessa metaboliter är än så länge mycket begränsad och möjliggör därför inte att dessa metaboliter medtages i den nuvarande riskbedömningen.

Riskbedömningen av PCB har genomförts på två olika sätt

*** Bedömning av risken vid exponering för PCB-blandningar** med användande av data från studier både på människa och djur. De olika effekter som kan utnyttjas för en sådan bedömning är immunotoxicitet hos djur, cancer hos människa och djur samt utvecklings- och beteendestörningar hos människa och djur.

*** Bedömning av risken vid exponering för enskilda PCB-kongener.** I detta fall finns endast data från djurstudier tillgängliga för bedömning. Den tillgängliga databasen tillåter i dag inte heller att en sådan bedömning sker på annat än sådana kongener som verkar via samma mekanismer som de klorerade dioxinerna.

4.2 PCB-blandningar

De kritiska effekterna när det gäller bedömningen av PCB har identifierats som cancer, immunotoxicitet och beteendeeffekter.

4.2.1 Cancer

Positiva långtidsstudier på råttor har alla utförts med endast en dosnivå, 100 ppm av endera av två kommersiella blandningar (Aroclor 1260 eller Clophen A60), motsvarande ungefär 5 mg/kg kroppsvikt och dag. En ökad incidens av levertumörer har rapporterats i flera stammar. På grund av bristen på dos-responsdata från dessa djurstudier är det för närvarande omöjligt att utnyttja dessa data för en kvantitativ riskbedömning och man kan alltså inte bestämma en "no observed adverse effect level" (NOAEL). Skillnader mellan de kommersiella blandningarna och miljöexponeringen när det gäller kongensammansättning betyder också att den prediktiva betydelsen av dessa studier är begränsad när det gäller bedömningen av risken vid miljöexponering. Det är emellertid uppenbart att de uppskattningar som gjorts av människans intag av PCB tyder på att detta ligger flera storleksordningar lägre än den dos som har utlöst en carcinogen respons i djurförsöken.

Ett fåtal epidemiologiska studier på yrkesexponerade arbetare har indikerat en ökad incidens av cancer i lever och gallgångar. Emellertid har all exponering i dessa studier skett för kommersiella PCB-blandningar som alltså skiljer sig från de som förekommer i livsmedel. Därutöver så har dessa PCB-blandningar i varierande omfattning varit förorenade med andra klorerade föreningar, speciellt polyklorerade dibensofuraner (PCDFs), vilket kan ha bidragit till de observerade effekterna. Sammantaget med bristen på acceptabla exponeringsmätningar betyder det att man inte kan utnyttja dessa kvalitativa data för den aktuella riskbedömningen.

4.2.2 Immunotoxicitet

Långtids-studier med lågdosexponering för en kommersiell blandning (Aroclor 1254) har visat på uppkomst av måttliga men statistiskt signifikanta effekter på vissa immunologiska parametrar hos Rhesusapor. Betydelsen för vår hälsa av dessa fynd är svår att bedöma eftersom det inte är känt hur dessa förändringar är relaterade till immunsystemets funktion.

4.2.3 Beteendeeffekter

Hyperaktivitet och försämrad inlärning har rapporterats från försök med Rhesus-apbarn som exponerats för olika Aroclor-blandningar i fosterlivet och under amning. Aporna i dessa studier exponerades för kommersiella blandningar av PCB (Aroclor 1248 eller 1016). Kongensammansättningen hos dessa blandningar skiljer sig avsevärt från den blandning man ser i de flesta biologiska prov, inklusive fisk och modersmjölk. Det är därför svårt att utnyttja dessa apdata direkt för den aktuella riskbedömningen. Det finns

emellertid data från studier på råttor, mus och vaktel som stöder de iakttagelser som gjorts på apa.

Beteendeeffekter som liknar de som iakttagits hos apor har också rapporterats för barn, vilkas mödrar exponerats för PCB genom intag av PCB-kontaminerad fisk i Michigan, USA. De effekter som man har iakttagit på barnen var små men måste ändå betraktas som allvarliga. Emellertid är studien inte helt entydig sett ur epidemiologisk synpunkt. Det faktiska kausalsambandet mellan PCB-exponering och effekterna är inte fullt bevisat beroende på att det föreligger vissa betydelsefulla "confounders". Å andra sidan är ett kausalsamband absolut möjligt. Till yttermera visso föreligger data från en liknande studie som utförts i North Carolina, USA, som stödjer de iakttagelser som gjorts i Michigan-studien. Även om det finns stora osäkerheter inblandade i en dylik bedömning så skulle en lägsta observerade effekt-nivå (LOEL) för lätta neurotoxiska effekter hos barn till exponerade mödrar uppskattas vara i området 0.014-0.9 µg/kg kroppsvikt och dag. Detta kan jämföras med det uppskattade intaget i nordiska länder på omkring 0.2 µg/kg kroppsvikt och dag. Människor med högre intag av fisk än genomsnittligt kan ha avsevärt högre intag av PCB.

4.3 Dioxin-lika PCB

Flera non- och mono-*ortho*-substituerade PCB kongener inducerar effekter som liknar de som orsakas av klorerade dioxiner och dibensofuraner. I likhet med vad som har gjorts för klorerade dioxiner och dibensofuraner så kan toxiciteten av sådana PCB kongener uttryckas i termer av TCDD-ekvivalensfaktorer (TEFs), dvs delar av toxiciteten hos 2,3,7,8-tetraklorodibenso-p-dioxin (TCDD). För de kalkyler som genomförts i detta dokument har data väsentligen från *in vivo* studier utnyttjats. Det måste emellertid understrykas att de TEFs som man har erhållit fortfarande är baserade på akuta effekter vid relativt höga doser.

Tillämpas sådana TEFs på fisk- och modersmjölksprover så finner man att bidraget från PCB till den totala dioxintoxiciteten är av stor betydelse. Sålunda kan man konstatera att enbart non-*ortho*-substituerade PCB-kongener bidrar med lika mycket toxicitet som den samlade toxiciteten från dioxiner och dibensofuraner i fisk. I modersmjölk är det totala bidraget från non- och mono-*ortho*-substituerade PCB-kongener större än det från dioxiner och dibensofuraner. Det måste understrykas att än så länge har inte alla mono-*ortho*-substituerade PCB kongener analyserats. Det totala bidraget från PCB kan sålunda antas vara betydligt större om alla kongener medräknas.

4.4 Slutsatser

Utvärderingen av tillgängliga data på PCB har visat att den tillgängliga databasen inte medger att man genomför en traditionell riskbedömning, dvs det är inte möjligt att rekommendera ett tolerabelt dagligt intag vare sig för total-PCB eller för någon enskild kongen.

Den PCB-exponeringen som befolkningen i Norden för närvarande utsätts för torde emellertid ligga i samma storleksordning som den vid vilken man skulle kunna förvänta att subtil hälsopåverkan kan ske hos barn som exponeras under fosterlivet och möjligen också via modersmjölken. Ytterligare studier är dock nödvändiga för att klargöra om sådana effekter faktiskt förekommer och om så, huruvida de är reversibla och man måste också i så fall klargöra mekanismen bakom detta.

Till detta kommer att vissa non- och mono-*ortho*-substituerade PCB kongener uppvisar dioxinlik toxicitet. Tar man hänsyn till koncentrationen av dioxinlika PCB kongener så betyder det att den samlade risken från PCB-förorening i modersmjölk och vissa födoämnen förefaller vara mer betydande än risken som kommer från de klorerade dioxinerna och dibensofuranerna. Om den samlade toxiciteten från alla dessa dioxinliknande föroreningar beaktas så innebär detta att konsumtion av fisk från vissa förorenade områden kan medföra ett intag som överstiger det tolerabla dagliga intaget (TDI) på 5 pg TCDD-ekvivalenter per kg kroppsvikt (TWI 35 pg/kg/vecka) som tidigare rekommenderats av en nordisk expertgrupp. Det bör emellertid uppmärksammas att man har ansett att ett sådant TDI-värde inte skall användas när man bedömer intaget av PCB hos spädbarn som exponeras via modersmjölk under en begränsad tidsperiod (WHO/EURO 1988).

Om man tar hänsyn till alla de välkända fördelar som amning medför för spädbarnet så finner expertgruppen att amning bör fortsätta och uppmuntras trots förekomsten av PCB och andra klorerade föroreningar i modersmjölken. Det är emellertid uppenbart att storleken av säkerhetsmarginalen inte kan bedömas för närvarande och den information som finns tillgänglig utesluter inte möjligheten att det inte föreligger någon säkerhetsmarginal. Expertgruppen är medveten om allvaret i denna situation och det är således viktigt att ytterligare utreda och vidta alla möjliga åtgärder för att förebygga fortsatt PCB-kontaminering av vår miljö.

4.5 Rekommendation om fortsatt forskning

De beteendeeffekter som iakttagits efter PCB-exponering är uppenbarligen kritiska för riskbedömningen av dessa miljöföroreningar. Det finns emellertid flera oklarheter avseende data kring PCB. Dessa rör verkningsmekanismer, relativ potens hos de olika kongenerna, dos-responsförhållanden, variationer mellan arter, human exponering och möjligheterna till extrapolering från tillgängliga epidemiologiska studier. Vissa immuntoxiska effekter har också iakttagits vid förhållandevis låg PCB-exponering. Det är ännu oklart huruvida dessa effekter påverkar immunsystemet så att människans hälsa påverkas. Det är vidare anmärkningsvärt att det inte finns några cancer-studier av PCB som ger klarhet kring dos-respons-förhållanden. Sådana är viktiga för en meningsfull extrapolering till människa. Det är alltså synnerligen angeläget att söka bringa klarhet i dessa förhållanden. Sålunda har expertgruppen rekommenderat ett flertal studier inom olika områden som exponeringsmätningar, toxikologi och epidemiologi.

5 CHEMISTRY AND ANALYSIS

5.1 Chemical identity

Polychlorinated biphenyls (PCBs) are aromatic, synthetic chemicals not occurring naturally in the environment. They consist of the biphenyl structure with two linked benzene rings in which some or all of the hydrogen atoms have been substituted by chlorine atoms. The basic molecular structure, including the conventional numbering of the substituent positions, is shown in Figure 1.

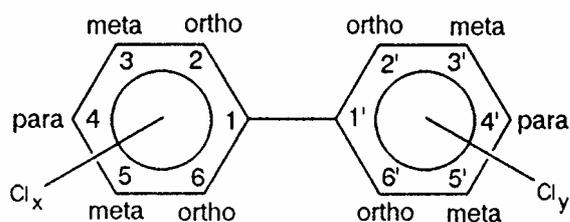


Figure 1. Structural formula of PCBs.

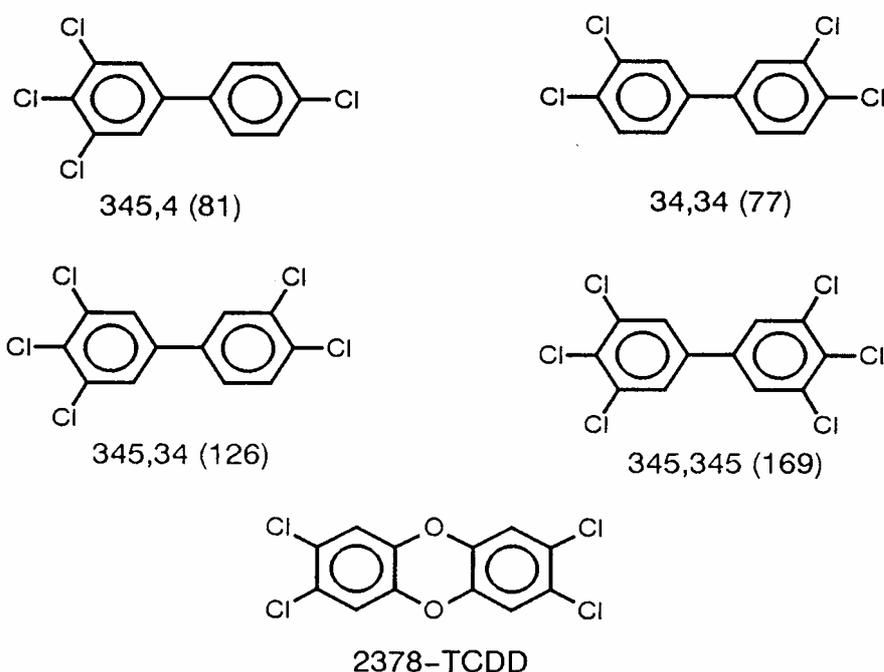


Figure 2. Structures of the PCB congeners substituted in both *para* and two or more *meta* positions and of TCDD. Numbers in parentheses refer to IUPAC number.

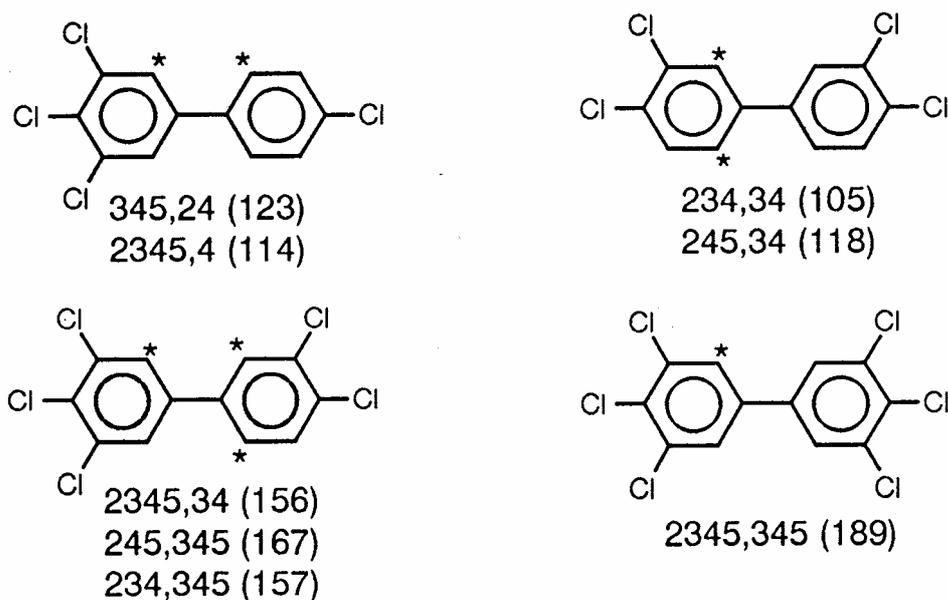


Figure 3. Structures of the mono-*ortho* PCB congeners. The possible positions for the *ortho* chlorine atom are marked with *. Numbers in parentheses refer to IUPAC number.

The chemical formula of PCBs is $C_{12}H_{10-n}Cl_n$, where n ranges from 1 to 10. Theoretically, 209 different congeners are possible, but only about 130 of these have been identified in commercial products. Ballschmiter and Zell (1980) proposed a numbering system for the PCB congeners which has been adopted by the International Union of Pure and Applied Chemists (IUPAC) (Table 1).

The PCB congeners without chlorine atoms at the *ortho*-positions can assume a coplanar conformation. The congeners 3,4,4',5-, 3,3',4,4'-, 3,3',4,4',5- and 3,3',4,4',5,5'-CB (non-*ortho* PCB congeners), which are also substituted in both *para* and at least two *meta* positions, are in their coplanar conformation approximate stereoisomers of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), the most toxic dioxin congener (Figure 2). Their mono-*ortho* analogs (Figure 3) are less, and the di-*ortho* analogs even less, likely to assume a coplanar conformation and thereby structurally resemble TCDD.

In this document, the non-, mono- and di-ortho nomenclature is used only for PCB congeners that are also chlorinated in both para and at least two meta positions (see Table 1).

5.2 Chemical and physical properties

All congeners of PCBs are lipophilic and have very low water solubilities. However, their lipophilicity increases with increasing degree of chlorination. Pure individual PCB congeners are colourless and often crystalline. Commercial PCB mixtures are clear to light yellow oils or resins and they do not crystallise, even at low temperatures.

Table 1. IUPAC numbers and chlorine atom positions of all PCB congeners (Ballschmiter and Zell 1980).

No.	Structure	No.	Structure	No.	Structure	No.	Structure
1	2	56	2,3,3',4'	111	2,3,3',5,5'	166***	2,3,4,4',5,6
2	3	57	2,3,3',5	112	2,3,3',5,6	167**	2,3',4,4',5,5'
3	4	58	2,3,3',5'	113	2,3,3',5',6	168***	2,3',4,4',5',6
4	2,2'	59	2,3,3',6	114**	2,3,4,4',5	169*	3,3',4,4',5,5'
5	2,3	60	2,3,4,4'	115	2,3,4,4',6	170***	2,2',3,3',4,4',5
6	2,3'	61	2,3,4,5	116	2,3,4,5,6	171	2,2',3,3',4,4',6
7	2,4	62	2,3,4,6	117	2,3,4',5,6	172	2,2',3,3',4,5,5'
8	2,4'	63	2,3,4',5	118**	2,3',4,4',5	173	2,2',3,3',4,5,6
9	2,5	64	2,3,4',6	119	2,3',4,4',6	174	2,2',3,3',4,5,6'
10	2,6	65	2,3,5,6	120	2,3',4,5,5'	175	2,2',3,3',4,5',6
11	3,3'	66	2,3',4,4'	121	2,3',4,5',6	176	2,2',3,3',4,6,6'
12	3,4	67	2,3',4,5	122	2',3,3',4,5	177	2,2',3,3',4',5,6
13	3,4'	68	2,3',4,5'	123**	2',3,4,4',5	178	2,2',3,3',5,5',6
14	3,5	69	2,3',4,6	124	2',3,4,5,5'	179	2,2',3,3',5,6,6'
15	4,4'	70	2,3',4',5	125	2',3,4,5,6'	180***	2,2',3,4,4',5,5'
16	2,2',3	71	2,3',4',6	126*	3,3',4,4',5	181	2,2',3,4,4',5,6
17	2,2',4	72	2,3',5,5'	127	3,3',4,5,5'	182	2,2',3,4,4',5,6'
18	2,2',5	73	2,3',5',6	128***	2,2',3,3',4,4'	183	2,2',3,4,4',5',6
19	2,2',6	74	2,4,4',5	129	2,2',3,3',4,5	184	2,2',3,4,4',6,6'
20	2,3,3'	75	2,4,4',6	130	2,2',3,3',4,5'	185	2,2',3,4,5,5',6
21	2,3,4	76	2',3,4,5	131	2,2',3,3',4,6	186	2,2',3,4,5,6,6'
22	2,3,4'	77*	3,3',4,4'	132	2,2',3,3',4,6'	187	2,2',3,4',5,5',6
23	2,3,5	78	3,3',4,5	133	2,2',3,3',5,5'	188	2,2',3,4',5,6,6'
24	2,3,6	79	3,3',4,5'	134	2,2',3,3',5,6	189**	2,3,3',4,4',5,5'
25	2,3',4	80	3,3',5,5'	135	2,2',3,3',5,6'	190***	2,3,3',4,4',5,6
26	2,3',5	81*	3,4,4',5	136	2,2',3,3',6,6'	191***	2,3,3',4,4',5',6
27	2,3',6	82	2,2',3,3',4	137***	2,2',3,4,4',5	192	2,3,3',4,5,5',6
28	2,4,4'	83	2,2',3,3',5	138***	2,2',3,4,4',5'	193	2,3,3',4',5,5',6
29	2,4,5	84	2,2',3,3',6	139	2,2',3,4,4',6	194***	2,2',3,3',4,4',5,5'
30	2,4,6	85	2,2',3,4,4'	140	2,2',3,4,4',6'	195	2,2',3,3',4,4',5,6
31	2,4',5	86	2,2',3,4,5	141	2,2',3,4,5,5'	196	2,2',3,3',4,4',5,6'
32	2,4',6	87	2,2',3,4,5'	142	2,2',3,4,5,6	197	2,2',3,3',4,4',6,6'
33	2',3,4	88	2,2',3,4,6	143	2,2',3,4,5,6'	198	2,2',3,3',4,5,5',6
34	2',3,5	89	2,2',3,4,6'	144	2,2',3,4,5',6	199	2,2',3,3',4,5,6,6'
35	3,3',4	90	2,2',3,4',5	145	2,2',3,4,6,6'	200	2,2',3,3',4,5',6,6'
36	3,3',5	91	2,2',3,4',6	146	2,2',3,4',5,5'	201	2,2',3,3',4',5,5',6
37	3,4,4'	92	2,2',3,5,5'	147	2,2',3,4',5,6	202	2,2',3,3',5,5',6,6'
38	3,4,5	93	2,2',3,5,6	148	2,2',3,4',5,6'	203	2,2',3,4,4',5,5',6
39	3,4',5	94	2,2',3,5,6'	149	2,2',3,4',5',6	204	2,2',3,4,4',5,6,6'
40	2,2',3,3'	95	2,2',3,5',6	150	2,2',3,4',6,6'	205***	2,3,3',4,4',5,5',6
41	2,2',3,4	96	2,2',3,6,6'	151	2,2',3,5,5',6	206	2,2',3,3',4,4',5,5',6
42	2,2',3,4'	97	2,2',3',4,5	152	2,2',3,5,6,6'	207	2,2',3,3',4,4',5,6,6'
43	2,2',3,5	98	2,2',3',4,6	153***	2,2',4,4',5,5'	208	2,2',3,3',4,5,5',6,6'
44	2,2',3,5'	99	2,2',4,4',5	154	2,2',4,4',5,6'	209	2,2',3,3',4,4',5,5',6,6'
45	2,2',3,6	100	2,2',4,4',6	155	2,2',4,4',6,6'		
46	2,2',3,6'	101	2,2',4,5,5'	156**	2,3,3',4,4',5		
47	2,2',4,4'	102	2,2',4,5,6'	157**	2,3,3',4,4',5'		
48	2,2',4,5	103	2,2',4,5',6	158***	2,3,3',4,4',6		
49	2,2',4,5'	104	2,2',4,6,6'	159	2,3,3',4,5,5'		
50	2,2',4,6	105**	2,3,3',4,4'	160	2,3,3',4,5,6		
51	2,2',4,6'	106	2,3,3',4,5	161	2,3,3',4,5',6		
52	2,2',5,5'	107	2,3,3',4',5	162	2,3,3',4',5,5'		
53	2,2',5,6'	108	2,3,3',4,5'	163	2,3,3',4',5,6		
54	2,2',6,6'	109	2,3,3',4,6	164	2,3,3',4',5',6		
55	2,3,3',4	110	2,3,3',4',6	165	2,3,3',5,5',6		

* Non-ortho congener[#], ** mono-ortho congener[#], *** di-ortho congener[#]
[#] also chlorinated in both *para* and at least two *meta* positions

PCBs are practically fire resistant because of their high flash points (170-380°C). They form vapours which are heavier than air, but are not explosive. They have low electrical conductivity, high thermal conductivity and high resistance to thermal degradation. On the basis of these properties they are used as cooling liquids in electrical equipment. Like many organochlorine compounds, they are highly persistent and accumulate within food chains. Investigations in many parts of the world have revealed widespread distribution of PCBs in the environment.

5.3 Commercial mixtures and impurities

PCBs are manufactured by chlorination of biphenyl in the presence of a suitable catalyst. Depending on the reaction conditions, the degree of chlorination varies between 21% and 68% (w/w). The product is always a mixture of different congeners.

Individual manufacturers have their own system of identification for their products. In the Aroclor series, a four digit code is used. Biphenyls are generally indicated by the figure 12 in the first two positions, whilst the last two numbers indicate the percentage of chlorine by weight in the mixture. An exception is Aroclor 1016, which is a distillation product of Aroclor 1242, containing only 1% of congeners with five or more chlorine atoms. In other commercial products the codes often indicate the approximate mean number of chlorine atoms in the components. Thus, Clophen A60, Phenochlor DP6 and Kanechlor 600 have an average of 6 chlorine atoms per molecule (59% w/w).

Commercial PCBs are not sold on a composition specification basis, but on their physical properties. The absolute composition, as well as the content of impurities, may, thus, vary from batch to batch.

Most commercial PCB mixtures are contaminated with other chlorinated compounds, especially the polychlorinated dibenzofurans (PCDFs), which occur at levels of up to 33 mg/kg (Table 2). In addition, polychlorinated naphthalenes (PCNs) and quaterphenyls (PCQs) have been identified in commercial PCB products (de Voogt and Brinkman 1989). As an illustration of this, the compositions of impurities in some PCB products and in the Yusho and Yu-Cheng oils are given in Table 2.

5.4 Analysis of PCBs

The procedure for the analysis of PCB includes the following steps: extraction, extract concentration, clean-up, chromatographic separation, identification and quantification. For the analysis of biological samples, separation of PCB from lipids is required prior to the determination.

Quantitation of total PCB has conventionally been performed by the pattern method, i.e. by comparing typically ≥ 4 peaks of the sample chromatogram to that of a commercial mixture, such as Clophen A50 in the "Jensen method" (Jensen *et al.* 1983) and Aroclor in the "Sawyer method" (Sawyer 1978). Dechlorination to biphenyl, as well as perchlorination to decachlorobiphenyl, have also been used for the quantification of total PCB (Himberg 1989).

Table 2. Concentrations of PCDF and PCN impurities in various PCB products and in the Yusho and Yu-Cheng oils (US/EPA 1990, E Jakobsson, personal communication).

Product	PCDF concentration (mg/kg)	PCN concentration (mg/kg)
Yusho oil (151-968 mg PCB/kg)	2-7 ^a	
Yusho oil (900 mg PCB/kg)	2.02 ^b	
Yu-Cheng oil (22-113 mg PCB/kg)	0.14-0.18 ^a	
Yu-Cheng oil (60-100 mg PCB/kg)	0.08-0.10 ^b	
Kanechlor 300	8.3 ^c	
Kanechlor 400	23.8 ^c	
Kanechlor 400 (unused)	33 ^a	
Kanechlor 400 (used)	20-510 ^a	
Kanechlor 500	6.1 ^c	
Kanechlor 600	1.1 ^c	
Aroclor 1016		6.5 ^d
Aroclor 1232		175.5 ^d
Aroclor 1241	5.9 ^c	
Aroclor 1242	4.5 ^c	103.4 ^d
Aroclor 1248	2.8 ^c	67.2 ^d
Aroclor 1248 (used)	12 ^c	
Aroclor 1254	5.6 ^c	3.5 ^d
Aroclor 1260	2.2 ^c	2.7 ^d
Aroclor 1262		1152.5 ^d
Aroclor 1264	16 ^c	
Clophen A30		871.7 ^d
Clophen A40		814.7 ^d
Clophen A50		1.8 ^d

^a Miyata *et al.* 1985, ^b Masuda *et al.* 1982, ^c Morita *et al.* 1977, ^d E Jakobsson, personal communication.

During the 1970s, improved analytical techniques and methods for the synthesis of pure standards of individual congeners made it possible to use single PCB congeners for quantification purposes (Jensen and Sundström 1974). At present, several recommended analytical procedures exist for the analysis of PCB in samples of biological origin. Various ways of extraction and clean-up of the extract are used, however, all acceptable methods are based on the determination of individual congeners.

There are several acceptable homogenization and extraction procedures for the isolation of lipid and lipid-soluble compounds from biological matrices. The percentage of extractable lipid is determined. The removal of lipid is of major importance in order to avoid interference during gas liquid chromatography (GLC) analysis, and this is achieved by gel permeation chromatography and/or column chromatography using aluminium oxide.

Clean-up processes can also be combined in a single aluminium oxide/silica gel column. Separation of other coextracted, lipid-soluble, persistent organochlorines that may interfere in the PCB analysis can be achieved by using a silica gel column, and then eluting with solvents of different polarity. Finally, group separation of PCBs can be performed by column chromatography using charcoal. This step is only necessary when non-*ortho* PCB congeners are to be determined, since they are present in concentrations 100 - 10 000 times lower than those of the mono-*ortho* and di-*ortho* congeners. Final separation of the PCBs is performed by temperature-programmed capillary gas chromatography (GC), with electron capture detection (EC) or mass spectrometry (MS).

Identification and quantification of the individual PCB congeners are performed by comparing the retention times and heights of peaks in the sample chromatogram with corresponding peaks in a chromatogram of a mixture of selected, pure reference PCB congeners. For the identification and quantification of the non-*ortho* PCB congeners, GC-MS should be used.

For quality assurance it is recommended that one or several suitable internal standards should be added, either to the matrix or to the extract prior to gas chromatography. It should be a prerequisite that laboratories engaged in producing PCB data for use in risk assessment should regularly participate in inter-laboratory analytical quality assurance testing of the analytical procedures used.

Comment

The method of quantifying total PCB, by comparing the sample peak pattern with that of a commercial mixture, is accurate when the sample under investigation has been directly contaminated by a commercial mixture. However, because of substantial differences in PCB patterns between biological samples and technical products, this method leads to errors in quantification from biological samples and also to differences between laboratories due to the use of different standards.

The use of perchlorination in the quantification of decachlorobiphenyl has, generally, been abandoned.

On the basis of the problems and differences in quantifying total PCB, data on the levels of PCB in samples has to be interpreted with the greatest of care. Comparisons can only be made between data from either the same laboratory, using the same validated technique and the same standards over a longer period, or between laboratories when very strict inter-laboratory controls have been made. Indications of trends can only be obtained when taking into account these basic considerations.

5.5 PCB patterns in technical and biological samples

The congener pattern of human (and other biological) samples differs from that of the commercial mixtures. Jensen and Sundström (1974) compared the relative concentrations of 60 congeners (≥ 4 chlorines) in Swedish human adipose tissue and in two of the commercial mixtures often used as analytical standards, Clophen A50 and A60 (Table 3). Safe *et al.* (1985) compared the relative concentrations of 88 congeners in human mother's milk and one of the commercial mixtures often used as analytical standard, Aroclor 1260 (Table 4).

Table 3. Relative concentrations (%) of individual PCB congeners in Clophen commercial mixtures and in human adipose tissue (source: Jensen and Sundström 1974). Only those congeners constituting at least 1% of total PCB in either matrix are shown.

Congener	IUPAC	A50	A60	Adipose tissue	Congener	IUPAC	A50	A60	Adipose tissue
2,2',3,4	41 ^a	1.2		0.66	2,2',3,3',4,6'	132	1.8	3.2	0.15
2,2',3,5'	44	1.9		1.1	2,2',3,3',5,6'	135	1.2	4.2	1.0
2,2',4,5'	49	1.4			2,2',3,3',6,6'	136	0.5	1.0	
2,2',5,5'	52	5.0			2,2',3,4,4',5'	138 ^{***}	5.1	11.3	14.0
2,3,4',6	64 ^a	2.1		0.56	2,2',3,4',5,5'	146	0.90	2.9	2.7
2,3',4',5	70	3.9		1.5	2,2',3,4',5',6	149	2.0	6.5	0.13
2,2',3,3',4	82	1.0			2,2',3,5,5',6	151	1.3	3.3	0.43
2,2',3,3',6	84	2.5	0.28	0.48	2,2',4,4',5,5'	153 ^{***}	4.2	12.9	21.5
2,2',3,4,5'	87	5.4	1.4	2.3	2,3,3',4,4',5	156 ^{**}	0.81	1.5	2.0
2,2',3,5,5'	92	2.2	1.1	1.2	2,3',4,4',5,5'	167 ^{**}	0.47	1.0	0.49
2,2',3,5',6	95	4.4	2.9	1.2	2,2',3,3',4,4',5	170 ^{***}	0.72	4.1	3.9
2,2',3',4,5	97	1.4			2,2',3,3',4,4',6	171	0.13	1.3	0.57
2,2',4,4',5	99	1.8		1.9	2,2',3,3',4,5,5'	172	0.23	0.90	1.2
2,2',4,5,5'	101	7.0	5.6	4.2	2,2',3,3',4,5,6'	174	0.33	3.7	
2,3,3',4,4'	105 ^{**}	3.6		1.9	2,2',3,3',4',5,6	177	0.27	2.1	1.3
2,3,3',4',6	110	7.6	2.9	4.7	2,2',3,4,4',5,5'	180 ^{***}	0.98	7.6	7.7
2,3',4,4',5	118 ^{**}	5.0	1.6	5.4	2,2',3,4,4',5',6	183	0.17	1.8	2.5
2,2',3,3',4,4'	128 ^{***}	1.3	2.0	0.81	2,2',3,4',5,5',6	187	0.39	3.3	3.5
2,2',3,3',4,5'	130	1.1	1.5		2,2',3,3',4,4',5,5'	194 ^{***}	0.35	0.67	1.7

^a Tentative structure, ^{**} Mono-ortho congener[#], ^{***} di-ortho congener[#], [#] also chlorinated in both *para* and at least two *meta* positions

Table 4. Relative concentrations (%) of individual PCB congeners in a commercial mixture and in human mother's milk (source: Safe *et al.* 1985). Only those congeners constituting at least 1% of total PCB in either matrix are shown.

Congener	IUPAC	Aroclor 1260	Mother's milk	Congener	IUPAC	Aroclor 1260	Mother's milk
2,4,4'	28	0.04	8.8 ^a	2,2',4,4',5,5'	153 ^{***}	9.6	12
2',3,4	33	0.09	2.2	2,3,3',4,4',5	156 ^{**}	0.45	4.87
3,4,4'	37	0.04	2.9	2,2',3,3',4,4',5	170 ^{***}	6.8	5.3
2,2',3,4	41	0.25	1.3	2,2',3,3',4,4',6/ 2,2',3,3',5,5',6,6'	171/202	1.2	0.37
2,2',5,5'	52	0.25	1.9	2,2',3,3',4,5,6'	174	5.5	0.39
2,4,4',5	74	0.03	11	2,2',3,3',4',5,6	177	1.9	0.61
2,2',3,5',6	95	2.7		2,2',3,3',5,5',6	178	1.2	
2,2',4,4',5	99	0.13	4.8	2,2',3,4,4',5,5'	180 ^{***}	9.1	5.3
2,2',4,5,5'	101	2.5	0.97	2,2',3,4,4',5',6	183	2.3	1.4
2,3,3',4',6	110	1.7	1.0	2,2',3,4,5,5',6	185	4.1	0.11
2,3',4,4',5	118 ^{**}	0.49	6.5	2,2',3,4',5,5',6	187	4.5	1.5
2,2',3,3',6,6'	136	1.4		2,3,3',4,4',5,5'	189 ^{**}	0.15	2.4
2,2',3,4,4',5'	138 ^{***}	6.5	10	2,2',3,3',4,4',5,5'	194 ^{***}	1.7	0.48
2,2',3,4,5,5'	141	2.5	0.29	2,2',3,3',4,4',5,6	195	3.1	0.31
2,2',3,4,5',6/ 2,2',3,3',5,6'	144/135	1.5	0.51	2,2',3,3',4,4',5,6'	196	2.5	0.18
2,2',3,4',5,5'	146	1.3	1.9	2,2',3,3',4,5,5',6'	201	2.9	0.85
2,2',3,4',5',6	149	7.4		2,2',3,4,4',5,5',6	203	3.1	0.79
2,2',3,5,5',6	151	2.5	0.59				

^a This congener constitutes only about 1.2% in Swedish mother's milk (Norén and Lundén 1991). ^{**} Mono-ortho congener, ^{***} di-ortho congener, ^{###} also chlorinated in both *para* and at least two *meta* positions

6 EXPERIMENTAL DATA

6.1 Toxicokinetics

6.1.1 Absorption

Several studies confirm that individual congeners and their mixtures are readily absorbed from the gastrointestinal tract of rodents and monkeys. Gastrointestinal absorption of individual congeners in the rat has been reported to vary between 66 and 96% (Tanabe *et al.* 1981). The degree of absorption decreases with increasing chlorination (Bergman *et al.* 1982). The effect of the vehicle on gastrointestinal absorption of PCB has not been systematically evaluated.

Several studies with PCB congeners, or mixtures, have demonstrated effective dermal absorption. In guinea pigs the absorption of mixtures was at least 33-56% during 16 days of exposure, whilst monkeys absorbed at least 20% during 28 days of exposure (Wester *et al.* 1983).

Rapid absorption and distribution, comparable to that after oral exposure, has been observed in rats exposed to PCB congeners via inhalation (Benthe *et al.* 1972).

6.1.2 Distribution

The distribution of PCBs in the body is dependent on the structure and the physicochemical characteristics of the individual congeners. In most animal species investigated there is an initial uptake in the liver and muscle, probably due to high blood perfusion in the liver and the relatively large volume of muscle (US/EPA 1990). Subsequently, the higher chlorinated congeners in particular are redistributed into adipose tissue and skin, reflecting their high affinity for tissues with a high lipid content. One week after an oral dose of 2,2',4,4',5,5'-CB, 81% was found in the body of rats (Wyss *et al.* 1986). The distribution within the body at this time was 64% in adipose tissue, 11% in skin, 5% in muscle, 1% in liver, whilst the lung, blood and brain only contained 0.1-0.3%. In rats, the congener 3,3',4,4',5-CB distributes especially to the liver, where 68% of an oral dose was found five days after exposure (Yoshimura *et al.* 1985). One month after exposure, more than 20% still remained in the liver.

In order to be able to compare tissue distribution patterns between congeners, the available data on the ratios between PCB concentrations in liver and adipose tissue are summarized in Table 5. The figures should, however, only be taken as rough illustrations as there are substantial differences in the experimental designs which obtained them.

Table 5. Ratios of PCB concentrations in liver and adipose tissue of rats reported for different congeners.

Congener	IUPAC	Ratio	Time after administration (days)	Reference
2,4',5	31	0.4	5	Lay <i>et al.</i> 1979
3,3',4,4' ^α	77*	0.15	5	Klasson-Wehler <i>et al.</i> 1989
"tetraCBs"		0.07	?	Hashimoto <i>et al.</i> 1976
"hexaCBs"		0.04	?	Hashimoto <i>et al.</i> 1976
2,2',4,4',6	100	0.06	8	Felt <i>et al.</i> 1979
2,2',3,3',6,6' [#]	136	0.8	1	Birnbaum 1983
2,2',4,4',5,5' [#]	153***	0.06	4	Birnbaum 1983
2,2',4,4',5,5'	153***	0.025	42-280	Wyss <i>et al.</i> 1986
2,2',4,4',5,5' ^α	153***	0.02	28	Biocca <i>et al.</i> 1981
2,2',3,3',6,6' ^α	136	0.04	28	Biocca <i>et al.</i> 1981
2,2',4,4',6,6' ^α	155	0.06	28	Biocca <i>et al.</i> 1981
3,3',4,4',5,5' ^α	169*	0.19	28	Biocca <i>et al.</i> 1981

^αmice, [#] adolescent rats

*,*** non- and di-ortho congeners, respectively, which are also chlorinated in both *para* and at least two *meta* positions

The ratio between the concentrations of 3,3',4,4',5-CB in liver and brain of rats has been reported to be 130-217 (on a wet weight basis). The ratio was even higher in rat pups exposed *in utero*, indicating a relatively efficient blood-brain barrier (Bernhoft *et al.* 1991).

The distribution of several PCB congeners in mice has been studied using autoradiography (Å Bergman, I Brandt, personal communication). The congeners 2,4',5-, 2,2',4,5'-, 2,2',5,5'-, 2,3',4,5'- and 2,2',4,5,5'-CB were found to accumulate in both pulmonary and renal tissues, whilst 2,2',3,4,4'-, 2,2',4,4',5-, 2,2',4,4',5,5'-, 2,2',3,3',6-, 2,2',3,5',6-, and 2,3,3',4',6-CB only accumulate in the lung. 2,4',5-CB accumulates in uterine fluid, 3,3',4,4'-CB in foetuses and 3,3',4,4',5-CB in the liver, whilst other congeners studied (4-, 2,4-, 2,2',3,3'-, 2,2',3,4'-, 2,2',3,5'-, 2,2',4,4'-, 2,3,3',4'-, 2,3',4,4'-, 2,3,3',4,4'-, 2,3',4,4',5'-, 2',3,4,4',5-, 2,2',3,4,4',6'-, 2,3',4,4',5',6-, 2,2',3,4,4',5,5'- and 2,2',3,3',4,4',5',6-CB) were distributed mainly to fatty tissues.

A study on mink dams, exposed to Clophen A50 during gestation, shows that mono- and di-ortho congeners were retained in the body (muscle), whilst other congeners present in Clophen A50 were not found in the tissue of the mink dams (Bergman *et al.* 1992).

6.1.3 Biotransformation

The rate limiting step in the elimination of PCBs is that of metabolism, which primarily occurs by the hepatic P450-dependent monooxygenase system. The different metabolic pathways of PCBs are shown in Figure 4.

Hydroxylated products are the major PCB metabolites and, based on the available studies, it can be concluded that hydroxylation mainly occurs at *para* or *meta* positions if these sites are unsubstituted.

Several hydroxylated metabolites (4-OH-3,3',4',5-, 5-OH-3,3',4,4'-, 4-OH-2,2',3,3',4'-, 4-OH-2,3,3',4'-, 4-OH-3,3',4'-CB) have been shown to bind to transthyretin (TTR) in plasma of rats and/or mice and, thereby, interfere with the transport of both vitamin A and thyroxin, whilst the unhydroxylated congeners do not bind (Brouwer and van den Berg 1986, Brouwer *et al.* 1988a, 1990, Willemsen *et al.* 1991).

Arene oxides have been proposed to occur as intermediates in the oxidation of PCBs. Arene oxides are reactive and can be converted both spontaneously and enzymatically to detoxified products (e.g. phenols, dihydrodiols, glutathione conjugates), which are excreted. Alternatively, they can form potentially toxic (cytotoxic, mutagenic, carcinogenic), covalently-bound substrate-macromolecular adducts.

Besides hydroxylation and subsequent conjugation, sulphur-containing metabolites (e.g. methyl sulphones) and partially dechlorinated metabolites have also been identified. Methyl sulphone metabolites have been shown to selectively accumulate in the Clara cells of rat lung (Lund *et al.* 1985). In mice, methyl sulphonyl metabolites of 2,4',5-, 2,2',4,5'- and 2,2',4,5,5'-CB accumulate in lung tissue (Bergman *et al.* 1979). These methyl-sulphonyl metabolites have also been found in liver, adipose and fetal tissues and have been identified in both environmental samples and in human milk. Both the rate of metabolism of PCB and the resultant metabolite pattern varies between different species. Schnellmann *et al.* (1985) have shown that the kinetic constants for PCB metabolism derived *in vitro* agree well with those obtained for *in vivo* metabolism and clearance for three congeners (4,4'-, 2,2',3,3',6,6'- and 2,2',4,4',5,5'-CB) in rats, dogs and monkeys.

6.1.4 Elimination

The excretion of PCB congeners is, to a large extent, dependent on the metabolism of PCBs to more polar compounds. The metabolism varies depending on the chlorination pattern of the congener. One illustration of this is the varying half-lives of different tetraCBs in mice: 2,2',3,3'- and 3,3',4,4'-CB - 0.9 days; 3,3',5,5'-CB - 2.1; 2,2',5,5'-CB - 3.4 and 2,2',4,4'-CB - 9.2 days (Mizutani *et al.* 1977). The biological half-lives of PCB congeners given orally to rats as a mixture of four Kanechlor products are presented in Table 6 (Tanabe *et al.* 1981). Most congeners show a biphasic elimination, where the initial half-life is relatively short for all congeners, but the later half-life is much longer and clearly structure-dependent.

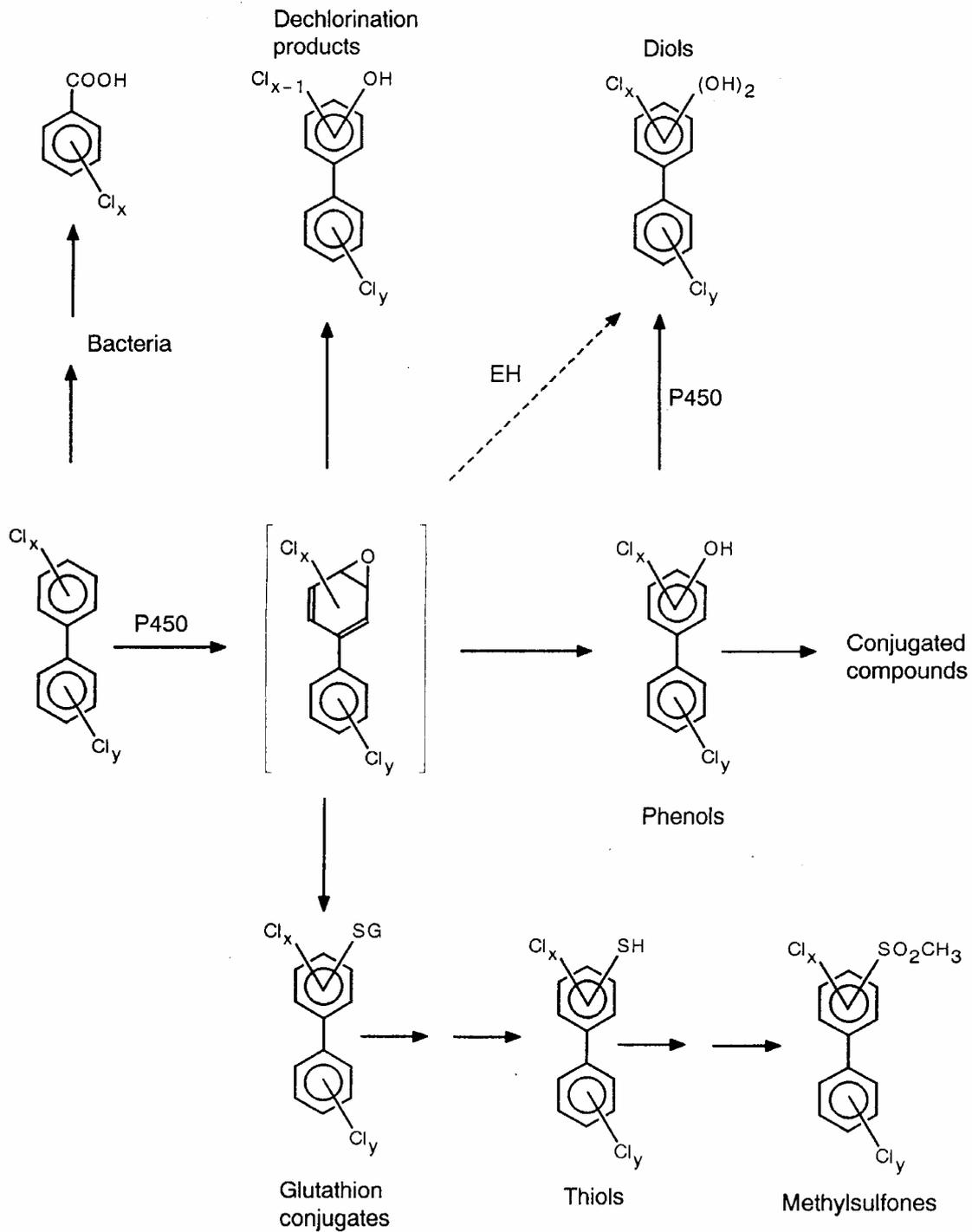


Figure 4. Metabolic pathways of PCBs.

Table 6. Whole body half-lives (days) of the first and second phases of elimination in rats given a mixture of four Kanechlor products (Tanabe *et al.* 1981).

Congener	IUPAC	t _{1/2} (I) (days)	t _{1/2} (II) (days)	Congener	IUPAC	t _{1/2} (I) (days)	t _{1/2} (II) (days)
2,2'	4	0.15	-	2,3',4,4',5	118**	6.6	>90
2,3'/2,4	6/7	0.34	-	2,2',3,3',4,4'	128***	6.3	>90
2,4'	8	0.18	-	2,2',3,3',4,5'	130	12	>90
2,2',3/2,3',6	16/27	0.21	-	2,2',3,3',5,6	134	1.9	-
2,2',4	17	0.21	-	2,2',3,3',5,6'	135	2.5	59
2,2',5	18	0.18	-	2,2',3,3',6,6'	136	2.6	-
2,2',6	19	0.11	-	2,2',3,4,4',5'	138***	-	>90
2,3,3'/2,4,4'	20/28	1.4	-	2,2',3,4,5,5'/2,2',4,4',5,5'	141/153***	-	>90
2,3',4	25	0.29	-	2,2',3,4',5,5'	146	-	>90
2,3',5/2',3,5	26/34	0.32	-	2,2',3,4',5,6'/2,2',3,5,5',6	148/151	2.7	23
2,4',6	32	0.23	-	2,3,3',4,4',5	156**	-	>90
2',3,4	33	0.20	-	2,3',4,4',5,5'	167**	-	>90
3,4,4'	37	0.34	-	2,2',3,3',4,4',5	170***	-	>90
2,2',3,4'	42	1.4	-	2,2',3,3',4,4',6	171	13	>90
2,2',3,5/2,2',5,5'	43/52	0.89	3.4	2,2',3,3',4,5,5'	172	-	>90
2,2',4,6	50	0.12	-	2,2',3,3',4,5,6'/2,2',3,4,4',5',6	174/183	9.3	>90
2,3,3',4'	56	2.4	25	2,2',3,3',4,6,6'	176	3.1	>90
2,3,3',6/2,3',4,6/2,3',5',6	59/69/73	3.8	70	2,2',3,3',4',5,6	177	-	>90
2,3,4,4'	60	0.29	-	2,2',3,3',5,5',6	178	-	>90
2,3',4',5/2,4,4',5	70/74	3.1	37	2,2',3,3',5,6,6'	179	3.3	66
2,2',3,3',4/2,3,3',4',6	82/110	2.5	64	2,2',3,4,4',5,5'	180***	-	>90
2,2',3,4,5'/2,2',3',4,5	87/97	2.1	-	2,2',3,4',5,5',6	187	-	>90
2,2',3,5,5'	92	2.1	-	2,2',3,3',4,4',5,5'	194***	-	>90
2,2',3,5',6	95	1.4	16	2,2',3,3',4,4',5,6'	196	9.4	>90
2,2',4,4',5	99	-	>90	2,2',3,3',4,5',6,6'	200	6.4	>90
2,2',4,5,5'	101	2.6	35	2,2',3,3',4,5,5',6'	201	-	>90
2,3,3',4,4'	105**	5.6	>90	2,2',3,3',5,5',6,6'	202	3.3	>90

** Mono-ortho congener[#], *** di-ortho congener[#] also chlorinated in both *para* and at least two *meta* positions

The half-life of the most slowly metabolized and eliminated congener, 2,2',4,4',5,5'-CB, has been reported to be about 450 days in the rat (Wyss *et al.* 1986).

Metabolites of all congeners studied so far are eliminated primarily via the bile and the faeces. However, the lower chlorinated PCB congeners are excreted to a greater extent (although less than 5%) via the urine than are the higher chlorinated PCB congeners. Depending on differences in metabolism, both the routes and the rates of elimination differ between species. For example, dogs excrete PCBs more rapidly and to a greater extent via the bile and faeces than does the monkey. The excretion rate and distribution pattern of 2,2',4,4',5,5'-CB is highly influenced by changes in the size of the adipose tissue compartment (Mühlebach *et al.* 1991).

6.1.5 Placental transport and elimination through milk

Several experiments in both rodents and monkeys demonstrate that PCBs cross the placental barrier and accumulate in fetal tissues (US/EPA 1990). At partus, approximately equal or lower levels of PCBs are found in the young as compared to in the dam, however, for 2,2',4,4',5,5'-CB, much lower levels were found in the fetus (Vodicnik and Lech 1980). In contrast, 3,3',4,4'-CB (as OH- and methyl-sulphonyl metabolites) has been shown to be transferred to a higher degree to the fetuses of mice, resulting in tissue concentrations which are higher than corresponding maternal levels (Darnerud *et al.* 1986, Klasson-Wehler *et al.* 1989). For 3,3',4,4',5-CB, most of the dose was found in the maternal liver with only traces found in the fetal livers (Klasson-Wehler *et al.* 1989).

In contrast to this, transfer of PCBs through nursing accounts for much higher exposure of the young than does placental transfer. In the rat, only 2.7% of an initial dose of 2,2',4,4',5,5'-CB was transferred through the placenta, whereas 39.2% was transferred via lactation (Ando 1978). Similarly, for 2,2',4,4'-CB, it was found that 75% of the maternal body burden was found in the suckling young, while only 1% had been transferred across the placenta in mice (Vodicnik 1986). Some PCB congeners (2,2',4,4',5,5'-, 2,2',3,4,4',5-, 2,2',3,3',4,4',5,5'-CB) are transferred to a higher degree than other congeners during lactation in mice (Larsen 1991). In studies with PCB mixtures, the postnatal exposure generally resulted in higher levels in the weaning young than in the mother. However, it is not investigated if the congener patterns are different, depending on possible differences in kinetics (e.g. absorption, metabolism), between neonatal and adult animals.

Comment

Most studies suggest that PCBs are efficiently absorbed by the gastrointestinal tract, the skin and the lungs. The absorbed PCBs are initially distributed to the highly perfused liver and muscle, but then redistributed to adipose tissue and skin. Excretion of PCB congeners depends on their rates of metabolism, which are primarily dependent on oxidative processes (e.g. hydroxylation). Metabolism is facilitated by the presence of at least one pair of unsubstituted, vicinal carbon atoms in the PCB structure. The metabolites are mainly eliminated in the bile and faeces and the elimination half-lives in rats ranges from less than one day to about 450 days.

PCBs cross the placenta, but tissue concentrations in newborn young are often lower than maternal concentrations. However, higher amounts are transferred to the young via the milk, resulting in tissue concentrations at weaning, which are higher than maternal levels.

However, it is yet to be investigated if the congener patterns in the weanlings and their mothers are similar.

6.2 Biochemical and toxic effects

Evaluation of the toxicity of commercial PCB mixtures is complicated by numerous factors, including congener composition, the varying degree of contamination with toxic compounds, such as PCDFs, and the differences in species susceptibility.

6.2.1 Acute toxicity

Only a few LD₅₀-values for individual congeners have been reported (Table 7). However, for commercial mixtures there are several studies reporting oral LD₅₀-values in rats ranging from 0.4-11 g/kg (Table 7).

For technical PCB-mixtures, death was reported to occur within three days after oral exposure, but in the case of intravenous administration the time to death was even shorter. LD₅₀-values increase with age, but do not vary between the sexes. Dermal LD₅₀-values for different Aroclors in rabbits were in the same range, or lower, than the oral LD₅₀-values in rats.

Comment

The short time to death for the PCB mixtures (less than three days) is in contrast to the delay in mortality seen with TCDD (weeks). As a delay in mortality (2-3 weeks) is also observed in rats exposed to the non-*ortho* congener 3,3',4,4',5-CB (H Hemming, personal communication), the short time to death obtained for mixtures probably reflects a different mechanism of acute toxicity which is related to the presence of both dioxin-like and non dioxin-like congeners in the mixtures.

Table 7. LD₅₀-values for individual congeners and commercial mixtures (H Hemming, personal communication, JE Kihlström, personal communication and modified from US/EPA 1990).

Congener/mixture	IUPAC	Species/strain	Route	LD ₅₀ (g/kg)
2,3,3',4,4'	105**	Rat/Wistar	oral	<0.012
2,3,3',4,4'	105**	Rat/SD	s.c.	<0.025
3,3',4,4',5	126*	Rat/SD	s.c.	0.0005-0.005
2,2',4,4',5,5'	153***	Rat/SD	s.c.	<0.1
2,4	7	Mouse/dd	oral	8
2,4',5	31	Mouse/NMRI	oral	3.1
2,2',5,5'	52	Mouse/NMRI	oral	1.8
2,3',4,4'	66	Mouse/CF-1	i.p.	2
2,2',4,5,5'	101	Mouse/NMRI	oral	4.5
2,3,3',4,4'	105**	Mouse/CF-1	i.p.	0.4
2,2',3,4',5',6	149	Mouse/NMRI	oral	5.8
2,2',4,4',5,5'	153***	Mouse/NMRI	oral	1.0
2,2',3,4,4',5',6	183	Mouse/NMRI	oral	2.0
3,3',4,4'	77*	Guinea pig/Hartley	oral	<0.001
2,2',4,4',5,5'	153***	Guinea pig/Hartley	oral	>0.010
3,3',4,4',5,5'	169*	Guinea pig/Hartley	oral	0.0005
2,3,3',4,4',5,5'	189**	Guinea pig/Hartley	oral	>0.003
Aroclor 1221		Rat/SD	oral	4
Aroclor 1232		Rat/SD	oral	4
Aroclor 1242		Rat/SD	oral	4-9
Aroclor 1248		Rat/SD	oral	11
Aroclor 1254		Rat/Wistar	oral	1-2
Aroclor 1254		Rat/Sherman	i.v.	0.4
Aroclor 1260		Rat/SD	oral	10
Aroclor 1260		Rat/Sherman	oral	1
Aroclor 1262		Rat/SD	oral	11
Aroclor 1268		Rat/SD	oral	11
Kanechlor 300		Rat/Wistar	oral	1
Aroclor 1221		Rabbit/?	dermal	2-3
Aroclor 1232		Rabbit/?	dermal	1-2
Aroclor 1242		Rabbit/?	dermal	0.8-1.3
Aroclor 1248		Rabbit/?	dermal	0.8-1.3
Aroclor 1260		Rabbit/?	dermal	1.3-2.0
Aroclor 1262		Rabbit/?	dermal	1.3-3.2
Aroclor 1268		Rabbit/?	dermal	2.5
Aroclors 1221, 1242, 1254		Mink/Pastel	oral	0.5-4

*,**,*** non-, mono- and di-ortho chlorinated congeners, respectively[#]

[#] also chlorinated in both *para* and at least two *meta* positions

6.2.2 Short- and long-term toxicity

6.2.2.1 General effects

The toxic effects commonly observed after acute, subchronic and chronic administration of PCB mixtures and/or individual congeners to animals include, a wasting syndrome (a progressive weight loss which is not simply related to decreased food consumption), effects on the liver, skin, immune system, vitamin A homeostasis, the reproductive system, the induction of oedema at various sites, disturbances of the gastrointestinal tract and thyroid gland and the induction of cancer and of different enzyme activities (Table 8 and Sections 5.2.2-4).

Species differences in the sensitivity to PCB toxicity have been identified from chronic exposure studies. The monkey, guinea pig and mink appear to be more sensitive to PCB toxicity than do rats and mice. The reason(s) for the variation in species sensitivity has (have) not been elucidated, but variation cannot be fully explained by different rates of metabolism.

In order to evaluate the relationship between the structure of individual congeners and their toxicological potency, Safe (1990) summarized the available studies which can be used for such a comparison (Table 9). Most of the studies are *in vitro* or short-term *in vivo* studies, however, a few studies on teratogenicity are also included. As in the case of the polychlorinated dibenzo-*p*-dioxins (PCDDs) and dibenzofurans (PCDFs), at least some of the toxic effects (e.g. enzyme induction, immunotoxicity) are suggested to depend on the binding of the PCB congener to the cytosolic aryl hydrocarbon (Ah) receptor (see Section 5.2.5). This binding is, in turn, dependent on the planarity and presence of lateral chlorines on the molecule. From the results of the studies on individual PCB congeners (Table 9), and from their structural similarities to 2,3,7,8-TCDD, Safe (1990) concluded that the non-*ortho* congeners 3,4,4',5-, 3,3',4,4'-, 3,3',4,4',5- and 3,3',4,4',5,5'-CB, which are substituted in both *para*, at least two *meta* and no *ortho* positions, are clearly the most toxic PCB congeners. Chlorination at one (mono-*ortho* PCB congeners) or two (di-*ortho* PCB congeners) *ortho* positions further decreases the toxic potency, due to a lower probability of attaining a coplanar conformation.

Comment

Overall, the same toxic effects are seen after PCB exposure, as after PCDD and PCDF exposure. From short-term studies with individual congeners it can be concluded that the congeners which are most structurally-related to TCDD, the non-*ortho* congeners with both *para* and at least two *meta* positions substituted, are the most toxic PCB congeners. Their mono-*ortho* analogues are less toxic and the di-*ortho* analogues even less effective. Congeners with more than two *ortho*-chlorines and congeners without *para* chlorines have not been shown to cause dioxin-like toxic effects. However, they have not yet been studied as thoroughly as the dioxin-like congeners.

Table 8. PCB-induced* effects reported for different species (extracted from WHO/IPCS 1990, US/EPA 1990).

Effect	Species
Wasting syndrome (reduced food intake and weight gain)	rat, mouse, monkey
<u>Skin</u> Chloracne Hyperkeratosis Hyperpigmentation Facial oedema Finger nail loss Alopecia Erythema Erosions and ulcerations Eczematous changes Metaplasia/atrophy of Meibomian glands Metaplasia/atrophy of sebaceous glands Prominent tarsal glands Keratinous cysts Dilatation of hair follicles	monkey rat, mouse, rabbit, monkey monkey rat, rabbit, monkey monkey rat, mouse, rabbit, monkey rat, mouse, rabbit, monkey mouse mouse monkey mouse, monkey monkey mouse, rabbit, monkey rat
<u>Gastrointestinal tract</u> Gastritis	mink, pig, monkey
<u>Lung</u> Peribronchial cell infiltration Cellular lipid vacuoles and lamellar bodies	rat rat
<u>Nervous system</u> ↓ Cholinergic receptors ↓ Dopamine level in brain ↓ Uptake of neurotransmitters ↑ Release of neurotransmitters ↓ Norepinephrine level in brain	mouse rat, monkey mouse mouse rat
<u>Lipid metabolism</u> ↑ Hepatic lipids ↑ Serum lipids ↓ Output of bile acids	rat, rabbit rat, rabbit, monkey rat
<u>Porphyrin metabolism</u> ↑ Hepatic porphyrins ↑ Excreted porphyrins	rat, mouse, rabbit rat, rabbit
<u>Vitamins</u> ↓ Vitamin A in liver, lung, serum, testes ↓ Thiamine (B1), Pyridoxal phosphate (B6) ↑ α-Tocopherol	rat, mouse, rabbit, pig rat rat

* The effects are mainly reported from studies using PCB mixtures

↑ increased, ↓ decreased

Table 9. Comparative toxic and biochemical potencies (ED₅₀ or EC₅₀) of non-ortho[#] and mono-ortho[#] PCB congeners (modified from Safe 1990). TCDD is included for comparison.

Response	Target species/cell	TCDD	3,3',4,4'	3,3',4,4',5	3,3',4,4',5,5'	2,3,3',4,4'	2,3,4,4',5	2,3',4,4',5	2',3,4,4',5	2,3,3',4,4',5	2,3,3',4,4',5'	2,3',4,4',5,5'
IUPAC			77	126	169	105	114	118	123	156	157	167
Reduced body weight gain	Rat (μmol/kg)	0.05	>500	3.3	15	750	180	1120	370	180	220	
Thymic atrophy	Rat (μmol/kg)	0.09	>500	0.95	8.9	1030	200	1550	2790	180	225	
Bursal lymphoid development	Chick embryo (μmol/kg)		0.17	0.012	0.83	<18		>18		<17	>17	>17
Thymic lymphoid development	Mouse fetuses (M)	2·10 ⁻¹⁰	3·10 ⁻⁷	2·10 ⁻⁹	2·10 ⁻⁷							
Splenic plaque forming cells	Mouse (μmol/kg)	0.0024								2		
Teratogenicity	Mouse (μmol/kg)		0.11 ^a		0.011-0.022							
AHH-induction	Rat (μmol/kg)	0.004	500	1.10	0.50	65	30	165	130	7	6	
AHH-induction	H-4-II E cells (M)	9.6·10 ⁻¹¹	3.5·10 ⁻⁸	2.4·10 ⁻¹⁰	6.0·10 ⁻⁸	8.8·10 ⁻⁸	3.9·10 ⁻⁶	1.2·10 ⁻⁵	9.7·10 ⁻⁷	2.1·10 ⁻⁶	7.1·10 ⁻⁷	1.3·10 ⁻⁵
AHH-induction	Chick embryo hepatocytes (M)	2.0·10 ⁻¹¹	2.2·10 ⁻⁹	2.0·10 ⁻⁹			1.0·10 ⁻⁷	5.0·10 ⁻⁸		1.4·10 ⁻⁵		
Receptor binding	Rat cytosol (M)	1.0·10 ⁻⁸	7.1·10 ⁻⁷	1.3·10 ⁻⁷	insoluble	4.3·10 ⁻⁶	4.1·10 ⁻⁶	9.1·10 ⁻⁶	1.4·10 ⁻⁵	7.1·10 ⁻⁶	5.0·10 ⁻⁶	1.6·10 ⁻⁵

[#]also chlorinated in both *para* and at least two *meta* positions

^afrom: Marks *et al.* 1989

6.2.2.2 Liver toxicity

The toxic effects of PCBs result both directly and indirectly from their presence in certain organs such as the liver, where they induce, to varying degrees, a variety of liver phase I and phase II xenobiotic metabolizing enzymes. In itself, enzyme induction may be viewed as an adaptive, protective mechanism. However, although enzyme induction generally leads to increased detoxication, in some instances induction may result in enhanced toxicity, due to an increased formation of reactive metabolites.

In the early 1970s it was reported that Aroclor 1254 and some related commercial PCBs were unique mixed-type inducers of the hepatic cytochrome P450 dependent monooxygenases. The induction was similar to that observed after coadministration of the classical inducers, phenobarbital (PB) and 3-methylcholanthrene (MC). The genes and gene products involved in this induction are described using many different nomenclatures in the literature (Table 10).

Table 10. Cytochromes P450 (CYP) gene products (monooxygenases) induced by PCBs in rats (Nebert *et al.* 1991).

Common name	Systematic name of gene and cytochrome	MC/PB-type	Older trivial names
P450 1A1	CYP1A1	MC	P450 _c , P450 _{BNF-B}
P450 1A2	CYP1A2	MC	P450 _d , P-448, P450 _{HCB}
P450 2B1	CYP2B1	PB	P450 _b , P450 _{PB-4} , P450 _{PB-B}
P450 2B2	CYP2B2	PB	P450 _e , P450 _{PB-5} , P450 _{PB-D}

The available data on the enzyme inducing properties of PCB congeners have been summarized by McFarland and Clarke (1989) (Table 11). However, it should be noted that some data are derived from *in vitro* studies and others from *in vivo* studies and the Table should only be used as a rough illustration.

As is proposed for TCDD, the mechanism of the MC-type enzyme induction of PCBs is based on the binding affinity of the congeners to the cytosolic Ah-receptor protein (see Section 5.2.5). The congeners that bind most strongly to the Ah-receptor also show the strongest degree of MC-induction. The most active congeners, with respect to MC-type induction, are the non-*ortho* congeners, 3,4,4',5-, 3,3',4,4'-, 3,3',4,4',5- and 3,3',4,4',5,5'-CB (Table 9). The least active of these 4 congeners, 3,4,4',5-CB, also shows PB-type induction. This mixed-type induction pattern is also shown by 3,4,4'-CB. All of the mono- and several di-*ortho* PCB congeners are mixed-type inducers, whilst other di-*ortho* congeners, such as 2,2',4,4',5,5'-CB, only induces PB-type enzymes (Table 11). Most other PCB-congeners are PB-type inducers or are inactive.

Table 11. Enzyme inducing properties of individual PCB congeners (McFarland and Clarke 1989).

Congener	IUPAC	Category	MC-type induction	PB-type induction
3,3',4,4'	77	Non-ortho[#]	+	-
3,4,4',5	81	-''-	+	+
3,3',4',5	126	-''-	+	-
3,3',4,4',5,5'	169	-''-	+	-
2,3,3',4,4'	105	Mono-ortho[#]	+	+
2,3,4,4',5	114	-''-	+	+
2,3',4,4',5	118	-''-	+	+
2',3,4,4',5	123	-''-	+	+
2,3,3',4,4',5	156	-''-	+	+
2,3,3',4,4',5'	157	-''-	+	+
2,3',4,4',5,5'	167	-''-	+	+
2,3,3',4,4',5,5'	189	-''-	+	+
2,2',3,3',4,4'	128	Di-ortho[#]	+	+
2,2',3,4,4',5	137	-''-	-	+
2,2',3,4,4',5'	138	-''-	+	+
2,2',4,4',5,5'	153	-''-	-	+
2,3,3',4,4',6	158	-''-	+	+
2,3,4,4',5,6	166	-''-	+	+
2,3',4,4',5,6	168	-''-	+	+
2,2',3,3',4,4',5	170	-''-	+	+
2,2',3,4,4',5,5'	180	-''-	-	+
2,3,3',4,4',5,6	190	-''-	-	+
2,3,3',4,4',5',6	191	-''-	-	+
2,2',3,3',4,4',5,5'	194	-''-	-	+
2,3,3',4,4',5,5',6	205	-''-	-	+

Congener	IUPAC	Category	MC-type induction	PB-type induction
3,3'	11		-	(+)
3,5	14		-	(+)
4,4'	15		-	(+)
3,4,4'	37		+	+
2,2',4,4'	47		-	+
2,2',5,5'	52		-	(+)
2,2',6,6'	54		-	(+)
2,3',4,4'	66		-	+
2,4,4',6	75		-	(+)
3,3',5,5'	80		-	(+)
2,2',3,4,5'	87		-	+
2,2',4,5,5'	101		-	+
2,3,4,4',6	115		-	+
2,3',4,4',6	119		+	+
2,2',3,3',5,5'	133		-	+
2,2',3,3',6,6'	136		-	(+)
2,2',3,5,5',6	151		-	(+)
2,2',4,4',5,6'	154		-	+
2,2',4,4',6,6'	155		-	(+)
2,3,3',4,5,5'	159		-	(+)
2,3,3',4',5,6	163		-	+
2,3,3',5,5',6	165		-	+
2,2',3,3',4,4',5,6	195		-	+

also chlorinated at both *para* and at least two *meta* positions
 (+) weak or non-inducer

The induction of hepatic, and in some cases also extrahepatic, microsomal enzymes has been observed in several animal species, but with distinct interspecies variations being evident. As an example of the varying potencies of different congeners, a reconstituted mixture of the PCB congeners which were found in mother's milk was 7 times more

effective in inducing MC-type enzymes than Kanechlor 500, when equal concentrations of total PCB were compared. This also reflects the preferential bioconcentration of the relatively toxic congeners 2,3,3',4,4'-, 2,3',4,4',5'- and 2,3,3',4,4',5'-CB (Parkinson *et al.* 1980).

Most studies have reported toxic effects of PCBs (mainly mixtures) in the liver. The liver damage is characterised by, for example, increased liver size, fatty degeneration and focal necrosis. The liver enlargement is associated with hepatocyte enlargement and an increase in smooth endoplasmic reticulum and/or increased enzyme activity. Similar hepatotoxic effects have been reported for several species including rats, mice, guinea pigs, rabbits, pigs and monkeys (Table 12), although the species differ in their susceptibility to these effects. One non-dioxin-like congener, 2,2',3,3',5,5'-, as well as 2,2',4,4',5,5'-CB, have been shown to cause liver enlargement, increased smooth endoplasmic reticulum and midzonal hepatic lipid accumulation in rats (Kohli *et al.* 1979). However, the dioxin-like congener, 3,3',4,4',5,5'-CB, causes qualitatively different pericentral lipid accumulation. Also, 2,2',4,4',6,6'-CB caused fatty changes and necrosis in mice (Biocca *et al.* 1981).

Table 12. Hepatotoxic effects of PCBs* reported in various species.

Effect	Species
Liver enlargement	rat, mouse, guinea pig, rabbit, pig, monkey
Hepatocyte hypertrophy	rat, mouse, rabbit, monkey
Pleiomorphic hepatocytes	rat, mouse
Fatty degeneration, lipid vacuoles in hepatocytes	rat, mouse, guinea pig, monkey
Proliferation of the smooth endoplasmic reticulum	rat, mouse, rabbit, monkey
UV fluorescence (porphyrin)	rat, rabbit
Brown pigment in macrophages	rat
Fibrosis	rat, rabbit
Oval cell proliferation	rat, mouse
Bile duct/gall bladder epithelial changes	rat, mouse, monkey
Increased serum alkaline phosphatase	rat
Increased serum transaminases	rat, rabbit, monkey

*The effects are mainly reported from studies using PCB mixtures

Comment

Hepatic enzyme induction and liver pathology occur in all species studied, although they differ in their susceptibility to these effects. The effects are the same as those reported for PCDD and PCDF exposure. MC-type induction and most pathological effects are probably mainly caused by the dioxin-like PCB congeners. However, in studies with PCB mixtures the effects might be partly caused by PCDF impurities.

6.2.2.3 Immunotoxicity

The immunotoxic potency of different congeners follows the same structure-activity relationships as MC-type enzyme induction (Table 9), indicating that immunotoxicity of PCBs might be dependent upon the expression of the Ah-receptor and on the ability of the PCB congener to bind to the receptor.

The different immunotoxic effects which have been reported (mainly for PCB mixtures) are summarized in Table 13.

Table 13. PCB-induced* immunotoxic effects reported for different species.

System	Effect	Species
Sensitivity to infections	↑	rat
Thymic weight	↓	rat, mouse, guinea pig, rabbit, pig, monkey
Splenic weight	↓	rat, mouse, guinea pig, pig
Number of germinal centres in spleen and lymphnodes	↓	rat, monkey
Number of bone marrow cells	↓	monkey
Number of leukocytes/lymphocytes	↓	guinea pig, monkey
Number of splenic plaque forming cells	↓	mouse
Myeloic/erythroid cell ratio	↑	monkey
T-helper/T-suppressor cell ratio	↓	mouse
T-helper cell activity	↓	mouse
Splenic cytotoxic T-cell response	↓	mouse
Lymphocyte proliferative response	↓	mouse
Serum IgA, IgG	↓	rat, mouse, rabbit
Antibody production	↓	guinea pig, monkey

* The effects are mainly reported from studies using PCB mixtures

↑ increased, ↓ decreased.

In rhesus monkeys, exposure to Aroclor 1254 for 55 months caused a dose-related decrease in the anamnestic (IgM and IgG) response to sheep red blood cells (Tryphonas *et al.* 1991). Lymphoproliferation was also dose-relatedly decreased when the monkeys were exposed to mitogens. The suppression of IgM was evident already in the lowest dose group, 5 µg/kg/d, which corresponded to a blood level of 10 µg PCB/kg (21 mg/kg blood fat).

In mice exposed to 300 mg PCB per kg diet for 28 days, both 2,2',4,4',6,6'- and 2,2',4,4',5,5'-CB caused thymic atrophy, whilst 2,2',3,3',6,6'-CB did not (Biocca *et al.* 1981). 3,3',4,4',5,5'-CB caused thymic atrophy already at 3 mg/kg.

Comment

Although the studies on immunotoxicity cannot be used for quantitative descriptions of dose-effect/dose-response relationships, some of them are useful in describing relative toxicity and for comparisons between congeners.

6.2.2.4 Neurotoxicity

There are a few studies reporting PCB-induced effects on the levels of and function of different transmitter substances in the central nervous system (Table 8). Aroclor 1016 caused decreased dopamine concentrations in the caudate, putamen, substantia nigra and hypothalamus of macaque monkeys (Seegal *et al.* 1990). In these regions, only the congeners 2,4,4'-, 2,2',4,4'- and 2,2',5,5'-CB were detected. These congeners, but not 3,3',4,4'- and 3,3',4,4',5-CB, were shown to reduce dopamine concentrations *in vitro* also. Aroclor 1260 caused these effects in monkeys (Seegal *et al.* 1991a). In this case, mostly di-*ortho* substituted hexa- and hepta chlorinated congeners were found in the brain. Decreased levels of dopamine have been observed in the rat brain after exposure to Aroclor 1254 (Seegal *et al.* 1991b). When 43 individual PCB congeners were screened *in vitro* in order to study the structure-activity relationships for the effect on dopamine levels, 2,2'-CB was found to be most potent (EC₅₀ 64 µM, Shain *et al.* 1991). It was indicated that congeners with *ortho*- or *ortho*- and *para*-chlorine substitutions were the most potent, and that metabolites were not responsible for the observed effects.

6.2.2.5 Reproductive and developmental effects

Exposure to PCB has been reported to cause several effects on different processes in reproduction and the development of the embryo/foetus/young. Most effects are specific to fertility and to the development of off-spring. In addition, mice suffer teratogenic effects, such as hydronephrosis and cleft palate. The quality of most studies, except the teratogenic studies (included in Table 9), and the behavioral effects (described later in more detail), do not allow for any quantitative risk assessment. The effects are summarized in Table 14.

Amongst mammals, teratogenic effects have only been observed in mice (Birnbaum *et al.* 1985, Marks and Staples 1980, Marks *et al.* 1981, 1989). These effects, and especially the induction of cleft palate, seem to be caused by the dioxin-like PCB congeners and show the same structure-activity relationship as enzyme induction and immunotoxicity, although teratogenicity has not been investigated as thoroughly as the other effects. Similarly, in chick embryos, teratogenic effects (e.g. eye and beak deformities) are induced by non-*ortho* and some mono-*ortho* PCB congeners, but not by 2,2',4,4',5,5'-CB (Brunström and Andersson 1988, Brunström 1990).

Other effects seen on reproduction and offspring development are mainly from studies with PCB mixtures, thus, no correlations to individual congeners can be performed.

Behavioural effects in the off-spring, such as hyperactivity, impaired learning and/or a "spinning syndrome", mostly after exposure to mixtures both pre- and postnatally, have been reported in rats, mice and monkeys. In a cross-fostering study in rats, behavioral toxicity in the off-spring occurred after prenatal and permanent exposure of Clophen A30 to the dams, whilst postnatal exposure caused no detectable behavioral changes (Lilienthal and Winneke 1991).

Table 14. Reproductive and developmental effects induced by exposure to PCB[#].

Effect	Species
<u>Male reproduction</u>	
↓ Fertility (postnatally exposed)	rat
↓ Matings/pregnancies	rat
↓ Testicular spermatozoan concentration	mouse
↓ Ventral prostate weight	rat
↓ Seminal vesicle weight	rat, mouse
<u>Female reproduction</u>	
Anovulation	rat
Effects on the oestrous cycle	rat, mouse, monkey
↓ Weights of uterus, ovaries, accessory glands	mouse
<u>Effects on offspring</u>	
↓ Implantations	rat*, mouse
↑ Resorptions	rat, mouse, rabbit, monkey
Abortions	guinea pig, rabbit, monkey
↑ Gestational length	rat
↓ Fetal development	mouse
↓ Litter size	rat, mouse, guinea pig, mink
↓ Fetal/perinatal survival	rat, mouse, guinea pig, mink, rabbit, monkey
↓ Weight/growth	rat, mouse, guinea pig, mink, monkey
Behavioural effects	rat, mouse, monkey
Hydronephrosis	mouse
Cleft palate	mouse

[#] The effects are mainly reported from studies using PCB mixtures

* Also when only males were exposed (Sager 1983), ↑ increased, ↓ decreased.

In Rhesus monkey infants, whose mothers were exposed to Aroclor 1248 during gestation and lactation, behavioural testing showed hyperactivity and retarded learning ability at 6-24 months of age (Bowman *et al.* 1978, 1981). However, at 44 months the monkeys were hypoactive and at 4-6 years of age, they showed impairments in a spatial learning and memory test (delayed spatial alternation, DSA) (Levin *et al.* 1988). Infants of the same mothers, but born when the mothers had been on a control diet for 0.5-1.5 years, also showed hyperactivity at 12 months of age and impaired learning in the DSA test at 4-6

years, despite a much lower body burden of PCBs (Bowman *et al.* 1981, Schantz *et al.* 1991). In addition, Aroclor 1016 has been demonstrated to cause these effects in the offspring of exposed monkeys (Schantz *et al.* 1991). As deficits in DSA performance are a sensitive indicator of dysfunction in the prefrontal cortex and as deficits are also seen after dopamine receptor blockade, the PCB-induced decreases in dopamine levels in the brain (Seegal *et al.* 1990, 1991a) might be associated with the learning deficits (Schantz *et al.* 1991).

The exposure of rats to 3,3',4,4',5-CB during gestation caused reduced litter size and birth weights, MC-type enzyme induction and effects on grip strength, raising of the head, walking and opening of the eyes, but no behavioral effects (learning, activity) (Bernhoft *et al.* 1991).

In studies with different congener fractions of Clophen A50 and Aroclor 1254 in minks which were exposed prior to and during gestation, no separate fraction (non-, mono-, di- to tetra-*ortho* congeners, di- and tricyclic impurities) caused statistically significant effects on reproduction, whilst combinations of the fractions did (Kihlström *et al.* 1992). Embryo mortality at different stages of development was observed, whilst no effects on ovulation, fertilization or implantation were found.

Comment

PCBs have several effects on both male and female reproductive functions, and on foetal and infant development. Reproductive aberrations have been reported at concentrations/doses from 2 mg Aroclor 1254 per kg diet (about 0.4 mg/kg and day) in the mink (Aulerich and Ringer 1977) and 0.09 mg Aroclor 1248 per kg and day in the Rhesus monkey (Barsotti *et al.* 1976). Behavioural/developmental disturbances (hyperactivity) in Rhesus monkey infants have been reported at doses of about 6 µg Aroclor 1248 per kg and day to the mother (Bowman *et al.* 1981).

Which of the PCB congeners are responsible for these effects are not yet clear.

6.2.2.6 Endocrine system

An underlying cause of some of the reproductive toxicities of PCBs may be alterations in hormonal levels and/or receptor affinities/levels (Table 15). Decreased levels of gonadal hormones can be explained by enhanced metabolism of steroids, which are the normal substrates for microsomal enzymes. In addition, effects on the thyroid gland and its function have been reported.

6.2.2.7 Vitamin A

Many symptoms of PCB-exposure resemble those of vitamin A deficiency (Kimbrough 1974, Thunberg *et al.* 1980). In addition, dietary exposure to PCB mixtures reduces vitamin A storage in several species (Brunström *et al.* 1991, Innami *et al.* 1974, Villeneuve *et al.* 1971). Studies in mink show that non- and mono-*ortho* PCB congeners can explain the vitamin A reducing effect of Clophen A50 (2 mg/day) in the liver and lung (Brunström *et al.* 1991). In contrast to this, Aroclor 1254 (1.6 mg/day), which contains considerably lower levels of the non-*ortho* PCB congeners, had no

Table 15. Endocrine effects induced by PCBs*.

Hormone	Parameter	Effect	Species
Progesterone	plasma concentration	↓	rat
	metabolism	↑	rat
	half-life	↓	rat, mouse, monkey
	LH-induced synthesis <i>in vitro</i>	↑	
Oestrogen	binding to uterine receptor	↓	rat
Oestradiol	plasma concentration	↓	monkey
Testosterone	metabolism	↑	rat
Androstenedione	metabolism	↑	
Corticosterone	plasma concentration	↑↓	rat, mouse
Thyroxine	plasma concentration	↓	rat, mouse
Thyroid gland	activity	↑	rat
	morphological changes		rat
	weight	↑	rat, pig

* The effects are mainly reported from studies using PCB mixtures

↑ increased, ↓ decreased

effect on tissue vitamin A levels in the mink (Håkansson *et al.* 1992). Studies with single PCB congeners in rodents clearly show that the non-*ortho* congeners and 2',3,3',4,5-CB decrease hepatic vitamin A levels (Azais *et al.* 1987, Bank *et al.* 1989, Brouwer *et al.* 1985, 1988a,b, Chen *et al.* 1992). In contrast to TCDD, some PCB congeners, both dioxin-like and non-dioxin-like, decrease serum vitamin A levels (Azais *et al.* 1987, Brouwer 1987, Chen *et al.* 1992).

Taken together, these data suggest that individual congeners in a PCB-mixture act additively with respect to effects on tissue vitamin A levels, and that different mechanisms of action are involved in the PCB-induced effects on the retinoid homeostasis. The effects of dioxin-like PCB congeners on hepatic vitamin A storage may be associated with their ability to bind to the Ah-receptor, whilst the lowering effect on serum vitamin A levels by different PCB congeners may be associated to the ability of their hydroxylated metabolites to bind to transthyretin and thereby interfere with the serum transport of vitamin A (Brouwer *et al.* 1988a).

6.2.3 Genotoxicity

There is no convincing evidence that PCBs induce point mutations, either in *Salmonella typhimurium* (Ames test) or in V79 Chinese hamster cells (Table I in the Appendix). Although most assays on cytogenetic effects are negative, some reports demonstrate a significant increase in chromosomal aberrations in mammalian cells, such as chromatid breaks and rearrangement (Table II in the Appendix). PCBs have been reported to bind to DNA both *in vivo* and *in vitro* and both single-stranded DNA-breaks and the induction of DNA repair have been detected in mammalian cells *in vitro* (Table III in the Appendix).

Comment

Most data indicate that PCBs have little, if any, *in vivo* genotoxic potential. However, some of the congeners, especially with low chlorination, may cause mutagenicity and DNA damage. A proposed mechanism for this genotoxicity is the metabolism of these compounds to arene oxide intermediates which are able to alkylate critical cellular macromolecules (Safe 1984). In general, these effects are observed in *in vitro* systems only.

6.2.4 Carcinogenicity

Results from several carcinogenicity experiments with dietary administration of PCBs in mice and rats are summarized in Table IV in the Appendix. Some of these are commented upon briefly below. Besides liver tumours, which are the most frequent tumours observed after PCB-exposure, stomach tumours have also been reported.

Mice: Indications of hepatocarcinogenic effects of the exposure of mice to PCBs were reported in the early 1970s (Nagasaki *et al.* 1972, Ito *et al.* 1973, Kimbrough and Linder 1974). These investigators found that Kanechlor 500 (500 mg/kg diet) and Aroclor 1254 (300 mg/kg diet) induced hepatocellular carcinomas after less than one year of exposure to the mixtures.

Perinatal exposure (i.p. injections) to the congener 2,2',5,5'-CB or its 2,2',5,5'-CB-3,4-oxide-metabolite did not induce lung adenomas in A/J mice after 28 weeks of observation (Preston *et al.* 1985). The assay system used is, however, probably not sensitive to nongenotoxic carcinogens and alkylating agents not requiring metabolic activation. These limitations may account for the lack of activity of these compounds in this model (Pereira and Stoner 1985). As for the 3,4-oxide metabolite, the doses employed were toxic, or close to toxic, which may also have influenced the outcome.

Rats: PCB mixtures have been shown to induce hepatic tumours in several long-term studies in rats. In male and female Sprague-Dawley rats given Aroclor 1260 (100 mg/kg diet for 16 months, 50 mg/kg for an additional 8 months), followed by a control diet for 5 months, hepatic tumours were frequently induced in the females (Norback and Weltman 1985). Kimbrough *et al.* (1975), using female Sherman rats fed with 100 mg Aroclor 1260 per kg diet for 21 months, found an increased incidence of hepatocellular carcinomas as compared to control animals.

In an experiment where male Wistar rats were fed 100 mg Clophen A30 or Clophen A60 per kg diet for approximately 800 days (Schaeffer *et al.* 1984), hepatocellular carcinomas developed in more than 50% of the Clophen A60-treated animals. Clophen A30 showed

no clear carcinogenic effect, but did induce numerous altered hepatic foci and neoplastic nodules. Marked time-related developmental trends from foci to neoplastic nodules, for Clophen A30, and further to hepatocellular carcinomas for Clophen A60, were obvious from the incidences of these lesions amongst the animals dying during and those sacrificed at the termination of the study.

Male and female Fisher 334 rats, fed on diets with 25, 50 or 100 mg Aroclor 1254 per kg diet for two years, were reported to develop hepatic tumours at the two highest dose levels (NCI 1978). However, there was no statistically significant difference from the control animals.

Several of the bioassays for cancer (Kimbrough *et al.* 1975, Norback and Weltman 1985, NCI 1978, Schaeffer *et al.* 1984) have recently been reevaluated by a panel of pathologists, applying today's accepted classification for liver pathology (IEHR 1991). The outcome of the evaluation was that only Aroclor 1260 and Clophen A60 can be considered to give a clear carcinogenic response. However, in many of the other studies, there were high incidences of hepatocellular proliferative lesions in both male and female rats which were related to the administration of the various mixtures. The summarized outcome of the reevaluation is given in Table 16.

6.2.4.1 Tumour initiation

The ability of various PCB-mixtures and individual congeners to initiate the formation of GGT-positive foci in F344 rats has been examined by Hayes *et al.* (1985). None of the PCBs generated GGT-positive foci, whilst known initiators were active in the assay system used (Table V in the Appendix).

6.2.4.2 Tumour promotion

The tumour promoting potential of PCBs have been studied extensively in two-stage carcinogenesis models in rat liver and also in mouse lung and skin. Studies on such effects in carcinogen-initiated animals, using manifest neoplasia or preneoplastic lesions as the experimental endpoints, are summarized in Tables VI and VII in the Appendix, and some of these are discussed in more detail below.

Mice: In male Swiss mice, a hepatic-promotive effect of a single intragastric dose of Aroclor 1254 (500 mg/kg) has been observed (Anderson *et al.* 1986). The promotive effects of PCBs have also been studied in mouse skin, but application of 100 µg of Aroclor 1254, twice weekly for 30 weeks to the skin of DMBA-treated, female CD1 mice, did not induce any papillomas (Berry *et al.* 1978). When 1 mg Aroclor 1254 was applied to the skin of MNNG-initiated, HRS/J hairless female mice twice weekly for 20 weeks, a small but statistically non-significant increase of the number of skin tumours was observed (Poland *et al.* 1982).

Table 16. A comparison of the results for chronic studies conducted in four strains of rats with Aroclor 1260, Clophen A60, Clophen A30 and Aroclor 1254 (IEHR 1991).

Chemical Strain Diet concentration	Aroclor 1260 Sherman 100 mg/kg diet		Aroclor 1260 Sprague-Dawley 100 mg/kg diet				Clophen Wistar 100 mg/kg diet			Aroclor 1254 Fischer 344 100 mg/kg diet			
	Female		Male		Female		Male			Male		Female	
	Control 187	Test 189	Control 31	Test 40	Control 45	Test 46	Control 120	A60 125	A30 128	Control 24	Test 23	Control 23	Test 24
Hepatocellular adenoma	0	135	0	4	1	29	6	85	14	0	1	0	1
Hepatocellular carcinoma	1	21	0	1	0	19	2	67	2	0	2	0	0
Hepatocellular adenoma and/or carcinoma	1	138	0	5	1	41	8	114	16	0	3	0	1
Cholangiocarcinoma	0	0	0	0	0	3	1	0	0	0	0	0	0
Centrilobular hepatocytomegaly	1	108	0	15	0	5	1	2	2	0	3	0	3
Foci/eosinophilic	7	173	1	16	5	36	51	101	98	0	4	0	6
Foci/basophilic	4	67	1	0	2	1	2	4	15	0	7	2	4
Foci/clear cell	14	67	4	0	1	0	7	28	39	0	0	0	2
Foci/mixed cell	1	38	0	2	0	0	7	28	49	0	8	0	5
Animals with foci	25	177	5	16	7	36	55	108	106	0	16	2	15

Rats: Several reports have demonstrated the abilities of various PCB-mixtures, such as Aroclor 1254 (Preston *et al.* 1981), Kanechlor 400 (Kimura *et al.* 1976) and Kanechlor 500 (Nishizumi 1976, Tatematsu *et al.* 1979, Ito *et al.* 1978) to promote the development of hepatic tumours in carcinogen-initiated rats.

Promotion of preneoplastic lesions

Investigations have been performed in order to study the ability of PCB mixtures and individual congeners to initiate and promote the growth of preneoplastic lesions using various two-stage models of liver carcinogenesis. The administration of PCB-mixtures, such as Aroclor 1254 and Clophen A50, to rats after their treatment with different initiating agents has been demonstrated to increase the number and size of altered hepatic foci (Table VII in the Appendix). In a study with Clophen A50, increased frequencies of enzyme-altered hepatic foci were found at doses of 2-100 mg/kg and week for adult rats and at 25-100 mg/kg and week for weanling rats (Oesterle and Deml 1984).

Promotive effects have been reported for most of the individual PCB congeners studied in this respect (Table VII in the Appendix). The non-*ortho* congener 3,3',4,4'-CB has been shown to be a more potent promoter than 4,4'- and the *ortho*-substituted congeners 2,2',4,4'-, 2,2',5,5'- and 2,2',4,4',5,5'-CB (Buchmann *et al.* 1986, Oesterle and Deml 1981, Sargent *et al.* 1991). In addition, the mono-*ortho* substituted congener 2,3,4,4',5-CB has been shown to be more potent than 3,3',4,4'- and 2,2',4,5'-CB as a promoter of the development of altered hepatic foci (Buchmann *et al.* 1991). However, in the same study 4-CB showed no promoting activity. Recently, Flodström and Ahlborg (1991) reported preliminary data showing a very strong liver tumour promoting activity of 3,3',4,4',5-CB, indicating that this congener is the most active PCB congener (about 10% of that of 2,3,7,8-TCDD) based on studies on altered foci development. In the same study, 2,3,3',4,4'-CB was shown to act as a tumour promoter although it was much less active than 3,3',4,4',5-CB.

6.2.4.3 Intercellular communication

Communication between cells is known to be dependent on permeable, intercellular junctions (gap junctions) which facilitate the transfer of ions, metabolites, nucleotides and other molecular signals between cells. Some *in vitro* assays for identification of potential tumour promoters are based on the observation that many established or potential tumour promoters can inhibit gap junctional intercellular communication.

The results of studies on cellular communication with both PCB mixtures and individual congeners are shown in Tables VIII and IX in the Appendix. Aroclor 1254 inhibits intercellular communication between primary B₆C₃F₁ mouse hepatocytes in a concentration-dependent manner (Ruch *et al.* 1987). Several individual congeners have been studied in different assays for their ability to inhibit intercellular communication. The results demonstrate that there is a correlation between the molecular structure of the congeners and the ability to inhibit gap junctional communication. In general, substitution in the *ortho* position is necessary for the inhibition of cell-cell communication (Tsushimoto *et al.* 1983, Swierenga *et al.* 1990, Hemming *et al.* 1991). Although both planar and non-planar congeners act as tumour promoters in altered hepatic foci (AHF) assays *in vivo*, chloro-substitution in the *ortho* position is essential for the ability to inhibit

intercellular communication *in vitro*. Different PCB congeners may, thus, act as tumour promoters by different mechanisms.

6.2.4.4 Modulation of carcinogenesis

The treatment of mice and rats with PCBs may modulate the effect of other carcinogens coadministered to these animals. Several reports demonstrate an inhibition of tumour formation when various PCB-mixtures are administered before the carcinogens in both mice and rats (Anderson *et al.* 1983, Kimura *et al.* 1976, Nishizumi 1980, Berry *et al.* 1979). When the PCBs and the carcinogens have been coadministered, either enhancement or inhibition of tumour incidences or preneoplastic lesion have been observed (Deml and Oesterle 1986, Makiura *et al.* 1974, Ito *et al.* 1973, Hayes *et al.* 1986). Several studies have demonstrated an antitumour activity of Aroclor 1254 (Hayes *et al.* 1987, Keck 1981, Kerkvliet and Kimeldorf 1977a,b). The modulation of carcinogenesis observed after pre- or co-treatment with PCBs has been suggested to be due to the induction of metabolizing enzymes, resulting in activation/deactivation of the carcinogens.

Comment

It has been shown that several PCB-mixtures have hepatocarcinogenic activity and that they are effective promoters of hepatocarcinogenesis in both mice and rats. Several individual PCB-congeners, representing various structural groups, have been shown to act as liver tumour promoters in model systems of multistage carcinogenesis in the rat. Thus, the promoting effects of PCBs have been demonstrated mainly in the liver, but there is also some evidence for promoting effects in the lung and the skin. Some PCB-congeners may act as promoters by their inhibitory effects on intercellular communication, whilst other congeners may act by a hitherto unknown mechanism in common with TCDD. No liver initiating effects of PCBs have been revealed.

6.2.5 Mechanism of toxicity

The similarity in the chemical structure and the common toxic and enzyme-inducing responses between the coplanar PCBs and the PCDDs/PCDFs, suggest a common mechanism of action. As is proposed for TCDD, this mechanism is based on the binding affinity of the PCB congener to the cytosolic Ah-receptor protein, followed by translocation of the toxicant-receptor complex to the nucleus, interaction with responsive genetic elements and resultant altered gene expression. However, so far, this chain has only been demonstrated for enzyme induction and it has not been established whether the induction leads directly or indirectly to toxicity, or whether the induction and toxicity are coordinated but independent aspects of a pleiotropic response.

The induction of monooxygenases is shown to be dependent on the position of and number of chlorine atoms in the molecule and the congeners that bind most strongly to the Ah-receptor also show the strongest CYP1A1/A2-type induction and the highest toxicity (e.g. acute toxicity, immunotoxicity, teratogenicity). The present state of our knowledge of this mechanism has recently been extensively reviewed (Banbury Report 1991).

Most studies suggest that the parent hydrocarbon initiates most of the common toxic responses, however, the toxicological significance of PCB metabolites is largely unknown.

6.2.6 Factors modifying toxicity

As PCBs can stimulate xenobiotic metabolizing enzyme activities, it can be expected that they may potentiate the action of those chemicals that undergo activation, and antagonize the action of those that are detoxified by these enzymes. Antagonism (e.g. due to enzyme induction or inhibition) has been observed in rodents exposed to drugs such as pentobarbital and hexachlorophene.

Cancer: Both inhibition of the carcinogenicity of known carcinogens and potentiation of carcinogenicity, in cases of coadministration with PCBs, have been explained by enhanced metabolism (see Section 5.2.4.4).

Enzyme inhibition: Two mixed-type enzyme inducers (2,2',3,4,4',5'- and 2,2',3,3',4,4'-CB) have been found to inhibit the MC-type induction *in vitro* of the most potent congeners 3,3',4,4'-, 3,3',4,4',5'- and 3,3',4,4',5,5'-CB (van Vliet 1990). However, concentrations of the di-*ortho* congener of at least 8-400 times that of the non-*ortho* congener are required for this inhibition. Such a concentration ratio is especially present for 2,2',3,4,4',5'-CB in human tissues, suggesting that such interactions between PCB congeners may occur.

Methylsulphonyl metabolites of PCBs have been shown to antagonize TCDD-induced, MC-type induction *in vitro* (Kiyohara *et al.* 1990). On the other hand, pretreatment with 2,2',4,4',5,5'-CB has been shown to elevate Ah-receptor levels and increase the inducibility of MC-type enzymes in rats and mice (Denomme *et al.* 1986).

Teratogenicity: In a teratogenicity study in C57Bl/6N mice, combined doses of TCDD (highly teratogenic) and 2,3,3',4,4',5-CB (slightly teratogenic) potentiated the effect seen with single compounds. No change in TCDD-teratogenicity was seen when 2,2',4,4',5,5'-CB (not teratogenic) was coadministered (Birnbaum *et al.* 1985). On the other hand, Aroclor 1254 given to C57Bl/6N mice before TCDD antagonized the teratogenic effect (cleft palate) induced by TCDD, but did not affect dexamethasone-induced cleft palate formation (Haake *et al.* 1987).

Immunotoxicity: The immunotoxicity of TCDD (inhibition of splenic plaque-forming cell response) has also been shown to be antagonized by co-treatment of the animal with 2,3,3',4,5,5'-CB or different PCB mixtures (Davis and Safe 1989, 1990).

Impurities: Highly toxic contaminants, such as PCDFs, have been identified in different commercial PCB mixtures. In many studies using PCB mixtures, the quantitative contribution of these impurities to the observed toxic responses is mainly unknown, as the biological and toxic effects induced in animals treated with PCBs and PCDFs are qualitatively similar. In general, the most toxic congeners of the PCDFs are much more potent than those of the PCBs. The toxic effects of PCB mixtures with a similar composition to that in the Yusho oil, with or without PCDFs, have been compared in rats and monkeys (Kunita *et al.* 1985). Less severe effects were seen with PCBs without contamination and only mixtures containing PCDFs caused dermal effects in the monkey. As these polychlorinated hydrocarbons seem to act through the same mechanism of action, questions arise as to the possible interactions between, as well as within, these groups.

Comment

The interactive effects that have been demonstrated *in vitro* are obviously of importance when bioassaying for dioxin-like activity. However, it is less clear what significance this may have *in vivo* at lower doses.

7 HUMAN DATA

Humans may be exposed to PCBs by direct contact with industrial products, accidental contamination of foodstuffs or from contaminated environmental components, either orally, dermally or via inhalation. In addition to the occupational exposures and the large exposures characteristic of PCB fires and point source environmental pollution, the Yusho and Yu-Cheng incidents in Japan (1968) and Taiwan (1979) caused considerable exposure of humans to PCBs (US/EPA 1990).

7.1 Toxicokinetics

Most studies describing the toxicokinetic properties of PCBs in humans indicate that the kinetics of PCBs are qualitatively similar in humans and experimental animals, such as the rat. However, the rates of metabolism and elimination seem to be slower in humans, as illustrated by the longer half-lives of certain congeners in humans (Table 18). However, the data-base thus far accumulated is very limited. Based on *in vivo* and *in vitro* comparative studies, Schnellmann *et al.* (1983, 1984) suggested that the metabolism of PCBs in humans would most closely resemble that of the rat and monkey, but not that of the dog.

7.1.1 Levels in human tissues

All routes of exposure to PCBs lead to the uptake and bioaccumulation of specific PCB congeners based on their chemical structures and stabilities. Kimbrough (1985) asserted that PCBs (measured as total PCB) tend to accumulate with increasing age of the person and increasing lipid content of the tissue.

A major problem associated with PCBs in humans has been the identification of the individual congeners in tissue samples. With few exceptions, all exposure studies have been related to a limited number of standards. Although there are qualitative differences in the PCB composition of human tissues, the congeners 2,2',4,4',5-, 2,3',4,4',5-, 2,3,3',4,4',5-, 2,2',3,4,4',5'-, 2,2',4,4',5,5'-, 2,2',3,3',4,4',5-, 2,2',3,4,4',5,5'- and 2,3,3',4,4',5,5'-CB are routinely identified and measured in human tissues (liver, adipose, serum and milk). Jensen (1991b) concluded that the congeners 2,4,4'-, 2,4,4',5-, 2,3',4,4',5-, 2,2',3,4,4',5'-, 2,2',4,4',5,5'-, 2,2',3,3',4,4',5- and 2,2',3,4,4',5,5'-CB dominate in human milk. In the adipose tissue of children (taken at surgery), six congeners constituted 53% of total PCB (1.6 mg/kg fat) and of the quantified congeners, 18% was 2,2',4,4',5,5'-, 16% 2,2',3,4,4',5,5'-, 16% 2,2',3,4,4',5'-, 1.7% 2,4,4'-, 1.2% 2,2',4,5,5'- and 0.4% 2,2',5,5'-CB (Teufel *et al.* 1990).

In tissues from occupationally- and accidentally-exposed individuals the PCB composition is highly dependent on the nature of the point source pollutant (i.e. the commercial PCB product). This means that workers exposed to the lower chlorinated products, such as Aroclor 1016, also accumulate low chlorinated congeners such as 2,4,4'- and 2,2',5,5'-CB. Furthermore, Wolff *et al.* (1986) reported that the PCB pattern in serum of people exposed through the food chain is different from that of occupationally-exposed persons. The pattern in mother's milk varies from area to area due to different exposure of the mothers tested. However, the pattern is always more or less different from that of the commercial

mixtures. In serum from consumers of sport fish in Wisconsin, a similar congener pattern was found as in the fish (perch, chinook salmon, walleye fish), although concentrations were higher in the fish than in the humans (Sonzogni *et al.* 1991).

The consumption of PCB contaminated fish not only increases the baseline body burden of PCB, but each meal also causes a temporary elevation in the serum concentrations of PCB (Humphrey 1988). Indeed, following a meal the serum PCB levels are maximal within 10 hours and then gradually decline over the succeeding 7 days.

As a rough illustration, some blood PCB levels reported for environmentally-exposed persons are summarized in Table 17. However, as concluded in the Section on PCB analysis, total PCB levels reported from different laboratories using different standards have to be interpreted and compared very cautiously.

Table 17. Total PCB concentrations in blood or serum of environmentally exposed persons.

Country/group	Blood/serum	Average concentration ± S.D. (range)	Reference
Norway/mothers	maternal serum	10 ± 7 µg/kg	Skåre <i>et al.</i> 1988
	cord serum	3 ± 1 µg/kg	Skåre <i>et al.</i> 1988
US/population	blood	5-7 µg/l	Kimbrough 1985
US/sport fishers*	serum	0.6-27.1 µg/l	Sonzogni <i>et al.</i> 1991
US/Michigan/mothers*	maternal serum	4.7 (1.1-14.3 ^a) µg/l	Jacobson <i>et al.</i> 1984a
	cord serum	2.0 (0.1-7.2 ^a) µg/l	Jacobson <i>et al.</i> 1984a
Japan/mothers	maternal blood	4.5 ± 2.9 µg/kg	Kodama and Ota 1980
	cord blood	1.1 ± 1.0 µg/kg	Kodama and Ota 1980

Total PCB levels reported from different laboratories have to be interpreted and compared very cautiously (see Section 4.4).

* Groups probably with higher intake of PCB through consumption of contaminated fish.

^a 95% confidence limits

7.1.2 Distribution

In general, many studies indicate that PCB levels are about the same in milk, blood, adipose tissue and muscle, calculated on a lipid basis (Jensen 1991a). However, certain congeners or their metabolites might have specific affinities to specific organs or cellular/subcellular sites. Masuda *et al.* (1974) reported PCB levels in tissues of Yusho patients, which derived concentration ratios between liver and adipose tissue of 0.04 and 1.03 on a whole tissue and lipid weight basis, respectively. The PCB congener pattern in the tissues might, however be different.

At an *in vitro* fertilization (IVF) clinic, PCB-concentrations have been analyzed in cervical mucus and follicular and seminal fluid from about 100 patients (Wagner *et al.* 1990). The highest concentration was found in the cervical mucus, being as high as in milk, although the lipid content of the mucus is 300 times lower than in milk. PCB in follicular fluid was higher for ideopathically-sterile women than for those with organic sterility or those who became pregnant. The results show that considerable concentrations of PCB may be present in some parts of the reproductive system. 2,2',6,6'-CB and Clophen (not specified) have been shown to decrease the motility of human sperm *in vitro* in both a concentration-

and time-dependent manner, at much lower levels than those found in the mucus (Roediger *et al.* 1989).

Comment

No data on the human distribution of individual congeners have been published.

7.1.3 Elimination

Half-lives in blood for a limited number of individual PCB congeners have been estimated in humans (Table 18). It should, however, be considered that the half-lives might be influenced by the varying body burdens and exposure situations (short-term, high accidental exposures compared to single, low-dose exposure at general environmental levels).

Table 18. Half-lives of different PCB congeners in human blood.

Congener	IUPAC	t _{1/2} (months)	Comment	Reference
2,2',4,4',5	99	9.8	Yu-Cheng	Chen <i>et al.</i> 1982
2,3,3',4,4'	105**	6.7	Yu-Cheng	Chen <i>et al.</i> 1982
2,2',3,4,4',5'	138***	10.7	volunteer	Bühler <i>et al.</i> 1988
2,2',4,4',5,5'	153***	11.3	volunteer	Bühler <i>et al.</i> 1988
2,2',3,4,4',5,5'	180***	4.1	volunteer	Bühler <i>et al.</i> 1988

**** ,*** mono- and di-ortho congener, respectively, which are also chlorinated in both *para* and at least two *meta* positions**

Half-lives of total PCB in blood were calculated for occupationally-exposed Japanese women and their children (Yakushiji *et al.* 1984). The half-lives in the children (1-13 years old) were much shorter than that in their mothers, 2.8 and 7.1 years, respectively. This is probably a result of the children's growth.

When studying the elimination of PCB congeners from the blood of intoxicated patients in Taiwan, Chen *et al.* (1982) found the same chlorination pattern-dependence for rapid metabolism and elimination as that described for rats. Because of the preferential elimination of certain PCB congeners, the PCB congener pattern of human fat and breast milk clearly differs from the pattern of common, commercial PCB-mixtures. Chromatograms of PCB congeners in human milk and of Aroclor 1260 are shown in Figures 5 and 6.

7.1.4 Placental transport and exposure via breast milk

Under environmental exposure circumstances, the levels of organohalogenes in human milk reflect, to a great extent, the levels in adipose tissue, a reservoir which is built up during several years and is mobilised during lactation (Jensen 1991a).

In a study on Japanese women (Kodama and Ota 1980), PCB levels increased in

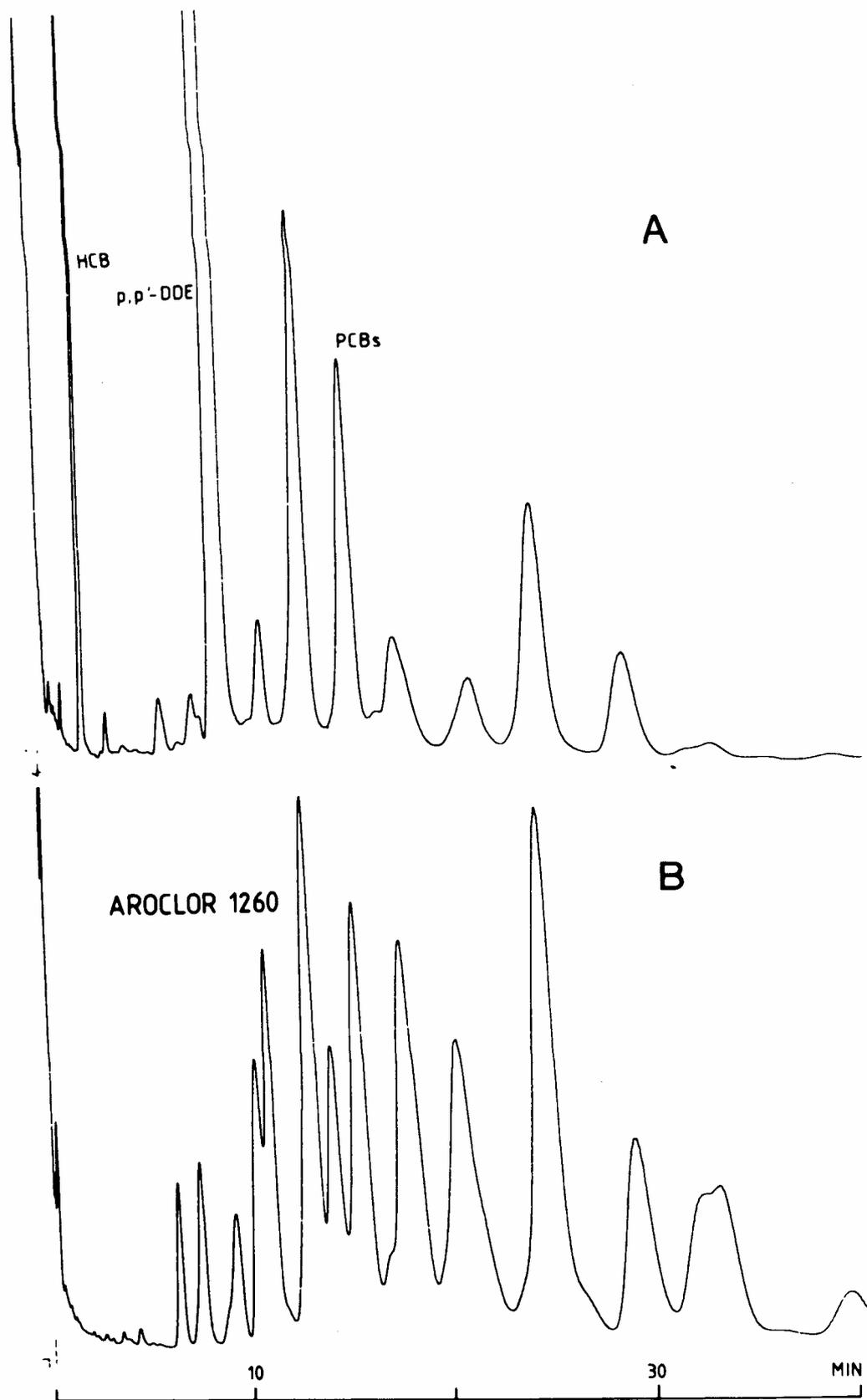


Figure 5. GC-EC chromatograms of Swedish human milk (A) and Aroclor 1260 (B) run on a packed column (Vaz 1991).

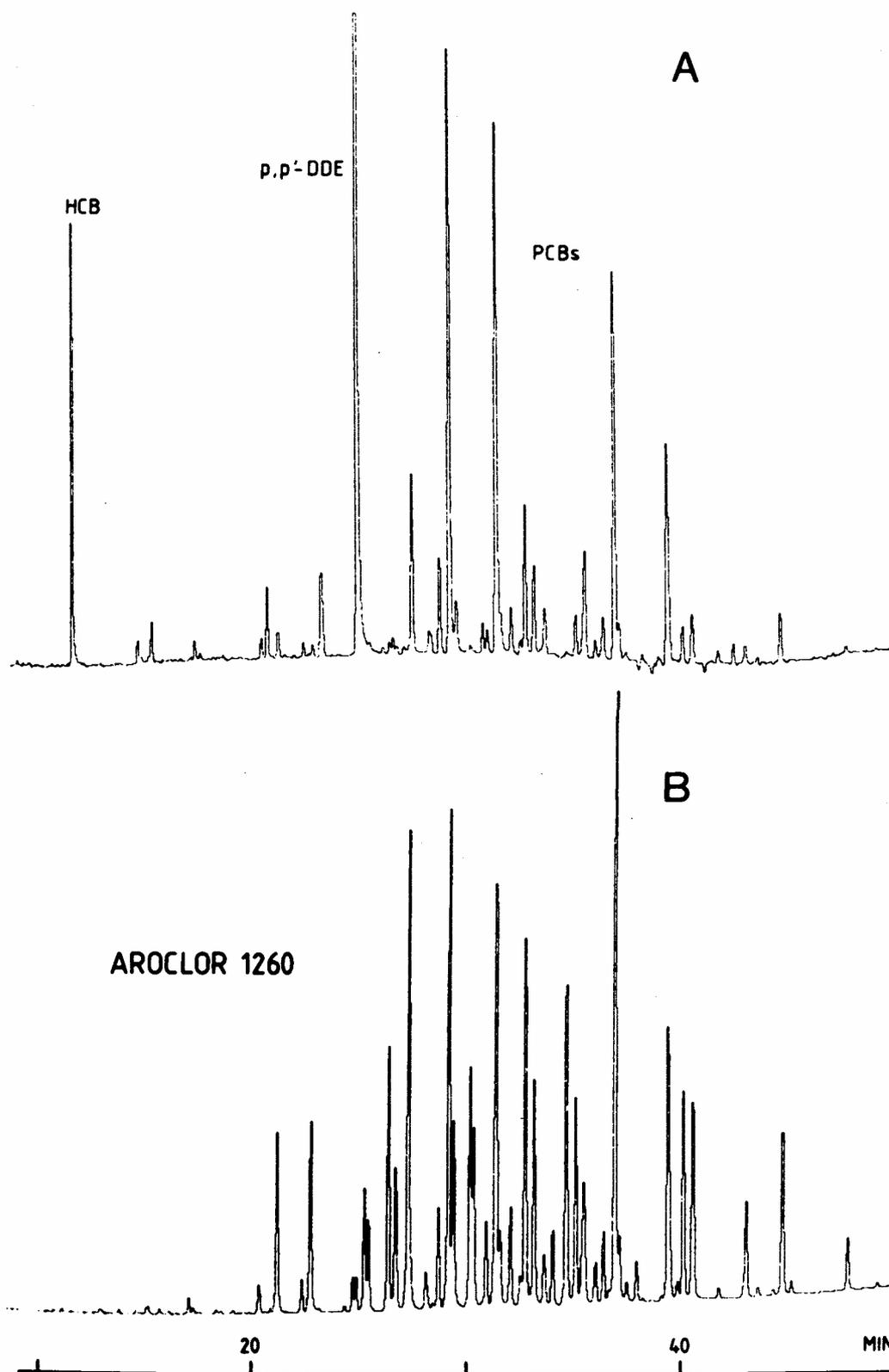


Figure 6. GC-EC chromatograms of Swedish human milk (A) and Aroclor 1260 (B) run on a fused silica SE 54 capillary column (Vaz 1991).

maternal blood during gestation and decreased after delivery and the levels in cord blood were lower than in the mother's blood (Table 19). These differences and changes in the blood PCB levels reflect, at least partly, normal differences and changes in blood lipid concentrations. The concentrations of PCB in the blood of infants rose gradually with ingestion of breast milk and exceeded their mothers' blood concentrations after 3 months (Table 19). The decrease in the mothers' blood levels during the first three months of lactation is probably due to both the excretion of PCB in milk and the decreasing lipid concentration in the blood occurring after delivery (Kodama and Ota 1980, Skåre *et al.* 1988). The PCB level in the blood of the breast-fed infants continued to increase until one year, but thereafter slowly decreased (at 2 and 3 years after birth). In two children breast-fed for a longer time, the PCB levels in their blood did not decrease. The PCB concentrations in the blood of bottle-fed infants remained low and the PCB levels in their mothers' blood did not decrease as much as in the lactating mothers' blood (Table 19).

Table 19. PCB concentrations ($\mu\text{g}/\text{kg}$, mean \pm S.D.) in whole blood of 76 Japanese mothers and their children (Kodama and Ota 1980).

Year	At delivery*		Breast-fed				
	Maternal blood	Cord blood	Mother 3 months	Child 3 months	Child 1 year	Child 2 years	Child 3 years
1974	5.1 \pm 3.0	1.5 \pm 1.3	2.9 \pm 2.4	3.3 \pm 2.0	4.0 \pm 2.4	3.2 \pm 2.4	2.2 \pm 1.6
1975	5.1 \pm 3.3	1.1 \pm 0.8	2.6 \pm 1.9	4.5 \pm 2.6	5.0 \pm 4.7	7.7 \pm 5.7	4.6 \pm 3.4
1976	3.6 \pm 2.1	0.8 \pm 0.6	1.5 \pm 0.7	2.6 \pm 1.1	4.8 \pm 3.8	4.5 \pm 2.6	NA
Year	At delivery*		Bottle-fed				
	Maternal blood	Cord blood	Mother 3 months	Child 3 months	Child 1 year	Child 2 years	Child 3 years
1974	5.1 \pm 3.0	1.5 \pm 1.3	NA	1.7 \pm 3.0	0.9 \pm 0.6	0.4 \pm 0.5	0.7 \pm 0.6
1975	5.1 \pm 3.3	1.1 \pm 0.8	4.1 \pm 1.0	1.9 \pm 0.8	ND	0.1	ND
1976	3.6 \pm 2.1	0.8 \pm 0.6	2.0 \pm 1.1	1.1 \pm 0.7	1.4 \pm 0.5	2.2 \pm 0.6	NA

* Blood values at delivery are average for the whole group (breast-fed + bottle-fed)

ND - not detected

NA - not analyzed

Higher blood levels in children, especially breast-fed children, than in their mothers have also been reported by Kuwabara *et al.* (1979). The PCB congener patterns were similar in the children and their mothers.

In a Norwegian study, similar levels of total PCB were found in adipose tissue and mother's milk on a per lipid basis, about 1 mg/kg fat (Skåre *et al.* 1988). The PCB concentration in cord serum was $\leq 50\%$ of that in maternal serum. However, calculated on a per lipid basis, the difference disappears because of the much lower ($>50\%$) lipid concentration in cord blood (Jensen 1991a). When the excretion of PCB in the milk of Norwegian women was followed, it was found that mothers decrease their body burden during lactation. The most marked decline in PCB concentration was seen during the first three weeks after delivery in primipara mothers. The initial concentration was 1.2 mg/kg milk fat, but after 120 days it had decreased to about 0.82 mg/kg milk fat. The concentration in milk of mothers breast-feeding their second child was about half of that in primipara mothers and no clear decline in the levels was seen during lactation (Skåre and Polder 1990).

A Japanese woman exposed to PCBs when working in a capacitor factory was chronically intoxicated (Yakushiji *et al.* 1978). Nine years after leaving the factory she conceived a child, but was recommended not to breast-feed. However, milk was collected for 16 months until lactation ceased. At delivery her maternal blood contained 57 μg PCB/kg, the cord blood 16 μg /kg, the placenta 56 μg /kg and omental fat 12.2 mg/kg. The PCB concentration in milk decreased from 370 to 170 μg /kg over the 16 months (13.6 to 3.8 mg/kg milk fat) and totally, 200 mg PCB was excreted in 818 litres of milk. PCB in blood of the mother decreased from about 60 μg /kg during gestation and at delivery to about 15 μg /kg at 5-16 months *post partum*. It was calculated that the infant would have ingested 45 μg PCB/kg and day if it had been breast-fed.

Comment

The presence of PCBs in human cord serum, placenta and fetal tissue indicates that there is no effective placental barrier against PCBs. The concentrations are, however, lower than the corresponding maternal levels, mainly due to a lower concentration of lipid in cord blood as compared to maternal blood (Jacobson *et al.* 1984a). As in experimental animals, PCB levels in breast-fed children at weaning are generally higher than the corresponding maternal levels. However, only total PCB levels have been measured. After weaning, the concentration of PCB in the child generally declines, mainly due to dilution in the growing fat deposits.

7.2 Toxic effects

There are great difficulties in assessing human health effects separately for PCBs, since frequently the much more toxic PCDFs were present in PCB mixtures to which the exposure occurred. The presence of PCDDs was occasionally seen in accidents with certain PCB mixtures.

There is little data reported in the literature regarding acute exposure or acute toxicity in humans. Most reports concern long-term, occupational or accidental exposure, such as the contamination of rice oil in Yusho and Yu-Cheng.

7.2.1 The Yusho and Yu-Cheng accidents

In June 1968, patients with chloracne appeared at the hospital in Fukuoka, Japan, and it was found that the disease originated from the consumption of a particular batch of rice oil. The disease was called Yusho (rice oil disease). The rice oil was found to be contaminated with about 375 mg/kg PCBs, which had entered the oil through a leak in a heat exchanger. Also PCDFs (11.6 mg/kg), PCDDs (ca 0.8 mg/kg) and polychlorinated quaterphenyls (PCQs) were found in the oil (Tanabe *et al.* 1989). The average estimated total intake was 633 mg PCBs, 3.3 mg PCDFs and 596 mg PCQs (roughly 157 µg/kg/day of PCBs, 0.9 µg/kg/day of PCDFs, 148 µg/kg/day of PCQs) (Hayabuchi *et al.* 1979). By 1982, nearly 2000 Yusho patients had been identified.

In 1979 a similar accident occurred on Taiwan which affected about 2000 persons. This incident was called Yu-Cheng. The concentrations of the compounds in rice-bran oil samples was 53-99 mg PCBs, 0.18-0.40 mg PCDFs and 25-53 mg PCQs/kg oil. The affected persons had consumed rice-bran oil contaminated with PCBs that was used as a heat transfer medium in the manufacture of the oil. The estimated average total intake was 973 mg PCBs, 3.8 mg PCDFs and 586 mg PCQs (Chen *et al.* 1985).

The most obvious clinical symptoms in Yusho and Yu-Cheng patients are the dermal effects. However, several other symptoms have been described in numerous other reports (Table 20).

A latency period of 71 days (range 20-190 days) was observed. The skin lesions were most often seen on the neck and upper chest, but in severe cases extended over the whole body. The severity and the extent of the skin lesions has improved slowly with time in the exposed population and, 15 years after the accident, only a few patients still had extensive chloracne.

Some patients suffered from a chronic bronchitis-like syndrome which persisted for several years and with a large amount of expectoration during the early stages of the disease. Pathophysiological findings revealed that the disease was mainly localised in the small airways.

The type and severity of effects and the latency time in Yu-Cheng patients were similar to those of Yusho. The average blood level of PCB was 89.1 µg/l in Yu-Cheng. One year after exposure, the PCB level had decreased to 39.3 µg/l.

PCDF congeners (e.g. the highly toxic congeners 2,3,7,8-TCDF, 2,3,4,7,8-PeCDF and 1,2,3,4,7,8-HxCDF) were identified in the blood and the tissues of both Yusho and Yu-Cheng patients, but not in unexposed persons. The presence of PCDFs in the rice oils and human tissues, together with the much higher toxicity of these compounds, suggest that the PCDFs caused most of the effects on health seen in the Yusho and Yu-Cheng patients.

Comment

The chronic bronchitis-like syndrome which persisted for several years in some Yusho patients and also in some occupationally-exposed patients, has not been detected in studies of dioxin-exposed groups.

Table 20. Signs and symptoms reported from the Yusho and Yu-Cheng accidents (US/EPA 1990).

Organ/system	Effect
Skin	hyperkeratosis hyperpigmentation acne
Meibomian glands	swelling hypersecretion
Nails, mucous membranes	pigmentation
Liver	↑ serum transaminases ↑ serum alkaline phosphatase ↓ serum bilirubin
Lungs	chronic bronchitis
Lipid	↑ serum triglycerides
Immune system	↑ susceptibility to infections ↓ IgA, IgM levels ↓ cellular immunity
Female reproduction	affected menstrual cycle
Nervous system	↓ conduction velocity in peripheral nerves sensory neuropathy
Placenta	enzyme induction
Neonatal infants	↓ birth weight hyperpigmentation of skin and mucous membranes gingival hyperplasia facial oedema exophthalmus dentition at birth abnormal calcification of the skull rocker bottom heel

↑ increased, ↓ decreased

7.2.2 Occupational exposure

One of the major problems in evaluating health effects in chemically-exposed workers is that they are often exposed to many chemical compounds.

In similarity to the poisonings in Yusho and Yu-Cheng patients, effects such as chloracne and other skin effects, chronic-bronchitis, immunosuppression and abnormal hepatic function have also been associated with occupational exposure to PCBs. As in the case of the Yusho and Yu-Cheng incidents, the contamination of the PCBs with PCDFs may, in many cases, be at least partly, the cause of these effects, especially in cases when the PCB has been heated. In the case of unheated, commercial PCBs the exposure to PCDFs might be very low, if any. The routes of exposure in occupational exposure (pulmonary, dermal) are different from those operating in the general population (gastrointestinal).

During acute exposure, irritative effects such as skin rash, itching, burning sensations, smarting and sweating have all been reported, as well as eye irritation. Transient irritation of the mucous membranes of the respiratory tract, as well as difficulties in breathing at high concentrations, have also been reported in emergency situations.

Both acute and chronic exposure to PCBs have been reported to cause neurological and non-specific psychological or psychosomatic effects such as headache, dizziness, nausea, depression, sleep and memory disturbances, nervousness, fatigue and impotence. These symptoms occurred in nearly 50% of workers exposed to PCBs for long periods. To what extent these symptoms are direct consequences of PCBs and related compounds and how much they are dependent on general conditions in emergency situations remains unclear (WHO/EURO 1987).

In a study of workers occupationally-exposed to PCBs, it was found that workers exposed for more than 10 years showed a statistically significant increase of chromosomal aberrations in their lymphocytes, and in workers exposed for periods longer than 15 years showed an increased frequency of sister chromatid exchanges (SCEs) in their lymphocytes (Kalina *et al.* 1989).

The PCB levels in the blood of many workers were much higher than those seen in Yusho patients. However, these workers showed no, or only slight, Yusho symptomology, whilst the Yusho patients showed symptoms for more than 15 years.

In order to give a general idea of the blood levels of PCBs in various populations, some studies are tabulated in Table 21. Variations in the analytical procedures used and other pitfalls that have been mentioned earlier makes it necessary to exert caution in comparing the values.

7.3 Cancer epidemiology

Only a few studies of the mortality of human populations exposed to PCBs either accidentally or occupationally have been conducted (Table X in the Appendix).

The most recently conducted study on the Yusho population is that of Kuratsune *et al.* (1987), where 1761 Yusho patients were studied (887 males; 874 females). Significantly increased incidences of deaths from cancer of the liver (9 observed; 1.61 expected) and of the respiratory system (8 obs; 2.45 exp) were observed in males but not in females. Comparisons were also made with local mortality rates (which did not change the study findings), showing a significantly increased mortality from liver cancer in

Table 21. Total PCB blood levels ($\mu\text{g/l}$) and symptoms in the general population and in PCB-exposed groups.

Group	Level[#]	Symptoms	Reference
General population	12.0 (10-27) 4.6 <20	none none not studied	Chase <i>et al.</i> 1982 Emmett 1985 Kreiss 1985
Non-fish-eaters	6.6 (<3-59.5)	not studied	Humphrey 1988
Exposed to contaminated fish	21.4 (<3-202.7)	not studied	Humphrey 1988
Occupationally exposed	80-100 21-117 33.4 (10-312) 81 18.2 (nd-424) 32.3 \pm 20.6 88-1359 12.2 41-1319 <200 \leq 40	dermatological abnormalities chloracne none none none minor liver enzymes minor enzyme affection some chloracne, liver affection none dermatological complaints breast-fed children affected	Fischbein and Wolff 1987 Hara 1985 Chase <i>et al.</i> 1982 Fischbein <i>et al.</i> 1985 Acquavella <i>et al.</i> 1986 Yakushiji <i>et al.</i> 1984 Maroni <i>et al.</i> 1984 Emmett 1985 Maroni <i>et al.</i> 1981 Ouw <i>et al.</i> 1976 Hara 1985
Yusho	1-30 (5 y post.exp.) 6 \pm 4 (11 y post.exp)	Yusho typical	Masuda 1985 Kashimoto <i>et al.</i> 1985
Yu-Cheng	39 \pm 17 (6 m post.exp) 38 (10-720) (9-18 m post.exp)	Yusho typical	Kashimoto <i>et al.</i> 1985 Chen <i>et al.</i> 1985

[#] Total PCB levels reported from different laboratories have to be interpreted and compared with each other very cautiously (see Section 4.4).

males (9 obs; 2.34 exp) but not in females (2 obs; 0.79 exp). When cancer cases occurring earlier than 9 years after the Yusho incidence were excluded, a significantly increased mortality due to liver cancer was still found (4 obs; 1.04 exp).

A study has been conducted on mortality due to cancer in workers engaged in the manufacture of electrical capacitors impregnated with PCBs in an Italian plant (Bertazzi *et al.* 1987). Various PCBs were used and exposure analysis showed very varying levels in the work environment. Air levels of 5200-6800 $\mu\text{g}/\text{m}^3$ had been measured in a few samples obtained in 1954. In 1977, serum from 37 workers was analyzed for PCB and the average levels were 280 (54% CI) and 140 (42% CI) $\mu\text{g}/\text{l}$. In 1984, the levels were 140 and 40 $\mu\text{g}/\text{l}$, respectively. Several cases of chloracne had been diagnosed in 1954 and 1977. Mortality was examined in workers who had worked for at least 1 week during the period 1946 - 1982. The expected deaths were calculated using both national and local mortality rates. In male workers, deaths due to cancer were significantly increased (14 obs; 7.6 exp). Of these, 6 were due to cancer of the gastrointestinal tract (2.2 exp). There were two cancers of liver/biliary tract. In addition, a significantly increased incidence of deaths due to cancer was observed in female workers (12 obs; 5.3 exp), and a significantly increased number of deaths from haematologic neoplasms was also found (4 obs; 1.1 exp). The authors were reluctant to draw definite conclusions from their findings because of the limitations, such as the small number of deaths studied.

A retrospective cohort mortality study of 2567 workers in two U.S. plants, where PCBs were used in the manufacture of electrical capacitors, was conducted by Brown and Jones (1981). In both plants PCBs were used for more than 30 years. The PCBs used were Aroclor 1254, 1242 and 1016. All workers included in the study were employed for at least 3 months in areas of the plants where PCBs were used. Exposure to other toxic contaminants in these plants was thought to be minimal, although trichloroethylene was used in some operations. Workers who were potentially exposed to trichloroethylene were not included in the analysis. The PCB concentrations (Aroclor 1016) in air were determined. In Plant 1, the time-weighted average (TWA) of personal air samples ranged from 24 to 393 $\mu\text{g}/\text{m}^3$, whereas in Plant 2 the samples ranged from 170 to 1260 $\mu\text{g}/\text{m}^3$. In an update of this study seven years later, the total mortality was lower than expected (295 obs; 318 exp), as was the number of deaths due to cancer (62 obs; 80 exp) (Brown, 1987). The number of deaths from cancers of the liver, gall bladder and biliary tract (5 obs; 1.9 exp) were significantly increased, and this was primarily restricted to female workers in one of the plants (Plant 2), in which higher PCB level was measured. There was no clear increase in risk associated with a longer length of employment or latency time. Several limitations of the study preclude further interpretations of the study findings with respect to PCB exposure. These included the small number of deaths studied, possible misclassification of the causes of the death, cause of death inconsistent with animal studies, and patterns of risk not completely consistent with that of an occupational carcinogen.

The remaining studies (Gustavsson *et al.* 1986, Shalat *et al.* 1989, Bahn *et al.* 1976, Davidorf and Knupp 1979, Fitzgerald *et al.* 1989) are inconclusive, and they suffer from diverse limitations such as the small number of cases and the short observation periods.

Comment

A few epidemiological studies on the possible association between the incidence of cancer and exposure to PCBs are available. Some of the studies indicate an increased incidence of cancer of the liver and biliary tract. However, there are several limitations in the present studies, such as the small groups studied, the limited observation periods, mixed exposure and other confounding variables. In all these studies, the PCB mixtures were contaminated, to various extents, with PCDFs in particular, which might have contributed to the observed effects.

7.4 Effects on newborns and infants

7.4.1 Yusho and Yu-Cheng

Pregnant Yusho women delivered in total 36 newborns with clinical signs of intoxication (Table 20). The same kind of effects were seen in children born to Yusho and Yu-Cheng mothers. The Yu-Cheng children gained height and weight more slowly than unexposed children. In addition to the clinical symptoms, the exposed children were delayed in their developmental milestones (Yu *et al.* 1991). Yu-Cheng children with neonatal symptoms had lower scores in developmental and cognitive tests (Rogan *et al.* 1988). The test scores decreased with increasing number of maternal symptoms. The behavioural effects were probably due to exposure *in utero*, since the effects were also found in bottle-fed infants.

7.4.2 Occupational exposure

Similar effects as seen in occupationally-exposed adults have been reported for children having been breast-fed for a long period by occupationally-exposed mothers (WHO/EURO 1987).

7.4.3 Environmental exposure

An important series of studies was made on a population eating fish from Lake Michigan (by Fein, Jacobson and coworkers). A total of 8482 pregnant women (96 % of all) attending four hospitals were interviewed concerning their intake of fish from the lake, which was contaminated with PCB (Swain 1991). A 4 % sample of women with high or moderate intake was drawn. In addition, subjects with no intake of local fish were studied. The outcome of pregnancy was thus investigated in a total of 313 women (242 fish consumers, 71 with no fish) (Fein *et al.* 1984). For the fish consumers, the intake of Lake Michigan fish was 6.7 ± 5.8 kg/year (mean \pm S.D.) and 4.1 ± 4.4 kg/year during pregnancy (Fein *et al.* 1984). These amounts are not simple amounts of fish, but are weighted for the PCB content of different fish species. These women had eaten Lake Michigan fish for an average of 16 years (Fein *et al.* 1984). A variety of fish intake scores were employed, which took into account both the amounts consumed and the PCB levels in different species. In many serum samples the concentrations were below the detection limit of the method. Maternal serum contained on average 4.7 (1.1-14.3, 95% confidence limits) μg PCB/l and cord serum 2.0 (0.1-7.2) μg PCB/l (63 % of all infants studied; Jacobson *et al.*

1984a). Maternal milk had an average level of 19.3 (5.4-63.1) µg PCB/l and 732.6 (293.4-1827.0) µg/kg milk fat (Jacobson *et al.* 1984a).

There were significant associations between the intake of fish and the levels of PCB in maternal serum and milk, and also between maternal and cord serum concentrations (Fein *et al.* 1984). In addition, there were significant associations between the intake of fish and cord serum levels, on the one hand, and i.e. gestational age, birth weight, and size for date, on the other. Furthermore, the behaviour of 242 studied newborns was associated with fish intake (Jacobson *et al.* 1984b). Moreover, there is some information on the health of the women themselves (Swain 1991). The investigators found that exposure to low levels of PCB from fish was associated with anaemia before pregnancy and oedema during pregnancy in the first 170 women examined (not reported in the publications by Jacobson and coworkers).

123 of the infants were restudied at the age of 7 months, especially with regards to visual recognition (preference for a new stimulus) (Jacobson *et al.* 1985). Again, there was an association between cord blood level of PCB and the score obtained (Figure 7A).

At the age of 4 years, 236 children were restudied. There were then associations between cord serum and milk levels of PCB, on the one hand, and poorer performance in verbal and numerical memory tests, on the other (McCarthy memory scale; Figures 7B,C; Jacobson *et al.* 1990a). Prenatal exposure to PCB was also correlated to lower body weight (Jacobson *et al.* 1990b). In addition, the PCB content in milk and the time of breast feeding and serum levels at age 4 were all associated with a composite activity rating (Figure 7D). The association with lactation was most marked for children exposed to high milk concentrations of PCB for more than 12 months. The most prevalent congeners in the serum of the children at 4 years of age were 2,3-, 2,4'-, 2,2',5-, 2,4,4'-, 2,4',5-, 2,2',4,4',5-, 2,3',4,4',5-, 2,2',3,4,4',5'-, 2,2',4,4',5,5'-, 2,3,3',4',5,6-, 2,2',3,3',4,4',5-, 2,2',3,4,4',5,5'-, 2,2',3,4,4',5,6'- and 2,2',3,4',5,5',6-CB (Jacobson *et al.* 1989). The serum levels at age 4 correlated with the PCB level in milk of their mothers and the duration of breast-feeding (0.6 µg/l for children breast-fed for up to 3 months, 5.5 µg/l for those fed more than 12 months; Jacobson *et al.* 1989).

The above data are important, particularly because the prospective follow-up design and the impressive dose-response relationships. The effects are not large, but must, especially on a population basis, be considered as adverse. In addition, the results are supported by the similarities of some of the effects with observations in infants poisoned by rice oil and those born to occupationally-exposed mothers. The neuro-behavioural findings also fit in with data obtained in monkeys.

Despite these correlations, there are some epidemiological problems with the above data. The non-participants and drop-outs are not fully described and there is a possibility of reversed causality. In addition, a major problem in this kind of study is the confounding control. The authors take into account 36 possible confounding variables (including PBB level in cord serum and socioeconomic factors, alcohol intake, and smoking). However, some important potential confounders, such as maternal intelligence and nutritional factors, were not studied. Moreover, other toxic compounds in the fish were not considered, such as methyl mercury. Some areas of Lake Michigan are affected by

mercury pollution (Glass *et al.* 1990). Also, increased levels of mercury have been found in fish from some areas (Department of Public Health, State of Michigan, unpublished data). In addition, the PCB exposure was probably confounded by PCDDs and PCDFs.

In a cohort of more than 800 children in North Carolina, psychomotor index correlated inversely with prenatal exposure to PCB (measured as the milk concentration of PCB at delivery), at both 6 and 12 months of age (Figure 8C; Gladen *et al.* 1988). Also neonatal hypotonicity and hyporeflexia (Figure 8A,B) were associated with prenatal PCB-exposure (Rogan *et al.* 1986). The effects had no association with exposure through breast-feeding. In a follow-up on the cohort at 3-5 years of age, no correlations between McCarthy developmental scores and either exposure to PCB via the placenta or by breast-feeding were found (Gladen and Rogan 1991).

Comment

In addition to the associations found between exposure to PCB and developmental effects in children, and the lack of correlations to other contaminants (DDE, PBB, lead), the qualitative similarities between effects in human and animal species further support that PCBs are the cause of the observed effects (Tilson *et al.* 1990).

To our knowledge, no studies on the levels of methyl-mercury have been performed in either of the two groups of children. The Michigan group (exposed through fish) should be expected to have an exposure to methyl mercury. In the case of North Carolina, the fish intake was probably low; whether there is a confounding by other agents than PCB is not known.

Due to different methods of PCB quantification used by various laboratories, it is difficult to compare PCB concentrations defined by different laboratories in different countries. In the Nordic countries only one study has been published where PCB concentrations in cord blood, maternal blood and mother's milk have been simultaneously determined (Skåre *et al.* 1988). The samples were collected in 1981 and PCBs were determined on a packed GC-column via pattern recognition using the commercial standard Aroclor 1254 (Sawyer 1978). Basically, the same method for PCB quantification was used in the Michigan study. The results, however, depend very much upon which standard is used and which peaks are selected. The choice of standard differs between the studies (Aroclor 1260 was used in the Michigan study) as probably also the number of peaks summed. In the Norwegian study, 1-4 major peaks were taken for comparison in the blood samples, whilst no such information from the Michigan study is available. In general, if 1-3 major peaks are selected, the results will be overestimated by a factor of at least 2 as compared to if a dozen peaks are selected. Thus, a difference of a factor 2-10 in PCB concentrations between the studies cannot be excluded. Whether the congener patterns are similar in Nordic and US tissue samples is not known. However, the major congeners seem to be the same (2,3',4,4',5-, 2,2',3,4,4',5'-, 2,2',4,4',5,5'-, 2,2',3,3',4,4',5- and 2,2',3,4,4',5,5'-CB).

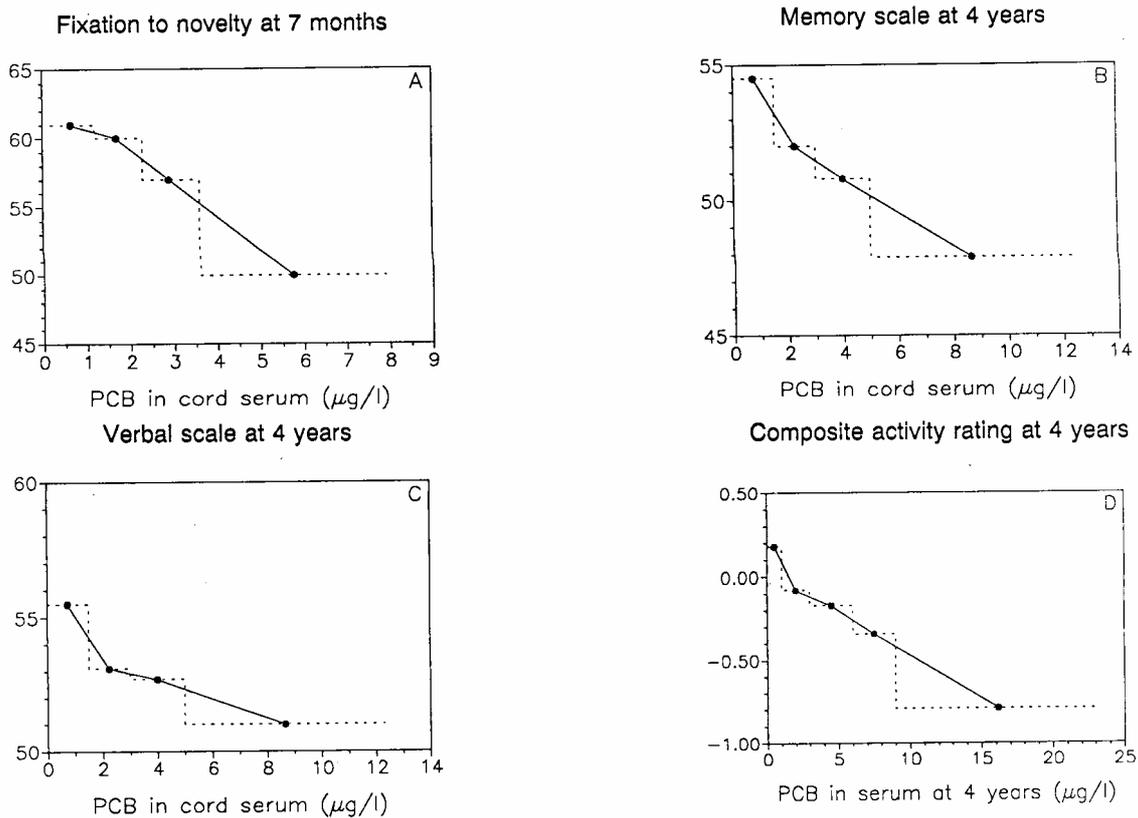


Figure 7. Dose-response curves from the Michigan study (Jacobson *et al.* 1985, 1990a,b). In the original data, dose levels are reported as ranges (illustrated as dotted lines in the Figures).

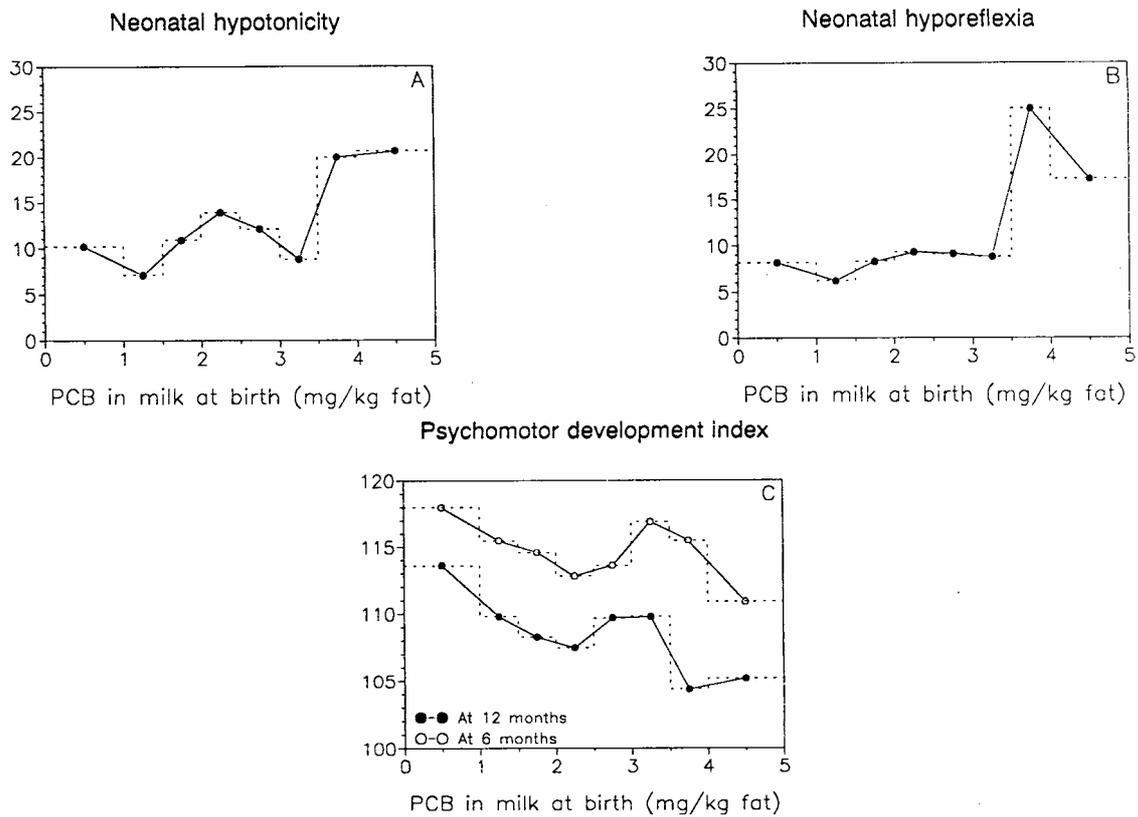


Figure 8. Dose-response curves from the North Carolina study (Rogan *et al.* 1986, Gladen *et al.* 1988). In the original data, dose levels are reported as ranges (illustrated as dotted lines in the Figures).

8 NORDIC LEVELS AND LIMITS

8.1 Human levels

The average concentrations of total PCB in human milk are typically between 0.5 and 1.5 mg/kg milk fat in the Nordic countries (Jensen 1991b). The levels of total PCB in Norwegian women, measured at delivery, were 0.95 mg/kg fat in adipose tissue, 10 µg/kg serum, 3-5 µg/kg cord serum and 0.8-1.2 mg/kg fat in mother's milk (Skåre *et al.* 1988). A limited amount of analytical data on individual PCB congeners in humans in the Nordic countries exists. Levels in Swedish mother's milk (Norén and Lundén 1991, R Vaz, personal communication) and Finnish serum and adipose tissue (Luotamo *et al.* 1991) are shown in Table 22. The concentrations of other tri- to heptaCBs identified in Finnish serum and adipose tissue are shown in Table XI in the Appendix. In Swedish blood samples, the level of 2,2',3,4,4',5'- and 2,2',4,4',5,5'-CB (combined) was 0.63-0.90 mg/kg fat, with these congeners being about 66% of the total PCB (S Jensen, personal communication).

The concentration of total PCB in Norwegian human milk has significantly decreased from 1982 (1.0 mg/kg milk fat) to 1986 (0.5 mg/kg milk fat) (Clench-Aas *et al.* 1988). Basically the same analytical methods were used in the surveys. Time trends (1972-1989) for individual PCB congeners in Swedish human mother's milk have been reported (Norén 1992; see Figures 9 and 10).

8.2 Levels in the environment and in food

Levels of total PCB in food have been measured for several years. In Denmark (1986/87), PCB (as Aroclor 1260) was determined in imported cheese (<0.10-0.32 mg/kg), the kidney fat of cattle (<0.10-0.29 mg/kg) and in cod liver (<0.10-2.07 mg/kg). The concentration in cod liver has declined by about 80% since 1975 and in herring the level has not been detectable (<0.10 mg/kg) since 1982/83 (Pesticide residues in Danish food 1989).

In Norway, the PCB-levels (sum of 22 congeners) in almost all samples of fat from pig, cattle and sheep were below the detection limit (0.04 or 0.01 mg/kg). For representative samples of different wild fish species the levels of these 22 congeners were detectable (Table 24, JU Skåre, personal communication), whilst the compounds concentrations in cultivated rainbow trout from the Norwegian west coast were not detectable. (The limits of quantification for each of 21 congeners analyzed was 0.5 µg/kg wet weight). Within the Swedish Dioxin Survey, different animal species have been analyzed for the non-*ortho* PCB congeners and for total PCB (Table 23, Asplund *et al.* 1990, C de Wit, personal communication). The mono-*ortho* congeners have not yet been analyzed.

In Finland, 88 different food samples have been analyzed for individual PCB congeners (Table 25, K Himberg, personal communication).

Table 22. Levels of PCB congeners in Swedish mother's milk (Norén and Lundén 1991, R Vaz, personal communication) and Finnish human serum and adipose tissue (Luotamo *et al.* 1991).

Congener	IUPAC	Swedish mother's milk (µg/kg) n=140 (Norén and Lundén)	Swedish mother's milk (µg/kg fat) n=140 (Norén and Lundén)	Swedish mother's milk (µg/kg fat) n=40 (Vaz)	Finnish human serum (µg/l)	Finnish human adipose tissue (µg/kg)
3,3',4,4'	77*	0.0007	0.027	NA	NA	NA
3,3',4,4',5	126*	0.0025	0.098	NA	NA	NA
3,3',4,4',5,5'	169*	0.0012	0.047	NA	NA	NA
2,3,3',4,4'	105**	0.16	6	NA	ND	10.10
2,3,4,4',5	114**	NA	NA	NA	0.02	27.9
2,3',4,4',5	118**	0.65	25	37-49	0.53	47.6
2',3,4,4',5	123**	NA	NA	NA	ND	1.30
2,3,3',4,4',5	156**	0.36	14	NA	ND	13.70
2,3,3',4,4',5,5'	189**	NA	NA	NA	ND	4.13
2,2',3,3',4,4'	128***	NA	NA	NA	ND	2.69
2,2',3,4,4',5	137***	NA	NA	NA	ND	3.93
2,2',3,4,4',5'	138***	3.0	116	130-200	1.28	190.00
2,2',4,4',5,5'	153***	3.93	151	150-220	0.99	179.00
2,2',3,3',4,4',5	170***	NA	NA	49-61	ND	61.40 [@]
2,2',3,4,4',5,5'	180***	1.66	64	78-110	ND	134.00
2,4,4'	28	0.21	8	NA	0.09	1.13
2,2',3,4',5,5',6	187	NA	NA	29-51	ND	44.80 ^α
Total PCB		16.9[#]	650[#]	NA	3.41^β	865.37^β

NA=not analyzed, ND=not detected, [@] Coelutes with 2,3,3',4,4',5,6^{***} (IUPAC 190),

^αCoelutes with 2,2',3,4,4',5,6' (IUPAC 182),

^β Sum of detected tri- to heptaCBs, [#]Quantified as Clophen A50,

^{*}, ^{**}, ^{***} non-, mono- and di-*ortho* congener, respectively, which are also chlorinated in both *para* and at least two *meta* positions

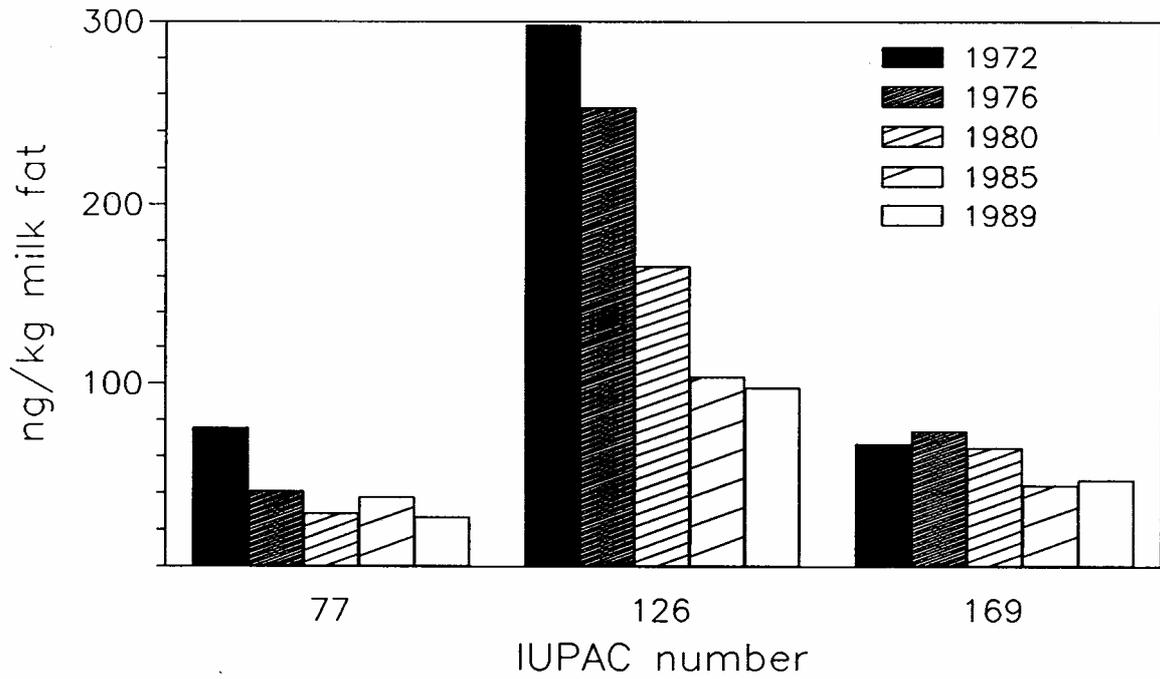


Figure 9. Average levels of non-ortho PCB congeners in Swedish mother's milk (Norén 1992).

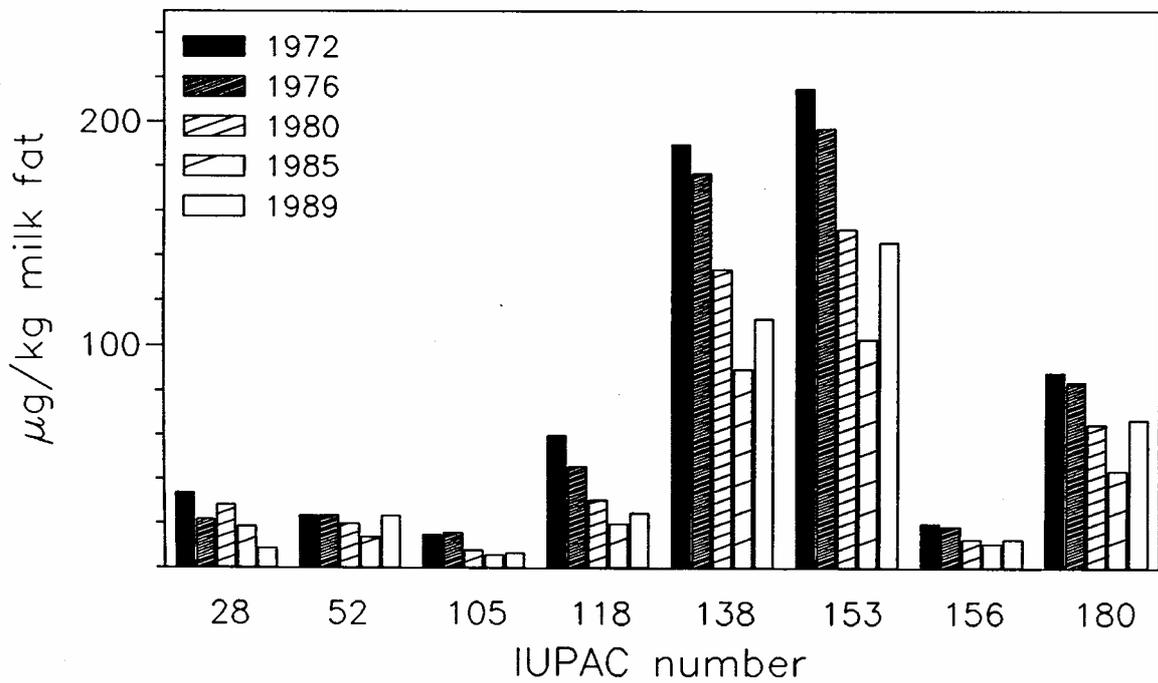


Figure 10. Average levels of certain PCB congeners in Swedish mother's milk (Norén 1992).

Table 23. Levels (ng/kg wet weight) of PCB congeners in different Swedish animal species (Asplund *et al.* 1990, C de Wit, personal communication).

Congener	IUPAC	Reindeer (suet)	Moose (muscle)	Whitefish (muscle)	Arctic char (muscle)	Bothnian herring (muscle)	Baltic herring (muscle)	Skagerak herring (muscle)
Lipid (%)		41	2.0	0.5	4.7	4.7	3.0	3.4
3,3',4,4'	77*	57	110	12	820	490	720	250
3,3',4,4',5	126*	96	5.7	2.2	320	66	81	29
3,3',4,4',5,5'	169*	18	3.0	1.4	56	18	21	6.8
2,2',4,4',5,5'	153***	7 000	1 200	980	56 000	18 000	16 000	5 100
2,2',3,4,4',5,5'	180***	3 700	280	440	22 000	6 800	5 800	1 200
Total PCB (LRGC)		34 000	NA	5 000	560 000	220 000	200 000	65 000

*,**,*** non- and di-*ortho* congener, respectively, which are also chlorinated in both *para* and at least two *meta* positions

NA - not analyzed

LRGC - Low Resolution Gas Chromatography

Table 24. Levels ($\mu\text{g}/\text{kg}$ wet weight, mean \pm SD) of PCB congeners in Norwegian fish (JU Skåre, personal communication).

Congener	IUPAC	Salmon muscle Vestlandet	Cod muscle Finmark	Cod liver Finmark	Mackerel muscle Vestlandet	Herring muscle Nordsjön
		$9 \pm 9\%$ fat	$0.2 \pm 0.0\%$ fat	$44 \pm 2\%$ fat	$28 \pm 7\%$ fat	$16 \pm 8\%$ fat
2,4,4'	28	1.7 ± 3		15.6 ± 4		0.7 ± 2
2,2',5,5'	52	0.8 ± 1		25.7 ± 3	1.5 ± 3	2.2 ± 4
2,4,4',5	74	1.5 ± 2		33.1 ± 10	0.8 ± 1	0.7 ± 1
2,2',4,4',5	99	8.0 ± 6	0.1 ± 0.1	241.5 ± 48	8.4 ± 3	9.8 ± 6
2,2',4,5,5'	101	5.8 ± 6		56.8 ± 24	1.8 ± 2	3.9 ± 2
2,3,3',4,4'	105**			30.8 ± 8		
2,3,3',4',6	110	5.8 ± 6		100.8 ± 31	3 ± 3	5.9 ± 4
2,3,4,4',5	114**	1.7 ± 3	0.1 ± 0.1	45.4 ± 6	0.7 ± 1	1.9 ± 2
2,3',4,4',5	118**	3.8 ± 4		94.8 ± 30	2.0 ± 2	1.3 ± 2
2,2',3,3',4,4'	128***	3.3 ± 2		116.9 ± 24	4.1 ± 4	4.1 ± 3
2,2',3,4,4',5'	138***	9.5 ± 5	2.0 ± 0.8	116 ± 25	8.8 ± 4	7.9 ± 4
2,2',3,4,5,5'	141	0.3 ± 0.6		8.1 ± 0.4		0.3 ± 0
2,2',4,4',5,5'	153***	9.5 ± 12	0.1 ± 0.1	124.8 ± 25	5.2 ± 1	7.8 ± 6
2,3,3',4,4',5	156**			10.1 ± 1	1.2 ± 2	

Congener	IUPAC	Salmon muscle Vestlandet	Cod muscle Finmark	Cod liver Finmark	Mackerel muscle Vestlandet	Herring muscle Nordsjön
		9 ± 9% fat	0.2 ± 0.0% fat	44 ± 2% fat	28 ± 7% fat	16 ± 8% fat
2,3,3',4,4',5'	157**	1.1 ± 2		13.3 ± 6	0.6 ± 1	
2,2',3,3',4,4',5	170***	0.6 ± 1		15.6 ± 4		
2,2',3,4,4',5,5'	180***	5.2 ± 3	1.5 ± 0.6	35.7 ± 4		2.8 ± 2
2,2',3,4,4',5',6	183			1.1 ± 1.5		
2,2',3,4',5,5',6	187	1.2 ± 1		13.1 ± 3	0.9 ± 0.2	0.98 ± 0
2,2',3,3',4,4',5,5'	194***			1.9 ± 0.2		
2,2',3,3',4,4',5,5',6	206			5.1 ± 2	0.9 ± 2	
Total PCB		57.1 ± 55	3.8 ± 2	1105 ± 257	39.9 ± 27	50.6 ± 33

, mono- and di-*ortho* congeners, respectively, which are also chlorinated in both *para* and at least two *meta* positions

Table 25. Average levels ($\mu\text{g}/\text{kg}$ wet weight) of PCB congeners in different foodstuffs in Finland (K Himberg, personal communication).

Congener	IUPAC	Baltic herring n = 9	Salmon n = 6	Other fish n = 20	Cattle n = 7	Pork n = 5	Inner organs n = 8	Chicken n = 4	Butter n = 2	Cheese n = 5	Margarine n = 4	Vegetable oil n = 3	Eggs n = 5	Pike [#] n = 4	Fish liver oil n = 5
2,4,4'	28	2.4	3.3	4.8	0.21	0.02	0.99	0.09	1.5	3.1	0.70	1.36	0.64	16	10
2,2',5,5'	52	3.7	5.7	2.9	0.04	0.11	0.45	0.14	1.6	8.3	0.70	0.19	0.09	35	23
2,2',4,5,5'	101	11	15	5.2	0.16	0.12	0.60	0.13	5.1	4.7	3.2	0.74	0.18	92	45
2,3',4,4',5	118 ^{**}	11	17	4.1	0.27	0.13	0.41	0.37	13	6.7	1.3	1.4	0.23	234	80
2,2',3,4,4',5'	138 ^{***}	24	33	8.8	0.12	0.45	0.70	1.3	12	5.8	3.6	0.53	0.51	99	158
2,2',4,4',5,5'	153 ^{***}	20	31	7.3	0.29	0.71	0.73	1.5	13	6.8	4.3	0.77	0.44	88	118
2,2',3,4,4',5,5'	180 ^{***}	8.2	9.1	3.5	0.07	0.30	0.33	0.79	3.4	NA	NA	0.13	0.15	16	50

n - number of analyzed samples

NA - not analyzed

[#] Samples of pike were collected from highly polluted waters

^{**},^{***} mono- and di-*ortho* congeners, respectively, which are also chlorinated in both *para* and at least two *meta* positions

8.3 Estimated intake of PCB

8.3.1 Mother's milk

Analysis of human milk from many countries has shown that in general, the average levels of total PCB lie in the range 0.5-1.5 mg/kg milk fat (Jensen 1991b). The breast-fed infant consumes about 160 g of milk per kg body weight each day. Since breast milk contains on average about 3% fat, this corresponds to about 4.8 g milk fat per kg per day. Consumption of 4.8 g milk fat containing 0.5-1.5 mg PCB/kg will therefore result in an intake of 2.4-7.2 µg PCB/kg body weight per day.

8.3.2 Fish and other foods

The analysis of foodstuffs in the Nordic countries for total PCB shows that the levels of these contaminants in foods of vegetable origin are below the limits of detection for routinely used analytical methods. The levels in milk fat, eggs and bovine and porcine fat are also generally below the limits of quantitation (0.05 mg/kg). Detectable levels are found in fish, especially fatty fish, e.g. salmon and herring. If one assumes that fish are the only important source of PCBs, the dietary intakes of persons consuming various amounts of different fish species will be as shown in Table 26. The intake has been calculated for two levels of fish consumption - 30 g/day (the average for Sweden) and 120 g/day (high intake, corresponding to 5-7 fish meals each week). Furthermore, it has been assumed that only fish of a single species has been consumed and that the consumer is an adult with a body weight of 60 kg.

Blood and breast milk from persons that do not eat fish contain detectable levels of PCBs (Norén 1983). Thus, exposure to PCBs also occurs via other foodstuffs and/or from non-dietary sources and the total intakes of PCBs will be somewhat higher than those shown in the Table.

The contribution from different food items to the total dietary intake of PCB has been estimated in Finland (Moilanen *et al.* 1986; Table 27). Of the total Finnish dietary intake of PCB (14.35 µg/day), fish accounts for 38%. For a person weighing 60 kg the total intake corresponds to 0.24 µg/kg and day.

Table 26. The calculated daily intake of total PCB from fish.

Fish species (location)	PCB level in fish µg/kg wet weight	PCB intake, ng/kg b.w. [#]	
		Normal fish consumption (30 g fish/day)	High fish consumption (120 g fish/day)
Herring (Swedish Westcoast)	87**	43.5	174
Herring (Baltic)	330**	165	660
Salmon (Baltic)	330**	165	660
Cod (Norwegian Westcoast)	4* (3-5)	2 (1.5-2.5)	8 (6-10)
Salmon (Norwegian)	57* (20-139)	28 (10-70)	114 (40-278)
Herring (Norwegian)	51* (15-93)	26 (8-46)	102 (30-186)
Mackerel (Norwegian)	40* (24-71)	20 (12-36)	80 (48-142)

A body weight of 60 kg is assumed

* Data from Table 24 (Skåre, personal communication)

** Data from the Swedish National Food Administration

Table 27. The estimated dietary intake of total PCB from different foods in Finland (Moilanen *et al.* 1986).

Food item	PCB intake	
	µg/day	% of total PCB intake
Baltic herring	4.0	28
Other fish	1.5	10
Dairy products	0.39	3
Fats and oils	3.02	21
Hens eggs	2.86	20
Meat products	2.21	15
Inner organs	0.38	3
Total	14.35	100

8.4 Limits for residues in food

In Sweden, the limits for total PCB (based on quantification according to Jensen *et al.* 1983) in food are:

Fish	Other foodstuffs
5.0 mg/kg salmon 5.0 mg/kg fish liver 2.0 mg/kg other fish	0.2 mg/kg meat 0.05 mg/kg milk 0.1 mg/kg butter and cheese 1.0 mg/kg egg 2.0 mg/kg liver from cattle and pig

Finland has congener-specific limits for PCB in fish and fish products as shown below (PNUN 1987):

Congener	IUPAC	Limit (mg/kg)
2,4,4'	28	0.6
2,2',5,5'	52	0.1
2,2',4,5,5'	101	0.2
2,3',4,4',5	118**	0.2
2,2',3,4,4',5'	138***	0.2
2,2',4,4',5,5'	153***	0.2
2,2',3,4,4',5,5'	180***	0.2
Other		0.6
Total		2.0

In Norway and Denmark, there is no official limit. Iceland is about to adopt a regulation similar to the Finnish one although they are considering to express the limits on a fat basis.

9 RISK ASSESSMENT

9.1 Introduction

The risk assessment from exposure to PCBs presents problems that are more complicated than usually encountered in dealing with a group of compounds. Indeed, it is certainly much more complicated than the earlier risk assessment of dioxins (Ahlborg *et al.* 1988).

The PCBs constitute a series of 209 individual congeners, varying in the number and sites of chlorine substitution. The biological effects caused by the various congeners differ, not only in potency but also qualitatively. Our knowledge of the mechanisms of toxicity indicates that some of the PCB congeners act by the same mechanisms as the chlorinated dioxins, i.e. the toxicity is probably mediated through interaction with the Ah receptor, and they are potent inducers of the P448 isoenzymes CYP1A1 and CYP1A2. Other PCB congeners presumably act by different mechanisms and are potent inducers of a different set of cytochromes, CYP2B1 and CYP2B2. In addition, there are PCB congeners that are intermediate in this respect, i.e. they elicit a mixed spectrum of enzyme induction.

Some typical toxic effects of PCBs, such as tumour promotion, are caused by PCB congeners of all these three classes (CYP1A1/2, CYP2B1/2 and mixed-type inducers), but the underlying mechanisms are probably different. Our knowledge of possible interactions between the various groups of PCBs is still very limited.

Almost all animal studies with PCB mixtures have been performed using commercially available PCBs. Due to differences between individual congeners, with regards to resistance to degradation and metabolism, the composition of a commercial mixture is different from the composition of the mixtures to which humans will be exposed to, especially from food.

A further complication in the risk assessment is the fact that many PCBs are metabolized to yield hydroxy- and methyl sulphone metabolites. The available data on the possible biological and toxicological effects of these metabolites are, however, very limited and preclude consideration of these metabolites in the present risk assessment.

The risk assessment of PCBs can, at present, be approached in at least two different ways.

*** Assessing the risk from the exposure to mixtures of PCBs** utilizing data from human studies and experimental animal studies. The various end-points that can be used for such an assessment are immunotoxicity in animals, cancer in humans and animals, and developmental/behavioural effects in humans and animals.

*** Assessing the risk from exposure to individual PCB congeners.** In this case, only data from animal studies are at present available for evaluation. Furthermore, the data-base today will only allow for this exercise to be performed on congeners acting through the same mechanisms as the chlorinated dioxins.

There are no convincing data indicating possible *in vivo* genotoxic actions of the PCBs. The dioxin-like PCB congeners presumably exert their toxic effects through a receptor-mediated mechanism. At very low doses we presume these PCB congeners to show highly non-linear dose-response relationships, i.e. virtual dose thresholds. We further presume that the other, non-dioxin-like congeners exhibit threshold dose responses.

9.2 Review of earlier risk assessments

Based on studies of liver cancer in rats, the United States Environmental Protection Agency (US/EPA) in their Drinking Water Criteria Document for Polychlorinated Biphenyls (PCBs) has calculated life-time cancer risks of 10^{-4} , 10^{-5} and 10^{-6} for water concentrations of 0.5, 0.05 and 0.005 μg Aroclor 1260 per litre, respectively (US/EPA 1990). It should be noted that this calculation is made for Aroclor 1260 only. Due to a deficient data base on toxicity and exposure to PCBs from drinking water in the US, recommendations for guidelines were not made for shorter exposure times.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) recently attempted to evaluate PCBs (FAO/WHO 1990). The Committee concluded that, due to the limitations of the available data, it was impossible to establish a precise numerical value for a tolerable intake for humans. However, it was concluded that the monkey was the most appropriate animal for use in studies with PCBs and that 0.04 mg/kg b.w./day was a no effect level in the monkey studies considered. It was also noted that some PCB mixtures were hepatocarcinogenic in rodent bioassays, but that available studies in humans were inconclusive with respect to an association between exposure to PCB and increased mortality due to cancer.

PCBs were evaluated by IARC in 1978 (IARC 1978) and updated in the IARC suppl. 7 (IARC 1987). IARC concluded that available studies suggested an association between human cancer and exposure to PCBs. However, due to various deficiencies in the database, the evidence was considered to be limited.

PCB mixtures, particularly with greater than 50% chlorination, have been found to produce benign and malignant liver neoplasms in mice and rats. The evidence for carcinogenicity in animals was considered to be sufficient, however, the overall classification of PCBs was 2A, i.e. probably carcinogenic to humans.

WHO/IPCS is still in the stage of editing their Environmental Health Criteria document for Polychlorinated Biphenyls (PCBs) and Polychlorinated Terphenyls (PCTs). Thus, the final evaluation is not yet available.

9.3 Mixtures of PCB

The critical endpoints for risk assessment of PCBs are identified as cancer, immunotoxic and behavioural effects.

9.3.1 Cancer

9.3.1.1 Animals

The available positive, long-term bioassays in the rat (Kimbrough *et al.* 1975, Norback and Weltman 1985, Schaeffer *et al.* 1984) have all been performed with one dose level, 100 ppm of either Aroclor 1260 or Clophen A60, roughly corresponding to 5 mg/kg b.w. and day. An increased frequency of liver tumours is reported in several strains. One study covering several dose levels (25, 50, 100 ppm) of Aroclor 1254 (NCI 1978) was found to be negative in a recent reevaluation of the pathology (IEHR 1991).

Due to the lack of dose-response data from animal bioassays, it is presently impossible to perform any quantitative risk evaluation including the establishment of a no observed adverse effect level (NOAEL). Discrepancies between the commercial mixtures and environmental exposures, with regards to congener composition, also imply that the predictive value of these studies are limited with respect to the judgement of the risks from environmental exposure.

However, intake estimates for humans indicate that human, non-occupational exposure (see Section 7.3) is several orders of magnitude lower than the tested carcinogenic dose of Aroclor 1260 or Clophen A60 (5 mg/kg b.w. and day).

9.3.1.2 Humans

A few epidemiological studies of occupationally-exposed workers have indicated an increased incidence of cancer of the liver and biliary tract. However, in all these studies the exposure occurred to commercial PCB mixtures, the compositions of which clearly differ from those of PCBs in food. In addition, the PCB mixtures were contaminated to various extents with other chlorinated compounds, especially PCDFs, which might have contributed to the observed effects. Taken together with the lack of good exposure measurements, it is not possible to use these qualitative data for the present risk assessment.

9.3.2 Immunotoxicity

9.3.2.1 Animals

Long-term, low-level exposure to Aroclor 1254 has been shown to produce moderate, but statistically significant, effects on certain immunological parameters in Rhesus monkeys. The significance to health of these findings is difficult to evaluate since it is not known how they are related to functional impairment of the immune system. However, the effects are already apparent at a daily dose of 5 µg/kg and day, corresponding to a whole blood total PCB-level of 10 µg/l. Keeping in mind that the PCB levels in the Rhesus monkey study were measured by a different method than used in the analysis of the Norwegian samples of human blood, the levels in the latter samples were approximately half of those of the monkeys (Skåre *et al.* 1988).

9.3.3 Behavioural effects

9.3.3.1 Animals

Hyperactivity and impaired learning ability have been reported for Rhesus monkey infants exposed to different Aroclors *in utero* and during lactation (Bowman and coworkers, see Section 5.2.2.5). The lowest dose studied (0.5 ppm Aroclor 1248 in the diet given to the dams), caused hyperactivity in their infants. The authors estimated the weekly intake for the mothers to be about 0.04 mg/kg, resulting in 6 µg/kg b.w. and day which, thus, represents a LOAEL (lowest observed adverse effect level).

The validity of these studies has been questioned. However, the experiments were performed with several cohorts of animals, although the number of animals in each cohort was rather limited, i.e. 3-5 animals plus controls. The outcome in all the studies was similar, i.e. an increase in behavioural activity. Studies of this type in monkeys have not been performed by other laboratories, but supportive data are available from studies in rats, mice and quails (for review, see Tilson *et al.* 1990).

The Rhesus monkeys in the studies by Bowman and coworkers were exposed to commercial mixtures of PCB (Aroclor 1248 or 1016). The congener patterns of these mixtures are, however, quite different from that seen in most biological samples, including fish and human milk. It is thus difficult to utilize the data on these monkeys directly for the present risk assessment.

9.3.3.2 Humans

Behavioural effects similar to those seen in monkeys have also been reported for human infants whose mothers were exposed to PCBs through the intake of contaminated fish (Michigan study, Jacobson and coworkers; see Section 6.4.3). The effects recorded in infants were slight, but should still be regarded as adverse. However, the study is not fully conclusive from an epidemiological point of view. Thus, the causal relationship between PCB and the effects are not proven due to some potentially important confounding factors (see Section 6.4.3). On the other hand, a causal relationship is definitely possible. Furthermore, supportive evidence comes from a similar study performed in North Carolina (Rogan and coworkers).

In a recent, crude risk assessment, Tilson *et al.* (1990) made a number of assumptions to estimate the exposure levels:

- * PCB in milk fat and blood fat is in steady state with body fat.
- * Body weight of the mothers is 60 kg.
- * 25 % of the body weight is fat.

The body burden can then be calculated from the level in milk or blood fat.

Tilson and coworkers also assumed that:

- * The PCB intake consists of equal daily doses over the life-time.

- * No excretion occurs except for pregnancy and lactation.
- * The mother is primiparous and 25 years old.

Using the effect on visual recognition memory at 7 months of age in the Michigan study, Tilson *et al.* (1990) roughly estimated a "NOAEL" of 3 µg/l umbilical cord serum. This means about 1 mg/kg fat (0.3 % fat in the serum). With the given assumptions above, the body burden is estimated to 15 mg and the corresponding average daily exposure will be 27 ng/kg body weight (see the equation below). Using the data from a more recent follow-up on the Michigan children, a "LOAEL" of 1.5-3.0 µg/l cord serum (0.5-1.0 mg/kg fat) can be estimated for short-term memory at 4 years of age. Using the same assumptions, this leads to an estimated average daily intake of 14-27 ng/kg body weight.

$$\frac{\frac{3 \mu\text{g PCB/l serum}}{3 \text{ g lipid/l serum}} * 25 \% \text{ fat} * 60\,000 \text{ g b.w.}}{25 \text{ years} * 365 \text{ days} * 60 \text{ kg b.w.}} = 0.027 \mu\text{g/kg b.w./day} = 27 \text{ ng/kg b.w./day}$$

In these calculations several factors must be viewed as overly conservative thus giving rise to an exposure figure which is too low. Thus, Tilson *et al.* (1990) assumed complete gastro-intestinal absorption, a distribution entirely into fat, and, - most importantly - no excretion. However, taken together the combined effect of these factors is presumably well below a factor of 10.

The Michigan mothers had an average serum PCB level of 5 µg/l, which is below the 10 µg/l found in 1981 in Norwegian subjects without particular exposure. However, these concentrations cannot be compared directly, as the analytical method used for evaluation may have a large impact on concentrations recorded; however, presumably not by more than a factor of 10 (see Section 6.4.3).

The Michigan data can also be very roughly evaluated on the basis of information on PCB levels in fish from Lake Michigan. Median values in various fish species were: trout 3 mg/kg, chinook salmon 1.5 mg/kg, coho salmon 0.8 mg/kg, and other fish (pike, walleye, perch, white fish) 0.2 mg/kg (Humphrey 1988). The approximate mean fish consumption was 6.7 kg/year (18 g/day) and 4.1 kg/year (11 g/day) during pregnancy. Assuming that all the fish consumed were trout, the PCB intake will correspond to 54 µg/day, i.e. about 0.9 µg/kg b.w./day. In this context, it may be mentioned that herring and salmon from the Baltic Sea contain about 0.3 mg total PCB per kg, whilst most other species of fish from Nordic waters (including cultivated salmon and trout) contain lower levels (Table 26).

If we assume that a) the conclusions drawn from the studies in Michigan and North Carolina are valid, and b) that the analytical methods used to determine PCBs in the USA, and those used in the Nordic countries are comparable, the different approaches will give LOELs for slight neurotoxic effects in infants in the range 0.014 - 0.9 µg/kg b.w./day for the mother.

This range may be compared with the average intake of PCB from fish of 0.16 µg/kg b.w./day if all fish eaten is herring or salmon from the Baltic. In subjects with a high

intake of fish the intake may be four times higher (Table 26). Similarly, a Finnish study (Moilanen *et al.* 1986) indicated a total PCB intake of about 0.24 µg/kg and day, of which about 40% would come from fish (Table 27).

9.4 Dioxin-like PCB congeners

9.4.1 The TEF concept

Table 28 compares the relative potencies of several non- and mono-*ortho* PCB congeners with that of 2,3,7,8-TCDD, with respect to the induction of AHH *in vivo*, weight loss and thymic atrophy. We assume that these effects are Ah receptor-mediated and, thus, highly correlated (as has been shown for the PCDDs/PCDFs). The values in Table 28 also could serve as a basis for suggesting toxic equivalency factors (TEFs) when the individual congeners are compared to 2,3,7,8-TCDD. It is evident that such TEFs differ considerably from those proposed by Safe (1990), who has given more weight to *in vitro* structure-activity relationships. In the case of 3,3',4,4'-CB especially, the discrepancy between Safe's TEF (0.01) and the TEF based on the *in vivo* data (0.0005) is striking. However, more credence should be given to the *in vivo* data, since these also include at least some of the manifestations of the toxicokinetics on the response parameters. However, it should be noted that these TEFs are still based on acute toxic effects at relatively high doses.

The whole concept of TEFs assumes that the combined effects of various congeners (i.e. of both polychlorinated dioxins, dibenzofurans and biphenyls) are additive. When TEFs are used, the risk assessment made for TCDD (which at present is based on the induction of hepatic tumours in rats) can be applied.

After a Swedish initiative, WHO/EURO arranged a small meeting in connection with the DIOXIN '91 congress (North Carolina, September 1991) to discuss the feasibility of having WHO/EURO taking responsibility for the development of TEFs for dioxin-like PCB congeners. The meeting decided to recommend WHO/EURO to do so and to organize a formal meeting, preferably in November 1992. The meeting also recommended that individual nations should refrain from instituting their own TEF-schemes but rather await the outcome of this meeting.

Table 28. Relative potency and proposed TEFs for PCB congeners based on reduced body weight gain, thymic atrophy and AHH-induction in rats (from Table 9) and TEFs proposed by Safe (1990).

Category	Congener	IUPAC	Weight reduction	Thymus atrophy	AHH induction <i>in vivo</i>	TEF <i>in vivo</i>	TEF (Safe 1990)
Non-ortho *	3,3',4,4'	77	<0.0001	<0.0002	0.000008	0.0005	0.01
	3,3',4,4',5	126	0.02	0.09	0.004	0.1 [#]	0.1
	3,3',4,4',5,5'	169	0.003	0.01	0.008	0.01	0.05
Mono-ortho **	2,3,3',4,4'	105	0.00007	0.00009	0.00006	0.0001	0.001
	2,3,4,4',5	114	0.0003	0.0004	0.0001	0.0005	0.001
	2,3',4,4',5	118	0.00004	0.00006	0.00002	0.0001	0.001
	2',3,4,4',5	123	0.0001	0.00003	0.00003	0.0001	0.001
	2,3,3',4,4',5	156	0.0003	0.0005	0.0006	0.001	0.001
	2,3,3',4,4',5'	157	0.0002	0.0004	0.0007	0.001	0.001
	2,3',4,4',5,5'	167	-	-	-	-	0.001
Di-ortho ***	All		-	-	-	-	0.00002

*,**,*** also chlorinated in both *para* and at least two *meta* positions

[#] based on tumour promotion activity (Flodström and Ahlborg 1991)

9.4.2 Contribution of PCBs to total TEQ levels in human milk and fish

For certain PCB-containing samples it is suggested that the toxic potential can be expressed in 2,3,7,8-TCDD equivalents (TEQs) using the appropriate toxic equivalency factors (TEFs). At present, very few data are available on the levels of a wide range of PCB congeners in human milk and other foods from the Nordic countries.

The outcome of the applications of the TEF models described in Table 28 is illustrated in Figure 11, as applied to pooled Swedish mother's milk where the contributions to TEQs from PCDDs, PCDFs and PCBs are shown. Figure 12 demonstrates these models applied to five different samples of Swedish fish. In Figure 12A, the TEQs are expressed as ng/kg wet weight and in Figure 12B the same data are expressed as ng/kg fat weight. It should be noted that wet weight data from fish vary considerably during the year due to variations in lipid content, whereas the data on a per fat weight basis remain rather constant.

When using the *in vivo* TEFs, the three non-*ortho* congeners (3,3',4,4'-, 3,3',4,4',5- and 3,3',4,4',5,5'-CB) contribute as much as the PCDDs/PCDFs to the TEQs in the fish, whilst in human milk, the PCDDs/PCDFs contribute twice as much. However, when the most important mono-*ortho* congeners are taken into account, the total contribution of PCB-derived TEQs in human milk is higher than that of PCDDs/PCDFs. Note that the figures shown for fish are based only on the analysis of the non-*ortho* congeners, 3,3',4,4'-, 3,3',4,4',5- and 3,3',4,4',5,5'-CB, and that not all mono-*ortho* PCB congeners have been analyzed in the milk. The total amount of TEQs may, thus, be appreciably higher if all congeners are taken into account.

In a recent Canadian study, TEQs in human mother's milk were determined using TEFs for PCDD/PCDFs and Safe's TEFs for PCBs (Dewailly *et al.* 1991). PCDD/PCDFs contributed with 13.26 ng TEQ/kg milk fat, non-*ortho* PCB congeners with 9.76, whilst three mono-*ortho* PCB congeners (2,3,3',4,4'-, 2,3',4,4',5- and 2,3,3',4,4',5-CB) contributed with 28.0 ng TEQ/kg milk fat. Using the TEFs based on *in vivo* experiments (Table 28), non-*ortho* PCB congeners contribute with 8.38 and the three mono-*ortho* congeners with 15.3 ng TEQ/kg milk fat. The association between the concentrations of non-*ortho* congeners and other PCB congeners as well as total PCB were determined. 3,3',4,4'-CB correlated poorly to the other congeners, while 3,3',4,4',5-CB was well predicted by other congeners and especially by 2,3,3',4,4'- and 2,3',4,4',5-CB. 3,3',4,4',5,5'-CB was strongly associated with hexa and hepta congeners as well as with total PCB (quantified as Aroclor 1260).

Tanabe *et al.* (1989) have shown that PCDFs contributed most to the total exposure of Yusho patients to TEQs (85.4%), while PCBs accounted for 13.4%. Similarly, the EROD-inducing potency of the PCDD/PCDF fraction of Yusho oil was 87% of that of whole Yusho oil, whilst the PCB fraction only accounted for 13% (Takayama *et al.* 1991). Of the PCBs, the non-*ortho* congeners, especially 3,3',4,4',5-CB, accounted for almost all of the induction.

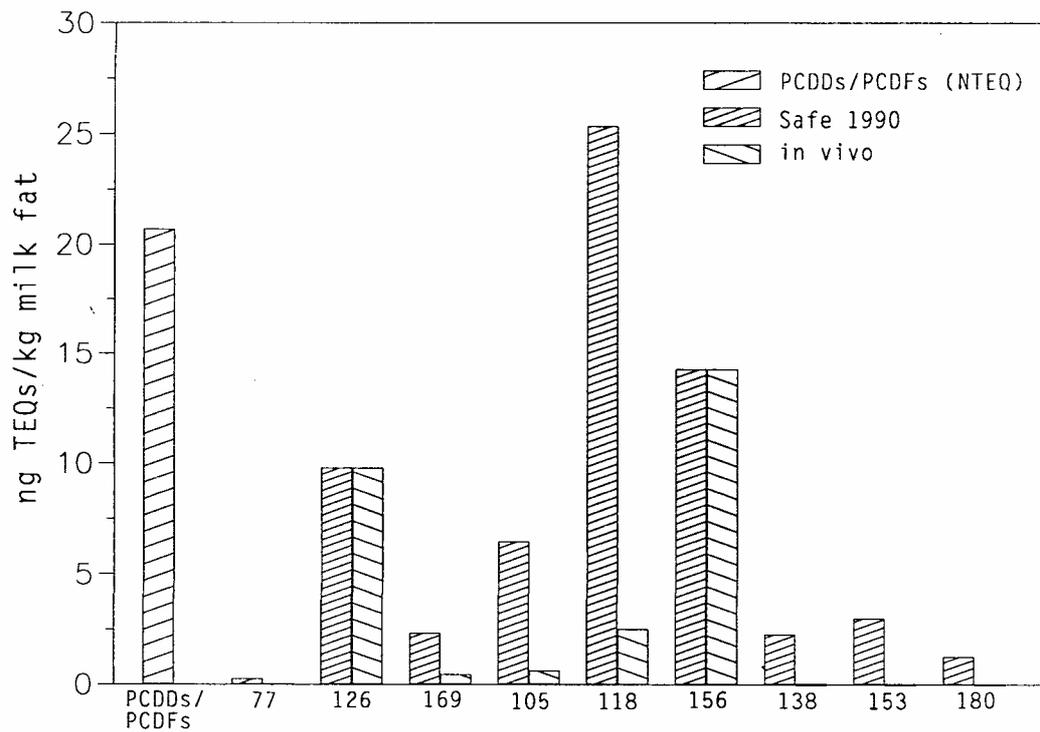


Figure 11. Toxic equivalents (ng/kg milk fat) calculated for PCDDs/PCDFs and for different dioxin-like PCB congeners in Swedish mother's milk (Norén and Lundén 1992).

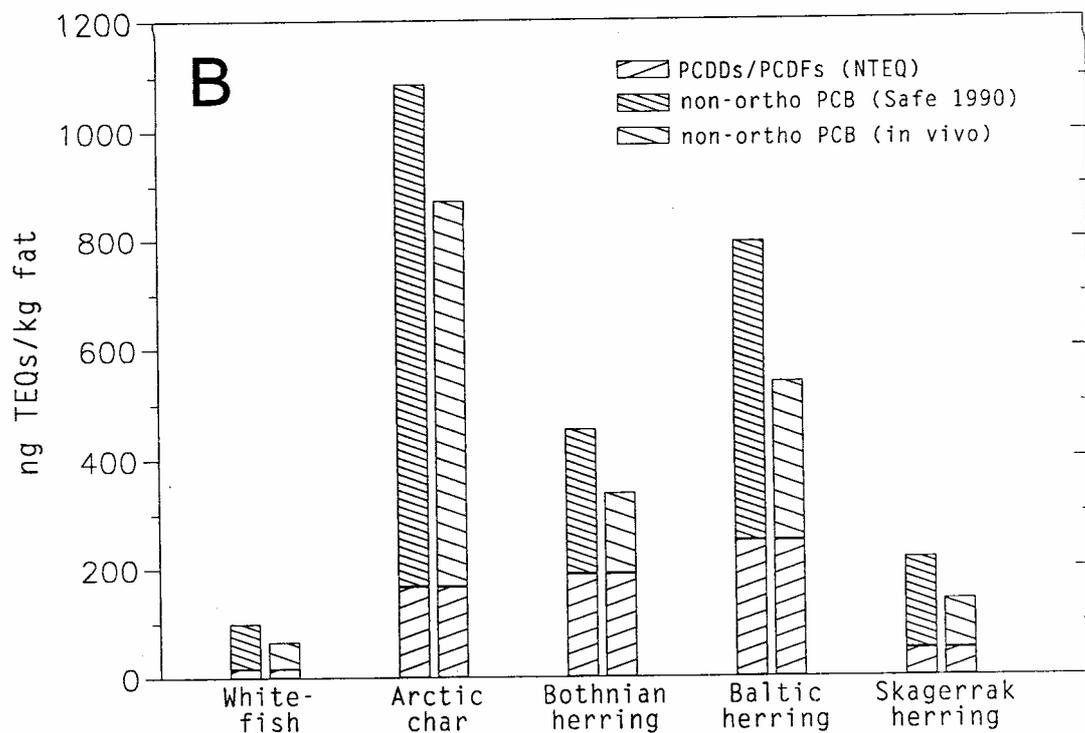
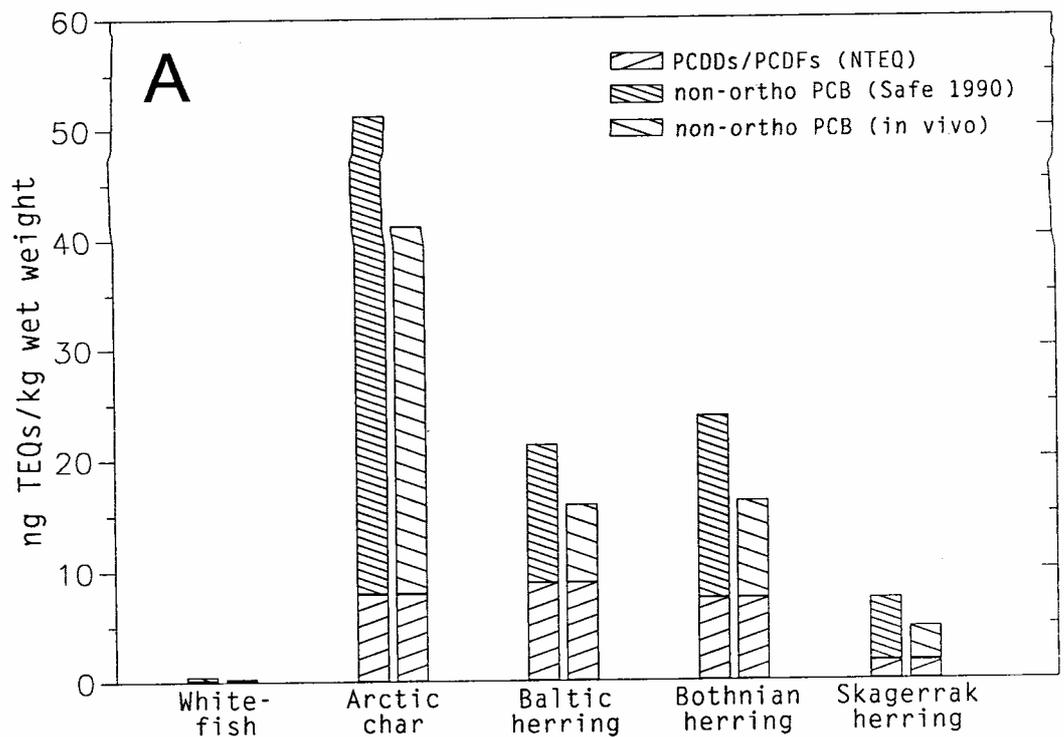


Figure 12. Toxic equivalents [ng/kg wet weight (A), ng/kg fat weight (B)] calculated for PCDDs/PCDFs and non-ortho PCB congeners in Swedish fish (Asplund *et al.* 1990, C de Wit, personal communication). Mono-ortho and di-ortho congeners have not yet been analysed.

9.5 General conclusion

The evaluation of the available data on PCBs has demonstrated that the present data-base does not allow a traditional risk assessment to be performed, i.e. it is not possible to recommend a tolerable daily intake of either total PCBs or of any individual congeners.

Furthermore, the evaluation of PCBs suggests that the present exposure of Nordic populations is of the same order of magnitude to that at which subtle health effects may occur in children exposed *in utero* and, possibly also, through breast-feeding. Further studies are necessary to clarify whether such effects actually occur and, if so, whether they are reversible and also to determine the mechanisms behind them.

In addition, certain non- and mono-*ortho*-substituted PCB congeners exhibit dioxin-like toxicity. When their concentrations are taken into account, the joint risk from the PCB congeners in human milk and certain other foods appears to be more important than that due to the polychlorinated dioxins and dibenzofurans (PCDDs/PCDFs) in the same food items. When the integrated toxicity of these dioxin-like pollutants is considered, the consumption of certain fish species from contaminated areas may lead to an intake which exceeds the tolerable daily intake (TDI) of 5 pg TCDD equivalents/kg b.w. (TWI 35 pg/kg b.w. and week) previously recommended by a Nordic Expert Group. However, it should be recognized that such a TDI has been considered non-applicable when dealing with the intake of PCBs by human infants from mother's milk during a limited period (WHO/EURO 1988).

Taking into account the many well-known benefits of breast-feeding for developing infants, the expert group recommend that breast-feeding should be continued and promoted in spite of the occurrence of PCBs and other chlorinated compounds in mother's milk. However, the magnitude of the safety margin cannot be determined at present, and the information available does not exclude the possibility that no safety margin may be present. The expert group recognizes the seriousness of this situation and it is thus important to further explore and implement all possible measures to prevent continued PCB contamination of the environment.

10 RECOMMENDATIONS FOR FURTHER RESEARCH

The neurobehavioural effects of the PCBs appear to be critical in the risk assessment of these environmental contaminants. However, there are a number of uncertainties in the data-base on the PCBs related to the mechanisms of action, relative congener potency, the dose-response relationships, inter-species effect relationships and the human exposure levels, as well as the validity of extrapolation from the two epidemiological studies. There is thus an urgent need to clarify these issues.

Certain immunotoxic effects are also seen at low doses of PCB-exposure. It is as yet uncertain whether these data indicate a functional impairment of the immune system which is of importance to human health. Thus, further studies are also necessary here in order to get a clearer picture of the situation.

The total lack of dose-response data in the carcinogenicity studies of the PCBs is remarkable. Such data are crucial for a meaningful extrapolation to the human situation.

The following types of activities should give important information which will aid in the risk assessment of PCBs.

10.1 Exposure studies

- * Congener-specific PCB levels in maternal serum, cord blood and breast milk in subjects with high intakes of fatty fish from the Baltic Sea or other polluted waters should be assayed.
- * Serum and adipose congener-specific PCB tissue levels in other subjects with high intakes of fatty fish from the Baltic Sea or other polluted waters should also be quantified.
- * Comparative studies of samples from other high-risk populations in the Nordic countries should be performed.
- * Interlaboratory quality control of the laboratories participating in PCB analysis is essential.
- * Reanalysis or recalculation should be performed, if possible, of fish and blood serum samples from the Michigan neurobehavioural study to obtain a better comparison with the current Nordic exposure situation.
- * The relationships between PCB intake and blood/fat levels in humans should be clarified.
- * There should be further studies on the dietary intake of PCBs.

- * Attempts to identify other possible important PCB exposure situations in addition to those via food should be made.
- * As complete as possible congener-specific analysis of a selected number of biological matrices to determine PCB-congener patterns should be performed. The following sample types should be given high priority: human serum and breast milk and major fish species.
- * There is a need for the development of criteria for the selection of which PCB congeners should be analyzed in biological samples. Based on current knowledge of toxicological potency and environmental persistence one scheme for the analysis of the following non-, mono- and di-*ortho*-PCBs is shown in Table 29. The congeners are shown in priority order for each group.

Table 29. The PCB congeners recommended to be analyzed in biological samples (shown in priority order for each group).

Non- <i>ortho</i> congeners [#]		Mono- <i>ortho</i> congeners [#]	
IUPAC	Chlorination	IUPAC	Chlorination
126	3,3',4,4',5	105	2,3,3',4,4'
169	3,3',4,4',5,5'	118	2,3',4,4',5
77	3,3',4,4'	156	2,3,3',4,4',5
		114	2,3,4,4',5
		157	2,3,3',4,4',5'
		167	2,3',4,4',5,5'
Di- <i>ortho</i> congeners [#]		Other congeners	
IUPAC	Chlorination	IUPAC	Chlorination
138	2,2',3,4,4',5'	28	2,4,4'
153	2,2',4,4',5,5'	47	2,2',4,4'
170	2,2',3,3',4,4',5	52	2,2',5,5'
180	2,2',3,4,4',5,5'	122	2'3,3',4,5
		101	2,2',4,5,5'

[#] also chlorinated in both *para* and at least two *meta* positions

10.2 Toxicological studies

- * Congener-specific, dose-response for neurobehavioural effects with special reference to *in utero* exposure should be studied.
- * Mechanisms for the neurobehavioural effects of PCBs should be clarified to more clearly define structure-activity relationships.

- * Congener-specific, dose-response immune function tests should be performed.
- * Effects on neurobehavioural tests and immune functions induced by fish oil PCB extracts and similar mixtures of pure congeners should be compared.
- * The dose-response relationships for PCB-induced carcinogenicity should be studied.
- * Congener-specific toxicokinetics should be studied in both animals and humans, especially during exposures *in utero* and during lactation.
- * An internationally-accepted toxic equivalency factor (TEF) model for the dioxin-like PCB congeners should be developed.
- * Possible interactive effects between PCB congeners should be studied.

10.3 Epidemiological studies

- * The pregnancy outcome and the neurobehavioural development in infants of mothers with a high intake of contaminated fatty fish should be studied.
- * Immunological effects should be studied in subjects with a high intake of contaminated fatty fish.
- * Cancer morbidity should be studied in subjects with varying intakes of fish from polluted waters.

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APPENDIX

Tables

Table I: Induction of point mutations in *Salmonella typhimurium* (Ames test).

TEST SUBSTANCE	STRAIN	METABOLIC ACTIVATION	RESULT	REFERENCE
Aroclor 1221	TA 1538	+	weak +(b)	Wyndham <i>et al.</i> 1976
Aroclor 1254	TA 98	-/+	-	Bruce and Heddle 1979
	TA 100	-/+	-	Heddle and Bruce 1977
	TA 1535	-/+	-	Schoeny <i>et al.</i> 1979
	TA 1537	-/+	-	
	TA 1538	-/+	-	Shahin <i>et al.</i> 1979
Aroclor 1268	TA 1538	+	-	Shahin <i>et al.</i> 1979
		+	-	Wyndham <i>et al.</i> 1976
Kanechlor 300	TA 98	-/+	-	Sugimura <i>et al.</i> 1976
	TA 100	-/+	-	
	TA 1535	NR	-	Odashima 1976
	TA 1536	NR	-	
	TA 1537	NR	-	
	TA 1538	NR	-	
Kanechlor 500	TA 98	-/+	-	Sugimura <i>et al.</i> 1976
	TA 100	-/+	-	
	TA 1535	NR	-	Odashima 1976
	TA 1536	NR	-	
	TA 1537	NR	-	
	TA 1538	NR	-	
4-CB	TA 98	-/+	-	Schoeny 1982
	TA 100	-/+	-	
	TA 1535	-/+	-	
	TA 1537	-/+	-	
	TA 1538	+	+(b)	Wyndham <i>et al.</i> 1976
2,2',4,4'-CB	TA 98	-/+	-	Schoeny 1982
	TA 100	-/+	-	
2,2',5,5'-CB	TA 1538	-/+	-	Wyndham <i>et al.</i> 1976
2,2',5,5'-CB and its metabolites (a)	TA 98	-/+	-	Hsia <i>et al.</i> 1978
	TA 100	-/+	-	
	TA 1535	-/+	-	
	TA 1537	-/+	-	
3,3',4,4'-CB	TA 98	-/+	-	Schoeny 1982
	TA 100	-/+	-	
2,2',4,4',6,6'-CB	TA 98	-/+	-	Schoeny 1982
	TA 100	-/+	-	
Biodegradation products of PCBs (c)	TA 98	-/+	-	Sayler <i>et al.</i> 1982
	TA 100	-/+	-	
	TA 1535	-/+	-	
	TA 1537	-/+	-	

(a) 4-hydroxy-2,2',5,5'-CB; 3,4-oxo-2,2',5,5'-CB

(b) negative results were obtained in repeated experiments

(c) *p*-chlorophenylglyoxylic acid; *p*-chloromandelic acid; three monochlorinated benzoic acids

NR not reported

Table II. Induction of cytogenetic damage by PCBs.

TEST SUBSTANCE	CONCENTRATION	EFFECT	TEST SYSTEM	REFERENCE
Aroclor 1242	1250, 2500 and 5000 mg/kg	-	chromosomal aberrations in bone marrow and spermatogonial cells of rat	Green <i>et al.</i> 1975a Green <i>et al.</i> 1973
Aroclor 1242	up to 2500 mg/kg	-	induction of dominant lethality in rat	Green <i>et al.</i> 1975b
Aroclor 1254	50, 100 and 300 mg/kg	+	chromosomal aberrations in fish	Al-Sabti 1985, 1986
Aroclor 1254	75, 150 and 300 mg/kg	-	chromosomal aberrations in bone marrow and spermatogonial cells of rat	Green <i>et al.</i> 1975a
Aroclor 1254	100 µg/ml	-	chromosomal aberrations in human lymphocytes <i>in vitro</i>	Hoopingarner <i>et al.</i> 1972
Aroclor 1254	up to 15000 mg/kg for micronuclei and 5000 mg/kg for sperm abnormalities	-	formation of micronuclei and sperm abnormalities in mouse	Heddle and Bruce 1977 Bruce and Heddle 1979
Aroclor 1254	50 mg/kg	-	chromosomal damage and rate of spermatogenesis in rat testis	Dikshith <i>et al.</i> 1975
Aroclor 1254	0.011, 0.11 and 1.1 µg/ml	+	chromosomal aberrations in human lymphocytes <i>in vitro</i>	Sargent <i>et al.</i> 1989
Aroclor 1254	up to 300 mg/kg	-	induction of dominant lethality in rat	Green <i>et al.</i> 1975b
Aroclor 1254	5, 50 and 500 mg/kg in diet	-	chromosomal aberrations in bone marrow and spermatogonial cells of rat	Garthoff <i>et al.</i> 1977
Clophen A30 Clophen A50	250 mg/l in diet	- -	chromosomal breakage or nondisjunction in <i>Drosophila melanogaster</i>	Nilsson and Ramel 1974
Kanechlor 300	NR	+(a) -	chromosomal aberrations in mammalian cells <i>in vitro</i> chromosomal aberrations in mouse bone marrow cells <i>in vivo</i>	Odashima 1976
Kanechlor 500	NR	- +(a)	chromosomal aberrations in mammalian cells <i>in vitro</i> chromosomal aberrations in mouse bone marrow cells <i>in vivo</i>	Odashima 1976
Kanechlor 500	100 mg/kg	-	micronuclei in polychromatic erythrocytes	Watanabe <i>et al.</i> 1982
2,2',5,5'-CB	1 µg/ml	-	chromosomal aberrations in human lymphocytes <i>in vitro</i>	Sargent <i>et al.</i> 1989
2,2',5,5'-CB	1 µg/ml	-	sister chromatid exchanges in human lymphocytes	Sargent <i>et al.</i> 1989
3,3',4,4'-CB	10 ⁻⁴ -10 ⁻¹ µg/ml	+	chromosomal aberrations in human lymphocytes <i>in vitro</i>	Sargent <i>et al.</i> 1989
3,3',4,4'-CB	10 ⁻⁵ -10 ⁻¹ µg/ml	-	sister chromatid exchanges in human lymphocytes	Sargent <i>et al.</i> 1989
2,2',4,4',5,5'-CB	1 µg/ml	+	chromosomal aberrations in human lymphocytes <i>in vitro</i>	Sargent <i>et al.</i> 1989
mixture of: 2,2',5,5'-CB and 3,3',4,4'-CB	up to 1 µg/ml	+(b)	chromosomal aberrations in human lymphocytes <i>in vitro</i>	Sargent <i>et al.</i> 1989
mixture of: 3,3',4,4'-CB and 2,2',4,4',5,5'-CB	10 ⁻⁵ µg/ml 3,3',4,4'-CB; 0.1 µg/ml 2,2',4,4',5,5'-CB	+(b)	chromosomal aberrations in human lymphocytes <i>in vitro</i>	Sargent <i>et al.</i> 1989
degradation product of PCBs: <i>p</i> -chlorophenyl-glyoxylic acid	25, 50, 100 and 200 µg/ml	-	sister chromatid exchanges in rabbit lymphocytes	Sayler <i>et al.</i> 1982

(a) no data was presented

(b) the PCB congeners were negative when tested separately

NR not reported

Table III. Induction of DNA damage by PCBs.

TEST SUBSTANCE	CONCENTRATION	EFFECT	TEST SYSTEM	REFERENCE
Aroclor 1254	500 mg/kg	+	reduced rate of sedimentation of DNA in liver primary cell cultures	Mendoza-Figueroa 1985
Aroclor 1254	300 mg/kg	-	DNA repair in rat hepatocytes	Kornbrust and Dietz 1985
Aroclor 1254	0.2 - 330 µg/ml	-	"-	Probst <i>et al.</i> 1981
Aroclor 1254	10 - 1000 µg/ml	+	single-stranded DNA breaks in rat hepatocytes	Sina <i>et al.</i> 1983
4-CB	10 µM	+	covalent binding to DNA <i>in vivo</i> ; DNA-repair in hamster cells (CHO)	Wong <i>et al.</i> 1979
4-CB	3 mM	+	binding to exogenous DNA after incubation with induced microsomal enzym fractions	Wyndham and Safe 1978
2,2',5,5'-CB and its metabolites (a)	1, 10, 20 and 100 µg/ml	+	single-stranded DNA breaks in L-929 cells <i>in vitro</i>	Stadnicki <i>et al.</i> 1979
2,2',3,3',6,6'-CB	7.28 mg/kg in diet	+	<i>in vivo</i> -binding to mouse liver DNA, RNA and proteins	Morales and Matthews 1979
2,2',4,4',5,5'-CB	"-	-	<i>in vivo</i> -binding to mouse liver DNA	Morales and Matthews 1979
2,2',4,4',5,5'-CB	NR	+	<i>in vitro</i> -binding to calf DNA and to rat liver microsomal proteins	Narbonne and Daubeze 1980

(a) 2,2',5,5'-tetrachlorbiphenyl-3,4-epoxide; a mixture of 3-hydroxy- and 4-hydroxy-2,2',5,5'-tetrachlorbiphenyl

NR not reported

Table IV. Induction of cancer in rat and mouse after oral exposure to PCBs.

TEST SUBSTANCE	CONCENTRATION IN DIET (PPM)	DURATION	SEX	SPECIES	EFFECT	FREQUENCY	REFERENCE
Aroclor 1254	300	11 months	males	BALB/cJ mice	hepatoma	controls: 0/58 300 ppm: 9/22	Kimbrough and Linder 1974
Aroclor 1254	25, 50, 100	105 weeks	males females	Fisher 344 rats	adenocarcinoma in stomach (males + females) hepatic tumours	controls: 0/47 25 ppm: 1/48 50 ppm: 3/48 100 ppm: 2/48 males: controls: 0/24 25 ppm: 0/24 50 ppm: 1/24 100 ppm: 3/24 females: 0/24 0/24 1/24 2/24	Morgan <i>et al.</i> 1981 Silberhorn <i>et al.</i> 1990 NCI 1978
Aroclor 1260	100	21 months	females	Sherman rats	hepatocellular carcinoma	controls: 1/173 100 ppm: 26/184	Kimbrough <i>et al.</i> 1975
Aroclor 1260	100 + 50	16 months + 8 months	males females	Sprague-Dawley rats	trabecular carcinoma adenocarcinoma -"	controls: 0/32 100+50 ppm: 2/46 controls: 0/49 100+50 ppm: 43/47	Norback and Weltman 1985
Aroclor 1260	50, 100	120 days	males	Wistar rats	adenofibrosis	controls: 50 ppm: 24/32 100 ppm: 16/32	Rao and Banerji 1988
Clophen A 30	100	up to 800 days	males	Wistar rats	hepatocellular carcinoma	controls: 1/53 100 ppm: 3/87	Schaeffer <i>et al.</i> 1984
Clophen A 60	100	up to 800 days	males	Wistar rats	hepatocellular carcinoma	controls: 1/53 100 ppm: 52/85	Schaeffer <i>et al.</i> 1984
Clophen A 60	10 - 200	32 weeks	males	C3H mice	tumours		Andersen <i>et al.</i> 1985
Kanechlor 300	100, 250, 500	32 weeks	males	dd mice	-		Ito <i>et al.</i> 1973 Nagasaki <i>et al.</i> 1972
Kanechlor 300	100, 500, 1000	52 weeks	males	Wistar rats	cholangiofibrosis	controls: 0/18 1000 ppm: 2/15	Ito <i>et al.</i> 1974

TEST SUBSTANCE	CONCENTRATION IN DIET (PPM)	DURATION	SEX	SPECIES	EFFECT	FREQUENCY	REFERENCE
Kanechlor 400	100, 250, 500	32 weeks	males	dd mice	-		Ito <i>et al.</i> 1973 Nagasaki <i>et al.</i> 1972
Kanechlor 400	38.5 - 616	159 - 560 days 255 - 538 days	females males	Donryu rats	multiple adenomateous nodules	controls: 0/6 females (>1200 mg/400 days): 6/6	Kimura and Baba 1973
Kanechlor 400 Kanechlor 500	100, 500, 1000	28 - 40 weeks 49 - 52 weeks	males	Wistar rats	cholangiofibrosis (chol) nodular hyperplasia (nod)	controls: 0/18 1000 ppm: chol: 2/10 nod: 3/10 1000 ppm: chol: 4/13 nod: 5/13	Ito <i>et al.</i> 1974
Kanechlor 500	100, 250, 500	32 weeks	males	dd mice	hepatocellular carcinoma	controls: 0/6 500 ppm: 5/12	Ito <i>et al.</i> 1973 Nagasaki <i>et al.</i> 1972
2,2',3,3',6,6'-CB	100	up to 29 months	males females	Sprague-Dawley rats	-		Weltman and Norback 1983
2,2',5,5'-CB	3,5 or 7 µmol i.p.	28 weeks	males females	A/J mice	-		Preston <i>et al.</i> 1985

Table V. Initiation of preneoplastic alterations by PCBs in rat liver.

TEST SUBSTANCE	INITIATOR-TREATMENT	PROMOTER-TREATMENT	MARKER FOR CELL ALTERATION	RESULTS	REFERENCE
Aroclor 1254	neonates: 1 or 3 oral doses of 500 mg PCBs/kg; adults: partial hepatectomy/single dose of 500 mg PCBs/kg	resistant hepatocytes, neonates: AAF/partial hepatectomy; adults: AAF/CCl ₄	GGT+	-	Hayes <i>et al.</i> 1985
reconstituted human breast milk mixture of PCB congeners	neonates: 3 oral doses of 134 mg PCBs/kg weekly for 3 weeks adults: partial hepatectomy/single dose of 134 mg/kg PCBs	resistant hepatocytes, neonates: AAF/partial hepatectomy; adults: AAF/CCl ₄	GGT+	-	Hayes <i>et al.</i> 1985
2,2',4,4'-CB	3 oral doses of 400 µmol PCB/kg/week for 3 weeks	resistant hepatocytes, neonates: AAF/partial hepatectomy	GGT+	-	Hayes <i>et al.</i> 1985
2,2',5,5'-CB	3 oral doses of 400 µmol PCB/kg/week for 3 weeks	resistant hepatocytes, neonates: AAF/partial hepatectomy	GGT+	-	Hayes <i>et al.</i> 1985
2,2',4,4',5,5'-CB	3 oral doses of 400 µmol PCB/kg/week for 3 weeks	resistant hepatocytes, neonates: AAF/partial hepatectomy	GGT+	-	Hayes <i>et al.</i> 1985

AAF - 2-acetylaminofluorene
 ATP - adenosine-triphosphatase
 BP - benzo[*a*]pyrene
 DENA - diethylnitrosamine
 G6P - glucose-6-phosphatase
 GGT - γ -glutamyl transpeptidase
 NNM - N-nitrosomorpholine

Table VI. Tumour promoting effects of PCBs.

TEST SUBSTANCE	SPECIES/TISSUE	EXPOSURE	INITIATOR	EFFECT	RESULTS	REFERENCE
Aroclor 1254	Sprague-Dawley rat/liver	100 ppm in diet during 18 weeks	DENA	liver carcinoma	64% liver carcinomas 16% in DENA-controls	Preston <i>et al.</i> 1981
Aroclor 1254 after elimination of PCDF contamination	-"	-"	-"	-"	84% liver carcinomas	
Aroclor 1254	infant Swiss mice/liver infant Swiss mice/lung	single doses of 50, 250 or 500 mg/kg by gastric intubation	DMNA	liver adenoma, liver carcinoma, alveolar adenoma	complex results two times increase of number of tumours over DMNA-controls	Anderson <i>et al.</i> 1986
Aroclor 1254	HRS/J hairless mice/skin	1 mg/mouse twice weekly during 20 weeks	MNNG	skin papilloma	non-significant increase of tumour incidence	Poland <i>et al.</i> 1982
Aroclor 1254	CD-1 mice/skin	100 µg applied twice weekly topically during 30 weeks	DMBA	skin papilloma	no promotive activity of PCBs	Berry <i>et al.</i> 1978
Kanechlor 400	Donryu rats/liver	400 ppm in diet during 6 months	MDAB	liver carcinoma	64% liver carcinoma 13% in MDAB controls 0% when PCBs was administrated prior to initiator	Kimura <i>et al.</i> 1976
Kanechlor 500	dd mice/liver	250 ppm in diet during 24 weeks coadministrated with initiator	α-BHC β-BHC γ-BHC	hyperplastic nodules, liver carcinoma	promotiv effect after α- and β- but not γ-BHC	Ito <i>et al.</i> 1973
Kanechlor 500	Wistar rats/liver	0.2ml 5% (v/v) twice weekly by gastric intubation during 4 weeks	DENA	tumours (including some liver carcinomas)	higher number of tumours and earlier appearance after treatment	Nishizumi 1976
Kanechlor 500	F344 rats/liver	500 or 1000 ppm in diet during 8 weeks	AAF	neoplastic nodules	increased number and area, increased frequency after partial hepatectomy	Tatematsu <i>et al.</i> 1979
non-specified PCBs	Fisher rats/liver	1000 ppm in diet during 8 weeks	AAF	neoplastic nodules	increased number, more pronounced after partial hepatectomy	Ito <i>et al.</i> 1978
non-specified PCBs	F344 rats/liver	0.05% in diet during 32 weeks	EHEN	neoplastic nodules, liver carcinoma	promotive effect of PCBs	Hirose <i>et al.</i> 1981
-"	kidney	-"	-"	neoplastic nodules, kidney tumour	no promotive effect	Hirose <i>et al.</i> 1981

AAF - 2-acetylaminofluorene, BHC - benzene hexachloride, DENA - diethylnitrosamine, DMNA - dimethylnitrosamine, EHEN - N-ethyl-N-hydroxyethylnitrosamine, MDAB - 3'-methyl-4-dimethylaminoazobenzene, MNNG - N-methyl-N'-nitrosoguanidine

Table VII. Promotion of preneoplastic alterations in rat liver by PCBs.

TEST SUBSTANCE	INITIATOR-TREATMENT	PROMOTER-TREATMENT	MARKER FOR CELL ALTERATION	RESULTS	REFERENCE
Aroclor 1254	Partial hepatectomy/DENA	1, 2 or 3 intraperitoneal injections of 500 mg PCBs/kg	GGT+	+	Pereira <i>et al.</i> 1982
Aroclor 1254	single dose of DENA	resistant hepatocytes: single dose of PCBs (16 mg/kg), 7 days later AAF and partial hepatectomy	GGT+	-(k)	Hayes <i>et al.</i> 1986
Clophen A 30 Clophen A 50	DENA for 12 days -"-	0.2 or 0.4 nM PCBs/kg/week for 7 weeks -"-	NR NR	+ +	Oesterle and Deml 1981
Clophen A 50	DENA for 12 days	50 or 100 mg of PCBs/kg/week for 7 weeks	ATP- GGT+	+(d)	Deml and Osterle 1982
Clophen A 50	Weanlings: single dose of DENA or NNM; adults: DENA for 12 days	100 mg of PCBs/kg once weekly for 1 up to 7 weeks	ATP- GGT+	+(e)	Oesterle and Deml 1983
Clophen A 50	Weanlings: single dose of DENA adults: DENA for 12 days	2 - 100 mg of PCBs/kg once weekly for 7 weeks	ATP- GGT+ glycogen+	+(f)	Oesterle and Deml 1984
Clophen A 50	single dose of DENA to female weanlings	0.1, 0.5, 1.0, 5 and 10 mg of PCBs/kg 3 times weekly for 11 weeks	ATP- GGT+ glycogen+	+(g)	Deml and Oesterle 1987
Clophen A 50	single dose of BP (200 mg/kg) and/or PCBs (500 mg/kg)	50 mg of PCBs/kg once weekly for 10 weeks	ATP- GGT+	+	Deml <i>et al.</i> 1983
4-CB	DENA (10 mg/kg/d) orally for 10 days	150 µmol PCB/kg i.p. once weekly for 8 weeks	ATP- GGT+	-	Buchmann <i>et al.</i> 1991
4,4'-CB	DENA for 12 days	0.2 or 0.4 nM PCB/kg/week for 7 weeks	NR	-	Oesterle and Deml 1981
4,4'-CB	single dose of DENA to female weanlings	64 mg of PCB/kg once weekly for 7 weeks	ATP-	+/(h)	Deml <i>et al.</i> 1985
2,2',4,4'-CB	DENA for 12 days	0.2 or 0.4 nM PCB/kg/week for 7 weeks	NR	+(i)	Oesterle and Deml 1981
2,2',4,4'-CB	partial hepatectomy/DENA	100 ppm PCB in diet for 27 weeks	GGT+	+	Preston <i>et al.</i> 1985
2,2',4,4'-CB	single dose of DENA	resistant hepatocytes: single dose of PCBs (50 µmol/kg), 7 days later AAF and partial hepatectomy	GGT+	-(k)	Hayes <i>et al.</i> 1986
2,2',4,5'-CB	DENA (10 mg/kg/d) orally for 10 days	150 µmol PCB/kg i.p. once weekly for 8 weeks	ATP- GGT+	+	Buchmann <i>et al.</i> 1991

TEST SUBSTANCE	INITIATOR-TREATMENT	PROMOTER-TREATMENT	MARKER FOR CELL ALTERATION	RESULTS	REFERENCE
,2',4,5'-CB	newborn rats: 5 mg of PCBs/kg/day for 3 weeks or single dose of DENA	50 mg of PCB/kg/week during 8 weeks (only after DENA initiation)	ATP-	+	Rose <i>et al.</i> 1985
2,2',5,5'-CB	DENA for 12 days	0.2 or 0.4 nM PCB/kg/week for 7 weeks	NR	+(i)	Oesterle and Deml 1981
2,2',5,5'-CB	partial hepatectomy/DENA	100 ppm PCB in diet for 27 weeks	GGT+	+	Preston <i>et al.</i> 1985
2,2',5,5'-CB	single dose of DENA to female weanlings	64 mg of PCB/kg once weekly for 7 weeks	ATP-	+/(h)	Deml <i>et al.</i> 1985
2,2',5,5'-CB	single dose of DENA	resistant hepatocytes: single dose of PCBs (50 µmol/kg), 7 days later AAF and partial hepatectomy	GGT+	-(k)	Hayes <i>et al.</i> 1986
2,2',5,5'-CB	partial hepatectomy/single dose of DENA	100 ppm of PCB in diet for 12 months	GGT+ ATP- PGST+ cyt P450 b/e+ cyt P450 c/d+ G6Pase-	+	Sargent <i>et al.</i> 1991
3,3',4,4'-CB	DENA (10 mg/kg/d) orally for 10 days	15 or 150 µmol PCB/kg i.p. once weekly for 8 weeks	ATP- GGT+	+	Buchmann <i>et al.</i> 1991
3,3',4,4'-CB	DENA in drinking water for 10 days	intraperitoneal injections (150 µmol/kg) of PCB once weekly for 8 weeks	ATP-	+	Buchmann <i>et al.</i> 1986
3,3',4,4'-CB	single dose of DENA	resistant hepatocytes: single dose of PCBs (50 µmol/kg), 7 days later AAF and partial hepatectomy	GGT+	-(k)	Hayes <i>et al.</i> 1986
3,3',4,4'-CB	NNM in drinking water for 4 weeks	a single intraperitoneal injection of PCB (200 mg/kg) after 7 weeks	ATP- GGT+	+	Wölfle <i>et al.</i> 1988
3,3',4,4'-CB	DENA for 12 days	0.2 or 0.4 nM PCB/kg/week for 7 weeks	NR	+	Oesterle and Deml 1981
3,3',4,4'-CB	NNM in drinking water for 7 weeks	5 intraperitoneal injections of PCB (50mg/kg/injection) after 22 weeks	G6P- G6P+	+/(j)	Kobusch <i>et al.</i> 1989
3,3',4,4'-CB	partial hepatectomy/single dose of DENA	0.1 ppm of PCB in diet for 12 months	GGT+ ATP- PGST+ cyt P450 b/e+ cyt P450 c/d+ G6Pase-	-	Sargent <i>et al.</i> 1991

TEST SUBSTANCE	INITIATOR-TREATMENT	PROMOTER-TREATMENT	MARKER FOR CELL ALTERATION	RESULTS	REFERENCE
2,3,3',4,4'-CB	partial hepatectomy/single dose of DENA	0.5, 1.5 or 5 mg of PCB/kg/week for 20 weeks (s.c. injections)	PGST+	+	Flodström and Ahlberg 1991
2,3,4,4',5-CB	ENA (10 mg/kg/d) orally for 10 days	75-150 µmol PCB/kg i.p. once weekly for 4 weeks	ATP- GGT+	+	Buchmann <i>et al.</i> 1991
3,3',4,4',5-CB	partial hepatectomy/single dose of DENA	10 or 100 µg of PCB/kg/week for 20 weeks (s.c. injections)	PGST+	+	Flodström and Ahlberg 1991
2,2',5,5'-CB + 3,3',4,4'-CB	partial hepatectomy/single dose of DENA	10 ppm 2,2',5,5'-CB + 0.1 ppm 3,3',4,4'-CB in diet for 12 months	GGT+ ATP- PGST+ cyt P450 b/e+ cyt P450 c/d+ G6Pase-	+	Sargent <i>et al.</i> 1991
2,2',4,4',5,5'-CB	newborn rats: PCB (5mg/kg/day) for 3 weeks or a single dose of DENA	50 mg of PCB/kg/week for 8 weeks (only after DENA initiation)	ATP-	+	Rose <i>et al.</i> 1985
2,2',4,4',5,5'-CB	single dose of DENA	resistant hepatocytes: single dose of PCBs (50 µmol /kg), 7 days later AAF and partial hepatectomy	GGT+	-(k)	Hayes <i>et al.</i> 1986
2,2',4,4',5,5'-CB	DENA in drinking water for 10 days	intraperitoneal injections (150 µmol/kg) of PCB once weekly for 8 weeks	ATP-	+	Buchmann <i>et al.</i> 1986

(d) stronger response in females than in males

(e) promotion was observed in both age groups

(f) dose-dependent promotion was observed in both age groups

(g) promotion was observed only with doses >1.0 mg/kg

(h) was reported as a weak promoter. No data were presented

(i) was reported as a weak promotive effect. No data were presented

(j) lower number of foci, but larger size

(k) reduced size of foci

ATP

- adenosin-triphosphatase

AAF

- 2-acetylaminofluorene

BP

- benzo[a]pyrene

DENA

- diethylnitrosamine

G6P

- glucose-6-phosphatase

GGT

- γ-glutamyl transpeptidase

NNM

- N-nitrosomorpholine

NR

- not reported

PGST

- placental glutathion S-transferase

Table VIII. Inhibition of intercellular communication by PCBs.

TEST SUBSTANCE	DOSE ($\mu\text{g/ml}$)	CELL LINE	EFFECT	REFERENCE
Aroclor 1254	0.1, 0.5, 1.0 and 5.0	B ₆ C ₃ F ₁ primary mouse hepatocytes	+ (transfer of ³ H-uridine between cells)	Ruch <i>et al.</i> 1987
2,2',5,5'-CB	10 - 35	human liver cells	-/+ (dye transfer)	Swierenga <i>et al.</i> 1990
	10 - 25	human skin cells	+	
3,3',4,4'-CB	3 - 20	human liver cells	- (dye transfer)	Swierenga <i>et al.</i> 1990
	3 - 30	human skin cells	-	
2,3,4,4',5-CB	5 - 50	human liver cells	+ (dye transfer)	Swierenga <i>et al.</i> 1990
	5 - 25	human skin cells	-/+	
2,2',4,4',5,5'-CB	<1.0 - >8.0	chinese hamster V79 cells	+ (metabolic cooperation)	Tsushimoto <i>et al.</i> 1983
2,2',4,4',5,5'-CB	5 - 25	human liver cells	+ (dye transfer)	Swierenga <i>et al.</i> 1990
	5 - 25	human skin cells	+	
3,3',4,4',5,5'-CB	0.25 - 2.0	chinese hamster V79 cells	- (metabolic cooperation)	Tsushimoto <i>et al.</i> 1983

Tabel IX. PCB congeners tested in the scrape loading/dye transfer assay using F-344 WB rat liver cells (Hemming *et al.* 1991).

TESTSUBSTANCE	DOSE(μ M)	EFFECT
2	25-100	+
4,4'	0-100	-
2,4'	25-50	+
2,2'	12.5-50	+
2,6	12.5-50	+
2,3',5	6.25-25	+
2,4,4'	30-50	+
3,3',4,4'	0-50	-
2,3,4,5	12.5-50	+
2,3',4,4'	12.5-50	+
2,3'4',5	12.5-50	+
2,2',4,5'	6.25-50	+
2,2',5,5'	6.25-50	+
2,2',6,6'	6.25-50	+
3,3',4,4',5	0-50	-
2,3,3',4,4'	6.25-25	+
2,3',4,4',5	25-100	+
2,2',3,3',4	6.25-25	+
2,2',4,4',5	12.5-50	+
2,2',4,5,5'	12.5-50	+
2,2',3,5',6	3.12-12.5	+
3,3',4,4',5,5'	0-50	-
2,3,3',4,4',5	12.5-100	+
2,3',4,4',5,5'	25-100	+
2,2',3,4,5,5'	12.5-50	+
2,2',3,3',4,4'	12.5-50	+
2,2',3,4,4',5'	12.5-50	+
2,2',4,4',5,5'	12.5-50	+
2,2',3,3',4',6	6.25-25	+
2,2',3,3',6,6'	3.12-25	+
2,2',4,4',6,6'	12.5-50	+
2,3,3',4,4',5,5'	0-50	-
2,2',3,3',4,4',5	6.25-50	+
2,2',3,3',5,6,6'	6.25-25	+

Table X. Cancer epidemiology.

POPULATION	NUMBER/SEX	EXPOSURE DATA	RESULTS	REFERENCE
Employees of a petrochemical plant where PCBs were used	72, 31 with high exposure (sex not reported)	no	3 cases of malignant melanoma (2 in the heavily exposed group), expected number: 0.04 out of 31	Bahn <i>et al.</i> 1976, 1977
Workers in 2 plants where PCBs were used in the manufacture of electric capacitors	2567 (1309 females; 1258 males)	yes	4 deaths in rectal cancer (1.19 expected); 3 in liver cancer (1.07 expected); increases were not statistically significant	Brown and Jones 1981
Update 7 years later	2588 (1318 females; 1270 males)	yes	statistically significant increase of number of deaths from cancer in liver, gallbladder and biliary tract (5 obs; 1.9 exp); number of deaths from all cancers lower than expected (62/80)	Brown 1987
Workers in a plant engaged in the manufacture of capacitors impregnated with PCBs	2100 (1566 females; 544 males)	yes	males: significantly increased number of deaths from all cancers (14 obs; 7.6 exp) and cancer in gastrointestinal tract (6 obs; 2.2 exp) females: significantly increased number of deaths from all cancers (12 obs; 5.3 exp) and hematologic neoplasms (4 obs; 1.1 exp) in comparison with the local population	Bertazzi <i>et al.</i> 1987
Workers exposed to PCB in a Swedish capacitor manufacture plant	142 males	yes	no indications on an increased cancer incidence or mortality from cancer	Gustavsson <i>et al.</i> 1986
Patients in the state of Ohio, USA, with ocular melanoma	698 (appr. 50 % of each sex)	no	no correlation between distribution of PCBs and incidence of ocular melanoma	Davidorf and Knupp 1979
Yusho patients from Japan exposed to PCBs from contaminated rice oil	1665 (sex not reported)	yes	11 out of 31 deaths were from malignant neoplasma (6.54 exp); 5 deaths from stomach and liver cancer	Urabe <i>et al.</i> 1979
-"-	1761 (874 females; 887 males)	no	males: significantly increased mortality from all cancers (33 obs; 15.51 exp), liver cancer (9 obs; 1.61 exp), cancer in respiratory system (8 obs; 2.45 exp) females: no significantly increased mortality from liver cancer (2 obs; 0.66 exp). No observed cancers in resp. system (0.85 exp)	Ikeda <i>et al.</i> 1986, Kuratsune <i>et al.</i> 1987
Workers in a Montsano plant for PCB production	89 (sex not reported)	not reported	no cases of liver cancers among 30 deaths; statistically significant increase of circulation diseases among white males; lung cancer incidence: 4 obs; 1.44 exp ? all cancers: ?	Brown 1987, Zack and Musch 1979
Workers maintaining electrical transmission equipment	3 cases (males)	no	3 kidney carcinomas	Shalat <i>et al.</i> 1989
Persons potentially exposed to PCBs from an electrical transformer fire	482 (sex not reported)	yes	males: 2 cancer cases (5.45 exp) females: 1 cancer case (1.11 exp)	Fitzgerald <i>et al.</i> 1989

Table XI. Levels of PCB congeners (the congeners not included in Table 22) in Finnish serum and adipose tissue (Luotamo *et al.* 1991).

Congener	IUPAC	Serum (µg/l)	Adipose (µg/kg)	Congener	IUPAC	Serum (µg/l)	Adipose (µg/kg)
2,2',3	16	0.05	0.11	2,3,3',4',6/2,3,3',5,5'/2,2',3,3',4	110/111/82	ND	2.26
2,2',4	17	ND	0.07	2,3',4,5',6/2,2',3',4,6	121/98	ND	1.47
2,2',5	18	0.11	0.14	2,2',3,3',4,5'	130	ND	4.32
2,3,4'	22	0.02	0.04	2,2',3,3',4,6	131	ND	3.93
2',3,4	33	ND	0.08	2,2',3,4,5,5'	141	ND	6.12
2,2',3,5'	44	ND	0.07	2,2',3,4,5',6/2,2',3,3',5,6'	144/135	ND	1.21
2,2',4,4'/2,2',4,5	47/48	ND	0.24	2,2',3,4',5,5'	146	ND	23.50
2,2',4,5'	49	ND	0.41	2,2',3,4',5',6	149	ND	1.42
2,2',5,5'	52	0.07	0.60	2,2',3,5,5',6	151	ND	1.46
2,3,4,4'/2,3,3',4'	60/56	ND	2.10	2,3,3',4,5,5'	159	ND	1.01
2,3',4,4'	66	0.04	1.36	2,2',3,3',4,4',6	171	ND	5.57
2,3',4',6/2,2',3,4/2,3',5,5'/2,3,4',6	71/41/72/64	ND	0.05	2,2',3,3',4,5,5'/2,3,3',4,5,5',6	172/192	ND	8.12
2,4,4',5	74	0.21	24.90	2,2',3,3',4',5,6	177	ND	10.80
2,2',3,4,6'	89	ND	1.24	2,2',3,3',5,5',6	178	ND	12.00
2,2',4,4',5	99	0.02	27.90	2,2',3,4,4',5',6	183	ND	21.30
2,2',4,5,5'	101	ND	1.87	2,3,3',4',5,5',6	193	ND	2.57

ND not detected

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