

PCBs, dioxins, and related compounds: summary of epidemiologic evidence
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1. Overall summary: Epidemiological evidence of associations between PCBs, PCDDs, PCDFs and related toxicants and adverse pregnancy outcome and child health and development

Outcome	Maternal high-level PCB/PCDF ^a	Maternal low-level PBB, PCB or TCDD ^b	Paternal occupational TCDD/related toxicants ^c	Lactational or childhood PCB or TCDD-TEQ
Spontaneous abortion	I	PCB – I TCDD – I	I	
Stillbirth	I	PCB – I	I	
Preterm birth	I	PCB – I TCDD – I	I	
Small for gestational age	I	PCB – I TCDD – I	I	
Neural tube birth defects		PCB – I TCDD – I	L	
Cardiac birth defects		TCDD – I	I	
Orofacial birth defects		TCDD – I	I	
Musculoskeletal birth defects			I	
Urinary tract birth defects		TCDD – I	I	

^a Ingestion of cooking oil containing high levels of PCB, PCDFs and related toxicants.

^b Background or occupational exposure.

^c Exposure to TCDD-contaminated chlorophenoxy herbicides (esp. 2,4,5-T) or chlorophenate wood preservatives.

Male genital birth defects		PCB – I TCDD – I	I	
Natal teeth	S	PCB/PCDD/PCDF-TEQ – I		
Hypomineralized enamel other developmental tooth defects	L	PCB – I PCB/PCDD/PCDF-TEQ – I		
Reduced postnatal growth in height	L	PCB – I PBB – I		Lactational PCB – I Childhood PCB – I
Cognitive function deficits, age 0-2	S	PCB – L		Lactational PCB – I
Cognitive function deficits, age ≥3	S	PCB – L		Lactational PCB – I
Neonatal hypotonia	S	PCB – L		
Psychomotor function deficits, age 0-2	L	PCB – L		Lactational PCB – I
Psychomotor function deficits, age ≥3		PCB – L		Lactational PCB – I
Visual function deficits	L	PCB – L		Lactational PCB – I
Auditory function deficits	L	PCB – L		Lactational PCB – I
Abnormal behaviours (hyperactivity, distractibility)	L	PCB – I		Lactational PCB – I
Delayed female pubic hair development		PCB – I PBB – I		Lactational PCB – I Childhood PCB – I Lactational PBB – I
Delayed female breast development		PCB – I PBB – I		Lactational PCB – I Childhood PCB – I Lactational PBB – I

Delayed menarche		PCB – I PBB – I		Lactational PCB – I Lactational PBB – I
Delayed male pubic hair development		PCB – I PBB – I		Lactational PCB – I Childhood PCB – I Lactational PBB – I
Delayed male external genitalia development		PCB – I		Lactational PCB – I Childhood PCB – I
Leukemia			I	Childhood PCB – I Childhood TCDD – I
Brain cancer			I	
Neuroblastoma			I	
Chloracne	L			High-level childhood TCDD – S
Lung infections	L	I		Lactational PCB – I
Middle ear infections	I	I		Lactational PCB – L
Asthma		I		Lactational PCB – I
Allergies		I		Lactational PCB – I

Sufficient evidence = based on peer-reviewed reports of expert groups or authoritative reviews that concluded that a causal relationship existed; limited evidence = relationships for which several epidemiologic studies, including at least one case-control or cohort study, showed fairly consistent associations and evidence of exposure-risk relationships after control for potential confounders; inadequate evidence = relationships for which epidemiologic studies were limited in number and quality (e.g., small studies, ecologic studies, limited control of potential confounders), had inconsistent results, or showed little or no evidence of exposure-risk relationships. Levels in parentheses are the author's interpretation of available evidence; other levels are based on expert group reviews.

^b Chlorophenolate wood preservatives were contaminated with TCDD.

2. Spontaneous abortion

Reviews

(Longnecker and others 1997), USA	Review of epidemiologic studies of PCBs, DDT and related organochlorines	PCBs and p,p' -DDE comprise the bulk of organochlorine residues in human tissues	Inconclusive evidence for associations between spontaneous abortion or stillbirth and ambient PCB exposure	Inadequate evidence for associations between early or stillbirth and maternal PCB exposure from Great Lakes fish consumption
(National Academy of Sciences 2005), USA	Literature review, potential health effects from phenoxy herbicides contaminated with TCDD	2,4-D and 2,4,5-T were contaminated with TCDD	There is insufficient evidence to determine if parental phenoxy herbicide exposure is associated with spontaneous abortion or stillbirths	

Original studies

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
(Wolfe and others 1995), USA	Retrospective cohort	Vietnam veterans and wives/partners; assessed pregnancy outcomes and infant mortality	1006 conceptions among men exposed to Agent Orange (a 50:50 mixture of 2,4-D and 2,4,5-T contaminated with TCDD) during 1962-71 and 1235 conceptions among an unexposed comparison group; 157 spontaneous abortions (GW<20) and 14 stillbirths (GW 20+) among exposed men (172 and 13 in comparison group)	Measured current serum TCDD on 94% of exposed men and 93% of comparison group and estimated levels at time of conception; serum TCDD levels: background (current level ≤ 10 ng/L), low (>10 and initial level ≤ 110 ng/L), high (>10 and initial level >110 ng/L)	Paternal race, maternal prenatal smoking, prenatal alcohol, parent's ages, paternal military occupation in Southeast Asia, history of spontaneous abortion before military service in Southeast Asia
Spontaneous abortion, relative risk, paternal serum TCDD high	1.0, 0.7-1.3				

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
(current >10 and initial >110 ng/L) vs background (<10 ng/L)					
(Axmon and others 2000), Sweden	Nested case-control	Cohort of Swedish fishermen's wives	438 east coast and 983 west coast fishermen's wives	East coast fatty fish consumption proxy for PCB exposure; measured plasma PCB-153 in 103 women (8 spontaneous abortions, 95 live births)	Maternal employment status, heavy lifting; maternal smoking and oral contraceptive use were not confounders
Mean maternal plasma PCB-153, cases vs controls	Stated that plasma PCB-153 levels were similar, $p=.40$ (Mann-Whitney test; paper included a graph but no data for mean/SD)				
(Yu and others 2000), Taiwan	Retrospective cohort	Women registered during the 1979 Yucheng incident and age 30-59 in 1993; comparison group of women not in registry; self-reported pregnancy history in 1993-94	14 early and 11 stillbirths among 356 exposed women; 22 early and 5 stillbirths among 312 comparison women	Measured serum PCB among registered women in 1979-81 55 th percentile serum PCB among exposed women was 49 $\mu\text{g/g}$; 21% of exposed women had PCBs $\geq 100 \mu\text{g/g}$ serum	Comparison group matched for neighbourhood of residence in 1979, age
Spontaneous abortion, % of women with history, Yucheng vs comparison group	6.8 vs 7.4%, $p>0.05$	Spontaneous abortion, baseline maternal serum PCB >46 vs $\leq 46 \mu\text{g/g}$ serum)	7/113 vs 7/127 = 6.2% vs 5.5% OR=1.12, 0.34-3.70		

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
(Schnorr and others 2001), USA	Retrospective cohort	Men occupationally exposed during production of Agent Orange	281 exposed men and 200 wives; comparison group of 260 unexposed neighbourhood men and 220 wives	Measured paternal serum TCDD levels in 1987 and extrapolated levels at time of conception Estimated median serum TCDD levels among occupationally exposed and comparison group men at conception were 254 ng/L (range 3-16,340 ng/L) and 6 ng/L (range 2-19 ng/L)	Maternal age, Hispanic ethnicity, thyroid medication
Odds of spontaneous abortion per 10-fold increment of paternal serum TCDD at conception	0.97, 0.88-1.09	Odds of spontaneous abortion by paternal serum TCDD at conception, referent = unexposed comparison men, serum TCDD <20 pg/g lipid	<20 0.77, 0.48-1.22 20-254 0.81, 0.40-1.63 255-1119 0.69, 0.30-1.58 ≥1120 0.95, 0.42-2.17	Odds of spontaneous abortion by paternal serum TCDD at conception <20 1.00 (referent) 20-254 1.05, 0.33-3.42 255-1119 0.88, 0.25-3.10 ≥1120 1.36, 0.39-4.81	
Eskenazi et al 2003, Seveso, Italy	Cohort	981 women age 40 yr or less at time of ICMESA chemical factory explosion (1976), followed to 1996-1998	97 spontaneous abortions among 769 pregnancies of 476 women	Median serum TCDD level soon after explosion was 47 (range 24-104 pg/g lipid)	Maternal age, education, history of spontaneous abortion
Spontaneous abortion during first 8 years of follow-up (the first serum TCDD half-life after exposure), odds	1.0, 0.6-1.6				

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
ratio per 10-fold increase in maternal serum TCDD					
(Sugiura-Ogasawara and others 2003), Japan	Case-control		45 cases with history of 3+ 1 st T spontaneous abortion, 2001-02; 30 healthy non-pregnant women with no history of live birth or infertility	Measured 18 PCBs, HCB, DDE, natural killer cell (NK) activity, antiphospholipid antibodies, antinuclear antibody, prolactin, progesterone, TSH, free T4 in prenatal maternal serum	
Mean organochlorine concentration (\pm SD) ng/g lipid, cases vs controls	PCBs 263.7 \pm 136.9 vs 319.9 \pm 189.7				
(Axmon and others 2004), Sweden	Retrospective cohort	165 sisters of Swedish east coast fishermen; provided blood sample in 2000	Self-reported pregnancy history in 1999; 16 spontaneous abortions among 165 planned first pregnancies of sisters of fishermen's wives + 121 pregnancies of fishermen's wives	Measured serum PCB-153; estimated level just before first planned pregnancy	
Mean preconceptional serum PCB-153, women with spontaneous abortion vs live births (sisters of fishermen's wives)	126 vs 218 ng/g lipid, p=.004	Mean preconceptional serum PCB-153, women with spontaneous abortion vs live births (fishermen's wives and their sisters)	146 vs 227 ng/g lipid, p=.005		
(Khanjani and Sim	Birth cohort	Representative sample	200 mother-infant pairs, 22	Breast milk samples Median	Maternal age, weight,

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
2007), Victoria, Australia		of Victoria live births	fetal deaths (any gestation length)	and range of breast milk PCBs (30, <10 to 220 µg/kg lipid)	education, prenatal smoking and drinking
OR, early or stillbirth, maternal breast milk PCB level vs <10 µg/kg lipid	10-50 µg/kg lipid 0.60, 0.17-2.14	>50 µg/kg lipid 1.07, 0.34-3.35 p-trend=.65			

Summary: Spontaneous abortion

Maternal high-level PCB/PCDF exposure, inadequate evidence

A retrospective cohort study of women who consumed cooking oil contaminated by high levels of PCBs, polychlorinated dibenzofurans (PCDFs) and related toxicants during the Yucheng incident in Taiwan revealed no association between spontaneous abortion and maternal preconceptional serum PCB levels (baseline maternal serum PCB >46 vs ≤46 µg/g lipid, crude OR=1.12, 95% CI 0.34-3.70) (Yu and others 2000).

Maternal background PCB exposure, inadequate evidence

Reviewers found inadequate evidence for an association between spontaneous abortion and background environmental PCB exposure (Longnecker and others 1997). In a Swedish retrospective cohort study of fishing families, spontaneous abortion was not associated with residence in a region with fish contaminated by relatively high PCB concentrations (1st trimester fetal death, OR=0.51, 95% CI 0.27-0.96; 2nd trimester, OR=0.90, 95% CI 0.44-1.83) (Axmon and others 2000). In the absence of body burden data, interpretation of these results is difficult. A case-control study nested within a cohort of Chinese textile workers revealed no association between spontaneous abortion and prenatal serum PCB (per 1 ng/100 g serum increment, OR=0.96, 95% CI 0.87-1.05) (Korrick and others 2001). In a small Japanese case-control study, spontaneous abortion was not associated with prenatal serum PCB concentration (mean serum PCB, cases vs controls, 263.7±136.9 vs 319.9±189.7 ng/g lipid) (Sugiura-Ogasawara and others 2003). In an Australian birth cohort study, pregnancy loss (spontaneous abortion or stillbirth) was not associated with breast milk PCB levels (≤50 µg/kg lipid vs undetectable, OR=0.60, 95% CI 0.17-2.14; >50 µg/kg, OR=1.07, 95% CI 0.34-3.35, p-trend=0.65) (Khanjani and Sim 2007).

Maternal TCDD exposure, inadequate evidence

A cohort study of women living in Seveso at the time of the 1976 factory explosion that released substantial amounts of TCDD found no association between spontaneous abortions and maternal preconceptional serum TCDD levels (per 10-fold increment, OR=1.0, 95% CI 0.6-1.6) (Eskenazi and others 2003).

Paternal occupational TCDD exposure, inadequate evidence

A literature review concluded that there was inadequate evidence for an association between spontaneous abortion and parental exposure to phenoxy herbicides potentially contaminated with TCDD (National Academy of Sciences 2005). This review focused mainly on health risks for Vietnam veterans potentially exposed to Agent Orange (a 50:50 mixture of 2,4-D and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) known to be contaminated with TCDD). A retrospective cohort study of veterans revealed no association between spontaneous abortion and paternal serum TCDD levels defined as background (current serum TCDD <10 pg/g lipid), low (current serum TCDD ≥10 and baseline level 10-109 pg/g lipid) and high (current serum TCDD ≥10 and baseline level ≥110 pg/g lipid)

(Wolfe and others 1995). The respective odds ratios for spontaneous abortion were background (OR=1.13, 95% CI 0.81-1.59), low (OR=1.32, 95% CI 0.94-1.86) and high (OR=0.99, 95% CI 0.68-1.43). There was also no association between spontaneous abortion and serum TCDD among wives of men highly-exposed during Agent Orange production (per 10-fold increment of preconceptual serum TCDD, OR=0.97, 95% CI 0.88-1.09) (Schnorr and others 2001).

3. Stillbirth

Original studies

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
(Wolfe and others 1995), USA	Retrospective cohort	Vietnam veterans and wives/partners; assessed pregnancy outcomes and infant mortality	1006 conceptions among men exposed to Agent Orange (a 50:50 mixture of 2,4-D and 2,4,5-T contaminated with TCDD) during 1962-71 and 1235 conceptions among an unexposed comparison group with known serum TCDD levels	Measured current serum TCDD on 94% of exposed men and 93% of comparison group and estimated levels at time of conception Serum TCDD levels: background (current level ≤ 10 ng/L), low (>10 and initial level ≤ 110 ng/L), high (>10 and initial level >110 ng/L)	Paternal race, maternal prenatal smoking, prenatal alcohol, parent's ages, paternal military occupation in Southeast Asia, history of spontaneous abortion before military service in Southeast Asia
Stillbirth, relative risk, paternal serum TCDD low or high vs background	0.45, 0.14-1.46 (calcd'd from data in report)				
(Dimich-Ward and others 1996), British Columbia	Nested case-control	Cohort of 19675 offspring of 9512 men exposed for at least one yr in a sawmill using chlorophenate wood preservatives, linked cohort and health outcome databases	867 preterm infants (< 37 wk), 2128 IUGR infants (10 th decile), 848 low birth weight infants (< 2500 g), 159 stillbirths, 300 neonatal deaths, 942 birth defects; 2 controls per case except for birth defects (5 controls per case)	Father's exposure to chlorophenate wood preservatives estimated from job titles and duration of employment in each job Chlorophenate wood preservatives known to be contaminated with PCDDs including TCDD	Sex, parental ages
Stillbirth, odds ratio per 100-hr increment in paternal occupational chlorophenate	1.0, 0.97-1.06				

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
exposure up to 3 mos before conception					
(Yu and others 2000), Taiwan	Retrospective cohort	Women registered during the 1979 Yucheng incident and age 30-59 in 1993; comparison group of women not in registry; self-reported pregnancy history in 1993-94	14 early and 11 stillbirths among 356 exposed women; 22 early and 5 stillbirths among 312 comparison women	Food cooked in oil contaminated by PCBs, PCDFs, PCTs and PCQs; measured serum PCB among registered women in 1979-81 55 th percentile serum PCB among exposed women was 49 µg/g; 21% of exposed women had PCBs ≥100 µg/g	Comparison group matched for neighbourhood of residence in 1979, age
Stillbirth, % of women with history, Yucheng vs comparison group	4.2 vs 1.7%, p=0.07	Stillbirth, baseline maternal serum PCB >46 vs ≤46 µg/g)	6/113 vs 5/127 = 5.3 vs 3.9% OR=1.35, 0.35-5.26		
(Korrick and others 2001), China	Nested case-control	Cohort of female Chinese textile workers	15 spontaneous abortion cases, 15 full-term controls; note this is a very small study	Measured maternal serum DDT and metabolites, PCBs and other organochlorines	Maternal age, BMI
Odds ratio increment per 1 ng/100 g serum maternal serum PCB increment	0.96, 0.87-1.05				
(Khanjani and Sim 2007), Victoria, Australia		Representative sample of Victoria live births	200 mother-infant pairs	Breast milk samples Median and range of breast milk PCBs (30, <10 to 220 µg/g lipid)	Maternal age, weight, education, prenatal smoking and drinking
Early or stillbirth,	0.60, 0.17-				

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
odds ratio, maternal breast milk PCB ≤ 50 and >50 $\mu\text{g/g}$ lipid vs non-detectable	2.14 1.07, 0.34-3.35 p-trend=0.65				

Summary: Stillbirth

Maternal high-level PCB/PCDF exposure, inadequate evidence

A retrospective cohort study of women exposed to high levels of PCBs, PCDFs and related toxicants during the Yucheng incident revealed no increased risk of stillbirths (maternal serum PCB >46 vs ≤ 46 ng/L, OR=1.35, 95% CI 0.35-5.26) (Yu and others 2000).

Maternal low-level PCB exposure, inadequate evidence

Reviewers found insufficient evidence for an association between stillbirth and background PCB exposure (Longnecker and others 1997). In a Swedish retrospective cohort study of fishing families, stillbirth was not associated with residence in a region with fish contaminated by relatively high PCB concentrations (OR=1.58, 95% CI 0.50-5.04) (Axmon and others 2000). In an Australian birth cohort study, pregnancy loss (spontaneous abortion or stillbirth) was not associated with breast milk PCB levels (≤ 50 $\mu\text{g/kg}$ lipid vs undetectable, OR=0.60, 95% CI 0.17-2.14; >50 $\mu\text{g/kg}$, OR=1.07, 95% CI 0.34-3.35, p-trend=0.65) (Khanjani and Sim 2007).

Paternal TCDD exposure, inadequate evidence

Compared to Vietnam veterans not exposed to Agent Orange, there were statistically non-significant elevated risks of stillbirth among exposure groups categorized as background (current and baseline TCDD ≤ 10 ng/L, OR=1.89, 95% CI 0.68-5.12) or low (current TCDD ≤ 10 ng/L and baseline ≤ 110 ng/L, OR=1.90, 95% CI 0.64-5.43); the odds ratio for the high TCDD category (current >10 ng/L and baseline >110 ng/L) was not calculated as there was only 1 exposed case father (Wolfe and others 1995). Among a cohort of British Columbia sawmill workers, stillbirths were not associated with paternal occupational exposure to chlorophenolate wood preservatives contaminated by TCDD and related toxicants (per 100-hr increment of exposure up to 3 mos before conception, OR=1.0, 95% CI 0.97-1.063) (Dimich-Ward and others 1996).

4. Preterm birth

Reviews

(Longnecker and others 1997), USA	Review of epidemiologic studies of PCBs, DDT and related organochlorines	PCBs and p,p' -DDE comprise the bulk of organochlorine residues in human tissues	Limited evidence for an inverse association between gestation length and occupational PCB exposure	Inconclusive evidence for an association between birth weight and background environmental PCB exposure
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Original studies

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
(Taylor and others 1989), upstate New York	Retrospective cohort	Women occupationally exposed to PCBs by inhalation and/or dermal contact in capacitor manufacturing plant during 1946-1977, age <55 in 1982; birth weight and gestation length verified through birth and/or medical records	190 live births among 200 directly exposed women (included all 140 women directly exposed for at least 1 yr); 207 live births among 205 indirectly exposed female employees	GM air PCB levels among directly and indirectly exposed women were 679 and 260 $\mu\text{g}/\text{m}^3$ in 1975 and 310 and 27 $\mu\text{g}/\text{m}^3$ in 1977; GM serum PCB in subsamples of directly/indirectly exposed women and unexposed comparison group were 302, 61 and 16 ng/g lipid; estimated serum PCB levels for all women in study	Maternal smoking, body mass index, height, pre-employment history of low birth weight, weight gain, infant sex, gestation length
Gestation length (days), direct vs indirectly exposed women	Indirect (low) exposure group, n=184 279.3 \pm 13.5 d Direct (high) exposure group, n=172 279.0 \pm 17.0 d	Cohen's d = 0.02, CI -0.19, 0.23, negligible effect	β = gestation length change (days) per unit change in ln estimated maternal serum PCB; univariate analysis (other covariates were not associated with gestation length)	β = -1.1 90% CI -2.0 to -0.1 p=0.02	
(Dimich-Ward and others 1996), British	Nested case-control	19675 offspring of 9512 men exposed for at least one yr in a	867 preterm infants (< 37 wk), 2128 IUGR	Chlorophenate wood preservatives known to be contaminated with	Sex, parental ages

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
Columbia		sawmill using chlorophenate wood preservatives; linked cohort and health outcome databases	infants (10 th decile), 848 low birth weight infants (<2500 g), 159 stillbirths, 300 neonatal deaths, 942 birth defects	PCDDs including TCDD; estimated cumulative exposure from job titles and duration of each job	
Preterm birth, odds ratio per 100-hr increment in paternal exposure	Up to 3 mos before conception 1.00, 0.99-1.001	During 3 preconception mos 0.99, 0.93-1.05			
(Michalek and others 1998), USA	Cohort	Vietnam veterans; assessed gestation length, birth weight and infant deaths based on birth, medical and death records	42 preterm births among 859 children of exposed Vietnam veterans and 54 preterm births among 1223 children of unexposed men	Serum TCDD levels: comparison grp, background (≤ 10 pg/g lipid), low (11-78 pg/g lipid) and high exposure groups (≥ 79 pg/g lipid)	Race, maternal smoking and alcohol during pregnancy, maternal age, paternal age, paternal military occupation
Preterm birth, odds ratio for high exposure vs comparison group	1.36, 0.75-2.39				
(Grandjean and others 2001), Faroe Islands	Birth cohort	Consecutive singleton term births at national hospital, 1994-95; assessed gestation length based on ultrasound, DNMP and clinical impression, birth weight measured by midwife	182 mother-infant pairs	Maternal serum PCB (28 congeners) tertiles: <0.6, 0.6-1.3, >1.3 ng/g lipid	Infant sex, parity, gestation length, maternal smoking, height, cord serum eicosapentaenoic acid
Mean gestation length vs increasing serum PCB tertile; p-value from regression analysis with gestation length as continuous	279.5, 281.3, 281.1 d p=0.09				

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
variable					
(Ribas-Fito and others 2002), Spain	Birth cohort	Births among women living in region with organochlorine production plant	70 mother-infant pairs, 1997-99	Median, 5 th and 95 th percentile maternal serum PCB (7 congeners) levels: 0.27, 0.11, 2.03 µg/L; note – local pop has high serum HCB levels	Infant sex, gestation length, maternal smoking, BMI, age
Mean maternal serum PCB (µg/L), preterm vs term infants	0.70 (n=4) vs 0.34 (n=66), p<0.10				
(Baibergenova and others 2003), New York state	Retrospective cohort	187 zip code areas in NY State with PCB-contaminated hazardous waste sites, all births during 1994-2000	Compared low (1500-2500g) and very low (<1500 g) birth weight rates in potentially exposed regions with those in the remainder of New York State except New York City	Residence in zip code with PCB-contaminated waste disposal site or in nearby regions	
% preterm births, regions with PCB-contaminated waste disposal sites vs unexposed regions	Contaminated regions 20080/224273 = 9.0% Comparison regions 56919/690981= 8.2%	OR=1.10, 1.08-1.11 (calc'd from data in paper)			
Eskenazi et al 2003, Seveso, Italy	Cohort	981 women age 40 yr or less at time of ICMESA chemical factory explosion (1976), followed to 1996-1998	30 preterm infants among 608 pregs incl 15 among 275 pregs during first 8 yr follow-up	Median serum TCDD level soon after explosion was 47 (range 24-104 ng/L)	Parity, history of low birth weight infant and maternal height, body mass index, age, education and

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
					smoking
Preterm delivery, odds ratio per 10-fold increase in maternal serum TCDD, first eligible pregnancy	First 8 yr after exposure 1.5, 0.5-4.8 all 22 yr after exposure 1.2, 0.6-2.5	Gestation length (days) vs maternal serum TCDD at baseline soon after the explosion	First 8 yr after expos $\beta=-1.0$ d, -3.1 to 1.2, n=275 all 22 yr after expos $\beta=-1.2$ d, -2.9 to 0.5, n=608		
(Lawson and others 2004), USA	Retrospective cohort	Wives of male workers exposed to TCDD during production of trichlorophenol and derivatives such as 2,4,5-T; comparison group of unexposed neighbourhood wives	51 preterm births among total of 1117 live singleton births of 217 referent wives and 176 worker wives	Exposed men: est'd mean TCDD at conception was 254 pg/g lipid (range 3-16,340); comparison grp – mean serum TCDD 6 pg/g (value assigned to workers before exposure)	Comparison group men matched on age, race and sex; adjusted for infant sex, maternal education, parity, prenatal cigarette smoking, gestation length
Preterm birth, odds per 10-fold increase in paternal serum TCDD	0.8, 0.6-1.1				
(Hertz-Picciotto and others 2005), San Francisco	Birth cohort (Child Health and Development Study)	Pregnant women who were members of Kaiser Health Plan during the 1960s	399 mother-child pairs born 1964-67	Maternal serum PCB (9 congeners – 105, 110, 118, 137, 138, 153, 170, 180, 187) – mean, median, 5 th , 95 th %'les 696, 616, 378, 1115 $\mu\text{g/g}$ lipid	Maternal age, education, height, BMI, parity, prenatal care, smoking, medications, hypertension, pre-eclampsia, child's race and sex
Multiple regression, gestation length (d) vs ln prenatal maternal serum PCB (i.e., odds ratio per 2.7-fold increase in maternal	Both sexes $\beta=-3.9\pm 2.0$ (SE) d	Boys $\beta=-3.0\pm 3.0$ d Girls $\beta=-4.4\pm 2.2$ d	Mean difference of gestation length (d), 90 th vs 10 th percentile maternal serum PCB	-4.2, -8.4 to 0.0 d n=40 in each subgroup	

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
serum PCB)					
(Longnecker and others 2005), USA	Cohort (U.S. Collaborative Perinatal Project)	Hospital prenatal clinics in 11 cities, 13 private practices in a 12 th city, singleton live births during 1959-65, 3-ml 3 rd trimester maternal serum sample available	1034 mother-infant pairs, recruited during 1959-65	Background sources; 3 rd T maternal serum PCBs (11 congeners – 28, 52, 74, 105, 118, 138, 153, 170, 180, 194, 203); median 2.8 µg/L (about 3-fold higher than current U.S.)	Study centre, maternal age, smoking and serum triglycerides, cholesterol, oxychlorodane and DDE, child race and sex
Preterm birth (gestation <37 wk), odds ratios, 95% CIs	Serum PCBs (µg/L) <2 2- 3- 4+	1.0 (referent) 0.92, 0.53-1.61 0.84, 0.44-1.62 1.11, 0.55-2.24	Logistic regression analysis, β = change in odds of preterm birth per unit change in maternal serum PCB (µg/L)	$\beta=0.04\pm0.09$ (SE)	
(Weisskopf and others 2005), USA	Retrospective cohort (Great Lakes Consortium)	511 mothers interviewed 1993-1995	Children born 1970-1993	Great Lakes fish contam'd with PCBs and other toxicants; maternal serum for 143 women 1994-1995	Child sex, maternal age, maternal education, parity, prepregnancy BMI, prenatal cigarette and alcohol use, weeks of breastfeeding
Multiple regression analysis, β = change in gestation length (wk) per unit increase in ln maternal serum PCB	$\beta = -0.08, -0.75$ to 0.59 wk				
(Khanjani and Sim 2007), Victoria, Australia	Cohort	Representative sample of Victoria live births	200 mother-infant pairs	Breast milk samples Median and range of breast milk PCBs (30, <10 to 220 µg/kg lipid)	Maternal age, weight, education, prenatal smoking and drinking
OR, preterm birth, maternal breast milk	≤ 50 1.41, 0.25-7.96				

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
PCB level ($\mu\text{g}/\text{kg}$ lipid) vs non-detectable	>50 2.30, 0.40-13.3 p-trend=0.43				
(Wolff and others 2007), New York City	Cohort	Enrolled at Mount Sinai Hospital during 1998-2002	404 mother-infant pairs	Mother-reported info on pesticide and other env exposures; maternal plasma DDE and PCB measured in a random subset of 194 women; maternal urinary OP metabolites measured; measured cord blood or maternal blood Pb	Mat age, race/ethnicity, BMI, preg wt gain, infant sex, gestation length
Gestation length vs log mat plasma PCB	$\beta=0.91\pm 0.49$ wk, p=.07	Gestation length vs log mat plasma PCB (lipid-adjusted)	$\beta=0.96\pm 0.52$ wk, p=.07		

Summary: Preterm birth, gestation length

Maternal high-level PCB/PCDF exposure, inadequate evidence

Follow-up to 1993-1994 of women exposed to high-levels of PCBs during the 1979 Yucheng incident revealed an elevated prevalence of stillbirths (exposed vs unexposed, 4.2 vs 1.7%, p=.07) (Yu and others 2000). This finding is consistent with an elevated risk possibly diluted by declining body burden of PCBs, PCDFs and related toxicants over 15 years.

Maternal occupational PCB exposure, inadequate evidence

Among women prenatally exposed to airborne PCBs during capacitor production, there was an inverse dose-response relationship of borderline statistical significance between gestation length and estimated serum PCB levels ($\beta=-1.1$ d, 90% CI -2.0 to -0.1) (Taylor and others 1989).

Maternal low-level PCB exposure, inadequate evidence

Reviewers noted inadequate evidence for an association between gestation length and prenatal background PCB exposure (Longnecker and others 1997). After adjustment for the relative concentration of docosahexaenoic acid (an n-3 polyunsaturated fatty acid in seafood) in cord serum phospholipids, gestation length was not associated with prenatal serum PCB levels in a small Faroe Islands birth cohort study (Grandjean and others 2001). A small Spanish birth cohort study revealed no association between preterm birth and mean maternal serum PCB levels (Ribas-Fito and others 2002). Preterm birth was weakly associated with maternal residence in zip code areas of New York State with PCB-contaminated hazardous waste disposal sites (crude OR=1.10, 95% CI 1.08-1.11); this study did not use exposure biomarkers and did not adjust for potential confounders (Baibergerova and others 2003). In a California pregnancy cohort study conducted during the 1960's (when population serum PCB levels were substantially higher than currently) gestation length was inversely associated with prenatal serum

PCB (per natural log serum PCB increment, $\beta=-3.9\pm 2.0$ d) (Hertz-Picciotto and others 2005). However, in a similar study with mothers recruited in 12 U.S. cities during 1959-65, preterm birth was not associated with prenatal serum PCB levels (≥ 4 vs < 2 $\mu\text{g/L}$, OR=1.11, 95% CI 0.55-2.24) (Longnecker and others 2005). There was also no association in cohort studies of Great Lakes fish eaters (change in gestation length per 2.7-fold maternal serum PCB increment, $\beta=-0.08$ weeks (95% CI -0.75 to 0.59) (Weisskopf and others 2005) or a representative sample of births in Victoria, Australia (preterm birth, breast milk PCB 10-49 vs < 10 $\mu\text{g/kg}$ lipid, OR=1.41, 95% CI 0.25-7.96; ≥ 50 vs < 10 $\mu\text{g/kg}$ lipid, OR=2.30, 95% CI 0.40-13.3; p-trend=.43) (Khanjani and Sim 2007). A birth cohort study in New York City found positive associations (i.e., favourable) between gestation length and log maternal plasma PCB levels ($\beta=0.91\pm 0.49$ wk, $p=.07$) (Wolff and others 2007).

Maternal TCDD exposure, inadequate evidence

Preterm birth during an 8-year follow-up of women exposed at Seveso was not associated with maternal serum TCDD levels (per log increment, OR=1.5, 95% CI 0.5-4.8); there was also no association between gestation length and maternal serum TCDD (per log increment, $\beta=-1.0$ d, 95% CI -3.1 to 1.2) (Eskenazi and others 2003).

Paternal occupational TCDD exposure, inadequate evidence

Preterm birth was not associated with exposure to potentially TCDD-contaminated chlorophenate wood preservatives among male sawmill workers (per 100-hr increment in cumulative exposure up to 3 months before conception, OR=1.00, 95% CI 0.99-1.001) (Dimich-Ward and others 1996) or with paternal serum TCDD levels in the study of U.S. veterans exposed to Agent Orange (serum TCDD at conception ≥ 79 vs ≤ 10 pg/g lipid, OR=1.36, 95% CI 0.75-2.39) (Michalek and others 1998). Similarly, preterm birth was not related to serum TCDD levels among men exposed during production of trichlorophenol and derivatives such as 2,4,5-T (per log serum TCDD increment, OR=0.8, 95% CI 0.6-1.1) (Lawson and others 2004).

5. Small for gestational age

Reviews

(Birnbaum 1995), USA	Literature review, developmental effects of dioxins in experimental animals and humans	Relatively high doses of TCDD and dioxin-like chemicals cause reduced fetal growth in several animal species		
(Brouwer and others 1995), Netherlands	Review of developmental toxicity of PHAHs in experimental animals and infants	Prenatal exposure to PCBs, PCDDs and PCDFs can cause reduced birth weight in humans and experimental animals		
(Guo and others 1995), Taiwan	Review of Yucheng, Michigan and North Carolina cohorts of children of women exposed to PCBs and related compounds	Yucheng – mean and median maternal serum PCB levels near end of pregnancy were 49 and 27 µg/L; Michigan – mean maternal and cord serum PCB levels, respectively, were 4.7-5.9 and 2.0-2.5 µg/L; North Carolina – median maternal and cord serum PCB levels were 9.1 and about 4 µg/L	IUGR associated with maternal PCB exposure in Yucheng and Michigan studies but not in North Carolina cohort	
(Longnecker and others 1997), USA	Review of epidemiologic studies of PCBs, DDT and related organochlorines	PCBs and p,p'-DDE comprise the bulk of organochlorine residues in human tissues	Inadequate evidence for an inverse associations between birth weight and occupational PCB exposure	Inconclusive evidence for an association between birth weight and background environmental PCB exposure
(Brouwer and others 1998), WHO Working Group	Health risks of PCDDs, PCDFs and PCBs	High-level prenatal maternal exposure from food cooked in oil contaminated with PCBs, PCDFs, PCTs and	Estimated maternal TCDD-TEQ body burden from PCDFs and dioxin-like PCBs during these incidents was 2-	

		PQTs in the Yusho and Yucheng incidents was associated with low birth weight	3 µg/kg body weight	
(National Academy of Sciences 2003), USA	Literature review, potential health effects from phenoxy herbicides contaminated with TCDD	2,4-D and 2,4,5-T were contaminated with TCDD	There is insufficient evidence to determine if paternal phenoxy herbicide exposure is associated with low birth weight	
(Guo and others 2004), Taiwan	Review of health effects among the cohort of persons exposed to food cooked in oil contaminated by PCBs, PCDFs, PCTs and PCQs during the 1979 Yucheng incident	Birth weight adjusted for gestation length was about 500 g lower among prenatally exposed Yucheng infants compared to an unexposed comparison group.		

Original studies

Reference	Design	Sampling frame	Subjects	Exposure	Covariates	
(Stockbauer and others 1988), Missouri, USA	Retrospective cohort	402 births among women in TCDD-contaminated regions (only 98 occurred after exposure), 804 infants of women living elsewhere in Missouri, 1972-1982; TCDD-contam soil used on roads during 1971-73	14 IUGR cases among 379 exposed births, 26 among 758 unexposed births	Birth records	Mat resid at birth in areas with soil TCDD ≥ 1 ng/g on or near property; max soil TCDD during 1982-85 was 241-2200 ng/g; high expos = mat resid ≥ 6 mos in region with soil TCDD >100 ng/g or >2 yr with soil TCDD 20-100 ng/g; low expos = soil TCDD <20 ng/g or resid for short periods in more contam regions	Matched for mat age, race, hosp, plurality, YOB; adj for var combs of mat educ, marital status, parity, infant sex, smk, prev preg loss GW <20 , prepreg wt
OR, IUGR, expos vs unexposed women	1.09, 0.50-2.28					
(Rogan and others 1988), Taiwan	Cohort	Yucheng children	127 Yucheng children, 115 unexposed neighbourhood controls, age 1 month to 8 yr	Prenatal maternal exposure to cooking oil heavily contaminated with PCBs, PCDFs and PCQs; infants had both prenatal and lactational exposure		
Mean birth wt, exposed vs unexposed infants; not adjusted for	Exposed 2749 \pm 46(SE) g, \pm 520(SD), n=128 Unexposed					

Reference	Design	Sampling frame	Subjects	Exposure	Covariates	
gestation length	3228±40(SE) g, ±429(SD), n=115					
(Taylor and others 1989), upstate New York	Retrospective cohort	Women occupationally exposed to PCBs by inhalation and/or dermal contact in capacitor manufacturing plant during 1946-1977, age <55 in 1982; birth weight and gestation length verified through birth and/or medical records	172 live births among directly exposed women (included all 140 women directly exposed for at least 1 yr); 184 live births among indirectly exposed female employees	Geometric mean airborne PCB levels in workplaces of directly and indirectly exposed women were 679 and 260 µg/m ³ in 1975 and 310 and 27 µg/m ³ in 1977 Geometric mean serum PCB levels in subsamples of directly and indirectly exposed employees and an unexposed reference group, respectively, were 302, 61 and 16 µg/g lipid; estimated serum PCB levels for all women in study	Maternal smoking, body mass index, height, pre-employment history of low birth weight, weight gain, infant sex, gestation length	
Birth weight, direct vs indirectly exposed women	Indirect (low) exposure group, n=184 3417±486 g Direct (high) exposure group, n=172 3313±456 g Cohen's d = 0.22, CI 0.01-0.43, small effect	Multiple regression, β = birth weight change (g) per unit change in ln estimated maternal serum PCB; adjusted for maternal smoking, previous low birth weight, height, BMI, weight gain during pregnancy, infant sex	β = -33±16 (SE) g, R ² = 0.19 90% CI -59, -7	Multiple regression, β = birth weight change (g) per unit change in ln estimated maternal serum PCB; adjusted for previous covariates plus gestation length	β = -24g 90% CI -49, 2 p=0.06	

Reference	Design	Sampling frame	Subjects	Exposure	Covariates	
(Dimich-Ward and others 1996), British Columbia	Nested case-control	19675 offspring of 9512 men exposed for at least one yr in a sawmill using chlorophenate wood preservatives; linked cohort and health outcome databases	867 preterm infants (< 37 wk), 2128 IUGR infants (10 th decile), 848 low birth weight infants (<2500 g), 159 stillbirths, 300 neonatal deaths, 942 birth defects	Father's exposure to chlorophenate wood preservatives estimated from job titles and duration of employment in each job Chlorophenate wood preservatives known to be contaminated with PCDDs including TCDD	Sex, parental ages, gestational age	
IUGR, odds ratio per 100-hr increment in paternal exposure	Up to 3 mos before conception 1.00, 0.99-1.001 During 3 preconception mos 1.00, 0.96-1.04	Low birth weight, odds ratio per 100-hr increment in paternal exposure	Up to 3 mos before conception 0.99, 0.994-0.999 During 3 preconception mos 1.01, 0.92-1.08			
(Rylander and others 1998), Sweden	Nested case-control	Retrospective cohort of east coast fishermen's wives	57 cases of low birth weight (1,500-2,750 g), 135 controls (birth weight 3250-4500 g)	Measured mother's serum or plasma PCB-153 levels 4-22 years after birth and estimated level at time of birth; correlation coefficient between plasma PCB-153 and total PCBs was 0.91; current median plasma PCB levels in case and control mothers were 190 (range 40-780) and 160 (range 20-570) ng/g	Cases and controls matched for infant sex, parity, year of birth; adjusted for maternal age and smoking during year of child's birth	

Reference	Design	Sampling frame	Subjects	Exposure	Covariates	
				lipid; estimated levels during years of infant births were 350 (range 70-1670) and 310 (range 30-1500) ng/g lipid		
Low birth weight, odds ratio, estimated maternal serum PCB-153 level during infant's YOB, >400 vs <400 ng/g fat; not adj for GL	2.3, 0.9-5.9					
(Vartiainen and others 1998), Finland	Cohort	Consecutive women at delivery in a maternity clinic in Helsinki and one in a rural province	167 mother-infant pairs	Breast milk (4 wk after delivery) – measured 17 PCDDs/PCDFs and 12 PCBs Mean breast milk levels among primiparous women in 1) urban region: PCBs – 496 ng/g lipid (range 173-1624); PCB-TEQ – 37 pg/g lipid (8.9-162); PCDD/PCDF-TEQ – 26 pg/g lipid (15-96) and 2) rural region: PCBs – 396 ng/g lipid (140-834); PCB-TEQ – 27 pg/g lipid (10-51); PCDD/PCDF-TEQ – 20 pg/g lipid (11-37)	Adjustment for maternal education made little difference; maternal smoking not a confounder; did not adjust for gestation length	
PCBs	Boys and girls	PCB-TEQ	Boys and girls	Total TEQ	Boys and girls	boys

Reference	Design	Sampling frame	Subjects	Exposure	Covariates	
Pearson's correlation coefficient between birth weight and breast milk PCBs; not adjusted for gestation length	$r=-0.10$, $p=0.22$, $n=166$	Pearson's correlation coefficient between birth weight and breast milk PCB-TEQ	$r=-0.02$, $p=0.77$, $n=166$	Birth weight (g) vs breast milk total dioxin TEQs (pg/g lipid)	Slope = -0.00228 g $r=-0.18$, $p = 0.022$, $n=166$	$r=-0.24$, $p=0.04$, $n=76$ girls $r=-0.08$, $p=0.45$, $n=90$
(Patandin and others 1998), Rotterdam, The Netherlands	Birth cohort; measured weight, length and head circumference at 10 d and 3, 7, 18 and 42 mos	Healthy term infants (37+ wk) born during 1990-92 in a large industrial city	105 breast-fed and 102 formula-fed infants	Measured cord and maternal plasma PCBs (118, 138, 153, 180) and breast milk PCBs (26 congeners) and PCDD/PCDFs (17 most abundant 2,3,7,8-substituted congeners); estimated total breast milk PCDD/PCDF/PCB-TEQ; used maternal and cord plasma to estimate prenatal exposure and breast milk levels plus duration of breastfeeding to assess lactational exposure; median PCB levels in maternal plasma, cord plasma and breast milk (2 nd wk after delivery) were 2.0 $\mu\text{g/L}$ (range 0.6-7.4), 0.4 $\mu\text{g/L}$ (range 0.1-2.1) and 392 ng/g lipid (range 174-1226); median total breast milk PCDD/PCDF/PCB-TEQ was 65 pg/g lipid	Parity, prenatal maternal alcohol and smoking, gestational age, parental height index	

Reference	Design	Sampling frame	Subjects	Exposure	Covariates	
				(range 28-155)		
Prenatal PCB exposures, birth wt (g) vs ln plasma PCB ($\mu\text{g/L}$); adj for gestation length	ln cord plasma PCB $\beta=-119.4\pm 53.7$ (SE) g, $p=0.03$, $n=179$	ln maternal plasma PCB $\beta=-123.1\pm 64.4$ (SE) g, $p=0.06$, $n=203$				
(Michalek and others 1998), USA	Cohort	Vietnam veterans; assessed gestation length, birth weight and infant deaths based on birth, medical and death records	859 children of exposed Vietnam veterans and 1223 children of unexposed men	Serum TCDD levels: comparison grp, background (≤ 10 pg/g lipid), low (11-78 pg/g lipid) and high exposure groups (≥ 79 pg/g lipid)	Race, maternal smoking and alcohol during pregnancy, maternal age, paternal age, paternal military occupation	
OR, IUGR vs paternal serum TCDD, ≥ 79 vs ≤ 10 pg/g lipid	0.9, 0.6-1.3					
(Seidler and others 1999), Germany	Birth cohort	3216 pregnant women, enrolled during gestation wk 15-28, 1987-1988	Physician-reported pregnancy outcome history, 194 SGA infants	Self-reported maternal occupational history; job-exposure matrix to assess exposure to PCBs and other toxicants	Maternal age, smoking, alcohol, BMI, parity	
OR, SGA vs maternal occupational PCB exposure yes/no	Unexposed 1.0 (ref) Exposed 1.2, 0.8-1.7	Trend analysis, OR vs exposure intensity score	p -trend=0.44			
(Rylander and others 2000),	Cohort	See Rylander and Hagmar 1999 above;	1719 infants of 1030 sisters of	See Rylander and Hagmar 1999 above Demonstrated	Maternal age, parity, smoking, infant sex	

Reference	Design	Sampling frame	Subjects	Exposure	Covariates	
Sweden		compared adverse pregnancy outcome risks in east coast relative to west coast cohort	east coast Swedish fishermen, 2682 infants of 1537 sisters of west coast Swedish fishermen	that fishermen's sisters had relatively high consumption of contaminated fish during early life		
Low birth weight, east vs west coast infants	1.6, 1.1-2.3	SGA, east vs west coast infants	1.4, 0.9-2.1			
(Grandjean and others 2001), Faroe Islands	Birth cohort	Consecutive singleton term births at national hospital, 1994-95; assessed gestation length based on ultrasound, DNMP and clinical impression, birth weight measured by midwife	182 mother-infant pairs	Marine fish, pilot whales; maternal serum PCBs (28 congeners) Geometric mean and interquartile range, maternal serum PCBs: 0.86, 1.05 µg/g lipid	Infant sex, parity, gestation length, maternal smoking, height, cord serum eicosapentaenoic acid	
Birth weight (g) vs log (?ln) maternal serum PCB (µg/g lipid); adj for gestation length	$\beta = -31.0 \pm 99.9$ (SE) g, $p = 0.76$, $n = 182$	Mean birth weight vs increasing serum PCB tertile; p-value from regression analysis with gestation length as continuous variable	<0.6 ng/g lipid 3691 g 0.6-1.3 3557 g >1.3 3606 g $p = 0.47$			
(Ribas-Fito and others 2002),	Cohort	Births among women living in one health	70 mother-infant pairs	Chlorinated solvent production plant; maternal	Covariates included infant sex, gestation	

Reference	Design	Sampling frame	Subjects	Exposure	Covariates	
Spain		region during 1997-99		serum PCBs (7 congeners) Median, 5 th and 95 th percentile maternal serum PCB levels: 0.27, 0.11, 2.03 µg/L	length, maternal age, BMI, gestational diabetes, prenatal smoking or alcohol, parents' education	
Birth weight (g) adjusted for gestational age vs log ₂ cord serum PCB levels (µg/L)	β=-5.6±36.1 (SE) g, n=70	SGA vs cord serum PCB (geometric mean)	SGA 0.28 µg/L, n=7 Non-SGA 0.37 µg/L, n=63			
(Baibergenova and others 2003), New York state	Retrospective cohort	187 zip code areas in NY State with PCB-contaminated hazardous waste sites	Compared low (1500-2500g) and very low (<1500 g) birth weight rates in potentially exposed regions with those in the remainder of New York State except New York City	Residence in zip code with PCB-contaminated waste disposal site or in nearby regions	Gestation length	
Difference in mean birth weight, regions with PCB-contaminated waste disposal sites vs unexposed regions	Contaminated regions 3386.7 g Comparison regions 3408.3 g Difference -21.6 g, p<0.001	Relative risk of low birth weight, regions with PCB-contaminated waste disposal sites vs unexposed regions (adj for gestation length)	All births 1.04, 1.02-1.07	Boys 1.06, 1.02-1.10 Girls 1.03, 0.99-1.07	Gestation length, maternal age, race, education, prepregnancy weight, SES, smoking	
Eskenazi et al	Cohort	981 women age 40 yr or	59 IUGR infants	Median serum TCDD level	Parity, history of low	

Reference	Design	Sampling frame	Subjects	Exposure	Covariates	
2003, Seveso, Italy		less at time of ICMESA chemical factory explosion (1976), followed to 1996-1998	among 608 pregs incl 28 among 275 pregs during the first 8 yr of follow-up	soon after explosion was 47 (range 24-104 ng/L)	birth weight infant and maternal height, body mass index, age, education and smoking	
SGA, first eligible pregnancy, odds ratio per 10-fold increase in maternal serum TCDD, first eligible pregnancy	First 8 yr after exposure 1.8, 0.7-4.3 all 22 yr after exposure 1.5, 0.9-2.6	Birth weight during first 8 years of follow-up vs maternal serum TCDD levels soon after exposure; adjusted for other covariates plus gestation length	First 8 yr after expos $\beta=-92$, -204 to 19, n=275 all 22 yr after expos $\beta=-4$, -68 to 60, n=608			
(Lawson and others 2004), New Jersey, Missouri, USA	Retrospective cohort	Wives of male workers exposed to TCDD during production of trichlorophenol or its derivatives; comparison group of unexposed neighbourhood wives; assessed birth weight of term infants (≥ 37 wk gestation)	1117 live singleton births of 217 referent wives and 176 worker wives; birth weight and gestation length based on birth records (82%) or mother's report	Estimated serum TCDD concentration at the time of conception based on serum TCDD at time of examination, dates exposed to TCDD-related processes, BMI; measured TCDD in sample of 79 men in comparison group Exposed men: median estimated serum TCDD at conception was 254 pg/g lipid (range 3-16340); mean referent estimated serum TCDD concentration was 6 pg/g (value assigned to pregnancies fathered by workers before exposure)	Comparison group men matched on age, race and sex; adjusted for infant sex, maternal education, parity, prenatal cigarette smoking, gestation length	

Reference	Design	Sampling frame	Subjects	Exposure	Covariates	
Mean birth weight: difference between comparison group and exposed men by serum TCDD category (pg/g lipid)	<20 -8±44(SD) g, n=264 20-254 -42±59 g, n=98	≥255 +83±52 g, n=144				
(Karmaus and Zhu 2004), Michigan	Retrospective cohort	Female anglers in Michigan of reproductive age after 1968; self-reported pregnancy history	168 mother-infant pairs	Sports-caught fish; serum PCB levels (based on Arochlor 1260 standard) measured during all 3 surveys; used value closest to date of delivery; serum organochlorine levels measured during 3 surveys between 1973 and 1991 10.7% of women had serum PCB level of 15+ µg/L	Infant sex, gestation length, birth year, maternal serum DDE, parity, age, height, education, smoking	
Adjusted birth weight from linear regression analysis, g	Maternal serum PCBs, µg/L <5 5-14 15-24 25-29	Adjusted birth weight, g (SE) 3520±103.3, n=84 3509±100.8, n=66 3537±202.0, n=11 2958±224.0, n=7	Wt diff between lowest and highest serum PCB = 562 g, p=0.02	Average birth weight difference, maternal serum PCB ≥25 vs <5 µg/gL	Boys -561g, p=0.02, n=6 Girls -241g, p=0.66, n=1	
(Hertz-Picciotto and others 2005), San Francisco	Birth cohort (Child Health and Development Study)	Pregnant women who were members of Kaiser Health Plan during the 1960s; children examined at birth and	399 mother-child pairs (211 girls, 188 boys) born 1964-67	Background sources; prenatal maternal serum PCBs (9 congeners – 105, 110, 118, 137, 138, 153, 170, 180, 187) Maternal	Maternal age, education, height, BMI, parity, prenatal care, smoking, medications,	

Reference	Design	Sampling frame	Subjects	Exposure	Covariates	
		re-examined at age 5 who fell within 3 strata: 194 with cognitive delay, 46 with hearing deficit, 159 randomly selected from others		serum PCB mean, median, 5 th , 95 th percentiles: 696, 616, 378, 1115 µg/g lipid	hypertension, pre-eclampsia, child's race and sex	
Multiple regression, birth weight (g) vs ln prenatal maternal serum PCB (µg/g lipid); not adjusted for gestation length	Both sexes β=-111±69 (SE) g	Boys β=-268±101 g Girls β=-26±73 g	Mean weight difference, maternal serum PCB ≥90 th vs ≤10 th decile, not adjusted for gestation length	Boys -290g, -504 to -76 g Girls -28g, -184 to 128 g		
Birth weight Z-score vs ln maternal serum PCB, adjusted for gestation length	Total β=-0.18±0.15 (SE) g	Boys, n=188 β=-0.53±0.21 Z	Girls, n=211 β=0.01±0.16 Z			
(Longnecker and others 2005), USA	Birth cohort (U.S. Collaborative Perinatal Project)	Hospital prenatal clinics in 11 cities, 13 private practices in a 12 th city, singleton live births during 1959-65, 3-ml 3 rd trimester maternal serum sample available	1034 mother-infant pairs, recruited during 1959-65	Background sources; 3 rd trimester maternal serum PCBs (11 congeners – 28, 52, 74, 105, 118, 138, 153, 170, 180, 194, 203) Median maternal serum PCB = 2.8 µg/L (about 3-fold higher than current U.S.)	Study centre, maternal age, smoking and serum triglycerides, cholesterol, oxychlorane and DDE, child race and sex	
SGA vs quartiles of maternal serum PCBs (µg/L),	<2 µg/L 1.0 (referent) 2-	Mean birth weight (SE), g vs maternal serum PCBs (µg/L)	<2 µg/L 3168±34 2-	Multiple regression analysis, β = change in birth weight (g) per unit	β=19.2±14.5 (SE)	

Reference	Design	Sampling frame	Subjects	Exposure	Covariates	
odds ratio	1.33, 0.68-2.60 3- 1.98, 0.94-4.17 ≥4 1.64, 0.73-3.68 logistic β=0.11±0.10		3181±29 3- 3192±35 ≥4 3238±37	change in maternal serum PCB (μg/L); similar values obtained when analysis limited to term births (stated without supporting data)		
(Tajimi and others 2005), Tokyo	Birth cohort	Tokyo	240 mother-infant pairs, 1999-2000, maternal age 25-34	Measured 14 PCDDs, 15 PCDFs and 12 coplanar PCB congeners in breast milk samples Median and range of total PCDD, PCDF and co-PCB TEQ (24.0, 4.2-67.0 pg/g lipid), PCDD and PCDF TEQ (13.8, 2.8-37.2) and co-PCB TEQ (9.9, 1.4-36.4)	Maternal age, parity, weight, smoking	
Multiple regression analysis, β = change in birth weight (g) per unit change in maternal breast milk PHAH concentration (pg/g lipid); not adjusted for gestation length but only 3/240	Coplanar PCB-TEQ β=-5.09±4.84 (SE) g PCDD/PCDF TEQ β=-2.01±4.16 g	PCDD/PCDF/co-PCB TEQ β=-2.30±2.62 g Octachlorodibenzo-p-dioxin β=-1.23±0.49 g	Note: max. OCDD level was 381 pg/g lipid			

Reference	Design	Sampling frame	Subjects	Exposure	Covariates	
infants were preterm						
(Weisskopf and others 2005), USA	Retrospective cohort (Great Lakes Consortium)	511 mothers interviewed 1993-1995	Children born 1970-1993; birth certificate info used to validate maternal-reported info on births	Great Lakes sport-caught fish are contaminated with PCBs and DDE; serum collected from 143 women 1994-1995; geometric mean, interquartile range and maximum PCB levels were 2.79, 1.43-5.11 and 21.1 µg/L; estimated serum PCB levels during earlier pregnancies using a toxicokinetic model	Child sex, maternal age, maternal education, parity, prepregnancy BMI, prenatal cigarette and alcohol use, weeks of breastfeeding, gestation length	
Multiple regression analysis, β = change in birth weight (g) per unit increase in ln maternal serum PCB (µg/L); adjusted for gestation length	β = 29, -110 to 168 g					
(Khanjani and Sim 2007), Victoria, Australia	Cohort	Representative sample of Victoria live births	200 mother-infant pairs	Breast milk samples Median and range of breast milk PCBs (30, <10 to 220 µg/kg lipid)	Maternal age, weight, education, prenatal smoking and drinking	
OR, SGA, maternal breast milk PCB (µg/kg)	≤ 50 0.87, 0.34-2.22					

Reference	Design	Sampling frame	Subjects	Exposure	Covariates	
lipid) vs non-detectable	>50 0.61, 0.22-1.66 p-trend=0.41					
(Wolff and others 2007), New York City	Cohort	Enrolled at Mount Sinai Hospital during 1998-2002	404 mother-infant pairs	Mother-reported info on pesticide and other env exposures; maternal plasma DDE and PCB measured in a random subset of 194 women	Maternal urinary OP metabolites measured; measured cord blood or maternal blood Pb	Mat age, race/ethnicity, BMI, preg wt gain, infant sex, gestation length
Birth wt adj for gestation length vs log mat plasma PCB	$\beta=17\pm 116$ g, p=.88	Birth wt adj for gestation length vs log mat plasma PCB (lipid-adjusted)	$\beta=29\pm 123$ g, p=.81			
(Sagiv and others 2007), Massachusetts, USA	Birth cohort	722 mother-infant pairs recruited at hospital near a Superfund site, New Bedford, Mass, 1993-98	Birth weight	Infant medical record	Residents of 4 towns near Superfund site (a contam'd harbor); cord serum PCBs (51 congeners), DDE, HCB	Infant sex, gestation length, mat age, parity, ht, prepreg BMI, prenatal mat smk, local fish consumption
Adjusted diff in mean birth wt (g), cord serum PCB quartiles 2-4 vs 1 (sum of 51 PCB congeners)	Q2 -16.0, -104.5 to 72.5 g Q3 -101.2, -194.5 to -7.9 g	Q4 -47.6, -152.9 to 57.7 g p-trend=.43	Adjusted diff in mean birth wt (g), cord serum PCB quartiles 2-4 vs 1 (sum of PCB-118, 138, 153, 180)	Q2 -65.0, -154.5 to 24.5 g Q3 -95.8, -189.6 to -2.0 g	Q4 -99.2, -204.2 to 5.8 g p-trend=.13	

Summary: Fetal growth deficit

Maternal high-level PCB/PCDF exposure, inadequate evidence

Birth weight was substantially lower among Yucheng infants (2749±46(SE) g) compared to unexposed infants (3228±40(SE) g) but there was no adjustment for gestation length (Rogan and others 1988).

Maternal occupational PCB exposure, inadequate evidence

Among infants of women occupationally exposed to airborne PCBs, there was an inverse association of borderline statistical significance between birth weight adjusted for gestation length and prenatal serum PCB levels estimated from those measured in a sub-sample of women (per 2.7-fold maternal serum PCB increment, $\beta=-24$ g, 90% CI -49 to 2) (Taylor and others 1989). A German birth cohort study found no association between FGD and prenatal PCB exposure inferred from a job-exposure matrix (exposed vs unexposed, OR=1.2, 95% CI 0.8-1.7) (Seidler and others 1999).

Maternal background PCB exposure, inadequate evidence

Reviewers found inadequate evidence for an inverse association between birth weight and maternal exposure to background environmental PCBs (Longnecker and others 1997). Studies published since this review provide inconsistent evidence for an association. In a study of Swedish fishermen wives, there was an association of borderline statistical significance between low birth weight and prenatal serum PCB-153 levels (>400 vs ≤400 ng/g lipid, OR=2.3, 95% CI 0.9-5.9) but there was no adjustment for gestation length (Rylander and others 1998). Birth weight adjusted for gestation length was inversely associated with cord plasma PCB levels in Holland (per 2.7-fold plasma PCB increment, $\beta=-119.4\pm53.7$ g, $p=.03$) (Patandin and others 1998). There was an increased risk of FGD (borderline statistical significance) among Swedish fishing families in a region where fish had relatively high PCB levels (contaminated vs less contaminated region, OR=1.4, 95% CI 0.9-2.1) (Rylander and others 2000). A retrospective cohort study in New York State found a weak but statistically significant association between low birth weight (adjusted for gestation length and other potential confounders) and prenatal residence in regions with PCB-contaminated hazardous waste disposal sites (OR=1.04, 95% CI 1.02-1.07) (Baibergenova and others 2003). In a retrospective cohort study of Lake Michigan female anglers, birth weight adjusted for gestation length was reduced among women in the highest serum PCB category (serum PCB 25-29 vs <5 µg/L, mean birth weight 2958±224.0 vs 3520±103.3 g, $p=.02$); when analyzed by gender, the association was significant among boys but not girls (Karmaus and Zhu 2004). Similarly, in a California birth cohort, birth weight adjusted for gestation length was inversely related to maternal serum PCB levels among boys but not girls (per 2.7-fold serum PCB increment, respective birth weight Z-scores for boys and girls were -0.53 ± 0.21 and 0.01 ± 0.16) (Hertz-Picciotto and others 2005). In a hospital-based cohort study near a Superfund site in Massachusetts, birth weight adjusted for gestation length was lower among infants in higher quartiles of cord serum PCB levels but the trend was not statistically significant (Q2 vs Q1, mean birth weight difference was -65.0, 95% CI -154.5 to 24.5 g; Q3 vs Q1, -95.8, 95% CI -189.6 to -2.0 g; Q4 vs Q1 -99.2, 95% CI -204.2 to 5.8 g; p -trend=.13) (Sagiv and others 2007).

A Finnish study found no association between birth weight and breast milk PCB levels (Pearson's $r=-0.10$, $p=.22$); analyses did not adjust for gestation length or other potential confounders (Vartiainen and others 1998). FGD was not associated with prenatal serum PCB levels in birth cohort studies in the Faroe Islands (per 2.7-fold maternal serum PCB increment, $\beta=-31.0\pm99.9$ g, $p=.76$) (Grandjean and others 2001) and Spain (per 2-fold cord serum PCB increment, $\beta=-5.6\pm36.1$ g) (Ribas-Fito and others 2002). A U.S. Collaborative Perinatal Project cohort study revealed elevated risks of FGD at higher maternal serum quartiles (4th vs 1st quartile, OR=1.64, 95% CI 0.73-3.68) but logistic regression based on PCB concentration as a continuous variable showed no association ($\beta=0.11\pm0.10$) (Longnecker and others 2005). In a Japanese birth cohort, birth weight among mostly term infants was not associated with breast milk PCB dioxin toxic equivalent (TEQ) levels ($\beta=-5.09\pm4.84$) (Tajimi and others 2005). A retrospective cohort study of parents engaged in Great Lakes sport fishing observed no association between birth weight adjusted for gestation length and maternal serum PCB levels (change in birth weight per 2.7-fold serum PCB increment, $\beta=29$ g, 95% CI -110 to 168) (Weisskopf and others 2005). In a representative sample of births in Australia, FGD was not related to breast milk PCB levels (≤50 µg/kg lipid vs non-detectable, OR=0.87, 95% CI 0.34-2.22; >50 µg/kg lipid, OR=0.61, 95% CI 0.22-1.66; p -trend=0.41) (Khanjani and Sim 2007). A recent birth

cohort study reported no association between birth weight adjusted for gestation length and log maternal plasma PCBs in New York City ($\beta=17\pm 116$ g, $p=.88$) (Wolff and others 2007).

Maternal TCDD exposure, inadequate evidence

Low birth weight at term was not associated with TCDD-contaminated soil (20-100 ng/g for 2+ yr or ≥ 100 ng/g for at least 6 mos) at or near the prenatal residence in Missouri (OR=1.09, 95% CI 0.50-2.28) (Stockbauer and others 1988). A birth cohort study of women exposed to TCDD at Seveso found a statistically non-significant increased risk of FGD during the first 8 years of follow-up (per \log_{10} maternal serum TCDD increment, OR=1.8, 95% CI 0.7-4.3) (Eskenazi and others 2003). In a Japanese birth cohort, birth weight among mostly term infants was not associated with breast milk total TEQ from polychlorinated dibenzo-p-dioxins, polychlorinated dibenzofurans and coplanar polychlorinated biphenyls ($\beta=-2.30\pm 2.62$) (Tajimi and others 2005).

Paternal occupational TCDD exposure, inadequate evidence

Birth weight adjusted for gestation length was not associated with paternal occupational exposure to chlorophenate wood preservatives known to be contaminated with TCDD and related toxicants (per 100-hr increment in cumulative exposure up to 3 months before conception, OR=1.00, 95% CI 0.99-1.001) (Dimich-Ward and others 1996). Among Vietnam veterans, FGD was not associated with paternal serum TCDD (≥ 79 vs ≤ 10 pg/g lipid, OR=0.9, 95% CI 0.6-1.3) (Michalek and others 1998). Birth weight adjusted for gestation length was not related to serum TCDD levels among men exposed during production of trichlorophenol and derivatives such as 2,4,5-T (mean birth weight difference, TCDD ≥ 255 vs < 20 pg/g lipid, 83 ± 52 g, $p>.05$) (Lawson and others 2004).

6. Birth defects

Reviews

Reviewers	Scope	Conclusions	
(Birnbaum 1995), USA	Literature review, developmental effects of dioxins in humans and experimental animals	No in-depth epidemiologic studies of pregnancy outcome of TCDD-exposed women; inadequate evidence to assess role of TCDD in human birth defects	Early gestational exposure to relatively low doses of TCDD and dioxin-like chemicals can cause birth defects (especially cleft palate) in experimental animals
Gestational or lactational exposure to relatively low doses of TCDD and dioxin-like chemicals can cause ureteral hyperplasia and hydronephrosis in experimental animals			
(Longnecker and others 1997), USA	Review of epidemiologic studies of PCBs, DDT and related organochlorines	PCBs and p,p' -DDE comprise the bulk of organochlorine residues in human tissues	Inconclusive evidence for an association between spina bifida and paternal TCDD exposure
(Brouwer and others 1998), WHO Working Group	WHO expert review of health risks of PCDDs, PCDFs and PCBs	High-level prenatal maternal exposure from food cooked in oil contaminated with PCBs, PCDFs, PCTs and PQTs was associated with microcephaly and natal teeth; estimated maternal TCDD-TEQ body burden from PCDFs and dioxin-like PCBs was 2-3 $\mu\text{g}/\text{kg}$ body weight	
(National Academy of	Literature review, potential	There is limited evidence for	There is insufficient

Sciences 2003), USA	health effects from phenoxy herbicides contaminated with TCDD; 2,4-D and 2,4,5-T were contaminated with TCDD	associations between phenoxy herbicide exposure and spina bifida in children of Vietnam veterans	evidence to determine if phenoxy herbicide exposure is associated with birth defects other than spina bifida
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6a. Neural tube birth defects

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
(Erickson and others 1984), Atlanta, USA	Case-control	Atlanta, births 1968-1980	7133 cases of major structural birth defects, 4246 healthy live birth controls	Self-reported info on Vietnam military service incl Agent Orange exposure; review of military records, subjective ratings of opportunity for exposure	Matched for race, year of birth, hospital of birth; adj for maternal age, education, alcohol use and family history of birth defects yielded similar results
OR, self-reported exposure vs non-exposure; paper did not report CIs or p-values	Total CNS 0.78, n=663	Anencephaly 0.80, n=142 Spina bifida 1.19, n=201	microcephaly 2.15, n=85		
(Wolfe and others 1995), USA	Retrospective cohort	Vietnam veterans and wives/partners	1006 conceptions among exposed men and 1235 among unexposed comparison group with known serum TCDD levels; assessed pregnancy outcomes and infant mortality	Measured current serum TCDD on 94% of exposed men and 93% of comparison group; est'd levels at conception; categorized as background (current level ≤ 10 pg/g lipid), low (>10 and initial level ≤ 110 pg/g lipid) and high (>10 and initial level >110 pg/g lipid)	Paternal race, maternal prenatal smoking, prenatal alcohol, parent's ages, paternal military occupation in Southeast Asia
OR, CNS defects, serum TCDD low or high (defined above) vs unexposed veterans or comparison grp	4.18, 0.96-21.3				

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
(calc'd from data in paper)					
(Dimich-Ward and others 1996), British Columbia	Nested case-control	Within cohort of 19675 offspring of 9512 men exposed for at least one yr in a sawmill using chlorophenate wood preservatives	942 birth defects; linked cohort and health outcome databases; 5 controls per case	Father's exposure to chlorophenate wood preservatives estimated from job titles and duration of employment in each job; chlorophenate wood preservatives known to be contaminated with PCDDs including TCDD	Sex, parental ages
OR, birth defects, 75 th vs 25 th percentile cumulative chlorophenate exposure during 3 mos before conception	NTD 1.27, 0.8-2.0	OR, birth defects, 75 th vs 25 th percentile cumulative chlorophenate exposure during pregnancy	NTD 1.24, 0.8-2.0		
(Croen and others 1997), California	Two case-control studies	Population-based, 1989-1991	1) 507 live born or stillborn neural tube birth defect (NTD) cases, 517 live birth controls, (2) 201 live born or stillborn conotruncal heart birth defect cases, 439 oral cleft defect cases, 455 live birth controls	Mother-reported periconceptual residential history; assessed maternal residential proximity to 764 hazardous waste disposal sites incl 105 National Priority List (NPL) sites; categorized chemicals and potential for human exposure at nearby residences	Various combinations of maternal race/ethnicity, education, alcohol, family income, periconceptual vitamin supplement use, neighbourhood educational attainment, employment status, infant sex
OR, NTDs, maternal residence <1 mi from a NPL site	1.4, 0.8-2.4	OR, NTDs, maternal residence <1 mi from a NPL site containing PCBs	3.5, 0.9-10.6		

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
(Cordier and others 2004), France	Retrospective cohort	94239 births (incl 1481 birth defects) in communities with solid waste incinerators, 470369 births (incl 6730 birth defects) in unexposed communities, 1988-1997; population-based birth defect registry		70 incinerators in study region; experts assessed potential for dioxin, metal and dust emissions based on capacity, continuous vs discontinuous operation, dust control, fume treatment, year operations began	YOB, maternal age, population density, avg family income
RR, NTDs, expert-rated hazard of incinerator emissions, medium and high vs low exposure	0.79, 0.37-1.69 0.83, 0.35-1.96 p-trend > 0.05				
(Suarez and others 2005), Texas	Case-control	Population-based, Mexican-American women, 1995-2000	87 NTD cases, 101 normal live birth controls	Maternal serum collected 1 yr after conception; assessed 7 individual congeners (99, 101, 110, 118, 138, 153, 180) and sum of 105, 118, 138, 153, 170, 180, 194	BMI, maternal age
OR, NTD vs sum of 7 PCBs	<LOD 1.0 (ref) LOD-15.4 ng/g lipid 0.4, 0.2-1.1	15.5-32.0 1.1, 0.5-2.3 >32 0.7, 0.3-1.6	OR, NTD vs individual PCBs, detectable vs non-detectable levels	PCB 99 1.6, 0.4-6.2 101 2.3, 0.6-8.1	110 2.0, 0.5-7.1 118 1.0, 0.5-2.0
138	180				

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
0.6, 0.3-1.2 153 0.7, 0.4-1.2	0.6, 0.2-1.7				

Summary: Neural tube birth defects

Maternal PCB exposure, inadequate evidence

In a population-based case-control study in California, NTDs were weakly associated with periconceptual maternal residential proximity to NPL sites containing PCBs (OR=3.5, 95% CI 0.9-10.6) (Croen and others 1997). A case-control study of Mexican-American women in Texas found no association between NTDs and individual or summed PCB congener concentrations in maternal serum (sum of 7 PCB congeners >32 ng/g lipid vs <LOD, OR=0.7, 95% CI 0.3-1.6) (Suarez and others 2005).

Maternal TCDD exposure, inadequate evidence

A retrospective cohort study of births in French communities with solid waste incinerators and unexposed comparison communities reported no association between NTDs and expert-rated hazard of incinerator emissions (high vs low exposure, OR=0.83, 95% CI 0.35-1.96) (Cordier and others 2004).

Paternal occupational TCDD exposure, limited evidence

A case-control study in Atlanta reported no association between anencephaly or spina bifida and self-reported paternal exposure to Agent Orange in Vietnam (respective ORs=0.80 and 1.19, CIs not stated) (Erickson and others 1984). In a retrospective cohort study of Vietnam veterans and partners, there was an elevated risk of CNS birth defects of borderline statistical significance among offspring of men with low or high TCDD categories (defined above) (compared to unexposed Vietnam veterans, OR=4.18, 95% CI 0.96-21.3, calculated from data in paper, only 5 exposed case fathers) (Wolfe and others 1995). Among male sawmill workers in British Columbia, NTDs were associated with maximum preconceptional chlorophenolate exposure intensity (hr/yr) (75th vs 25th percentile, OR=2.35, 95% CI 1.1-5.3) and less strongly with cumulative exposure (hr) during the 3 mos before conception (75th vs 25th percentile, OR=1.27, 95% CI 0.8-2.0) (Dimich-Ward and others 1996). The latter findings are consistent with a role for cumulative exposure to PCDD and PCDF contaminants that bioaccumulate in body lipids. An expert panel concluded that there was limited epidemiologic evidence for an association between spina bifida and paternal exposure to phenoxy herbicides potentially contaminated by TCDD (National Academy of Sciences 2003).

6b. Cardiac birth defects

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
(Wolfe and others 1995), USA	Retrospective cohort	Vietnam veterans and wives/partners	1006 conceptions among exposed men and 1235 among unexposed comparison group with known serum TCDD levels; assessed pregnancy outcomes and infant mortality	Measured current serum TCDD on 94% of exposed men and 93% of comparison group; est'd levels at conception; categorized as background (current level ≤ 10 pg/g lipid), low (>10 and initial level ≤ 110 pg/g lipid) and high (>10 and initial level >110 pg/g lipid)	Paternal race, maternal prenatal smoking, prenatal alcohol, parent's ages, paternal military occupation, Southeast Asia
OR, cardiovascular system birth defects, serum TCDD low or high (defined above) vs unexposed veterans or comparison grp (calc'd from data in paper)	Low or high serum TCDD 1.63, 0.79-3.31	Low serum TCDD 2.39, 1.02-5.24 High serum TCDD 0.95, 0.28-2.65			
(Dimich-Ward and others 1996), British Columbia	Nested case-control	Cohort of 19,675 offspring of 9,512 men exposed for at least one yr in a sawmill using chlorophenate wood preservatives; linked cohort and to birth and stillbirth records	178 cases cardiovascular system birth defects, 5 controls per case	Father's expos to chlorophenate wood preservatives known to be contaminated with PCDDs incl TCDD estimated from job titles and duration of employment in each job	Sex, parental ages
Cardiac birth defects, OR per 100 hr cumulative exposure during 3 mos preconception	Conotruncal and septal defects 0.94, ns	Valvular and other cardiac defects 1.00, ns	Cardiac defects, OR per 100 hr exposure during peak exposure year up to 3 mos before conception	Conotruncal and septal defects 0.95, ns	Valvular and other cardiac defects 0.99, ns
(Cordier and others 2004), France	Retrospective cohort	94239 births (incl 1481 birth defects) in communities with solid waste incinerators, 470369 births (incl 6730 birth defects) in		70 incinerators in study region; experts assessed potential for dioxin, metal and dust emissions based on capacity, continuous vs discontinuous operation,	YOB, maternal age, population density, avg family income

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
		unexposed communities, 1988-1997; population-based birth defect registry		dust control, fume treatment, year operations began	
RR, cardiac conotruncal defects, expert-rated hazard of incinerator emissions, medium and high vs low exposure	Medium exposure 0.99, 0.58-1.72 High exposure 0.97, 0.58-1.60 p-trend >.05	RR, other cardiac defects, expert-rated hazard of incinerator emissions, medium and high vs low exposure	Medium exposure 0.93, 0.63-1.38 High exposure 1.05, 0.72-1.53 p-trend > .05		

Summary: Cardiac birth defects

Maternal TCDD exposure, inadequate evidence

A retrospective cohort study of births in French communities with solid waste incinerators and unexposed comparison communities reported no association between cardiac birth defects and expert-rated hazard of incinerator emissions (high vs low exposure, conotruncal defects, OR=0.97, 95% CI 0.58-1.60; other cardiac defects, OR=1.05, 95% CI 0.72-1.53) (Cordier and others 2004).

Paternal occupational TCDD exposure, inadequate evidence

In a retrospective cohort study of Vietnam veterans and partners, there was an elevated risk of cardiovascular birth defects among offspring of men with low (OR=2.39, 95% CI 1.02-5.24) but not high serum TCDD levels (OR=0.95, 95% CI 0.28-2.65) (TCDD categories defined above) (Wolfe and others 1995). Among offspring of male sawmill workers, conotruncal and septal defects were not associated with preconceptional chlorophenolate exposure intensity (per 100 hr exposure during peak exposure year up to 3 mos before conception, OR=0.95, p>.05) or with cumulative exposure during the 3 mos before conception (per 100 hr exposure, OR=0.94, p>.05) (Dimich-Ward and others 1996).

6c. Orofacial birth defects

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
(Wolfe and others 1995), USA	Retrospective cohort	Vietnam veterans and wives/partners	1006 conceptions among exposed men and 1235 among unexposed comparison group with known serum TCDD levels; assessed pregnancy outcomes and infant mortality	Measured current serum TCDD on 94% of exposed men and 93% of comparison group; est'd levels at conception; categorized as background (current level ≤ 10 pg/g lipid), low (>10 and initial level ≤ 110 pg/g lipid) and high (>10 and initial level >110 pg/g lipid)	Paternal race, maternal prenatal smoking, prenatal alcohol, parent's ages, paternal military occupation in Southeast Asia
OR, cleft lip and/or cleft palate, serum TCDD low or high (defined above) vs unexposed veterans or comparison grp (calc'd from data in paper)	1.09, 0.42-2.62				
(Cordier and others 2004), France	Retrospective cohort	94239 births (incl 1481 birth defects) in communities with solid waste incinerators, 470369 births (incl 6730 birth defects) in unexposed communities, 1988-1997; population-based birth defect registry		70 incinerators in study region; experts assessed potential for dioxin, metal and dust emissions based on capacity, continuous vs discontinuous operation, dust control, fume treatment, year operations began	YOB, maternal age, population density, avg family income
RR, facial clefts, expert-rated hazard of incinerator emissions, medium and high vs	Medium exposure 0.79, 0.49-1.29	High exposure 1.01, 0.64-1.59 p-trend > 0.05			

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
low exposure					

Summary: orofacial birth defects

Maternal TCDD exposure, inadequate evidence

A retrospective cohort study of births in French communities with solid waste incinerators and unexposed comparison communities reported no association between facial clefts and expert-rated hazard of incinerator emissions (high vs low exposure, OR=1.01, 95% CI 0.64-1.59) (Cordier and others 2004).

Paternal occupational TCDD exposure, inadequate evidence

In a retrospective cohort study of Vietnam veterans and partners, there was no association between ear, face or neck defects and paternal serum TCDD categories (low or high serum TCDD vs unexposed or serum TCDD <10 pg/g lipid, OR=1.09, 95% CI 0.42-2.62 (calculated from data in paper)) (Wolfe and others 1995).

6d. Musculoskeletal birth defects

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
(Wolfe and others 1995), USA	Retrospective cohort	Vietnam veterans and wives/partners	1006 conceptions among exposed men and 1235 among unexposed comparison group with known serum TCDD levels; assessed pregnancy outcomes and infant mortality	Measured current serum TCDD on 94% of exposed men and 93% of comparison group; est'd levels at conception; categorized as background (current level ≤ 10 pg/g lipid), low (>10 and initial level ≤ 110 pg/g lipid) and high (>10 and initial level >110 pg/g lipid)	Paternal race, maternal prenatal smoking, prenatal alcohol, parent's ages, paternal military occupation in Southeast Asia
OR, musculoskeletal birth defects, serum TCDD low or high (defined above) vs unexposed veterans or comparison grp (calc'd from data in paper)	Low serum TCDD 1.08, 0.72-1.60	High serum TCDD 0.89, 0.58-1.32			

Summary: Musculoskeletal birth defects

Paternal occupational TCDD exposure, inadequate evidence

In a retrospective cohort study of Vietnam veterans and partners, there was no association between musculoskeletal birth defects and paternal serum TCDD levels categorized as low (current level >10 and initial level ≤ 110 pg/g lipid, OR=1.08, 95% CI 0.72-1.60) or high (current level >10 and initial level >110 pg/g lipid, OR=0.89, 95% CI 0.58-1.32, calculated from data in paper) (Wolfe and others 1995).

6e. Urinary tract defects

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
(Wolfe and others 1995), USA	Retrospective cohort	Vietnam veterans and wives/partners	1006 conceptions among exposed men and 1235 among unexposed comparison group with known serum TCDD levels; assessed pregnancy outcomes and infant mortality	Measured current serum TCDD on 94% of exposed men and 93% of comparison group; est'd levels at conception; categorized as background (current level ≤ 10 pg/g lipid), low (>10 and initial level ≤ 110 pg/g lipid) and high (>10 and initial level >110 pg/g lipid)	Paternal race, maternal prenatal smoking, prenatal alcohol, parent's ages, paternal military occupation in Southeast Asia
OR, urinary tract birth defects, serum TCDD low or high (defined above) vs unexposed veterans or comparison grp (calc'd from data in paper)	Low serum TCDD 1.97, 0.70-4.97	High serum TCDD 2.12, 0.81-5.12			
(Cordier and others 2004), France	Retrospective cohort	94239 births (incl 1481 birth defects) in communities with solid waste incinerators, 470369 births (incl 6730 birth defects) in unexposed communities, 1988-1997; population-based birth defect registry		70 incinerators in study region; experts assessed potential for dioxin, metal and dust emissions based on capacity, continuous vs discontinuous operation, dust control, fume treatment, year operations began	YOB, maternal age, population density, avg family income
RR, renal dysplasia, expert-rated hazard of incinerator emissions, medium and high vs low	1.05, 0.46-2.36 1.30, 0.57-2.97	RR, obstructive urinary tract defects, expert-rated hazard of incinerator emissions, medium and high vs low exposure	1.38, 0.65-2.93 1.93, 0.94-3.93 p-trend=0.07		

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
exposure	p-trend > 0.05				

Summary: Urinary tract birth defects

Maternal TCDD exposure, inadequate evidence

A retrospective cohort study of births in French communities with solid waste incinerators and unexposed comparison communities revealed that expert-rated hazard of incinerator emissions was associated with obstructive urinary tract defects (high vs low exposure, OR=1.93, 95% CI 0.94-3.93, p-trend=0.07) but not with renal dysplasia (OR=1.30, 95% CI 0.57-2.97) (Cordier and others 2004).

Paternal occupational TCDD exposure, inadequate evidence

In a retrospective cohort study of Vietnam veterans and partners, urinary tract birth defects were associated with paternal serum TCDD levels categorized as low (OR=1.97, 95% CI 0.70-4.97) or high (OR=2.12, 95% CI 0.81-5.12) (calculated from data in paper) (Wolfe and others 1995). These findings preclude firm inferences as the odds ratios were not statistically significant (there were only 17 cases among the 3 exposure categories) and there was no testing or adjustment for potential confounders. A review concluded that early gestational exposure to relatively low doses of TCDD and dioxin-like chemicals can cause ureteral hyperplasia and hydronephrosis in experimental animals (Birnbaum 1995).

6f. Male genital birth defects

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
(Wolfe and others 1995), USA	Retrospective cohort	Vietnam veterans and wives/partners	1006 conceptions among exposed men and 1235 among unexposed comparison group with known serum TCDD levels; assessed pregnancy outcomes and infant mortality	Measured current serum TCDD on 94% of exposed men and 93% of comparison group; est'd levels at conception; categorized as background (current level ≤ 10 pg/g lipid), low (>10 and initial level ≤ 110 pg/g lipid) and high (>10 and initial level >110 pg/g lipid)	Paternal race, maternal prenatal smoking, prenatal alcohol, parent's ages, paternal military occupation in Southeast Asia
OR, urinary tract birth defects, serum TCDD low or high (defined above) vs unexposed veterans or comparison grp (calc'd from data in paper)	Hypospadias 1.66, 0.41-6.10				
(Dimich-Ward and others 1996), British Columbia	Nested case-control	Within cohort of 19675 offspring of 9512 men exposed for at least one yr in a sawmill using chlorophenate wood preservatives	942 birth defects; linked cohort and health outcome databases; 5 controls per case	Father's exposure to chlorophenate wood preservatives estimated from job titles and duration of employment in each job; chlorophenate wood preservatives known to be contaminated with PCDDs including TCDD	Sex, parental ages
OR, birth defects, 75 th vs 25 th percentile cumulative chlorophenate	Genital organs 1.29, 0.9-1.5 Cryptorchidism	OR, birth defects, 75 th vs 25 th percentile cumulative chlorophenate exposure during pregnancy	Genital organs 1.3, 1.0-1.7 Cryptorchidism		

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
exposure during 3 mos before conception	1.16, 0.8-1.6		1.4, 1.0-1.9		
(Hosie and others 2000), Mannheim, Germany	Case-control	Pediatric surgical cases	18 cases cryptorchidism, 30 controls	Measured DDT/DDE, PCBs (28, 52, 101, 138, 153, 180), toxaphenes, HCH, chlorinated cyclodienes, HCB and other chlorinated benzenes in adipose tissue samples Median and ranges of contaminants ($\mu\text{g}/\text{kg}$ lipid) in controls: PCBs – 561, 52-2965	
Cryptorchidism	Median adipose tissue PCB levels, cases vs controls	558 vs 561 $\mu\text{g}/\text{kg}$ lipid, $p>0.05$			
(Cordier and others 2004), France	Retrospective cohort	94239 births (incl 1481 birth defects) in communities with solid waste incinerators, 470369 births (incl 6730 birth defects) in unexposed communities, 1988-1997; population-based birth defect registry		70 incinerators in study region; experts assessed potential for dioxin, metal and dust emissions based on capacity, continuous vs discontinuous operation, dust control, fume treatment, year operations began	YOB, maternal age, population density, avg family income
RR, hypospadias, expert-rated hazard of incinerator emissions, medium and high vs low exposure	0.59, 0.28-1.23 1.12, 0.53-2.35 p-trend $>.05$				

Summary: Male genital birth defects

Maternal PCB exposure, inadequate evidence

A small German case-control study observed no association between cryptorchidism and infant adipose tissue PCB levels (median concentrations, cases vs controls, 558 vs 561 $\mu\text{g}/\text{kg}$ lipid, $p>.05$) (Hosie and others 2000).

Maternal TCDD exposure, inadequate evidence

A retrospective cohort study of births in French communities with solid waste incinerators and unexposed comparison communities reported no association between hypospadias and expert-rated hazard of incinerator emissions (high vs low exposure, $\text{OR}=1.12$, 95% CI 0.53-2.35, $p\text{-trend}>.05$) (Cordier and others 2004).

Paternal occupational exposure to TCDD, 2,4,5-T or chlorophenate wood preservatives, inadequate evidence

In a retrospective cohort study of Vietnam veterans, genital tract birth defects were not associated with paternal serum TCDD levels categorized as low or high ($\text{OR}=1.66$, 95% CI 0.041-6.10, calculated from data in paper) (Wolfe and others 1995). Among male infants of British Columbia sawmill workers exposed to chlorophenate wood preservatives known to be contaminated with TCDD and related toxicants, genital tract defects were weakly associated with hours of exposure during the 3 preconceptional months (75th vs 25th percentile, $\text{OR}=1.29$, 95% CI 0.9-1.5) (Dimich-Ward and others 1996).

6g. Congenital tooth abnormalities

Reference	Design	Sampling frame	Subjects	Exposure	Covariates	
(Rogan and others 1988), Taiwan	Retrospective cohort study		127 Yucheng children, 115 unexposed neighbourhood controls, age 1 month to 8 yr; conducted physical examinations	Yucheng children exposed prenatally and lactationally to PCBs, PCDFs and PCQs		
Prevalence of natal teeth, exposed vs unexposed	11/127 vs 0/113 OR= ∞ , 3.0- ∞					
(Lan and others 1989), Taiwan	Retrospective cohort study		18 children prenatally exposed to PCBs, 44 unexposed children; examined for missing permanent teeth	Mothers of exposed children prenatally consumed cooking oil contaminated by PCBs, PCDFs and related toxicants		
Prevalence of missing tooth germ, exposed vs unexposed children	5/18 vs 1/44 OR=16.5, 1.6-411					
(Alaluusua and others 1999), Finland	Cohort		102 children age 6-7; dental exams for hypomineralized enamel defects in permanent molars that are mineralized	Measured breast milk (collected at 4 wk postpartum) PCDDs/PCDFs (17 congeners), PCBs (33 congeners); calc.	Sum of TEQ from PCDDs/PCDFs and PCBs: mean=48.8 \pm 29.1(SD), range 7.7-258 pg/g milk lipid	

Reference	Design	Sampling frame	Subjects	Exposure	Covariates	
			during first 2 yrs of life	TCDD-TEQ; used duration of BF plus milk TCDD-TEQ to estimate lactational exposure		
Observed hypomineralized enamel defects in 17 children	Enamel defects were associated with ranked level of lactational exposure to TCDD-TEQ from PCDDs/PCDFs and PCBs; p-values from regression analysis (only data provided)	PCDD/PCDF-TEQ P=.004 PCB-TEQ p=.07				
(Alaluusua and others 2002), Finland	Case-control; neonatal dental examination	Recruited mother-infant pairs in 4 hospitals in Helsinki and southern Finland during 1997-2000	14 infants with natal or neonatal teeth, 12 normal controls	Measured 17 PCDD/PCDF and 36 PCB congeners in breast milk 4-8 wk after delivery; median PCDD/PCDF- and PCB-TEQs, respectively, in controls were 8.6 (IQ range 6.0-10.0) and 5.3 (IQ range 3.5-6.2) pg/g lipid		
Mean breast milk PCDD/PCDF- or PCB-TEQ, natal/neonatal teeth case vs control mothers	PCDD/PCDF-TEQ 11.9 vs 8.6, Mann-Whitney p=.70	PCB-TEQ 7.2 vs 5.3, Mann-Whitney p=.59				

Reference	Design	Sampling frame	Subjects	Exposure	Covariates	
(Wang and others 2003), Taiwan	Cohort study	Women prenatally exposed during Yucheng incident; unexposed children	73 Yucheng children, 75 unexposed children; conducted dental examinations incl x-rays at age 7-11 in 1992	Maternal prenatal exposure to food cooked in oil contaminated with PCBs, PCDFs, PCTs and PCQs	Measured maternal total serum PCBs and children's total serum PCBs and PCDF-TEQ at age 6-10 (2,3,4,7,8-PnCDF and 1,2,3,4,7,8-HxCDF)	Matched for neighbourhood, age, sex, maternal age, parents' education and occupation
Prevalence of neonatal teeth by exposure status	Maternal serum PCB (ng/g) Comparison grp <10 10-36 ≥37	Prevalence 0.0 5.3 11.5 13.0 p-trend=.003	Prevalence of neonatal teeth by exposure status	BF duration (wk) Comparison FF BF short BF long	Prevalence 0.0 14.3 0 10 trend=.08	
Prevalence of developmental tooth defects by exposure status	Maternal serum PCB (ng/g) Comparison group Exposed group <10 10-36 ≥37	Prevalence 2.7% 9.1 11.5 24 p-trend=.001	Childhood serum PCDF-TEQ (pg/g) Comparison group Exposed group 85-455 481-3830	Prevalence 2.7% 6.3 20 p-trend=.01	Childhood serum PCB (ng/g) Comparison group Exposed group <3 3-83	Prevalence 2.7% 6.3 20 p-trend=.01
(Alaluusua and others 2004), Seveso	Retrospective cohort	Persons exposed to TCDD as children	48 persons from contaminated regions and 65 from surrounding non-contaminated region examined for dental abnormalities		Serum TCDD at baseline 23-26,000 ng/g lipid among persons from contaminated regions	

Reference	Design	Sampling frame	Subjects	Exposure	Covariates	
OR, developmental enamel defects, serum TCDD \geq 238 ng/kg lipid vs <238 ng/kg lipid or from uncontaminated region	2.4, 1.3-4.5	25/27 of persons with developmental enamel defects were age <5 at exposure				

Summary: Developmental tooth abnormalities

Natal teeth

Maternal high-level PCB/PCDF exposure, sufficient evidence

Prenatal consumption of cooking oil contaminated with high levels of PCBs, PCDFs and related toxicants in Taiwan was associated with natal teeth (prevalence, exposed vs unexposed, 11/127 vs 0/113, OR= ∞ , 95% CI 3.0 to ∞) (Rogan and others 1988). Further investigation revealed a dose-response relationship between a history of natal teeth and maternal serum PCB levels (0.0% among unexposed children; 5.3, 11.5 and 13.0% among those with increasing maternal serum PCB tertiles, p-trend=.003) (Wang and others 2003).

High-level lactational PCB/PCDF exposure, inadequate evidence

Among Yucheng children, there was an irregular relationship between a history of natal teeth and breastfeeding duration (0.0% among unexposed children; 14.3% among formula-fed Yucheng children and 0 and 10%, respectively, among Yucheng children breastfed for shorter or longer periods, p-trend=.08) (Wang and others 2003).

Maternal background PCB/PCDD/PCDF exposure, inadequate evidence

In a small Finnish cohort, natal teeth were not associated with breast milk TCDD-TEQ exposure from PCDDs/PCDFs or PCBs (cases vs non-cases, mean PCDD/PCDF-TEQ 11.9 vs 8.6 pg/g milk lipid, p=.11; mean PCB-TEQ 7.2 vs 5.3 pg/g milk lipid, p=.31) (Alaluusua and others 2002).

Hypomineralized enamel and other developmental tooth defects

Maternal high-level PCB/PCDF exposure, limited evidence

Prenatal consumption of cooking oil contaminated with high levels of PCBs, PCDFs and related toxicants in Taiwan was associated with missing permanent tooth germ (exposed vs unexposed, 5/18 vs 1/44. OR=16.5, 95% CI 1.6-411, calculated from data in paper) (Lan and others 1989). Further investigation revealed a dose-response relationship between the prevalence at age 7-11 of other developmental tooth defects (fusion, microdontia, pigmentation, enamel hypoplasia, impaction) and maternal serum PCB levels (2.7% among unexposed children; 9.1, 11.5 and 24.0% among increasing maternal serum PCB tertiles, p-trend=.001) (Wang and others 2003).

Maternal background PCB exposure, inadequate evidence

A cross-sectional study of Slovenian children found a higher prevalence of enamel defects among residents of a PCB-contaminated region compared with those from a relatively uncontaminated region (22 vs 13%, $p < .001$) (Jan and Vrbic 2000). Unfortunately, this study did not assess the relationship between enamel defects and biomarkers of PCB exposure.

Maternal PCDD/PCDF/PCB-TEQ or TCDD exposure, inadequate evidence

A small Finnish cohort study (102 children) showed that hypomineralized enamel defects at age 6-7 were associated with total lactational TCDD-TEQ exposure from PCDDs/PCDFs and PCBs; the statistical significance was stronger for PCDD/PCDF-TEQ ($p = .004$) than PCB-TEQ ($p = .07$); this short communication did not include other statistical data on the strength of these associations or potential confounders (Alaluusua and others 1999). A small retrospective cohort study of persons exposed before age 10 to TCDD at Seveso revealed an association between developmental tooth enamel defects (opacities or hypoplasia) and serum TCDD at baseline soon after the incident (≥ 238 vs < 238 pg/g lipid, OR=2.4, 95% CI 1.3-4.5) (Alaluusua and others 2004).

7. Postnatal growth – reviews

Reviewers			
(Guo and others 2004), Taiwan	Review of health effects among the cohort of persons exposed to food cooked in oil contaminated by PCBs, PCDFs, PCTs and PCQs during the 1979 Yucheng incident	Compared to an unexposed comparison group, prenatally exposed Yucheng children had height deficits up to age 13	
(Guo and others 1995), Taiwan	Review of Yucheng, Michigan and North Carolina cohorts of children of women exposed to PCBs and related compounds	Yucheng – mean and median maternal serum PCB levels near end of pregnancy were 49 and 27 µg/L; Michigan – mean maternal and cord serum PCB levels, respectively, were 4.7-5.9 and 2.0-2.5 µg/L; North Carolina – median maternal and cord serum PCB levels were 9.1 and about 4 µg/L	Postnatal growth in height was reduced among children of exposed women in the Yucheng cohort (did not comment on results of other 2 cohorts)
(Longnecker and others 1997), USA	Review of epidemiologic studies of PCBs, DDT and related organochlorines	PCBs and ρ,ρ' -DDE comprise the bulk of organochlorine residues in human tissues	Prenatal mixed exposure to high levels of PCBs, PCDFs and related organochlorines in the Yusho and Yucheng incidents was associated with reduced stature during childhood

Original studies

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
(Rogan and others 1988), Taiwan	Cohort	127 Yucheng children, 115 unexposed neighbourhood controls, age 1 month to 8 yr	Physical examinations	Yucheng children exposed prenatally and lactationally to PCBs, dibenzofurans and related toxicants	

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
Height at follow-up lower among children of exposed mothers	-3% (CI -4 to -1)				
(Jacobson and others 1990b), Michigan	Birth cohort	Women who consumed PCB-contaminated Lake Michigan fish; farm families exposed to PCB- or PBB-contaminated farm products	236 children of women who consumed contaminated fish, 87 children of farm families; assessed weight at age 4 yr	Mean PCB and PBB levels in cord and 4-yr serum were 2.5 and 2.1 µg/L and in breast milk was 836 µg/L	Combinations of child sex, maternal and paternal height and weight, maternal age, gravidity, examiner, SES, maternal employment, marital status, smoking, breast milk PBB level, child's serum PBB and DDT and blood lead
Height and head circumference at age 4 yr vs any PCB exposure index	Result stated without supporting data				
(Guo and others 1994), Taiwan	Cohort	Mothers exposed to PCBs during 1978-1979 Yucheng incident	55 prenatally exposed children age 6-13 yr, matched comparison group	Mean maternal serum PCB level close to delivery was 51 ng/g serum (range 2-341); mean serum PCB levels among 6 exposed and 10 unexposed children were 3.0 and 0.5 ng/g serum; corresponding serum PCDF levels among 9 exposed children and 10 unexposed children were 823 and 40 pg/g lipid	Groups matched for neighbourhood, age, sex, maternal age, parental education and occupation
Difference in average height,	Age 6-13 yr -3.1 cm, p<.01				

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
exposed vs unexposed children					
(Patandin and others 1998), Rotterdam, The Netherlands	Birth cohort	Healthy term infants (37+ wk) born during 1990-92 in a large industrial city	105 breast-fed and 102 formula-fed infants; measured weight, length and head circumference at 10 d and 3, 7, 18 and 42 mos	Measured 4 PCBs (118, 138, 153, 180) in cord and maternal plasma and 26 PCBs and 17 PCDD/PCDFs in breast milk; median PCBs in maternal plasma, cord plasma and breast milk (2 nd wk after delivery) were 2.0 µg/L (range 0.6-7.4), 0.4 µg/L (range 0.1-2.1) and 392 ng/g lipid (range 174-1226); median total breast milk PCDD/PCDF/PCB-TEQ was 65 pg/g lipid (range 28-155)	Parity, prenatal maternal alcohol and smoking, gestational age, parental height index
Height gain by age 3 mos in formula-fed infants	Prenatal exposure: β -coefficient (standard deviations relative to national norms) per unit change in natural log cord plasma PCB levels (µg/L)	β =-0.28 cm, SE 0.12, p=0.03	Height gain by age 3 mos in breastfed infants	Prenatal PCB and cumulative lactational PCDD/PCB-TEQ exposure: β -coefficient (standard deviations relative to national norms) per unit change in cord blood PCB (µg/L) or PCDD/PCB-TEQ (pg/g lipid)	PCBs β =0.002 cm, SE 0.19, p=0.99 PCDD/PCB-TEQ β =-0.05 cm, SE 0.31, p=0.88
Height gain from age 3 to 7 mos in breastfed infants	Cumulative lactational exposure: β -coefficient (standard deviations relative to national norms) per unit change in cord blood PCB (µg/L) or PCDD/PCB-TEQ (pg/g lipid)	PCBs β =-0.21 cm, p=.04	Growth in height at age 7-18 mos and at age 18-42 mos was not associated with prenatal PCB or lactational PCDD/PCB-TEQ exposure (stated without supporting data)		

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
(Gladen and others 2000), North Carolina	Birth cohort; self-reported height and weight solicited by questionnaire beginning in 1992 for max. 5 yr	Mother-infant pairs recruited from general population in 1978-82	594 youth surveyed annually beginning at age 12-14	Measured PCBs and DDE in breast milk, maternal and cord blood and placenta and converted to equivalent concentration in breast milk lipid; median PCB concentration – 1.7 µg/g lipid (range 0.5-5.5); median cumulative lactational PCB exposure – 5.0 mg (range 0.2-23)	Age, maternal weight, race, breast feeding
Girls	Average height by increasing prenatal PCB level (0-1, 1-2, 2-3, 3+ µg/g lipid)	165, 164, 164, 164 cm p-trend=.75	Girls	Average height by increasing cumulative lactational PCB intake (formula-fed, 0-5, 5-10, 10+ mg)	166, 163, 164, 164 cm p-trend=.13
Boys	Average height by increasing prenatal PCB level	169, 169, 170, 166 cm p-trend=.24	Boys	Average height by increasing cumulative lactational PCB intake	169, 168, 169, 169 cm p-trend=.92
(Karmaus and others 2002), Germany	Retrospective cohort	3 repeat surveys during 1994-1997 of 343 children (age 7-8 yr in 1994) and their parents	Assessed growth in height and weight since birth in relation to blood organochlorines measured at age 7-8 yr	Measured blood PCB (7 congeners) and DDE levels at age 7-8 yr in 1994 PCB and DDE levels highly correlated (Spearman r = 0.64)	Child age, maternal age, parental education and height, birth weight, birth order, environmental tobacco smoke exposure, prenatal maternal smoking, breast-feeding duration, body mass index
Growth in height from birth to age 10-11 yr vs blood PCB levels among boys or girls at					

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
baseline (data not shown in report)					
(Blanck and others 2002), Michigan, USA	Cohort study; assessed mother or self-reported height and weight of daughters at age 5-24 in 1997	Daughters of women exposed to beef, poultry and dairy products contaminated by polybrominated biphenyls (PBBs) during 1973-1974	328 daughters	Measured mother's PBB (2,2',4,4',5,5'-hexabromodiphenyl) and PCB levels in 1976-81 Median and 90 th percentile maternal serum PBB 1.1 and 7.0 µg/L (range ND-1020); median and 90 th percentile maternal PCB 5.0 and 9.0 µg/L (range ND-78); estimated levels during pregnancy.	Daughter's age, height (in analysis of weight), breastfeeding status and mother's education, age at daughter's birth and height or BMI
Regression, change in height vs prenatal maternal serum PCB level category	5-8 vs <5 µg/L β=-0.04 inch, -0.8 to 0.7 ≥ 9.0 vs <5 µg/L β =0.2 inch, -0.8 to 1.3	Regression, change in height vs prenatal maternal serum PBB level category	1-6 vs <1 µg/L β =-0.33 inch, -1.0 to 0.4 ≥ 7.0 vs <1 µg/L β =0.61 inch, -0.5 to 1.7		
(Grandjean and others 2003), Faroe Islands	Birth cohort		182 singleton term infants; measure height and weight at ages 18 and 42 mos	Measured serum PCB at age 54 mos as an index of cumulative lactational PCB exposure	Birth weight, gestational age, sex, parity, maternal weight and height, diabetes, smoking, alcohol, child's age, BMI
Change in height at age 42 mos per doubling of serum PCB at age 54 mos	-0.63 cm (CI -1.12, -0.13)				
(Lamb and others 2006), New York	Cohort	NYC subset of African-American	Measured height at birth and ages 1, 4, 7	3 rd trimester maternal sera analyzed for PCBs (24 congeners) and	Maternal prepreg weight, preterm status, serum

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
City		mother-infant pairs in the National Collaborative Perinatal Project recruited in 1959-62	and 17 yr	DDE/DDT; median PCB 8.4 µg/L, mean/SD 9.2/3.5 µg/L	triglyceride and cholesterol, maternal height
Regression analysis, unit change in natural log of height at each age per unit change in natural log of maternal serum PCBs	Girls -0.6 cm, -3.2 to 2.0 Boys 0.5 cm, -1.4 to 2.3				
(Rylander and others 2007), Sweden	Nested case-control	Retrospective cohort of Swedish fishermen's wives; linked to Swedish Medical Birth Register, 1973-91	238 children with low birth wt (LBW, 1500-2750 g); 476 children with normal birth wt (NBW, 3250-4500 g); assessed parent, child-health centre and school-reported height at age 4 and 7	Measured plasma PCB-153 among mothers of 48 LBW and 109 NBW children in 1995 and extrapolated to value in year of child's birth	Matched for gender, parity, YOB
Mean difference in height at age 4 for maternal plasma PCB-153 ≥ 250 vs < 250 ng/g lipid	LBW infants $\beta = -0.21$ cm, -2.91 to 2.49 NBW infants $\beta = 0.35$ cm, -1.08 to 1.79	Height at age 7 vs maternal plasma PCB-153	LBW infants $\beta = -1.69$ cm, -6.06 to 2.69 NBW infants $\beta = -0.31$ cm, -2.05 to 1.43		

Summary: reduced postnatal growth in height

High-level maternal PCB/PCDF exposure, limited evidence

Compared to unexposed children, Yucheng children up to age 8 were 3% shorter (95% CI -4 to -1) (Rogan and others 1988). Further follow-up revealed a persistent height deficit up to ages 6-13 (exposed vs unexposed, difference -3.1 cm, $p < .01$) (Guo and others 1994). Reviewers concluded that growth in height during childhood was reduced among offspring of women prenatally exposed to cooking oil highly contaminated by PCBs, PCDFs and related toxicants (Guo and others 1995; Longnecker and others 1997).

Background maternal PCB exposure, inadequate evidence

The Dutch birth cohort study reported that cord blood PCB was inversely associated with growth in height from birth to age 3 months (change in height per unit change in natural log PCB, $\beta = -0.28 \pm 0.12$ cm, $p = .03$) but not with height changes during months 3-7, 7-18 or 18-42 (Patandin and others 1998). A Michigan birth cohort study found no association between height at age 4 and prenatal PCB exposure (stated without supporting data) (Jacobson and others 1990b). The North Carolina birth cohort study observed no association between prenatal PCB exposure and height at age 12-14 in girls or boys (average height vs increasing prenatal maternal PCB level, p -trend was 0.75 for girls and 0.24 for boys) (Gladen and others 2000). In another Michigan birth cohort, there was no association between prenatal serum PCB and height of daughters age 5-24 (PCB ≥ 9.0 vs ≤ 5.0 $\mu\text{g/L}$, $\beta = 0.2$ inches, 95% CI -0.8 to 1.3) (Blanck and others 2002). A birth cohort study in New York City revealed no association between height at intervals up to age 17 and 3rd trimester maternal serum PCB concentrations (unit change in natural log of height at each age per unit change in natural log of maternal serum PCBs, girls, -0.6 cm, 95% CI -3.2 to 2.0; boys, 0.5 cm, 95% CI -1.4 to 2.3) (Lamb and others 2006). A retrospective cohort study of Swedish fishermen's wives revealed no association between maternal plasma PCB-153 concentrations and child height at age 4 or 7 (normal birth weight children, mean difference in height at age 7, maternal plasma PCB-153 ≥ 250 vs < 250 ng/g lipid, $\beta = -0.31$, 95% CI -2.05 to 1.43) (Rylander and others 2007).

Lactational or childhood PCB exposure, inadequate evidence

A Michigan birth cohort study found no association between height at age 4 and lactational PCB exposure (stated without supporting data) (Jacobson and others 1990b). The Dutch birth cohort study reported that growth in height from 3-7 months was inversely related to cumulative lactational dioxin-TEQ based on cord blood PCDD/PCB concentrations and breast-feeding duration (weeks) (change in height per unit change in cumulative exposure, $\beta = -0.21$ cm, $p = .04$); changes in height from birth to age 3 months, 7-18 and 18-42 months were not associated with lactational PCDD/PCB-TEQ exposure (Patandin and others 1998). The North Carolina birth cohort study observed no association between cumulative lactational PCB exposure and height at age 12-14 (average height vs increasing lactational PCB intake, p -trend was 0.13 for girls and 0.92 for boys) (Gladen and others 2000). The North Carolina birth cohort study observed no association between lactational PCB exposure and height at age 12-14 (Gladen and others 2000). A German retrospective cohort study found no association between growth in height from birth to age 10-11 and blood PCB levels at age 7-8 (result stated without supporting data) (Karmaus and others 2002). In a small Faroe Islands birth cohort, growth in height from birth to age 42 months was inversely associated with lactational PCB exposure (change in height per doubling of serum PCB at age 54 mos, -0.63 cm, 95% CI -1.12 to -0.13) (Grandjean and others 2003).

Maternal PBB exposure, inadequate evidence

A Michigan birth cohort study reported no association between prenatal serum PBB and height of daughters at age 5-24 (change in height, PBB ≥ 7.0 vs ≤ 1.0 $\mu\text{g/L}$, $\beta = 0.61$ inches, 95% CI -0.50 to 1.7) (Blanck and others 2002).

8. Neuropsychological function

8a. Cognitive function

Reviews

Reviewers	Scope	Comments or conclusions	Conclusions
(Guo and others 1995), Taiwan	Review of Yucheng, Michigan and North Carolina cohorts of children of women exposed to PCBs and related compounds	Yucheng – mean and median maternal serum PCB levels near end of pregnancy were 49 and 27 µg/L; Michigan – mean maternal and cord serum PCB levels, respectively, were 4.7-5.9 and 2.0-2.5 µg/L; North Carolina – median maternal and cord serum PCB levels were 9.1 and about 4 µg/L	Mental development index scores among infants reduced among exposed infants in the Yucheng cohort; high cord serum PCB levels in the other 2 cohorts associated with visual recognition memory but not mental development index score deficits
(Schantz 1996), USA	Review of PCBs and developmental neurotoxicity	Prenatally exposed Yucheng children had IQ deficits but these were not associated with current childhood or maternal serum PCB levels	Noted inverse associations between reduced Brazelton Neonatal Assessment Battery scores and prenatal PCB levels in the Michigan birth cohort (statistically significant) and the North Carolina birth cohort (borderline statistical significance)
(Jacobson and Jacobson 1997), Michigan	Comparison of Michigan and North Carolina birth cohort studies; reanalyzed Michigan data using average PCB levels in cord and maternal serum and breast milk; neither study assessed PCDD/PCDF exposure. The Michigan study assessed a broader range of potential confounders; the NC study included the same set of potential confounders in all analyses; neither study controlled for maternal smoking; the NC cohort mothers were upper middle class and prevalence of smoking was only 11% whereas the	Most cord serum PCB levels were below detection limits (67% in Michigan, 88% in NC); prenatal PCB exposure indices in previous reports were based on maternal serum and breast milk in NC and on cord and maternal serum in Michigan	Cognitive function during infancy: Michigan – visual recognition memory (Fagan test) at age 7 mos inversely associated with cord serum PCB levels NC – Fagan test not used

	Michigan mothers were middle class and 31% smoked		
(Brouwer and others 1998; Brouwer and others 1998), WHO	Review of health risks to infants of perinatal exposure to PHAHs by a World Health Organization working group	Estimated maternal TCDD-TEQ body burden from PCDFs and dioxin-like PCBs was 2-3 µg/kg body weight, i.e., two orders of magnitude higher than background environmental exposure levels.	High-level prenatal exposure to PCBs, PCDFs and related organochlorines during the Yusho and Yucheng incidents caused reduced reduced IQ in children
Although prenatal exposure to ambient levels of PCBs or mixtures of PCBs and related organochlorines has been associated with reduced cognitive development scores in infants and children, most of the individual results were within normal limits. Cohort studies in The Netherlands found no associations between mental development indices at age 18 mos and breast milk TCDD-TEQs from dioxin-like PCBs, PCDDs and PCDFs.	Perinatal exposure of rodents and monkeys to individual (PCB-77, 118, 126 or 169) or mixed PCBs caused adverse neurobehavioral effects including impaired discrimination learning, altered open field activity and delayed spatial alternation	Perinatal exposure of monkeys to TCDD at 5 or 25 PPT in diet caused retarded learning of discrimination (shape) reversals	Perinatal exposure of rodents to PCB 169 or mixed PCBs during early gestation caused reduced striatal dopamine levels in offspring up to several weeks postnatally and severe reductions in fetal and neonatal brain T4 levels
(Foster and others 2000), USA	Review of potential impact of prenatal exposure to environmental contaminants on thyroid function and brain development	PCBs and TCDD have neurotoxic effects and alter thyroid function during critical periods of thyroid hormone-dependent brain development	Thyroid hormones are essential for neuronal proliferation, migration and differentiation in discrete brain regions; thyroid hormones regulate development of cholinergic and dopaminergic systems serving the cerebral cortex and hippocampus
(World Health Organization 2000), Geneva	Assessment of the health risk of PHAHs and re-evaluation of the tolerable daily TEQ intake (TDI)	Effects seen in highly exposed Yusho and Yucheng children included global persistent developmental delays	2 U.S. and 2 Dutch birth cohorts exposed to background PCB levels have shown neurodevelopmental delays
Among breast-fed infants in the Rotterdam/Groningen Dutch cohort, those with higher exposures based on breast milk TEQs tended to have poorer	Animals – sensitive health effects of TCDD and dioxin-like substances include developmental cognitive deficits	Health effects of TCDD and dioxin-like substances in animals occur at dioxin-TEQ body burden levels in the range 3-73 ng/kg, i.e.,	

neuropsychological test results		overlapping with dioxin TEQ body burdens in human populations exposed to background PHAH levels in industrialized countries	
(Boersma and Lanting 2000; Boersma 2001), The Netherlands	Review of results from Dutch birth cohort study up to age 6 yr including Bayley Scales of Infant Development at ages 18 mos, Kaufman Assessment Battery for Children at 42 mos and McCarthy Scales at age 6 yr	Assessed prenatal exposure by summing the concentrations of 4 non-coplanar PCBs in maternal and cord plasma; assessed postnatal exposure from PCBs (26 congeners) and PCDDs (17 congeners) in breast milk and formula and plasma PCB levels at age 42 mos	Median maternal and cord plasma PCB levels among breast- and formula-fed groups, respectively, were 2.2 and 0.43 µg/L and 1.9 and 0.34 µg/L; median breast milk PCB and total dioxin/PCB-TEQ levels in the breast-fed group were 405 ng/g lipid and 63 pg/g lipid vs non-detectable in the formula-fed group
Groups matched for maternal pregnancy history (no complications), parity (0 or 1), gestation length (37-42 wk), Caucasian race; note: breast-feeding mothers had much higher education and prevalence of prenatal alcohol use and much lower prevalence of prenatal smoking	Mental development index scores at 18 mos not associated with prenatal or postnatal PCB/dioxin exposure indices		
(Ribas-Fito and others 2001), Spain	Systematic review of 7 cohort studies of PCB exposure and childhood neuropsychological function	Among the 5 studies that evaluated cognitive function at age 4 years, 4 studies found inverse associations with prenatal PCB exposure.	Lactational PCB exposure was not clearly related to any indicator of neuropsychological function.
(Schantz and others 2003), USA	Review of PCB exposure and childhood neuropsychological function	Most epidemiologic studies have found associations between cognitive deficits and prenatal maternal environmental PCB exposure.	Major knowledge gap with respect to PCB congener-specific developmental neurotoxicity in experimental animals.
(Longnecker and others 2003), USA	Review of PCB levels in 10 epidemiological studies of neurodevelopment	Range of median maternal serum PCB-153 levels in the 10 studies was 30-450 ng/g lipid. The median level in the Faroe Islands study (450 ng/g lipid) was 3-4X those in most other studies. Levels	Such differences could partially explain inconsistent findings regarding health effects of prenatal PCB exposure in epidemiologic studies.

		in the two recent US studies were about 10% of those in the Faroe Islands study and a third of those in four earlier US studies or recent studies in the Netherlands, Germany and northern Quebec.	
(Guo and others 2004), Taiwan	Review of health effects among the cohort of persons exposed to food cooked in oil contaminated by PCBs, PCDFs, PCTs and PCQs during the 1979 Yucheng incident	Compared to unexposed children, prenatally exposed Yucheng children had Bayley Scale psychomotor and cognitive deficits at age 12-30 mos, higher activity scores at age 3-12, Stanford-Binet cognitive deficits at age 4-5, WISC cognitive deficits at age 6-7 and Raven's scale spatial ability deficits at age 6-8.	

Cognitive function, children age 0-2

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Jacobson and others 1985), Michigan	Birth cohort	123 white middle-class infants, recruited during 16-month period	Conducted Fagan test of visual recognition memory	75% of mothers had consumed at least 11.8 kg of Lake Michigan (LM) fish known to be contaminated with PCBs over a 6-yr period; other mothers had not consumed LM fish	Measured PCBs and PBBs in cord serum and breast milk; assessed lactational exposure from info on breast milk PCB levels and duration of breastfeeding	Identified and controlled for 3 potential confounders: SES, mat age, parity
Change in Fagan visual recognition memory test score per unit change in cord serum PCB	$\beta = -0.35$ points, $F(1,76) = 10.2$, $p < .005$	Association persisted after forcing birth weight, gestation length and neonatal Brazelton scale score into multiple regression model	Change in Fagan visual recognition memory test score per unit change in lactational PCB exposure	$F(3,80) = 1.18$, $p > .05$ (β not stated)		
(Rogan and others 1988), Taiwan	Cohort study	Survey (1985) of children of women exposed during 1979 to contaminated cooking oil	100 Yucheng children avg age 32 mos (range 1-82 mos), 106 unexposed neighbourhood controls avg age 31 mos; Bayley Scales at age 6-30 mos, Stanford-Binet at age 30-72 mos and WISC and Rutter scales at older ages	Yucheng children of women exposed during 1979 (up to 6 yr before pregnancy) to cooking oil contaminated by PCBs, dibenzofurans and related toxicants		Groups matched for neighbourhood, sex, age, birth order and family SES

Mean (\pm SE) MDI score, children of exposed vs unexposed women	100 \pm 2.5(SE), n=45, SD=16.8 106 \pm 2.4, n=45, SD=16.1	t-value of difference in means = 1.67, p=.10				
(Gladden and others 1988), North Carolina	Birth cohort	See Rogan et al 1986 above; conducted Bayley Scales of Infant Development	Assessed 706 infants at both ages 6 and 12 mos, 82 at age 6 mos only, 14 at age 12 mos only	Assessed prenatal PCB and DDE exposure from breast milk levels at or near birth and cumulative postnatal exposure from breast milk levels and lactation duration		Maternal age, race, education, occupation, smoking and alcohol; child sex, gestational length, birth weight, head circumference at birth, neonatal jaundice, breastfeeding duration, number of older siblings, number of abnormal reflexes neonatally, age, study center
Prenatal exposure: change in MDI score per unit change in breast milk PCB level at birth (μ g/g lipid)	Age 6 mos β =0.12 \pm 0.44, p=.78 Age 12 mos β =-0.54 \pm 0.54, p=.32	Lactational exposure: change in MDI score per 1 mg breast milk PCBs ingested from birth to age at test	Age 6 mos β =-0.18 \pm 0.20, p=.36 Age 12 mos β =-0.06 \pm 0.16, p=.70			
(Koopman-Esseboom and others 1996), Rotterdam, the Netherlands	Birth cohort (part of larger Dutch PCB/Dioxin Study)	Conducted Bayley Scales of Infant Development at age 3, 7 and 18 mos	207 mother-infant pairs (105 breastfed, 102 formula-fed)	Measured 4 PCBs (118, 138, 153, 180) in maternal plasma during last month of pregnancy and in cord blood; measured 17 PCDD and 24 PCB congeners in breast milk during	Mean cord and maternal plasma PCB levels were 0.5 and 2.2 ng/g plasma and the mean breast milk PCB/PCDD-TEQ was 67 pg/g lipid	Gestational age, parity, HOME score, maternal education, breast feeding duration

				2 nd postnatal week and computed total PCB-TEQ		
Age 7 mos: MDI vs ln maternal plasma PCB (4 non-coplanar congeners, ng/g)	$\beta=2.3\pm 1.7$ points, $p=.18$ (favourable effect)					
(Winneke and others 1998), Germany	Birth cohort	Mother-infant pairs recruited from 3 Dusseldorf hospitals	171 mother-infant pairs; Bayley Scales of Infant Development and Fagan Test of Infant Intelligence (a test of visual recognition memory) at age 7 mos		Mean levels of PCBs 138, 153 and 180 in cord plasma and maternal milk samples at ages 2 and 4 weeks were 0.55 $\mu\text{g/L}$ and 427 ng/g lipid	Maternal age, BMI, education, vocabulary and birth weight, HOME score, Apgar score, cord blood lead, breast feeding duration
Change in MDI at age 7 mos per unit change in cord plasma PCB ($\mu\text{g/L}$) and breast milk PCB (ng/g lipid)	Cord plasma PCB $\beta=0.06\pm 0.38$ (SE) points, $p=.43$ Breast milk PCB $\beta=-0.69\pm 0.41$ (SE) points, $p=.05$	Change in Fagan visual recognition test score at age 7 mos per unit change in cord plasma PCB ($\mu\text{g/L}$) and breast milk PCB (ng/g lipid)	Cord plasma PCB $\beta=0.93\pm 1.13$ points Breast milk PCB $\beta=-0.20\pm 1.19$, $p=.43$			
(Darvill and others 2000), New York State	Birth cohort (Oswego Newborn and Infant Development Project); conducted Fagan Test of Infant Intelligence at ages 6 and 12 mos	See Stewart et al. 2000 above	247 infants	Measured cord blood PCBs (total and highly chlorinated congeners), HCB, mirex, DDE, lead, breast milk PCBs (86 mothers), maternal hair Hg	Median and 75 th percentiles: breast milk PCBs – 153/249 ng/g lipid; cord blood PCBs – 0.53/1.11 ng/g wet wt, DDE – 0.10/0.18 ng/g wet wt, lead – 1.7/2.0 $\mu\text{g/dL}$; maternal hair mercury -	HOME score, parental ages, maternal education, height, weight, prepregnancy weight, weight gain during pregnancy, nutrition scale, herbal tea, caffeine, vitamin and non-prescription drug use, stress before pregnancy, smoking,

					0.5/0.7 µg/g	prenatal child sex, parity, birth weight, cord blood DDE, lead and erythrocyte protoporphyrin, maternal blood mercury
Linear trend analysis, Fagan score vs cord blood total PCBs (ng/g wet wt)	Age 6 mos F(1,214)=4.87, p=.01 Age 12 mos F(1,207)=2.04, p=.08	Linear trend analysis, Fagan score vs breast milk total PCBs (ng/g lipid)	Age 6 mos β=0.065, t=0.37, p=.71 Age 12 mos β=-0.075, t=-0.51, p=.30	Linear trend analysis, Fagan score vs cord blood highly chlorinated PCBs (ng/g wet wt)	Age 6 mos F(1,214)=1.20, p>0.05 Age 12 mos F(1,207)=4.08, p=.02	
(Walkowiak and others 2001), Germany	Birth cohort	171 mother-infant pairs recruited in 3 Dusseldorf hospitals, 1993-95; 1 st or 2 nd born term infants, 5' Apgar ≥78	Conducted Bayley Scales at ages 7, 18, 30 and 42 mos and Kaufman Assessment Battery at age 42 mos; n=116 at 42 mos	Cord serum, breast milk and child serum (age 42 mos) PCB levels (congeners 138, 153, 180)	Median and 95 th percentile PCB levels: cord serum 0.4/0.8 µg/L; milk - 404/679 ng/g lipid; child serum -1.2/3.4 µg/L	Parental education, sex, maternal IQ, HOME score, parity, prenatal maternal smoking and BMI
Multiple regression analysis of MDI vs log ₂ breast milk PCB (ng/g lipid)	age 7 mos β=-3.61, t=-1.26, p=.10 age 18 mos β=-4.11, t=-1.56, p=.06	age 30 mos β=-4.98, t=-1.80, p=.035 age 7-30 mos β=-4.19, t=-1.99, p=.025	MDI score differences, age 30 mos, 95 th vs 5 th percentile breast milk PCB (i.e., ≥679 vs ≤173 ng/g lipid)	MDI -8.3, -16.5 to 0.0		
(Daniels and others 2003), 1959-66 Collaborative Perinatal Project, USA	Birth cohort (Collaborative Perinatal Project,)	Children of about 42,000 women recruited during pregnancy at 12 U.S. hospital, 1959-66;	1065 randomly selected children and 194 with Bayley PDI scores at least 1 SD above	Maternal sera collected every 8 wk during pregnancy, at delivery and 6 wk	Median and 95 th percentile maternal PCB - 2.7 and 6.3 µg/L	Research centre, maternal education, triglycerides, cholesterol, birth order; results not

		3 rd trimester frozen maternal serum sample available	or below the group mean; conducted Bayley Scales at age 8 mos	postpartum; analyzed PCBs in 3 rd trimester sera (11 congeners – 28, 52, 74, 105, 118, 138, 153, 170, 180, 194, 203)		affected by including maternal serum DDE, race, prepregnancy BMI, breastfeeding
Regression analysis of MDI at age 8 mos vs 3 rd trimester maternal serum PCB; β = increase of MDI per $\mu\text{g/L}$ increase in maternal serum PDB	$\beta=0.10$, $SE=0.26$, $p=.71$					

Summary: Cognitive function deficits, children age 0-2

High-level maternal PCB/PCDF exposure, sufficient evidence

Compared to unexposed children, Yucheng children had a statistically non-significant Bayley MDI score deficit at ages 6-30 months (difference in mean Bayley MDI 6.0 points, $t=1.67$, $p=.10$; t and p calculated from data in paper) (Rogan and others 1988). A WHO expert group concluded that high-level prenatal exposure to PCBs, PCDFs and related compounds caused childhood cognitive deficits and persistent global developmental delays, mild behaviour disorders and hearing deficits (Brouwer and others 1998; World Health Organization 2000).

Background maternal PCB exposure, limited evidence

In the Michigan cohort, the Fagan test of visual recognition memory at 7 months was inversely associated with cord serum PCB levels (change in MDI score per unit change in cord serum PCB, $\beta=-0.35$ points, $F(1,76)=10.2$, $p<.005$) (Jacobson and others 1985). The authors stated that, unlike the Bayley MDI, the Fagan test during infancy is predictive of childhood cognitive function, likely because it measures visual discrimination and short-term memory which are essential for information processing (Jacobson and Jacobson 1996a). In the North Carolina birth cohort, Bayley MDI scores at ages 6 and 12 months were not associated with breast milk PCB levels (change in MDI score at age 12 months per unit change in breast milk PCB at birth ($\mu\text{g/g}$ lipid), $\beta=-0.54\pm 0.54(\text{SD})$, $p=.32$) (Gladden and others 1988). A birth cohort study in the Netherlands revealed a favourable but statistically non-significant relationship between Bayley MDI scores at age 7 months and maternal plasma PCB (sum of 4 non-coplanar congeners) (change in MDI per natural log increment of maternal plasma PCB, $\beta=2.3\pm 1.7$, $p=.18$) (Koopman-Elseboom and others 1996). In a German birth cohort, Bayley MDI at age 7 months was inversely associated with breast milk PCB concentrations at 2 and 4 weeks after delivery (change in MDI per unit change in breast milk PCB, $\beta=-0.69\pm 0.41(\text{SE})$, $p=.05$) but not with cord plasma PCB (change in MDI per unit change in cord plasma PCB, $\beta=0.06\pm 0.38(\text{SE})$, $p=.43$) (Winneke and others 1998). In the Oswego birth cohort, Fagan Test of Infant Intelligence scores at ages 6 and 12 months were not associated with breast milk total PCBs (change in Fagan test score at age 12 months per unit change in breast milk PCB, $\beta=-0.075$ points, $t=-0.51$, $p=.30$); this study did not assess cumulative lactational PCB exposure (Darvill and others 2000). However, the latter study observed inverse relationships between Fagan scores and cord blood total PCBs (change in Fagan test score at age 12 months per unit change in cord blood PCB, $F(1,207)=2.04$, $p=.08$) and cord blood highly chlorinated PCBs (change in Fagan test score at age 12 months per unit change in cord blood highly chlorinated PCB,

$F(1,207)=4.08$, $p=.02$); the study did not report β values for the latter analyses). In a German birth cohort, breast milk PCB concentrations about 2 weeks postpartum were inversely associated with Bayley MDI scores at 7, 18 or 30 months (change in MDI scores at age 7, 18 or 30 months per \log_2 breast milk PCB increment, $\beta=-4.19$, $t=-1.99$, $p=.025$) (Walkowiak and others 2001). Further analysis showed that compared to infants of mothers in the 5th percentile of breast milk PCBs (≤ 173 ng/g lipid), infants of mothers in the 95th percentile (≥ 679 ng/g lipid) had an average MDI score deficit of 8.3 points (95% CI 0.0 to 16.5). In the U.S. Collaborative Perinatal Project birth cohort, Bayley MDI scores at age 7-10 months were not associated with 3rd trimester maternal serum PCB levels (change in MDI score at age 8 months per unit increase in maternal serum PCB ($\mu\text{g/L}$), $\beta=0.10\pm 0.26(\text{SE})$, $p=.71$) (Daniels and others 2003).

Lactational or childhood PCB exposure, inadequate evidence

In the Michigan cohort, the Fagan test of visual recognition memory at 7 months was not associated with lactational PCB exposure (β not stated, $F(3,80)=1.18$, $p>.05$) (Jacobson and others 1985). In the North Carolina cohort, Bayley MDI scores at 6 and 12 months were not associated with cumulative lactational PCB exposure from birth to age at test (change in MDI score at age 12 months per 1 mg cumulative breast milk PCB intake, $\beta=-0.06\pm 0.16(\text{SE})$, $p=.70$; this study did not include the Fagan test (Gladden and others 1988). In the Dutch cohort, Bayley MDI at age 18 months was not associated with lactational PCB exposure (result stated without supporting data) (Koopman-Esseboom and others 1996). The Oswego birth cohort study reported no association between Fagan Test of Infant Intelligence scores at ages 6 and 12 months and PCB levels in breast milk samples collected at 1-3 months postpartum, an index of postnatal exposure (Darvill and others 2000). In the German birth cohort, cumulative lactational PCB dose was not associated with Bayley MDI scores at 7, 18 or 30 months (result stated without supporting data) (Walkowiak and others 2001).

Cognitive function, original studies, children age ≥ 3

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Rogan and others 1988), Taiwan	Cohort study	Survey (1985) of children of women exposed during 1979 to contaminated cooking oil	100 Yucheng children avg age 32 mos, 106 unexposed neighbourhood controls avg age 31 mos (range 1-82 mos); conducted Stanford-Binet at age 30-72 mos and WISC and Rutter scales at older ages	Yucheng children of women exposed during 1979 (up to 6 yr before pregnancy) to cooking oil contaminated by PCBs, dibenzofurans and related toxicants		Groups matched for neighbourhood, sex, age, birth order and family SES
WISC full-scale IQ, children age 6-7 of exposed vs unexposed women	84 \pm 2.9 (SE), n=21 SD=13.3 88 \pm 2.4 (SE), n=21 SD=11.0	Difference in mean IQ, t=1.06, df=40, p=.29				
(Jacobson and others 1990a), Michigan	Birth cohort		236 children, age 4 yr; conducted McCarthy Scales of Children's Abilities	Most mothers had consumed organochlorine-contaminated Lake Michigan sports fish	Cord and maternal serum and breast milk PCB levels and duration of breastfeeding; avg cord serum PCB=2.5 \pm 2.0 (SD) μ g/L, mat serum 5.9 \pm 3.6 μ g/L, maternal milk 836 \pm 388 μ g/L; at age 4 mean serum PCB was 5.1 \pm 3.9 μ g/L for children	Maternal age, gravidity, examiner

					breastfed for at least 6 mos vs 0.3±0.7 µg/L for non-breastfed children	
Multiple regression analysis, McCarthy General Cognitive Index vs log cord serum PCB	$\beta=-0.11$, $p=.22$	Multiple regression analysis, McCarthy General Cognitive Index vs serum PCB at age 4 yr	No association between CGI or any subscale and serum PCB at age 4; stated without supporting data			
(Jacobson and Jacobson 1996b), Michigan	Birth cohort	313 mother-infant pairs recruited in 1980-81	Conducted WISC-R and spelling, arithmetic and word/passage comprehension tests on 212 children at age 11 yr	Serum samples at age 4 and 11 yr tested for PCBs, PBBs and 7 organochlorine pesticides (only DDT/DDE was detected); breast milk at 0.2-4.5 mos post-delivery	Developed a composite measure of prenatal exposure based on PCB levels in cord and maternal serum and breast milk; breast milk PCB categories for dose-response analysis were 0.50, 0.50-0.74, 0.75-0.99, 1.00-1.24 and ≥ 1.25 µg/g lipid	SES, maternal education, vocabulary and marital status, HOME score
Mean WISC-R full-scale IQ deficit at age 11, highest vs lower prenatal PCB indices (breast milk PCB ≥ 1.25 µg/g lipid or cord serum PCB ≥ 4.7 µg/L or maternal serum PCB ≥ 9.7 µg/L vs lower PCB levels)	-6.2 points, $p=.007$, exposed $n=30$, unexposed $n=21$	Multiple regression analysis, WISC-R full-scale IQ at age 11 vs breast milk PCB level (5 categories defined above)	$\beta=-0.17$, $n=178$, $p=.02$	Full-scale IQ at age 11 at least 1 SD below mean, breast milk PCB ≥ 1.25 vs < 1.25 µg/g lipid, odds ratio (calculated from data in paper)	5.14, 1.93-13.69	
(Patandin and others 1999), Rotterdam and Groningen, The	Birth cohort	418 mother-infant pairs, 1 st or 2 nd born term infants, half	384 children at age 42 mos; conducted Dutch	See Lanting et al 1998 above	Median and 95 th percentiles: maternal plasma PCBs –	Study centre, HOME score, parity, maternal

Netherlands		breast-fed and half formula fed, recruited during 1990-92	version of Kaufman Assessment Battery for Children (K-ABC) on all and Reynell Language Developmental Scales (RLDS) on Rotterdam children only (n=190)		2.0/3.8 µg/L; cord plasma – 0.4/0.9 µg/L; child plasma PCBs at age 42 mos – 0.4/1.5 µg/L; breast milk PCBs (same 4 congeners as in plasma) – 405/723 µg/kg lipid; breast milk 20 non-dioxin-like PCBs – 545/914 µg/kg lipid; breast milk coplanar PCB-TEQ – 15/32 ng/kg lipid; breast milk total dioxin-TEQ – 33/60 ng/kg lipid	age, parental verbal IQ and education, sex, prenatal maternal smoking and alcohol use
Multiple regression analysis, change in K-ABC score per unit change in ln 3 rd trimester maternal plasma PCBs (µg/L, sum of 118, 138, 153, 180)	Total group $\beta=-4.56\pm 1.62(\text{SE})$, n=373, p=.005	Breastfed group $\beta=-2.20\pm 2.14$, n=195, p=.30	Formula-fed group $\beta=-8.69\pm 2.49$, n=178, p=.0006			
(Walkowiak and others 2001), Germany	Birth cohort	171 mother-infant pairs recruited in 3 Dusseldorf hospitals, 1993-95; 1 st or 2 nd born term infants, 5' Apgar ≥ 78	Conducted Bayley Scales at ages 7, 18, 30 and 42 mos and Kaufman Assessment Battery at age 42 mos; n=116 at 42 mos	Cord serum, breast milk (at 2 wk postpartum) and child serum (age 42 mos) PCB levels (congeners 138, 153, 180); assessed lactational PCB exposure from breast milk PCB levels and months of breastfeeding	Median and 95 th percentile PCB levels: cord serum 0.4/0.8 µg/L; milk – 404/679 ng/g lipid; child serum – 1.2/3.4 µg/L	Parental education, sex, maternal IQ, HOME score, parity, prenatal maternal smoking and BMI

Change in Kaufman-ABC index at age 42 mos per unit change in log ₂ breast milk PCB (ng/g lipid)	$\beta=-4.30$, $t=-1.93$, $p=.028$	Change in Kaufman-ABC index at age 42 mos per unit change in postnatal PCB exposure, adjusted for prenatal PCB exposure	Serum PCB at age 42 mos $t=-2.01$, $p=.025$	Lactational PCB dose $T=-1.89$, $p=.03$		
(Vreugdenhil and others 2002), Rotterdam and Groningen, The Netherlands	Birth cohort	418 mother-infant pairs recruited during 1990-92 (see Huisman et al. 1995a above), 1 st or 2 nd born infants only	372 children examined at age 6-7 yr; 194 had been breast-fed and 178 formula-fed; conducted Dutch version of the McCarthy Scales of Children's Abilities	Maternal and cord plasma – 4 non-coplanar PCBs (118, 138, 153, 180); breast milk – 6 dioxin-like (77, 105, 118, 126, 156, 169) and 20 non-dioxin-like PCBs, 17 PCDDs and PCDFs	Median cord and maternal plasma PCBs were 0.4 and 2.0 $\mu\text{g/L}$; mean breast milk PCDD/PCDF and PCB TEQ levels were 30.2 and 16.1 pg/g lipid	Study centre, maternal parity, age at birth, parental education and verbal IQ, HOME score, child sex, type of feeding during infancy, duration of breast feeding, age at examination
Multiple regression analysis, McCarthy General Cognitive Index (GCI) at age 7 vs ln maternal plasma PCB (μL)	All children $\beta=-0.14\pm 1.58(\text{SE})$, $p=.93$	Breastfed children $\beta=-0.01\pm 2.00$, $p=.996$ Formula fed children $\beta=-0.30\pm 2.22$, $p=.89$	CGI vs ln maternal plasma PCB plus PCB times maternal age plus PCB times maternal age ²	PCB $\beta=-147.5\pm 50.4$ PCB*mat age $\beta=9.37\pm 3.41$ PCB*mat age ² $\beta=-0.15\pm 0.06$	Negative effects of prenatal PCB exposure on GCI in children born to younger mothers	
(Jacobson and Jacobson 2003), Michigan, USA	Birth cohort	Children of women with prenatal history of consumption of Lake Michigan sports-caught fish	167 children examined at age 11	Prenatal exposure based on avg z-score of cord, maternal serum and breast milk total PCBs; postnatal exposure based on serum PCBs at age 4	Mean and SD PCB concentrations: cord and maternal serum – 2.7 ± 2 and 15.9 ± 3.8 ; ng/ml; breast milk – 0.859 ± 0.388 $\mu\text{g/g}$ lipid	SES, maternal age, parity, gravidity, education, vocabulary score, HOME score, employment, alcohol, smoking, child sex, school grade at age 11, other variables

Executive function at age 11: Wisconsin card sort categories completed vs prenatal PCB exposure (see above)	Prenatal PCB $\beta=-0.04$, $p>.05$ Postnatal PCB $\beta=0.01$, $p>.05$	Executive function at age 11: Stroop Color-Word test vs PCB	Prenatal PCB $\beta=-0.15$, $p<.10$ Postnatal PCB $\beta=-0.08$, $p>.05$			
(Stewart and others 2003), New York State	Birth cohort (Oswego Newborn and Infant Development Project)	Children of women with prenatal history of consumption of Lake Ontario sports-caught fish	212 children re-examined at ages 38 and 54 mos	Cord blood total and highly chlorinated PCBs (170, 172, 174, 177, 179, 180, 181, 183, 185, 187, 190, 194, 195, 196, 199, 203, 206), breast milk total PCBs, maternal hair mercury, cord blood lead	50 th and 75 th percentiles: cord blood total and highly chlorinated PCBs – 0.52/1.11 and 0.05, 0.18 ng/g wet wt; breast milk total PCBs – 153 and 249 ng/g lipid; cord blood lead 1.7/2.0 $\mu\text{g}/\text{dL}$; maternal hair mercury in second half of pregnancy 0.5/0.7 $\mu\text{g}/\text{g}$	Parental education, parity, SES, maternal IQ, smoking, alcohol, ETS exposure, cord serum DDE, HCB, mirex, mercury, cord blood lead, parental age and height, HOME score, child sex, birth weight, head circumference, gestation length and several other variables
McCarthy general cognitive index (CGI), age 38 mos	Linear trend analysis, GCI vs cord blood highly chlorinated PCBs (lipid adjusted)	Inverse association $F(1,165)=7.33$, $p=.008$		McCarthy general cognitive index (CGI), age 54 mos	Linear trend analysis, GCI vs cord blood highly chlorinated PCBs	$F(1,166)=1.25$, $p>.05$
McCarthy general cognitive index (CGI), age 38 mos	Linear trend analysis, cord blood PCB times maternal hair mercury (first half of pregnancy) interaction	PCB*mat hair Hg (1 st half of pregnancy) $\beta=-0.50$, $p=.008$	PCB*mat hair Hg (2 nd half of pregnancy) $\beta=-0.31$, $p=.16$			
(Vreugdenhil and others 2004a),	Birth cohort; conducted	Recruited 207 mother-infant pairs,	83 children in the 1 st and 4 th	Prenatal maternal plasma PCBs	Median and range maternal plasma	Maternal prenatal alcohol, gestation

Rotterdam, The Netherlands	neuropsychological tests at age 9	1990-92, 1 st or 2 nd born term infants	maternal plasma PCB quartiles examined at age 9	(118, 138, 153, 180)	PCBs: 1 st Q – 1.40, range 0.6-1.9 µg/L; 4 th Q – 3.2, 2.5-5.1 µg/L	length, infant sex, parity, parental education, parental verbal IQ and age
Tower of London test, 4 th vs 1 st quartile maternal plasma PCBs	Executive function $\beta=-1.85$, SE=0.67, p=.007	Tower of London test, breastfed 17+ wk vs formula-fed	Executive function $\beta=-1.81$, SE=0.73, p=.015			
(Gray and others 2005), USA	Cohort (U.S. Collaborative Perinatal Project)	894 mother-child pairs (49% White, 47% Black, 4% other race); recruited at hospital prenatal clinics in 11 cities and 13 private practices in a 12 th city, singleton live births during 1959-1965, 3-ml 3 rd trimester maternal serum sample available	Examined random sample of children at age 7 plus 61 children with low IQ and 101 children with high IQ (full-scale IQ at least 1 SD below or above mean)	Background sources; 3 rd trimester maternal serum PCBs (11 congeners – 28, 52, 74, 105, 118, 138, 153, 170, 180, 194, 203); analyzed PCB as a continuous linear variable on wet- and lipid-weight bases	Median maternal serum PCB = 2.8 µg/L (about 3-fold higher than current U.S.)	Study centre, maternal age, race, parity, SES, education, smoking, serum triglycerides, cholesterol, heptachlor epoxide, child sex, meconium at birth, unfavourable emotional environment, breastfeeding duration
Multiple regression analysis; change in WISC full scale IQ at age 7 per unit change in maternal serum PCB (µg/L)	Crude estimate 1.31±0.30(SE) Partially adjusted estimate 0.61±0.27 Fully adjusted estimate 0.22±0.25	Multiple regression analysis; change in WISC full scale IQ at age 7 per unit change in maternal serum PCB (µg/g lipid)	Crude estimate 6.81±2.34 Partially adjusted estimate 4.80±2.09 Fully adjusted estimate 1.90±1.92, p>.05			

Summary: Cognitive function deficits, children age ≥ 3

High-level maternal PCB/PCDF exposure, sufficient evidence

Compared to unexposed children, Yucheng children age 6-7 had lower WISC full-scale IQ scores at age 6-7 (mean IQ, exposed vs unexposed, 84 vs 88, $t=1.06$, $df=40$, $p=.29$) (Rogan and others 1988). Yucheng children also had increased auditory event-related P300 potential latencies and reduced P300 amplitudes; such neurophysiological changes have been linked to cognitive deficits, attention deficit disorder and reading disability (Chen and Hsu 1994). Reviewers concluded that prenatal high-level maternal exposure to PCBs, PCDFs and related toxicants were associated with persistent cognitive function deficits (Longnecker and others 1997) and a WHO expert group concluded that this is a causal relationship (Brouwer and others 1998).

Background maternal PCB exposure, limited evidence

Reviewers noted that there were inverse associations between cognitive function scores and prenatal PCB exposure indices in 4 of the 5 studies that were published by 1999 and assessed this relationship (Ribas-Fito and others 2001). Other reviewers concluded that the growing weight of evidence from epidemiologic studies supports an inverse association between childhood cognitive scores and prenatal PCB exposure levels but noted that there have been few attempts to assess the role of specific PCB congeners or classes of congeners (Schantz and others 2003). In the Michigan birth cohort, McCarthy GCI scores at age 4 were not associated with cord serum PCB (change in GCI per unit change in cord serum PCB, $\beta=-0.11$, $p=.22$) (Jacobson and others 1990a). Follow-up of the Michigan cohort at age 11 revealed an inverse dose-response relationship between WISC-R full-scale IQ and breast milk PCB levels at birth (IQ vs 5 categories of increasing breast milk PCBs, $\beta=-0.17$, $p=.02$) (Jacobson and Jacobson 1996b). This study also reported an inverse association of borderline statistical significance between executive function scores at age 11 and prenatal PCB exposure (change in Stroop Color-Word test score per unit change in prenatal PCB, $\beta=-0.15$, $p<.10$) (Jacobson and Jacobson 2003). The latter study observed no association between another test of executive function at age 11 and prenatal PCB exposure (change in Wisconsin card sort categories completed per unit change in prenatal PCB, $\beta=-0.04$, $p>.05$). In the Dutch cohort, Kaufman ABC scores at age 42 months were inversely associated with maternal 3rd trimester plasma PCBs (per natural log PCB increment, $\beta=-4.56\pm 1.62$, $p=.005$); this association was stronger among the subgroup of formula-fed infants ($\beta=-8.69\pm 2.49$, $p=.0006$) than the breastfed group ($\beta=-2.20\pm 2.14$, $p=.30$) (Patandin and others 1999). McCarthy GCI scores at age 7 in the Dutch cohort were not associated with 3rd trimester maternal plasma PCBs (per natural log PCB increment, $\beta=-0.14\pm 1.58$) (Vreugdenhil and others 2002). This study reported inverse associations between Tower of London test scores at age 9 and maternal plasma PCBs (change in score, 4th vs 1st quartile maternal plasma PCB, $\beta=-1.85\pm 0.67$ (SE), $p=.007$) (Vreugdenhil and others 2004a). In the German birth cohort, breast milk PCB concentrations about 2 weeks postpartum were inversely associated with Kaufman ABC scores at age 42 months (per \log_2 breast milk PCB increment, $\beta=-4.30$, $t=-1.93$, $p=.03$) (Walkowiak and others 2001). In the Oswego Newborn and Infant Development cohort, cord blood highly chlorinated PCB concentrations were inversely associated with McCarthy GCI scores at 38 months (linear trend test, $F(1,165)=7.33$, $p=.008$) but not at 54 months (linear trend test, $F(1,166)=1.25$, $p>.05$) (Stewart and others 2003). In the U.S. Collaborative Perinatal Project cohort, WISC full-scale IQ at age 7 was not associated with 3rd trimester maternal serum PCB in a fully adjusted model (change in IQ per unit change in maternal serum PCB ($\mu\text{g/g lipid}$), $\beta=1.90\pm 1.92$ (SE), $p>.05$) (Gray and others 2005).

Lactational PCB exposure, inadequate evidence

In the Michigan birth cohort, McCarthy GCI scores at age 4 were not associated with current serum PCB (stated without supporting data) (Jacobson and others 1990a). This study reported no association between executive function scores at age 11 and postnatal PCB exposure (e.g., change in Wisconsin card sort categories completed per unit change in serum PCB at age 4, $\beta=0.01$, $p>.05$) (Jacobson and Jacobson 2003). In the German birth cohort, lactational PCB exposure was inversely associated with Kaufman ABC scores at age 42 months (change in Kaufman-ABC index per unit change in current serum PCB, $t=-2.01$, $p=.03$; β -coefficient not reported) (Walkowiak and others 2001).

General findings

Reviewers concluded that prenatal and lactational exposure to PCBs, PCDDs and PCDFs can cause neuropsychological and neuromotor deficits in humans and in experimental animal with LOAELs in the range of background general population dioxin-TEQ body burdens (Brouwer and others 1995). Cord plasma and breast milk non-coplanar PCB congener levels have also been associated with cognitive deficits in children age 6-7 (Vreugdenhil and others 2002). Such congeners were the most potent in reducing dopamine content and disrupting calcium metabolism in neurons *in vitro* (Tilson and Kodavanti 1997). Inconsistent findings in epidemiologic studies may arise from PCB exposure intensity differences; for instance, average prenatal serum PCB-153 levels in 10 epidemiologic studies of neurodevelopment varied from 30 to 450 ng/g lipid, being highest in the Faroe Islands birth cohort study and lowest in two U.S. studies (Longnecker and others 2003).

8b. Psychomotor function

Reviews

Reviewers	Scope	Comments or conclusions	Conclusions
(Guo and others 1995), Taiwan	Review of Yucheng, Michigan and North Carolina cohorts of children of women exposed to PCBs and related compounds	Yucheng – mean and median maternal serum PCB levels near end of pregnancy were 49 and 27 µg/L; Michigan – mean maternal and cord serum PCB levels, respectively, were 4.7-5.9 and 2.0-2.5 µg/L; North Carolina – median maternal and cord serum PCB levels were 9.1 and about 4 µg/L	Psychomotor development index scores among infants reduced among exposed infants in the Yucheng cohort; high cord serum PCB levels in the other 2 cohorts associated with psychomotor index score deficits
(Schantz 1996), USA	Review of PCBs and developmental neurotoxicity		Noted small delays in psychomotor development among infants in the highest prenatal PCB exposure category in the North Carolina birth cohort study
(Longnecker and others 1997), USA	Review of epidemiologic studies of PCBs, DDT and related organochlorines	PCBs and ρ,ρ' -DDE comprise the bulk of organochlorine residues in human tissues	Evidence from 3 birth cohort studies is suggestive of an association between prenatal exposure to background PCB levels and neonatal hypotonia and hyporeflexia; the relative importance of PCBs vs dioxins or other contaminants associated with PCBs is not clear
(Jacobson and Jacobson 1997), Michigan	See Jacobson and Jacobson 1997 above	Psychomotor function, neonates: NC – association between reduced muscle tone and abnormally weak reflexes and prenatal PCB exposure indices Michigan – decreased autonomic regulation, responsiveness to external stimuli and reflexes associated with maternal Lake Michigan fish consumption but not with PCB levels in cord/maternal serum	Psychomotor function, age <3: NC – Bayley psychomotor development index scores at ages 6, 12 and 24 mos lower in highest prenatal PCB exposure category; no dose-response relationship Michigan – Bayley scales only conducted at age 5 mos – scores not associated with prenatal PCB exposure
(Brouwer and others 1998), The Netherlands	Review of health risks to infants of perinatal exposure to PHAHs by a World Health Organization working group	High-level exposure to PCBs, PCDFs and related organochlorines during the Yusho and Yucheng incidents caused reduced muscle tone and hyperactivity	Although prenatal exposure to ambient levels of PCBs or mixtures of PCBs and related organochlorines has been associated with reduced psychomotor development scores in infants and children, most of the individual results

			were within normal limits. Cohort studies in The Netherlands found no associations between mental development indices at age 18 mos and breast milk TCDD-TEQs from dioxin-like PCBs, PCDDs and PCDFs.
(World Health Organization 2000), Geneva	Assessment of the health risk of PHAHs and re-evaluation of the tolerable daily TEQ intake (TDI)	Effects seen in highly exposed Yusho and Yucheng children included global persistent developmental delays	2 U.S. and 2 Dutch birth cohorts exposed to background PCB levels have shown neurodevelopmental delays and neurobehavioral effects including neonatal hypotonia. Among breast-fed infants in the Rotterdam/Groningen Dutch cohort, those with higher exposures based on breast milk TEQs tended to have poorer neuropsychological test results
(Boersma and Lanting 2000; Boersma 2001), The Netherlands	See Boersma and Lanting 2000 and Boersma 2001 above		Neurologic optimality scores at age 18 mos inversely associated with prenatal but not postnatal PCB/PCDD exposure indices
(Ribas-Fito and others 2001), Spain	Systematic review of 7 cohort studies of PCB exposure and childhood neuropsychological function	In all 4 studies that evaluated it, abnormal neonatal reflexes were associated with prenatal PCB exposure; among the 5 studies that evaluated psychomotor development during infancy, 4 studies found inverse associations with prenatal PCB exposure.	Lactational PCB exposure was not clearly related to any indicator of neuropsychological function.
(Guo and others 2004), Taiwan	Review of health effects among the cohort of persons exposed to food cooked in oil contaminated by PCBs, PCDFs, PCTs and PCQs during the 1979 Yucheng incident	Compared to unexposed children, prenatally exposed Yucheng children had Bayley Scale psychomotor deficits at age 12-30 mos	27 pairs of Yucheng and comparison children were similar with regard to abnormalities on neurological examination.

Psychomotor function, original studies, children age 0-2

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Rogan and others 1988), Taiwan	Cohort study	Survey (1985) of children of women exposed during 1979 to contaminated cooking oil	100 Yucheng children avg age 32 mos, 106 unexposed neighbourhood controls avg age 31 mos; Bayley Scales at age 6-30 mos, Stanford-Binet at age 30-72 mos and WISC and Rutter scales at older ages	Yucheng children of women exposed during 1979 (up to 6 yr before pregnancy) to cooking oil contaminated by PCBs, dibenzofurans and related toxicants		Groups matched for neighbourhood, sex, age, birth order and family SES
PDI score, children of exposed vs unexposed women, mean±SE	101±2.7(SE), n=45, SD=18.1 108±2.1, n=45, SD=14.1	Difference in mean PDI scores, t=2.05, df=88, p=.04				
(Gladen and others 1988), North Carolina	Birth cohort	See Rogan et al 1986 above; conducted Bayley Scales of Infant Development	Assessed 706 infants at both ages 6 and 12 mos, 82 at age 6 mos only, 14 at age 12 mos only	Assessed prenatal PCB and DDE exposure from breast milk levels at or near birth and cumulative postnatal exposure from breast milk levels and lactation duration		Maternal age, race, education, occupation, smoking and alcohol; child sex, gestational length, birth weight, head circumference at birth, neonatal jaundice, breastfeeding duration, number of older siblings, number of abnormal reflexes neonatally, age, study center

Prenatal exposure: change in PDI score per unit change in breast milk PCB level at birth ($\mu\text{g/g}$ lipid)	Age 6 mos $\beta=-0.96\pm0.46$, $p=.04$ Age 12 mos $\beta=-1.34\pm0.61$, $p=.03$	Lactational exposure: change in PDI score per mg breast milk PCBs ingested from birth to age at test	Age 6 mos $\beta=-0.27\pm0.20$, $p=.17$ Age 12 mos $\beta=-0.27\pm0.18$, $p=.13$			
(Rogan and Gladen 1991), North Carolina	Birth cohort	See Rogan et al 1986 above	Conducted Bayley Scales of Infant Development at ages 18 (n=676) and 24 mos (n=670)	Assessed prenatal PCB and DDE exposure from breast milk levels at or near birth and cumulative postnatal exposure from breast milk levels and lactation duration		Sex, race, age at examination, number of older siblings, maternal age, education, occupation, smoking, alcohol use
Prenatal exposure: differences in mean PDI scores for infants of women with highest vs lowest breast milk PCB levels (≥ 4 vs < 1 $\mu\text{g/g}$ lipid)	Age 18 mos $-4.0\pm 3.9(\text{SE})$	Age 24 mos -7.9 ± 4.5				As above
(Guo and others 1994), Taiwan	Cohort	Children of women exposed during Yucheng incident born during 1985-1991	66 children born 7-12 yr after parental exposure, 66 unexposed children, avg age 3.6 yr; conducted Chinese Child Developmental Inventory and Rutter's Child Behavior Scale A	Either parent exposed to cooking oil contaminated by PCBs, dibenzofurans and related toxicants		Groups matched for neighbourhood, age, sex, mother's age, parental education
Motor scores, children of Yucheng women vs	Gross motor 27.4 ± 0.6	Fine motor 31.5 ± 1.0				

children of unexposed women, mean±SE (reduced score = adverse effect)	28.2±0.6 Difference of mean scores, t=-1.5, p=.14	32.6±0.9 Difference of mean scores, t=-1.3, p=.20				
(Huisman and others 1995a), The Netherlands	Birth cohort	Rated neurologic optimality score based on performance on 60 items related to 2 clusters – reflexes and postural tone; 4 infants had definite and 20 had suspected neurologic abnormalities	418 mother-infant pairs (209 breast-fed and 209 formula-fed); infants examined 10-21 days after birth	Median cord and maternal plasma PCB levels were 0.4 and 2.0 µg/L (4 non-coplanar PCBs: 118, 138, 153, 180)	Mean breast milk PCDD/PCDF and PCB TEQ levels were 30.2 and 16.1 pg/g lipid	Maternal age, alcohol, study centre
Odds of suboptimal neonatal neurologic score per doubling of maternal or cord plasma PCB levels	Maternal plasma PCB levels (4 non-coplanar congeners) 1.11, 0.74-1.65	Odds of suboptimal neonatal neurologic score per doubling of breast milk PCB and TEQ levels (pg/g lipid)	Total PCB-TEQ 3.21, 1.37-7.48 PCDD/PCDF-TEQ 3.12, 1.36-7.18	Neonatal neurologic optimality score deficits vs breast milk coplanar PCB-TEQ levels (odds ratio)	1.7 (CI 1.0-2.9)	
(Huisman and others 1995b), The Netherlands	Birth cohort	Pregnant women recruited in Groningen and Rotterdam, 1990-1992	418 mother-infant pairs (209 breast-fed, 209 formula-fed); rated neurologic optimality score at age 18 mos	Median cord and maternal plasma PCB levels were 0.4 and 2.2 µg/L (4 non-coplanar PCBs: 118, 138, 153, 180)	Median breast milk PCDD/PCDF and PCB TEQ levels were 29 and 33 pg/g lipid	Paternal education, parity, study centre, paternal smoking
Change in neurologic optimality score at 18 mos per unit change in log cord serum levels of 4 non-coplanar PCBs	β =-0.149±0.049 (SE), p=.003	Neurologic optimality scores not associated with lactational exposure to 4 coplanar PCBs or PCB/PCDD/PCDF-TEQ	Result stated without supporting data			
(Koopman-Esseboom and others 1996),	Birth cohort (part of larger Dutch	Conducted Bayley Scales of Infant	207 mother-infant pairs (105	Measured 4 PCBs (118, 138, 153,	Mean cord and maternal plasma	Gestational age, parity, HOME score,

Rotterdam, the Netherlands	PCB/Dioxin Study)	Development at age 3, 7 and 18 mos	breastfed, 102 formula-fed)	180) in maternal plasma during last month of pregnancy and in cord blood; measured 17 PCDD and 24 PCB congeners in breast milk during 2 nd postnatal week and computed total PCB-TEQ	PCB levels were 0.5 and 2.2 ng/g plasma and the mean breast milk PCB/PCDD-TEQ was 67 pg/g lipid	maternal education, breast feeding duration
Age 3 mos: PDI vs ln maternal plasma PCB (4 non-coplanar congeners, ng/g)	$\beta=-4.8\pm 2.0$, $p=.02$	Age 3 mos: PDI vs ln breast milk PCB-TEQ (pg/g lipid) , adjusted for breastfeeding duration	$\beta=-7.4\pm 4.0$, $p=.07$	PDI at age 3 mos vs duration of breastfeeding	$\beta=0.91\pm 0.91$, $p=.32$	
Age 7 mos: PDI vs ln maternal plasma PCB (4 non-coplanar congeners, ng/g)	$\beta=2.3\pm 1.7$, $p=.18$	Age 7 mos: PDI vs high breast milk PCB-TEQ levels, adjusted for breastfeeding duration	770-1289 pg-weeks/g lipid $\beta=-9.5\pm 3.9$, $p=.01$ 1290-4340 pg-weeks/g lipid $\beta=-7.7\pm 4.9$, $p=.12$	PDI at age 7 mos vs duration of breastfeeding, adjusted for breast milk PCB-TEQ levels	$\beta=2.0\pm 0.9$, $p=.02$	
(Winneke and others 1998), Germany	Birth cohort	Mother-infant pairs recruited from 3 Dusseldorf hospitals	171 mother-infant pairs; Bayley Scales of Infant Development and Fagan Test of Infant Intelligence (a test of visual recognition memory) at age 7 mos		Mean levels of PCBs 138, 153 and 180 in cord plasma and maternal milk were 0.55 $\mu\text{g/L}$ and 427 ng/g lipid	Maternal age, BMI, education, vocabulary and birth weight, HOME score, Apgar score, cord blood lead, breast feeding duration
PDI at age 7 mos vs	Cord plasma	Breast milk PCB				

log cord plasma PCB ($\mu\text{g/L}$) and log breast milk PCB (ng/g lipid), adjusted for BF duration	PCB $\beta=0.009\pm 0.63$, $t=0.01$, $p>.9$	$\beta=-0.71\pm 0.63$, $t=-1.12$, $p=.13$				
(Steuerwald and others 2000), Faroe Islands	Birth cohort	182 births at one hospital during 1994-1995	Conducted neurologic examination at age 2 wk	Measured PCBs (138, 153, 180) in maternal serum (GM 1.12, range 0.63-1.87 $\mu\text{g/g lipid}$) and breast milk (GM 1.52, IQ range 0.87-2.52 $\mu\text{g/g lipid}$)		
Neonatal neurologic optimality scores vs maternal serum or breast milk levels of 3 non-coplanar PCBs ($\mu\text{g/g lipid}$); Spearman's rank correlation coefficient	Maternal serum PCB $R=0.03$, $n=173$, ns	Breast milk PCB $R=-0.03$, $n=168$, ns				
(Stewart and others 2000), New York State	Birth cohort (Oswego Newborn and Infant Development Project)	Mother-infant pairs, recruited 1991-94; conducted Neonatal Behavioral Assessment Scale (NBAS) on postnatal days 1 and 2	293 neonates: 141 with mothers who consumed Lake Ontario fish and 152 with mothers who did not	Measured cord blood PCBs (total and highly chlorinated congeners), HCB, mirex, DDE, lead, breast milk PCBs, maternal hair Hg	Median and 75 th percentiles: cord blood PCBs – 0.53/1.11 ng/g wet wt	HOME score, parental education, SES, paternal age, prepregnancy weight, weight gain during pregnancy, stress during early gestation, smoking, ETS, caffeine, prenatal vitamin and prescription drug use, child sex, birth weight, head circumference
NBAS: abnormal	Linear trend	$F(1,262)=2.81$, $p=.095$				

reflex score on postnatal day 2	analysis, score vs. cord blood highly chlorinated PCB concentration (ng/g wet wt)					
(Walkowiak and others 2001), Germany	Birth cohort	171 mother-infant pairs recruited in 3 Dusseldorf hospitals, 1993-95; 1 st or 2 nd born term infants, 5' Apgar ≥ 78	Conducted Bayley Scales at ages 7, 18, 30 and 42 mos and Kaufman Assessment Battery at age 42 mos; n=116 at 42 mos	Cord serum, breast milk and child serum (age 42 mos) PCB levels (congeners 138, 153, 180)	Median and 95 th percentile PCB levels: cord serum 0.4/0.8 $\mu\text{g/L}$; milk – 404/679 ng/g lipid; child serum –1.2/3.4 $\mu\text{g/L}$	Parental education, sex, maternal IQ, HOME score, parity, prenatal maternal smoking and BMI
Multiple regression analysis of PDI vs \log_2 breast milk PCB (ng/g)	age 7 mos $\beta=-3.13$, $t=-1.19$, $p=.12$ age 18 mos $\beta=-4.78$, $t=-1.71$, $p=.045$	age 30 mos $\beta=-4.73$, $t=-1.68$, $p=.05$ age 7-30 mos $\beta=-4.61$, $t=-2.22$, $p=.015$	PDI score differences, age 7-30 mos, 95 th vs 5 th percentile breast milk PCB (i.e., ≥ 679 vs ≤ 173 ng/g lipid)	PDI deficit = -9.1 points, -17.2 to -1.02	Multiple regression analysis of PDI vs lactational PCB exposure based on breast milk levels and BF duration	No associations between Bayley PDI and lactational PCB exposure (stated without supporting data)
(Daniels and others 2003), 1959-66 Collaborative Perinatal Project, USA	Birth cohort (Collaborative Perinatal Project,)	Children of about 42,000 women recruited during pregnancy at 12 U.S. hospital, 1959-66; 3 rd trimester frozen maternal serum sample available	1065 randomly selected children and 194 with Bayley PDI scores at least 1 SD above or below the group mean; conducted Bayley Scales at age 8 mos	Maternal sera collected every 8 wk during pregnancy, at delivery and 6 wk postpartum; analyzed PCBs in 3 rd trimester sera (11 congeners – 28, 52, 74, 105, 118, 138, 153, 170, 180, 194, 203)	Median and 95 th percentile maternal PCB - 2.7 and 6.3 $\mu\text{g/L}$	Research centre, maternal education, triglycerides, cholesterol, birth order; results not affected by including maternal serum DDE, race, prepregnancy BMI, breastfeeding
Regression of PDI at	$\beta=0.47$, $SE=0.32$,					

age 8 mos vs 3 rd trimester maternal serum PCB; β = increase of PDI per $\mu\text{g/L}$ increase in maternal serum PDB	$p=.14$					
(Ribas-Fito and others 2003), Spain	Birth cohort	Recruited 102 mother-infant pairs in one hospital, serving a region near a pesticide factory, 1997-99	92 infants examined at age 13 mos (27 formula-fed, 65 breastfed); conducted Bayley and Griffiths Scales of Infant Development and Griffith's Mental Development Index at age 13 mos 13 m	Measured cord serum ρ,ρ' -DDE, HCB and PCBs (28, 52, 101, 118, 138, 153, 180)	PCB levels not stated	Maternal age, prenatal smoking and alcohol, education, migration, paternal occupation, infant sex, kindergarten attendance, breastfeeding history
Multivariate linear regression coefficient, change of Bayley PDI score per doubling of cord serum PCB ($\mu\text{g/L}$)	$\beta=-2.84\pm 1.72$ (SE), $p<0.1$					

Summary: psychomotor function deficits, children age 0-2

Neonatal hypotonia

High-level exposure, sufficient evidence

A WHO working group concluded that high-level prenatal exposure to PCBs, PCDFs and related compounds caused neonatal hypotonia (Brouwer and others 1998).

Low-level maternal PCB exposure, limited evidence

A recent review concluded that the evidence from birth cohort studies suggests an association between neonatal hypotonia and hyporeflexia and background PCB exposure levels (Longnecker and others 1997). A review of 7 cohort studies noted that abnormal neonatal reflexes were associated with PCB exposure in all 4 studies that assessed it (Ribas-Fito and others 2001).

Psychomotor function, age 0-2

High-level maternal PCB/PCDF exposure, limited evidence

Compared to unexposed children, Yucheng children age 6-30 months had lower Bayley Scale psychomotor development index (PDI) scores (mean PDI score, exposed vs unexposed children, $101 \pm 2.7(\text{SE})$ vs 108 ± 2.1 , mean difference $t=2.05$, $df=88$, $p=.04$ (t and p calculated from data in paper) (Rogan and others 1988). Further investigation showed that Yucheng children age 7 had small and statistically non-significant gross (exposed vs unexposed, Chinese Child Developmental Inventory (CCDI) scores, $27.4 \pm 0.6(\text{SE})$ vs 28.2 ± 0.6 , $t=-1.5$, $p=.14$) and fine motor function deficits (exposed vs unexposed, CCDI scores, $31.5 \pm 1.0(\text{SE})$ vs 32.6 ± 0.9 , $t=-1.3$, $p=.20$) (Guo and others 1994; Lai and others 1994; Lai and others 2001)

Low-level maternal PCB exposure, limited evidence

A WHO working group concluded that childhood psychomotor function was inversely associated with low-level prenatal exposure to PCBs and related compounds but noted that most of the individual neuropsychological test results were within normal limits (Brouwer and others 1998). Among reviewed studies, a North Carolina birth cohort study revealed inverse associations between Bayley PDI scores at ages 6 and 12 months and breast milk PCBs soon after birth (an index of prenatal PCB exposure) (change in PDI score at age 6 months per unit change in breast milk PCB ($\mu\text{g/g}$ lipid), $\beta=-0.96 \pm 0.46$, $p=.04$; at age 12 months, $\beta=-1.34 \pm 0.61$, $p=.03$) (Gladden and others 1988; Rogan and Gladden 1991). The PDI deficits at ages 18 and 24 months of infants of women with the highest breast milk PCB levels, compared to those with the lowest levels, were not statistically significant (18 months, deficit = $-4.0 \pm 3.9(\text{SE})$; 24 months, deficit -7.9 ± 4.5) (Rogan and Gladden 1991). In a Dutch birth cohort, suboptimal neonatal neurologic scores at 10-21 days after birth (based in part on reflexes and postural tone) were not associated with maternal or cord serum individual or aggregate levels of 4 non-coplanar PCB congeners (per doubling of maternal or cord serum non-coplanar PCBs, $\text{OR}=1.11$, 95% CI 0.74-1.65) (Huisman and others 1995a). However, suboptimal scores were associated with breast milk PCB-TEQ and PCDD/PCDF-TEQ levels (per doubling of breast milk PCB-TEQ levels (pg/g lipid), $\text{OR}=3.21$, 95% CI 1.37-7.48; per doubling of breast milk PCDD/PCDF-TEQ, $\text{OR}=3.12$, 95% CI 1.36-7.18). At this age, maternal and cord serum and breast milk PCB levels all reflect prenatal exposure. Continued follow-up of the whole Dutch birth cohort revealed a persistent inverse association between neurologic optimality scores at age 18 months and cord plasma levels of 4 non-coplanar congeners (change in score per log increment of cord serum PCBs, $\beta=-0.149 \pm 0.049$, $p=.003$) (Huisman and others 1995b). Within the Rotterdam component of the Dutch cohort, there was an inverse association between Bayley PDI scores at age 3 months and maternal plasma levels of 4 non-coplanar PCBs (per natural log PCB increment, $\beta=-4.8 \pm 2.0$, $p=.02$) but not at age 7 months ($\beta=2.3 \pm 1.7$, $p=.18$) (Koopman-Esseboom and others 1996). A small German birth cohort study observed no association between Bayley PDI scores at age 7 months and cord plasma levels of 3 non-coplanar PCBs (change in PDI per log increment of cord plasma PCBs, $\beta=0.009 \pm 0.63$, $p>.9$) (Winneke and others 1998). The Oswego birth cohort study observed an association between abnormal reflexes on postnatal day 2 and cord blood levels of highly chlorinated PCB congeners ($F(1,262 \text{ df})=2.81$, $p=.095$) (Stewart and others 2000). In the latter study, cord blood levels of highly chlorinated PCB congeners, but not cord blood levels of total PCBs or lightly chlorinated PCBs, correlated with maternal Lake Ontario fish consumption and with breast milk levels of highly chlorinated congeners. Highly chlorinated PCBs are very persistent and appear to reflect cumulative and total PCB exposure. A small Faroe Islands birth cohort study found no association between neonatal optimality scores at age 2 weeks and maternal serum or breast milk PCB levels (Spearman's rank correlation coefficients, scores vs maternal serum or breast milk PCBs, $R=0.03$ and -0.03 , respectively, $p>.05$) (Steuerwald and others 2000). In a German birth cohort, Bayley PDI scores at ages 7-30 months were inversely associated with breast milk PCBs, an index of prenatal exposure (per \log_2 increment, $\beta=-4.61$, $t=-2.22$, $p=.015$) (Walkowiak and others 2001). There was no association between 3rd trimester maternal serum PCBs (11 congeners) and Bayley PDI at age 8 months in the U.S. Collaborative Perinatal Project (change in Bayley PDI per unit change in maternal serum PCBs ($\mu\text{g/L}$), $\beta=0.47 \pm 0.32$, $p=.14$) (Daniels and others 2003). In a small Spanish birth cohort, there was a statistically non-significant inverse association between Bayley PDI at age 13 months and cord serum PCBs (7 congeners) (change in Bayley PDI per doubling of cord serum PCB ($\mu\text{g/L}$), $\beta=-2.84 \pm 1.72$, $p<.10$) (Ribas-Fito and others 2003). The U.S. study was much larger than the Spanish cohort and included women recruited during 1959-1966 when population serum PCB levels were substantially higher than recently (median and 95th percentiles were 2.7 and 6.3 $\mu\text{g/L}$).

Low-level lactational PCB exposure, inadequate evidence

A North Carolina birth cohort study revealed no association between Bayley PDI scores at ages 6 and 12 months and cumulative lactational PCB exposure (change in PDI score at age 6 months per mg PCB ingested, $\beta=-0.27 \pm 0.20$, $p=.17$; at age 12 months, $\beta=-0.27 \pm 0.18$, $p=.13$) (Gladden and others 1988; Rogan and

Gladen 1991). In a Dutch birth cohort, suboptimal neonatal neurologic scores at 10-21 days after birth (based in part on reflexes and postural tone) were associated with breast milk PCB-TEQ and PCDD/PCDF-TEQ levels (per doubling of breast milk PCB-TEQ levels (pg/g lipid), OR=3.21, 95% CI 1.37-7.48; per doubling of breast milk PCDD/PCDF-TEQ, OR=3.12, 95% CI 1.36-7.18) (Huisman and others 1995a). Within the Rotterdam component of the Dutch cohort, there was an inverse association of borderline statistical significance between Bayley PDI scores at age 3 months and breast milk PCB-TEQ (per natural log increment, $\beta=-7.4\pm 4.0$, $p=.07$), adjusted for breastfeeding duration (Koopman-Esseboom and others 1996). At age 7 months, PDI scores were inversely and significantly associated with breast milk PCB-TEQ levels, adjusted for breastfeeding duration (medium vs lowest category, $\beta=-9.5\pm 3.9$, $p=.01$; highest vs lowest category, $\beta=-7.7\pm 4.9$, $p=.12$) (Koopman-Esseboom and others 1996). A small German birth cohort study observed an statistically non-significant inverse relationship between Bayley PDI scores at age 7 months and breast milk levels of 3 non-coplanar PCBs (change in PDI per log increment of breast milk PCBs, $\beta=-0.71\pm 0.63$, $p=.13$, adjusted for breastfeeding duration) (Winneke and others 1998). In the German birth cohort, Bayley PDI scores at age 7-30 months were not associated with cumulative lactational PCB dose (stated without supporting data) (Walkowiak and others 2001).

Psychomotor function, original studies, children age ≥ 3

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Lanting and others 1998b), The Netherlands	Birth cohort	418 mother-infant pairs, half breast-fed and half formula fed	394 children age 42 mos; conducted neurologic exams at age 2 wk and 42 mos; assigned neurologic optimality scores	PCBs 118, 138, 153, and 180 in maternal and cord plasma and child plasma at age 42 mos; PCBs (6 dioxin-like ⁴ and 20 other congeners) and PCDD/PCDFs (17 congeners) in breast milk collected 2 wk postpartum; lactational exposure estimated by product of weeks of breast-feeding and children's current plasma PCB levels	See Patandin et al 1999 below	Study centre, obstetric optimality score
Neurologic optimality scores vs PCB/TEQ exposure indices (only 12 children had neurologic abnormalities, mostly mild ones)	No associations between NOS scores and cord, maternal or current serum levels of 4 non-coplanar PCBs	No associations between NOS scores and PCB-TEQ in breast milk	Results stated without supporting data			
(Grandjean and others 2001), Faroe Islands	Birth cohort	Mother-infant pairs recruited at 3 hospitals in 1986-87, singleton births	435 children examined at age 7 yr; conducted neuropsychological tests	Measured cord tissue PCBs (138, 153, 180) and multiplied by 2 to estimate total PCBs; cord blood DDE, mercury	Cord tissue PCB – median 1.02 $\mu\text{g/g}$ lipid (interquartile range 0.53-1.71); cord blood DDE – median 0.71	Age, sex, and, as necessary, maternal IQ, IUGR, parental education and employment, day care, computer

⁴ PCBs 77, 105, 118, 126, 156, 169

					$\mu\text{g/g}$ lipid; cord blood mercury – median 25.7 $\mu\text{g/L}$	acquaintance
Fine motor function Multiple regression coefficients, test score vs log cord tissue PCBs ($\mu\text{g/g}$ lipid)	Finger tapping, preferred hand $\beta=-0.76$, $p=.30$	Hand-eye coordination errors $\beta=0.04$, $p=.26$				
(Vreugdenhil and others 2002), Rotterdam and Groningen, The Netherlands	Birth cohort	418 mother-infant pairs recruited during 1990-92 (see Huisman et al. 1995a above), 1 st or 2 nd born infants only	372 children examined at age 6-7 yr; 194 had been breast-fed and 178 formula-fed; conducted Dutch version of the McCarthy Scales of Children's Abilities	Maternal and cord plasma – 4 non-coplanar PCBs (118, 138, 153, 180); breast milk – 6 dioxin-like (77, 105, 118, 126, 156, 169) and 20 non-dioxin-like PCBs, 17 PCDDs and PCDFs	Median cord and maternal plasma PCBs were 0.4 and 2.0 $\mu\text{g/L}$; mean breast milk PCDD/PCDF and PCB TEQ levels were 30.2 and 16.1 pg/g lipid	Study centre, maternal parity, age at birth, parental education and verbal IQ, HOME score, child sex, type of feeding during infancy, duration of breast feeding, age at examination
McCarthy Scales – motor score β -coefficient from multiple regression analysis of motor scores vs ln prenatal maternal plasma PCB concentration	All children $\beta=-2.45$, $\text{SE}=1.45$, $p=.09$, adjusted for BF duration	Breastfed children $\beta=-1.28$, $\text{SE}=1.84$, $p=.49$, adjusted for BF duration	Formula-fed children $\beta=-3.92$, $\text{SE}=2.04$, $p=.06$			

Summary: Psychomotor function deficits, age ≥ 3

Background maternal PCB exposure, inadequate evidence

A Dutch birth cohort study found no associations between neurologic optimality scores at age 42 months and cord or maternal levels of 4 non-coplanar PCBs (results stated without supporting data) (Lanting and others 1998b). Further follow-up of this cohort revealed a statistically non-significant association between McCarthy motor subscale scores at age 6-7 and 3rd trimester maternal plasma levels of 4 non-coplanar PCBs (per natural log PCB increment, all children, $\beta = -2.45 \pm 1.45$, $p = .09$, adjusted for breastfeeding duration); this association was somewhat stronger among the formula-fed subgroup ($\beta = -3.92 \pm 2.04$, $p = .06$) (Vreugdenhil and others 2002). In the Faroe Islands birth cohort, fine motor function test scores at age 7 were not associated with log cord tissue levels of 3 non-coplanar PCBs, adjusted for cord blood mercury levels and other potential confounders (finger tapping score, preferred hand, $\beta = -0.76$, $p = .30$; hand-eye coordination errors, $\beta = 0.04$, $p = .26$) (Grandjean and others 2001).

Background lactational PCB exposure, inadequate evidence

A Dutch birth cohort study found no associations between neurologic optimality scores at age 42 months and breast milk PCB-TEQ levels (results stated without supporting data) (Lanting and others 1998b). Further follow-up of this cohort revealed an association of borderline statistical significance between McCarthy motor subscale scores at age 6-7 and 3rd trimester maternal plasma levels of 4 non-coplanar PCBs among formula-fed but not among breastfed children (per natural log PCB increment, formula-fed, $\beta = -3.92 \pm 2.04$, $p = .06$; breastfed, $\beta = -1.28 \pm 1.84$, $p = .49$, adjusted for breastfeeding duration) (Vreugdenhil and others 2002).

8c. Sensory function

Reviews

Reviewers	Scope	Comments or conclusions	Conclusions
(Brouwer and others 1998; Brouwer and others 1998), WHO	Review of health risks to infants of perinatal exposure to PHAHs by a World Health Organization working group	Estimated maternal TCDD-TEQ body burden from PCDFs and dioxin-like PCBs was 2-3 µg/kg body weight, i.e., two orders of magnitude higher than background environmental exposure levels.	High-level prenatal exposure to PCBs, PCDFs and related organochlorines during the Yusho and Yucheng incidents caused central auditory processing deficits in children

Original studies

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Chen and Hsu 1994), Taiwan	Cohort	27 Yucheng children and matched comparison group, age 7-12 yr	Conducted Chinese version of WISC-R and neurologic examinations and measured auditory, visual and somatosensory evoked potentials	Yucheng children were exposed prenatally and lactationally to PCBs, dibenzofurans and related toxicants		Groups matched for age, sex, birth order, parental education and occupation
Visual-evoked potential latencies (ms), right eye, N145, Yucheng vs unexposed children	148.7±15.0(SD) ms, n=27 153.1±19.2 ms, n=27	Difference in mean visual-evoked potential latencies, t=0.94, p=.35	Auditory-evoked potential latencies (ms), Yucheng vs unexposed children	356.0±36.9 ms, n=27 329.3±25.5 ms, n=27	Difference in mean auditory-evoked potential latencies, t=3.09, p=.003	
(Grandjean and others 2001), Faroe Islands	Birth cohort	Mother-infant pairs recruited at 3 hospitals in 1986-87, singleton births	435 children examined at age 7 yr; conducted neuropsychological tests	Measured cord tissue PCBs (138, 153, 180) and multiplied by 2 to estimate total PCBs; cord blood DDE, mercury	Cord tissue PCB – median 1.02 µg/g lipid (interquartile range 0.53-1.71); cord blood DDE – median 0.71 µg/g lipid; cord blood mercury – median 25.7	Age, sex, and, as necessary, maternal IQ, IUGR, parental education and employment, day care, computer acquaintance

					µg/L	
Visual-evoked potential latencies: 30' latency vs log cord tissue PCBs (ng/g wet wt.), adjusted for age, sex, cord blood Hg	N75 β=0.74 ms, p=.26 P100 β=1.44 ms, p=.22	N145 β=3.35 ms, p=.11		Auditory evoked potential latencies: latency vs log cord tissue PCBs (ng/g wet wt.), adjusted for age, sex, cord blood Hg	20 Hz, III β=0.02 ms, p=.68 20 Hz, V β=0.07 ms, p=.08	40 Hz, III β=0.05 ms, p=.34 40 Hz, V β=0.03 ms, p=.54
(Vreugdenhil and others 2004b), Rotterdam, The Netherlands	Birth cohort; measured P300 auditory-evoked potential latencies	See Vreugdenhil et al 2004 above	60 children examined at age 9	See Vreugdenhil et al 2004 above	See Vreugdenhil et al 2004 above	Maternal alcohol, infant sex, parental education and age at assessment
Adjusted mean difference in auditory-evoked potential latencies (msec) between children of women in 4 th vs 1 st prenatal plasma PCB quartiles	P300Fz 14.3±9.5(SE), p=.14 P300Cz 25.6±9.6, p=.01	P300Pz 22.0±9.4, p=.02	Adjusted mean difference in auditory-evoked potential latencies (msec) between children who were breastfed 17+wk vs formula-fed	P300Fz -19.8±10.8, p=.07 P300Cz -20.2±10.9, p=.07	P300Pz -22.5±10.6, p=.04 Note favourable association	
(Longnecker and others 2004), USA	Cohort (U.S. Collaborative Perinatal Project)	Hospital prenatal clinics in 11 cities, 13 private practices in a 12 th city, singleton live births during 1959-65, 3-ml 3 rd trimester maternal serum sample available; random sample of 615 children at age 7 plus 195 with sensorineural hearing loss (SNHL)	810 mother-child pairs (55% White, 43% Black, 2% other race) ; children examined at birth and age 4 mos, 8 mos and 1, 3, 4 and 7 years	Background sources; 3 rd trimester maternal serum PCBs (11 congeners – 28, 52, 74, 105, 118, 138, 153, 170, 180, 194, 203); analyzed PCB as a continuous linear variable on wet- and lipid-weight bases	Median maternal serum PCB = 2.8 µg/L (about 3-fold higher than current U.S.)	Study centre, maternal serum triglycerides, cholesterol, race, child sex

Sensorineural hearing loss ⁵	Maternal serum PCB ($\mu\text{g/L}$) <1.25 1.25- 2.5- 3.75- 5+	1 1.5, 0.8-3.0 1.1, 0.6-2.3 1.6, 0.7-3.6 1.1, 0.5-2.6 p-trend=0.76				
(Saint-Amour and others 2006), Nunavik, Quebec	Birth cohort	483 newborns recruited at baseline	110 examined at age 5-6; measured visual evoked potentials	Measured cord plasma PCBs (14 congeners with highest concentrations) and 11 chlorinated pesticides or their metabolites, cord blood Pb and Se, blood and hair Hg; selected PCB-153 as marker for PCB exposure (most prevalent congener, highly correlated with other congeners)		Maternal alcohol, marijuana, non-verbal reasoning abilities, parity, child sex, height at birth and hemoglobin at testing time, highest grade completed by primary caregiver, number of children and adults in home
Change in latency (ms) per natural log cord plasma PCB-153 increment	At 95% contrast N75 $\beta=0.10$ ms, $p>.05$ P100 $\beta=2.50$ ms, $p<.01$ N150 $\beta=0.57$ ms, $p>.05$	At 30% contrast N75 $\beta=0.54$ ms, $p>.05$ P100 $\beta=1.12$ ms, $p<.01$ N150 $\beta=1.42$ ms, $p>.05$	At 12% contrast N75 $\beta=-0.44$ ms, $p>.05$ P100 $\beta=3.22$ ms, $p<.05$ N150 $\beta=5.58$ ms, $p<.05$	No associations between cord PCB-153 and visual evoked potential latencies or amplitudes	Result stated without supporting data	

⁵ Hearing threshold ≥ 13.3 dB averaged across both ears at 1000, 2000 and 4000 Hz with no evidence of conductive hearing loss.

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Summary: Sensory function deficits

Visual function

High-level maternal PCB/PCDF exposure, limited evidence

Yucheng children age 7-12 prenatally exposed to high levels of PCBs, PCDFs and related toxicants had visual-evoked potential latencies similar to those of unexposed children (mean visual-evoked potential latencies, 148.7±15.0 ms vs 153.1±19.2 ms, $t=0.94$, $p=.35$) (Chen and Hsu 1994).

Background maternal PCB exposure, limited evidence

In the Faroe Islands birth cohort, there was no association between visual-evoked potential latencies at age 7 and umbilical cord tissue levels of 3 non-coplanar PCBs (change in latency per log increment cord tissue levels of 3 non-coplanar PCBs, N75 $\beta=0.74$ ms, $p=.26$; P100 $\beta=1.44$ ms, $p=.22$; N145 $\beta=3.35$ ms, $p=.11$) (Grandjean and others 2001). A Quebec birth cohort study reported no association between VEP latencies and cord plasma PCB-153 levels (result stated without supporting data) (Saint-Amour and others 2006).

Lactational PCB exposure, inadequate evidence

The Quebec birth cohort study observed associations between P100 and N150 VEP latencies and current child blood PCB levels, independent of potential confounders including maternal alcohol or marijuana use and current child blood mercury levels (change in latency per natural log increment of cord plasma PCB-153, 12% contrast, N75 $\beta=-0.44$ ms, $p>.05$; P100 $\beta=3.22$ ms, $p<.05$; N150 $\beta=5.58$ ms, $p=.05$) (Saint-Amour and others 2006). Current plasma PCB levels in young children with a history of breastfeeding mainly reflect lactational exposure.

Auditory function

High-level maternal PCB/PCDF exposure, limited evidence

Yucheng children age 7-12 prenatally exposed to high levels of PCBs, PCDFs and related toxicants had increased auditory-evoked potential latencies compared to those of unexposed children (mean auditory-evoked potential latencies, 356.0±36.9 ms vs 329.3±25.5 ms, $t=3.09$, $p=.003$) (Chen and Hsu 1994).

Background maternal PCB exposure, limited evidence

In the Faroe Islands birth cohort, there was no association between auditory-evoked potential latencies at age 7 years and umbilical cord tissue levels of 3 non-coplanar PCBs (change in latency per log increment cord tissue levels of 3 non-coplanar PCBs, 20 Hz III $\beta=0.02$ ms, $p=.68$; 20 Hz V $\beta=0.07$ ms, $p=.08$; 40 Hz III $\beta=0.05$ ms, $p=.34$; 40 Hz V $\beta=0.03$ ms, $p=.54$) (Grandjean and others 2001). Among children age 9 in the Rotterdam component of the Dutch birth cohort study with 4th quartile maternal plasma levels of 4 non-coplanar PCBs, mean auditory-evoked potential latencies were greater than those of children with 1st quartile maternal plasma levels (adjusted mean latency difference, P300Fz 14.3±9.5 ms, $p=.14$; P300Cz 25.6±9.6 ms, $p=.01$; P300Pz 22.0±9.4 ms, $p=.02$) (Vreugdenhil and others 2004b). In the U.S. Collaborative Perinatal Project cohort, sensorineural hearing loss at age 8 was not associated with maternal serum PCB levels over the range <1.25 to ≥ 5 $\mu\text{g/L}$ ($p\text{-trend}=.76$) (Longnecker and others 2004).

Lactational PCB exposure, inadequate evidence

Among children age 9 in the Rotterdam component of the Dutch birth cohort study, those who were breastfed for at least 17 weeks had reduced auditory-evoked potential latencies compared to those who were formula-fed (adjusted mean latency difference, P300Fz -19.8±10.8 ms, $p=.07$; P300Cz -20.2±10.9 ms, $p=.07$; P300Pz -22.5±10.6 ms, $p=.04$) (Vreugdenhil and others 2004b).

8d. Abnormal behaviours

Reviews

Reviewers	Scope	Comments or conclusions
(Schantz 1996), USA	Review of PCBs and developmental neurotoxicity	Prenatally exposed Yucheng children had increased activity levels and behaviour problems but severity of effects were not associated with current childhood or maternal serum PCB levels
(Longnecker and others 1997), USA	Review of human health effects of DDT and PCBs	Noted that exposed children showed disordered behaviour and were hyperactive
(Guo and others 2004), Taiwan	Review of health effects among the cohort of persons exposed to food cooked in oil contaminated by PCBs, PCDFs, PCTs and PCQs during the 1979 Yucheng incident	Compared to unexposed children, prenatally exposed Yucheng children had higher Rutter scale problem behaviour scores at ages 3 and 9, higher activity scores at age 3-12

Original studies

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Chen and others 1994), Taiwan	Cohort	See Yu et al. 1994 above, 115 Yucheng children and matched comparison group	Conducted Rutter's Child Behavior Scale A and Werry-Weiss-Peters Activity Scale (WWPAS) twice annually during 1985-1991; children were age 3-11 yr when tested			
Yucheng children had mean Rutter total problem behaviour scores 11-63% higher	Yucheng children born up to 6 yr after mother was exposed had similar increase	Yucheng children had WWPAS scores 8-53% higher than controls at each age	Behaviour and activity scores not associated with maternal serum PCB levels or	Result stated without supporting data		

than controls at each age tested (average of 28% across all ages tested)	in total problem behaviour scores	tested	detectable PCBs in children's serum			
(Jacobson and Jacobson 1996b), Michigan	Birth cohort	313 children at baseline (see Jacobson et al. 1990 above)	Conducted WISC-R and spelling, arithmetic and word/passage comprehension tests on 212 children at age 11 yr	See Jacobson et al. 1996 above; serum samples at age 4 and 11 yr tested for PCBs, PBBs and 7 organochlorine pesticides (only DDT/DDE was detected)	Developed a composite measure of prenatal exposure based on PCB levels in cord and maternal serum and breast milk; breast milk PCB categories for dose-response analysis were 0.50, 0.50-0.74, 0.75-0.99, 1.00-1.24 and ≥ 1.25 $\mu\text{g/g}$ lipid	SES, maternal education, vocabulary and marital status, HOME score, prenatal smoking and alcohol use, number of children in household, child's sex, grade and current hair mercury level, prenatal PCB exposure index
WISC-R subscale for freedom from distractibility score at age 11 vs maternal or cord serum PCB level (5 categories)	$\beta = -0.17$, $p = .02$	WISC-R subscale for freedom from distractibility score at age 11 vs breast milk PCB levels, adjusted for BF duration	No association – result stated without supporting data	WISC-R subscale for freedom from distractibility scores at age 11 vs prenatal serum PCB and serum PCB at age 4	Report states that scores were associated with prenatal serum PCB ($p = .02$) but not serum PCB at age 4; does not state β 's	
(Grandjean and others 2001), Faroe Islands	Birth cohort	Mother-infant pairs recruited at 3 hospitals in 1986-87, singleton births	435 children examined at age 7 yr; conducted neuropsychological tests	Measured cord tissue PCBs (138, 153, 180) and multiplied by 2 to estimate total PCBs; cord blood DDE, mercury	Cord tissue PCB – median 1.02 $\mu\text{g/g}$ lipid (interquartile range 0.53-1.71); cord blood DDE – median 0.71 $\mu\text{g/g}$ lipid; cord blood mercury – median	Age, sex, and, as necessary, maternal IQ, IUGR, parental education and employment, day care, computer acquaintance

					25.7 µg/L	
Attention: continuous performance test Avg reaction time (msec) vs cord tissue PCBs (µg/g lipid)	Not adjusted for cord blood Hg $\beta=7.2, p=.41$ Adjusted for cord blood Hg $\beta=-7.2, p=.45$					
(Jacobson and Jacobson 2003), Michigan, USA	Birth cohort		167 children examined at age 11; conducted continuous performance test, assessed behaviour during cognitive testing and by mother-reported information on hyperactivity	Prenatal exposure based on avg z-score of cord, maternal serum and breast milk total PCBs; postnatal exposure based on serum PCBs at age 4; measured blood lead at age 4	Mean and SD PCB concentrations: cord and maternal serum – 2.7 ± 2.1 and $1.5.9\pm 3.8$; ng/ml; breast milk – 0.859 ± 0.388 µg/g lipid	SES, maternal age, parity, gravidity, education, vocabulary score, HOME score, employment, alcohol, smoking, child sex, school grade at age 11, other variables
Change in reaction time per unit change in PCB level	Prenatal $\beta=0.04, p>.05$ postnatal $\beta=.02, p>.05$	Change in mother-reported attentiveness score per unit change in prenatal PCB, adjusted for serum PCB at age 4	Total sample $\beta=-0.13, p>.05$ BF <6 wk $\beta=-0.39, p<.05$			
(Vreugdenhil and others 2004a), Rotterdam, The Netherlands	Birth cohort; conducted neuropsychological tests at age 9	Recruited 207 mother-infant pairs, 1990-92, 1 st or 2 nd born term infants	83 children in the 1 st and 4 th maternal plasma PCB quartiles examined at age 9	Prenatal maternal plasma PCBs (118, 138, 153, 180)	Median and range maternal plasma PCBs: 1 st Q – 1.40, range 0.6-1.9 µg/L; 4 th Q – 3.2, 2.5-5.1 µg/L	Maternal prenatal alcohol, gestation length, infant sex, parity, parental education,

						parental verbal IQ and age
Standardized response time test (index of processing speed and sustained attention), 4 th vs 1 st quartile maternal plasma PCB levels	Response time (RT) $\beta=26.6\pm12.8(\text{SE})$ ms, $p=.04$	Standardized response time test (index of processing speed and sustained attention), BF short vs FF	Response time (RT) $\beta=18.9\pm13.8$ ms, $p=.18$	Standardized response time test (index of processing speed and sustained attention), BF long vs FF	Response time (RT) $\beta=20.4\pm14.0$ ms, $p=.15$	
Standardized response time test (index of processing speed and sustained attention), BF long vs BF short	Response time (RT) $\beta=1.53\pm15.7$ ms, $p=.92$					

Summary: Abnormal behaviours

High-level maternal PCB/PCDF exposure, limited evidence

Four reviews of epidemiologic studies noted that high-level maternal exposure to PCBs, PCDFs and related toxicants during the Yusho and Yucheng incidents was associated with persistent problem behaviours including hyperactivity (Brouwer and others 1998; Guo and others 2004; Longnecker and others 1997; Schantz 1996). There appears, however, to have been no association between problem behaviours and prenatal or postnatal PCB exposure indices (stated without supporting data) (Chen and others 1994).

Background maternal PCB exposure, inadequate evidence

A Michigan birth cohort study found an inverse association between freedom from distractibility at age 11 and prenatal but not postnatal PCB exposure levels (change in WISC-R subscale for freedom from distractibility per unit change in cord or maternal serum PCB level (5 categories), $\beta=-0.17$, $p=.02$) (Jacobson and Jacobson 1996b). Further follow-up of this cohort revealed no association between reaction time and prenatal or postnatal PCB levels in the whole group; however, there was an inverse association between mother-reported attentiveness and prenatal PCB levels among the subgroup of infants who were breastfed less than 6 weeks (change in score per unit change in prenatal PCB level, $\beta=-0.39$, $p<.05$) (Jacobson and Jacobson 2003). The Faroe Islands birth cohort study found an inverse association between attention scores (measured using the continuous performance test) at age 7 and umbilical cord tissue PCB levels (change in reaction time per log increment of cord tissue levels of 3 non-coplanar PCBs, $\beta=-7.2$, $p=.45$, adjusted for cord blood mercury) (Grandjean and others 2001). In the Rotterdam component of the Dutch birth cohort, sustained attention scores at age 9 were inversely associated with maternal plasma PCB levels (change in reaction time, 4th vs 1st quartile maternal plasma levels of 4 non-coplanar PCBs, $\beta=20.4\pm14.0$ ms, $p=.15$) (Vreugdenhil and others 2004a).

Lactational PCB exposure, inadequate evidence

The Michigan birth cohort study found no association between freedom from distractibility at age 11 and serum PCB at age 4 (an index of lactational exposure) when adjusted for prenatal serum PCB levels; the report does not give data for β related to freedom from distractibility at age 11 vs serum PCB at age 4

(Jacobson and Jacobson 1996b). In the Rotterdam component of the Dutch birth cohort, sustained attention scores at age 9 were not associated with breastfeeding duration (change in reaction time, breastfed long vs short, $\beta=1.53\pm 15.7$ ms, $p=.92$) (Vreugdenhil and others 2004a).

9. Pubertal development

Review of toxicologic studies

Reviewers	Scope	Conclusions
(Brouwer and others 1998), The Netherlands	Review of health risks to infants of perinatal exposure to PHAHs by a World Health Organization working group	Perinatal exposure of rodents to TCDD caused reduced anogenital distance, delayed testis descent and reduced sperm counts in male offspring and clitoral clefting in female offspring
		Perinatal exposure of male rodents to TCDD caused partial demasculinization of sexual behaviour during adulthood; no effect of same exposure on sexual behaviour of female offspring during adulthood

9a. Delayed pubertal development: females – original studies

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Gladen and others 2000), North Carolina	Birth cohort; annual questionnaire for self-assessed Tanner stage of pubertal development beginning in 1992 for max. 5 yr	Mother-infant pairs recruited from general population in 1978-82	594 youth surveyed annually beginning at age 12-14	Measured breast milk, maternal blood, cord blood and placental PCB and DDE levels; computed average PCB concentration in all biological samples and converted to equivalent concentration in breast milk lipid	Median PCB concentration – 1.7, range 0.5-5.5 µg/g lipid; median cumulative lactational PCB exposure – 5.0, range 0.2-23 mg, among those breastfed as infants	Age, maternal weight, race, breast feeding
Menarche: average age at menarche by increasing prenatal	12.7, 13.0, 13.0, 12.6 p-trend=.46	Menarche: average age at menarche by increasing cumulative	12.9, 12.8, 13.0, 12.8 p-trend=.69	Breast development: average age at Tanner stage B3 by	11.1, 11.4, 11.6, 10.1 p-trend=.41	

PCB level (0-1, 1-2, 2-3, 3+ µg/g lipid)		lactational PCB intake (formula-fed, 0-5, 5-10, 10+ mg)		increasing prenatal PCB level		
Breast development: average age at Tanner stage B3 by increasing cumulative lactational PCB intake	11.9, 11.4, 11.5, 11.6 p-trend=.69	Female pubic hair development: average age at Tanner stage H3 by increasing prenatal PCB level	12.0, 12.2, 12.1, 10.5 p-trend=.31	Female pubic hair development: average age at Tanner stage H3 by increasing cumulative lactational PCB intake	12.6, 11.6, 11.9, 11.7 p-trend=.08	
(Blanck and others 2000), Michigan	Cohort study; information from mothers and daughters age 18+ on daughter's ages at pubertal changes with aid of Tanner stage drawings	Daughters of mothers enrolled in the Michigan PCB registry during 1976-79; exposed via animal and dairy products to PBBs inadvertently added to cattle feed in 1973	327 daughters age 5-24	Maternal serum PBBs and PCBs: 14% of mothers sampled at daughter's birth and others sampled later – the latter values were extrapolated backwards to estimate levels at daughter's birth	Estimated mean prenatal serum concentrations: PBBs – 17 µg/L (range ND to 1142); PCBs – 5.6 µg/L (range ND to 78)	Various combinations of maternal age at menarche, maternal serum PCBs, maternal age at daughter's birth, maternal education, prenatal alcohol and smoking, household income, daughter's age, usual physical activity, years of farm chemical use
Menarche: Cox proportional hazards model: ratios of likelihoods of being postmenarchial and 95% CIs	Mat. serum PBB (µg/L) ≤1 >1-6 ≥7 ≤1 >1-6 ≥7	Formula-fed 1.0 0.9, 0.6-1.6 0.8, 0.3-1.8 Breastfed 1.2, 0.7-1.9 1.5, 0.7-3.1 3.4, 1.3-9.0		Pubic hair stage: ordinal logistic regression analysis, likelihood of Tanner stage H2 or greater by maternal serum PCB category, odds ratios and 95% CIs	Mat. serum PBB (µg/L) ≤1 >1-4 ≥5 ≤1 >1-4 ≥5	Formula-fed 1.0 0.4, 0.1-1.7 0.9, 0.2-4.3 Breastfed 0.7, 0.2-1.9 2.4, 0.4-15.3 19.5, 2.8-138

Breast development: ordinal logistic regression analysis, Tanner stage vs maternal serum PCB, odds ratios and 95% CIs	Mat. serum PBBB ($\mu\text{g/L}$) ≤ 1 $>1-4$ ≥ 5 ≤ 1 $>1-4$ ≥ 5	Formula-fed 1.0 0.5, 0.2-1.9 0.5, 0.2-1.9 Breastfed 0.7, 0.2-1.8 2.5, 0.4-12 1.2, 0.2-6.4				
(Staessen and others 2001), Antwerp, Belgium	Cross-sectional; physician-assessed Tanner stage of sexual maturation, also measured testicular volume	Recruited adolescents in 1999 who were life-long residents of 2 areas near sources of environmental pollutants (smelter, waste incinerators, crematory, printing works); comparison group from a non-contaminated area	100 adolescents from contaminated regions, 100 from unexposed region, age 15-19	Measured serum PCBs (138, 153, 180) and TCDD-like compounds (calux <i>in vitro</i> assay of AhR activation), urinary cotinine, cadmium, benzene and toluene metabolites, 1-hydroxypyrene, β_2 -microglobulin, blood lead, cadmium, cystatin C	Geometric mean serum levels in 2 exposed and comparison regions: PCBs – 278, 259, 234 pM/g lipid; dioxin-TEQ – 30, 46, 25 pg/g lipid	Age, BMI, parental SES, use of oral contraceptives (girls)
Female breast development	Less than adult breast development: odds ratio per doubling of serum dioxin activity	2.3, 1.2-4.5				
(Den Hond and others 2002), Belgium	Cross-sectional, see Staessen et al. 2001 above,	Recruited adolescents in 1999 who were life-long residents of 2 areas near sources of environmental pollutants (smelter,	100 adolescents from contaminated regions, 100 from	Measured serum PCBs (138, 153, 180) and TCDD-like compounds (calux <i>in vitro</i> assay of AhR activation), urinary	Geometric mean serum levels in 2 exposed and comparison regions: PCBs – 278, 259, 234 pM/g lipid;	Age, BMI, oral contraceptive use (girls), parental social class

		waste incinerators, crematory, printing works); comparison group from a non-contaminated area	unexposed region, age 15-19	cotinine, cadmium, benzene and toluene metabolites, 1-hydroxypyrene, β_2 -microglobulin, blood lead, cadmium, cystatin C	dioxin-TEQ – 30, 46, 25 pg/g lipid	
Females: less than adult breast development	PCB congener 138 153 180 all 3 Serum dioxin	OR per doubling of serum level 0.8, p=0.43 0.8, p=0.64 0.7, p=0.45 0.7, p=0.49 2.3, p=0.02	Female pubic hair growth	PCB congener 138 153 180 all 3 Serum dioxin	OR per doubling of serum level 1.1, p=0.71 1.3, p=0.43 1.0, p=0.99 1.2, p=0.59 1.0, p=0.97	
(Vasiliu and others 2004), Michigan, USA	Cohort study; assessed mother-reported age at menarche of daughters	Daughters of women who consumed Lake Michigan sports fish as identified during 3 surveys between 1973 and 1991	213 daughters age 20-50	Measured mother's PCB (Aroclor 1260 standard) and DDE levels repeatedly during 1973-91; estimated levels during relevant pregnancy	Median, 5 th and 95 th percentile serum levels for mothers of daughters with age at menarche of 12-14 were: PCBs – 2.9, 0, 13 $\mu\text{g/L}$; DDE- 4.2, 0.4, 15 $\mu\text{g/L}$. Paper does not give data for all mothers combined.	Maternal serum DDE or PCB, height, age at delivery, education, daughter's birth weight, year of birth, breastfeeding history
Age at menarche	β -coefficient (years) from regression of age at menarche vs maternal serum PCB ($\mu\text{g/L}$) and covariates	-0.01, SE 0.04 p=0.76				

Summary: Delayed pubertal development, females*Delayed pubic hair development*

Prenatal, lactational or childhood PCB exposure, inadequate evidence

The North Carolina birth cohort study reported that adolescent girls with high lactational PCB exposure had *lower age at onset of pubic hair* of borderline statistical significance (average age at Tanner stage H3, highest vs lowest lactational PCB exposure (estimated from breast milk PCB levels and breastfeeding duration), 11.7 vs 12.6, p-trend over 4 cumulated exposure categories was 0.08) (Gladden and others 2000). There was no association with maternal or cord serum PCB (average age at Tanner stage H3, highest vs lowest maternal or cord serum PCB level, 10.5 vs 12.0, p-trend over 4 exposure categories was 0.31). In a Belgian cross-sectional study of adolescents, delayed pubic hair development was not associated with current serum level of TCDD-like activity (per doubling of serum CALUX assay for TCDD activity, OR=1.0, p=.97) or with serum PCBs (per doubling of sum of 3 non-coplanar PCB congeners, OR=1.2, p=.59) (Den Hond and others 2002).

Prenatal or lactational PBB exposure, inadequate evidence

A Michigan birth cohort study observed an association between maternal serum PBB levels and likelihood of Tanner pubic hair development stage H2 or greater among breast-fed (maternal serum PCB ≥ 5 vs ≤ 1 $\mu\text{g/L}$, OR=19.5, 95% CI 2.8-138) but not formula-fed daughters (OR=0.9, 95% CI 0.2-4.3) (Blanck and others 2000). The wide confidence intervals of these odds ratio reflect the small numbers of breast-fed or formula-fed subjects in the highest maternal serum PBB category.

Delayed breast development

Prenatal, lactational or childhood PCB exposure, inadequate evidence

The North Carolina study found no association between age at breast development and maternal or cord serum PCB level (average age at Tanner stage B3, highest vs lowest maternal or cord serum PCB level, 10.1 vs 11.1, p-trend over 4 exposure categories was 0.41) or cumulative lactational PCB exposure (average age at Tanner stage B3, highest vs lowest cumulative lactational PCB dose, 11.6 vs 11.9, p-trend over 4 cumulated exposure categories was 0.69) (Gladden and others 2000). A Belgian cross-sectional study of youth age 15-19 observed an association between delayed breast development and serum TCDD activity (per doubling of serum CALUX assay TCDD activity, OR=2.3, p=.02) but not with serum PCBs (per doubling of sum of 3 non-coplanar PCB congeners, OR=0.7, p=.49) (Den Hond and others 2002).

Prenatal or lactational PBB exposure, inadequate evidence

The Michigan birth cohort study observed no association between maternal serum PBB levels and likelihood of Tanner breast development stage B2 or greater among breast-fed (maternal serum PCB ≥ 5 vs ≤ 1 $\mu\text{g/L}$, OR=1.2, 95% CI 0.2-6.4) or formula-fed daughters (OR=0.5, 95% CI 0.2-1.9) (Blanck and others 2000).

Delayed menarche

Prenatal or lactational PCB exposure, inadequate evidence

The North Carolina birth cohort study reported no association between age at menarche and indices of transplacental or lactational PCB exposure (average age at menarche, highest vs lowest maternal or cord serum PCB level, 12.6 vs 12.7, p-trend over 4 exposure categories was 0.46) or cumulative lactational PCB exposure (average age at menarche, highest vs lowest cumulative lactational PCB dose, 12.8 vs 12.9, p-trend over 4 cumulated exposure categories was 0.69) (Gladden and others 2000). The Michigan cohort observed no association between age at menarche and maternal serum PCB levels (change in age at menarche per unit change in maternal serum PCB, $\beta=-0.01\pm 0.04$ years, p=.76) (Vasiliiu and others 2004).

Prenatal or lactational PBB exposure, inadequate evidence

A Michigan birth cohort study observed an association between maternal serum PBB levels and likelihood of being post-menarche among breast-fed (≥ 7 vs ≤ 1 $\mu\text{g/L}$, OR=3.4, 95% CI 1.3-9.0) but not formula-fed daughters (OR=0.8, 95% CI 0.3-1.8) (Blanck and others 2000).

9b. Delayed pubertal development: males – original studies

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	
(Gladen and others 2000), North Carolina	Birth cohort; annual questionnaire for self-assessed Tanner stage of pubertal development beginning in 1992 for max. 5 yr	Mother-infant pairs recruited from general population in 1978-82	594 youth surveyed annually beginning at age 12-14	Measured breast milk, maternal blood, cord blood and placental PCB and DDE levels; computed average PCB concentration in all biological samples and converted to equivalent concentration in breast milk lipid	Median PCB concentration – 1.7, range 0.5-5.5 µg/g lipid; median cumulative lactational PCB exposure – 5.0, range 0.2-23 mg, among those breastfed as infants	
Boys: average age at Tanner genital development stage G3 by increasing prenatal PCB level	13.0, 12.5, 12.6, 12.4 p-trend=.78	Boys: average age at Tanner genital development stage G3 by increasing cumulative lactational PCB intake	12.4, 12.1, 12.7, 11.5 p-trend=.07			
Boys: average age at Tanner pubic hair development stage H3 by increasing prenatal PCB level	13.1, 13.0, 13.1, 13.1 p-trend=.93	Boys: average age at Tanner pubic hair development stage H3 by increasing cumulative lactational PCB intake	12.9, 12.5, 12.9, 12.5 p-trend=.35			
(Den Hond and others 2002), Belgium	Cross-sectional, see Staessen et al. 2001 above,	Recruited adolescents in 1999 who were life-long residents of 2 areas near sources of environmental pollutants (smelter, waste incinerators, crematory, printing works); comparison group from a non-contaminated area	100 adolescents from contaminated regions, 100 from unexposed region, age 15-19	Measured serum PCBs (138, 153, 180) and TCDD-like compounds (calux <i>in vitro</i> assay of AhR activation), urinary cotinine, cadmium, benzene and toluene metabolites, 1-hydroxypyrene, β ₂ -	Geometric mean serum levels in 2 exposed and comparison regions: PCBs – 278, 259, 234 pM/g lipid; dioxin-TEQ – 30, 46, 25 pg/g lipid	Age, BMI, contraceptive use (girls), parental social class

				microglobulin, blood lead, cadmium, cystatin C		
Males: less than adult genital development	PCB congener 138 153 180 all 3 Serum dioxin	OR per doubling of serum level 3.5, p=0.04 4.3, p=0.06 2.6, p=0.21 3.8, p=0.06 1.3, p=0.46	Male pubic hair growth	PCB congener 138 153 180 all 3 Serum dioxin	OR per doubling of serum level 1.4, p=0.33 3.5, p=0.04 3.4, p=0.05 2.7, p=0.06 1.1, p=0.62	
(Mol and others 2002), Faroe Islands	Birth cohort; pediatrician assessed Tanner stage pubertal changes and testicular volume; morning urine sample examined for presence of sperm	Mother-infant pairs recruited at 3 hospitals, 1986-87	196 boys examined at avg age 14	Cord tissue – sum of PCBs (138, 153, 180) times 2 to estimate total PCBs	Cord tissue PCB tertiles were <1.5, 1.5-3.0 and >3.0 ng/g	Age, testicular size, serum testosterone
Spermaturia	Logistic regression analysis: morning urine spermaturia vs cord tissue PCBs	$\beta=0.18$, SD=0.66, p=0.79		Pubic hair	Tanner stage	1.9, 2.4, 1.9 p-trend=0.6
Testicular volume	Mean volume by cord tissue PCB tertile (low to high)	6.8, 8.9, 7.5 ml p-trend=0.30		External genitals	Tanner stage	2.1, 2.5, 2.1 p-trend=0.2

Summary: Delayed pubertal development, males

Delayed pubic hair development

Prenatal, lactational or childhood PCB exposure, inadequate evidence

The North Carolina birth cohort study reported slightly earlier attainment of Tanner pubic hair development stage H3 among breast-fed boys with high lactational PCB exposure (average age at H3, highest vs lowest cumulative lactational PCB dose, 12.5 vs 12.9, p-trend=.35); there was no association with transplacental PCB exposure (average age at H3, highest vs lowest cord or maternal serum PCB level, 13.1 vs 13.1, p-trend=.93) (Gladden and others 2000). A Belgian cross-sectional study of youth age 15-19 reported an association between non-attainment of adult-stage pubic hair development and current serum PCBs (per doubling of sum of 3 non-coplanar congeners, OR=2.7, p=.06) but not serum TCDD activity (OR=1.1, p=.62) (Den Hond and others 2002). In a small birth cohort study

in the Faroe Islands, Tanner stage of pubic hair and genital development among boys age 14 was not associated with cord tissue PCB levels (average Tanner stage by ascending cord tissue PCB tertile, 1.9, 2.4, 1.9, p-trend=.63) (Mol and others 2002).

Delayed external genitalia development

Prenatal, lactational or childhood PCB exposure, inadequate evidence

The North Carolina birth cohort study reported slightly earlier attainment of Tanner male genital development stage G3 among breast-fed boys with high lactational PCB exposure (average age at G3, highest vs lowest cumulative lactational PCB dose, 11.5 vs 12.4, p-trend over 4 PCB dose categories was 0.07); there was no association with transplacental PCB exposure (average age at G3, highest vs lowest cord or maternal serum PCB level, 12.4 vs 13.0, p-trend=.78) (Gladen and others 2000). In a small birth cohort study in the Faroe Islands, external genital development among boys age 14 was not associated with cord tissue PCB levels (mean testicular volume by ascending cord tissue PCB tertile, 6.8, 8.9, 7.5 ml, p-trend=.30; average Tanner stage of external genital development by ascending cord tissue PCB tertile, 2.1, 2.5, 2.1, p-trend=.25) (Mol and others 2002). A Belgian cross-sectional study of youth age 15-19 reported an association between non-attainment of adult-stage male genital development and current serum PCBs (per doubling of sum of 3 non-coplanar congeners, OR=3.8, p=.06) but not serum TCDD activity (OR=1.3, p=.46) (Den Hond and others 2002).

10. Cancer

Reviews (mainly adult cancer)

Reviewers	Scope	Conclusions
(International Agency for Research on Cancer 1987), Lyon	Expert group review of toxicologic and epidemiologic studies of carcinogenicity of PCBs in adults	Limited evidence of carcinogenicity in humans, especially for hepatobiliary cancers, and sufficient evidence in animals (mainly liver cancers); IARC concluded that PCBs can cause cancer in experimental animals and can probably cause cancer in humans
(International Agency for Research on Cancer 1997), Lyon	Expert group review of toxicologic and epidemiologic studies of carcinogenicity of PCDDs and PCDFs	TCDD is a human carcinogen; there is limited evidence of increased cancer risks in highly exposed humans and sufficient evidence of carcinogenicity in experimental animals in which it is a multisite carcinogen and acts through the aryl hydrocarbon receptor that functions similarly in humans and animals
TCDD tissue levels are similar in highly exposed human populations in which increased cancer risks were observed and in exposed rats that developed tumours in carcinogenicity tests.	Other PCDDs and PCDFs are not classifiable as to their carcinogenicity in humans.	
(National Academy of Sciences 2003), USA	Literature review, potential health effects from phenoxy herbicides contaminated with TCDD.	There is sufficient evidence for associations between phenoxy herbicide exposure and chronic lymphocytic leukemia, soft tissue sarcoma, non-Hodgkin's lymphoma and Hodgkin's disease in adults.
There is limited evidence for associations between phenoxy herbicide exposure and respiratory	There is insufficient evidence to determine if phenoxy herbicide exposure is associated with hepatobiliary, nasal/nasopharyngeal, bone, skin, breast, female reproductive tract, testicular, bladder or	There is insufficient evidence to determine if phenoxy herbicide exposure of adults is associated with childhood cancer in their offspring.

and prostate cancers and multiple myeloma in adults	renal cancers or leukemia other than chronic lymphocytic leukemia in exposed adults.	
(National Academy of Sciences 2005), USA	Literature review, potential health effects from the herbicides 2,4-D, 2,4,5-T, cacodylic acid and picloram and TCDD, a potential contaminant of 2,4-D and 2,4,5-T (especially the latter). The evidence was drawn from occupational, environmental and veterans studies in which individuals were exposed to the herbicides used in Vietnam, to their components or to their contaminants.	There is insufficient evidence to determine if parental phenoxy herbicide or TCDD exposure is associated with childhood cancer in their offspring.

10a. Childhood leukemia

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Scheele and others 1992), Germany	Case-control		38 childhood leukemia cases, 15 controls	Measured organochlorine compounds in pooled bone marrow samples (16 pools for cases, 5 pools for controls)	Median concentrations ($\mu\text{g/g}$ lipid): PCBs - 2.9, DDE - 1.1, hexachlorobenzene - 0.26, dieldrin - 0.06, hexachlorocyclohexane - 0.09	
Mean bone marrow PCB concentration, leukemia cases vs controls	4.21 vs 3.38 mg/kg lipid, $p=.28$					
(Pesatori and others 1993), Seveso, Italy	Cohort; assessed cancer incidence during 1977-1986	Persons age 0-19 at time of 1976 chlorophenol plant explosion	15,360 person-years at risk	Explosion contaminated the town of Seveso with TCDD	Avg soil TCDD levels in two contaminated zones and surrounding referent region (R) were 15-580, 1.7-4.3 and 0.9-1.4 $\mu\text{g}/\text{m}^2$	
Incidence of hematopoietic cancers	Expected number based on cancer rates in region R	O/E (8/4.1) = 1.6, 0.7-3.4				
(Heacock and others 2000), British Columbia	Case-control	Nested within cohort of 23,829 male workers in sawmills that used chlorophenolate wood preservatives contaminated by PCDDS and PCDFs, employed at	40 cases of cancer among workers' children age <20, diagnosed during 1969-93, 200 healthy	Cumulative hours of chlorophenolate exposure based on job title and duration	Exposure index validated on subsample by measuring urinary chlorophenolate metabolites	Controls matched by sex and YOB

		least 1 yr during 1950-85	controls randomly selected from other offspring			
Childhood leukemia	Cumulative exposure (hr) <3000 3000+	1.0 0.8, 0.2-3.6				

Summary: leukemia

Childhood PCB exposure, inadequate evidence

A small German case-control study of childhood leukemia found no association with bone marrow PCBs (mean concentration, cases vs controls, 4.21 and 3.38 $\mu\text{g/g}$ lipid, $p=.28$) (Scheele and others 1992).

Paternal occupational exposure to PCDDs, PCDFs and related toxicants, inadequate evidence

Among children of sawmill workers in British Columbia, Canada, leukemia was not associated with duration of paternal occupational exposure to chlorophenolate wood preservatives known to be contaminated with PCDDs, PCDFs and other toxicants (≥ 3000 vs < 3000 hours cumulated exposure, OR=0.8, 95% CI 0.2-3.6) (Heacock and others 2000). An expert panel found insufficient evidence for an association between paternal phenoxy herbicide exposure and childhood cancer (National Academy of Sciences 2003).

Childhood TCDD exposure, inadequate evidence

Follow-up of Seveso residents age 0-19 at the time of the 1976 chlorophenol plant explosion revealed a statistically non-significant excess of leukemia and other hematopoietic cancers (SIR=1.6, 95% CI 0.7-3.4) (Pesatori and others 1993). Much longer follow-up is needed to assess the risk of cancer after longer latent periods.

10b. Childhood brain cancer

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Heacock and others 2000), British Columbia	Case-control	See Heacock et al 2000 above				
Childhood brain cancer	Cumulative exposure (hr) <3560 3560+	1.0 1.5, 0.4-6.9				

Summary: brain cancer

Paternal occupational exposure to PCDDs, PCDFs and related toxicants, inadequate evidence

Among children of sawmill workers in British Columbia, Canada, brain cancer was not associated with duration of paternal occupational exposure to chlorophenolate wood preservatives known to be contaminated with PCDDs, PCDFs and other toxicants (≥ 3560 vs < 3560 hours cumulated exposure, OR=1.5, 95% CI 0.4-6.9) (Heacock and others 2000).

10c. Neuroblastoma

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Kerr and others 2000), New York State	Case-control	Population-based, NY State minus NY City, 1976-87; controls selected from live birth registry matched for YOB	183 neuroblastoma cases, 372 controls, age <15	Hospital records; all cases histologically confirmed	Mother-reported parental occupa and work-related exposures during preg; assessed expos using a list of 25 potential workplace carcinogens	Child's age, parental age, educ
OR, neuroblastoma, self-reported pat occupl dioxin exposure, yes/no	6.9, 1.3-68.4 (7 exp case fa)					

Summary: neuroblastoma

Paternal occupational exposure to TCDD, inadequate evidence

A case-control study in New York State revealed an association between neuroblastoma and self-reported paternal occupational to dioxin (yes/no, OR=6.9, 95% CI 1.3-68.4) (Kerr and others 2000).

11. Chloracne

Reviews

Reviewers	Scope	Conclusions
(Longnecker and others 1997), USA	Review of epidemiologic studies of PCBs, DDT and related organochlorines	PCBs and ρ,ρ' -DDE comprise the bulk of organochlorine residues in human tissues. Relatively high-level PCB exposure probably causes chloracne. High-level dioxin exposure causes chloracne.
(Agency for Toxic Substances and Disease Registry 1998), USA	Review of health effects of PCDDs in animals and humans	The most obvious health effect in people postnatally exposed to relatively large amounts of TCDD is chloracne.
(Sweeney and Mocarelli 2000), USA, Italy	Review of 6 epidemiologic studies of persons exposed to TCDD with biologic measurements of body burden	Postnatal TCDD exposure caused chloracne at dose levels that produced no other obvious health effects; all of the Seveso cases were children age <17 and all but one were age <11.
(National Academy of Sciences 2005), USA	Literature review, potential health effects from the herbicides 2,4-D, 2,4,5-T, cacodylic acid and picloram and TCDD, a potential contaminant of 2,4-D and 2,4,5-T (especially the latter). The evidence was drawn from occupational, environmental and veterans studies in which individuals were exposed to the herbicides used in Vietnam, to their components or to their contaminants.	There is sufficient evidence that TCDD exposure can cause chloracne.

Original studies

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Rogan and others 1988), Taiwan	Retrospective cohort	1979 Yucheng incident; follow-up in 1985; 127 pregnancies among 74	127 Yucheng children, 115 unexposed neighbourhood	History of exposure prenatally and lactationally to		

		exposed women; 115 children from 96 unexposed families	comparison children, age 1 month to 8 yr; conducted physical examinations	PCBs, dibenzofurans and related toxicants		
Prevalence of acne at birth or acne scars at birth or follow-up, children of exposed vs unexposed mothers	At birth 16/125 vs 0/114, p<.001	At follow-up 20/117 vs 10/106, p=.05 (one-tailed Fisher's exact test)				
(Hsu and others 1995), Taiwan	Retrospective cohort	Prenatally exposed Yucheng children, comparison group of unexposed children	88 exposed and 86 unexposed children examined by dermatologist in 1991			Groups matched for neighbourhood, age, sex, maternal age, parental SES
Prevalence of chloracne scars, comedones, exposed vs unexposed children	10 vs 8.1%, p>.05					

Summary: chloracne

High-level prenatal PCB/PCDF exposure, limited evidence

Chloracne occurred among children prenatally exposed to high levels of PCBs, PCDFs and related toxicants during the Yucheng incident (prevalence of acne or acne scars at age 1 month to 8 years, exposed vs unexposed children, 20/117 vs 10/106, p=.05) (Rogan and others 1988). When followed to age 12-14, the prevalence of chloracne scars and comedones among Yucheng children was similar to that of an unexposed comparison group (exposed vs unexposed, prevalence 10.0 vs 8.1%, p>.05) (Hsu and others 1995).

High-level childhood TCDD exposure, sufficient evidence

Reviewers and 2 expert panels concluded that high-level TCDD exposure causes chloracne (Agency for Toxic Substances and Disease Registry 1998; Longnecker and others 1997; National Academy of Sciences 2005; Sweeney and Mocarelli 2000). One reviewer concluded that TCDD caused chloracne at doses that cause no other obvious health effects and observed that all of the Seveso chloracne cases were children age <17 (Sweeney and Mocarelli 2000). Thus children appear to be more susceptible to chloracne after TCDD exposure compare to adults.

12. Childhood respiratory tract infections

Reviews

Reviewers	Scope	Conclusions
(Longnecker and others 1997), USA	Review of epidemiologic studies of PCBs, DDT and related organochlorines	Inadequate evidence for an association between infectious diseases during infancy and prenatal environmental PCB exposure
(Tryphonas 1998), Canada	Review of literature on environmental toxicants with potential adverse effects on the immune system during childhood; focuses on PCBs and dioxins	Although PCBs and dioxins may be immunosuppressive, there is insufficient evidence for an association between ambient exposures and infectious diseases
(Brouwer and others 1998), The Netherlands	Review of health risks to infants of perinatal exposure to PHAHs by a World Health Organization working group	High-level exposure to PCBs, PCDFs and related organochlorines during the Yusho and Yucheng incidents were associated with increased risk of bronchitis among infants.
(Holladay 1999), USA	Review of literature on prenatal exposure to immunotoxicants and risk of autoimmune disease	Gestational TCDD exposure causes severe, persistent immune suppression in rodents.

Childhood respiratory tract infections – original studies

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Rogan and others 1987), North Carolina	Birth cohort	912 children born 1978-82	802 infants followed to age 1; mother-reported info	Measured PCB and DDE levels in breast milk, maternal serum, cord blood and placenta; est'd PCB/DDE breast milk levels at birth and cumulated lactational exposure		
Prevalence of middle ear infections during	Bottle-fed	Prevalence (%) 58				

infancy vs cumulative lactational PCB exposure	<1 mg 1-<2 2-<3 3-<4 ≥5	50 65 48 47 47				
(Rogan and others 1988), Taiwan	Retrospective cohort	Yucheng children born 1978-85; prenatally exposed to PCBs, PCDFs, PCDQs and related toxicants	127 Yucheng children of 74 exposed women, 115 unexposed neighbourhood children, physical examinations			
History of illness by age 6 mos, exposed vs unexposed children	Bronchitis or pneumonia 30/124 vs 5/115, OR=7.02, 2.74-21.0, p<.001					
(Chao and others 1997), Taiwan	Retrospective cohort		103 Yucheng children, 96 comparison children, age 8-15 yr; in 1993, otolaryngologic exam to identify middle ear abnormalities	Measured serum organochlorine levels		
Prevalence of clinical signs of chronic otitis media, exposed vs unexposed children	44/103 vs 18/96, OR=3.23, 1.70-6.23, p<.001	Serum PCDF ≥400 ng/kg lipid, Yucheng middle ear cases vs non-cases	5/15 vs 0/15, OR=∞, 1.46-∞, p=.04	Serum PCB ≥4 mg/kg lipid, Yucheng middle ear cases vs non-cases	5/15 vs 4/15, OR=1.38, 0.27-7.23, p=.86	
(Yu and others 1998), Taiwan	Retrospective cohort		105 Yucheng and 101 control children, age 8-16	Measured serum PCB/PCDF levels for 31 Yucheng children		

			yr; parent-reported illness during previous 6 mos	in 1992		
Avg frequency of illness during previous 6 mos, exposed vs unexposed children	Otitis media 0.67±3.88 vs 0.03±0.22, ns					
(Dewailly and others 2000), Nunavik, Quebec	Birth cohort	Inuit infants born in 2 hospitals during 1989-90	171 mother-infant pairs; 98 breastfed, 73 formula fed; mother- and nurse-reported infections during first year of life	Measured PCBs (sum of 138, 153, 180), DDE, mirex, heptachlor epoxide, chlordane, HCB, endrin and dieldrin in breast milk from women who breastfed; no measurements on women who formula fed	Geometric mean and third tertile maternal plasma levels µg/kg lipid): PCBs – 621, >873; DDE – 962, >1320; HCB – 107, >146; dieldrin – 30, >43; mirex – 14, >18	Authors stated that logistic regression analysis including breastfeeding duration, maternal age and duration of previous breastfeeding yielded similar results (data not shown)
Middle ear infection among BF infants – at least once before age 12 mos	Relative risk for 2 nd and 3 rd relative to 1 st tertile, breast milk PCBs	1.25, 0.89-1.75 1.28, 0.92-1.77		Middle ear infection among BF infants – at least 3 times before age 12 mos	Relative risk for 2 nd and 3 rd relative to 1 st tertile, breast milk PCBs	1.56, 0.48-5.60 1.65, 0.49-5.57
(Weisglas-Kuperus and others 2000), The Netherlands	Birth cohort	207 mother-infant pairs recruited in 1990-92, 1 st or 2 nd born term infants, half breastfed, half formula fed	175 children, age 42 mos; parent-reported physician-diagnosed infectious diseases	Prenatal exposure based on maternal and cord plasma – 4 non-coplanar PCBs (118, 138, 153, 180); postnatal exposure based on breastfeeding duration and breast milk levels of 6 dioxin-like (77,	Medians and ranges: maternal plasma PCBs – 2.1, 0.6-7.4 µg/L; cord plasma PCBs – 0.4, 0.1-2.1 µg/L; plasma PCBs at age 42 mos – 0.4, 0.1-5.9 µg/L; breast milk planar PCB TEQ – 15, 4-46 pg/g	Breast/formula feeding, duration of breast feeding, maternal parity, education, paternal occupational class, parental smoking, family history of allergy, day care attendance, child

				105, 118, 126, 156, 169), 20 non-dioxin-like PCBs and 17 PCDDs and PCDFs	lipid; breast milk total PCB and PCDD/PCDF TEQ – 36, 10-87 pg/g lipid	sex
History of 1 or more ear infections	Multiple logistic analysis: odds ratios per unit increase in PCB concentration	Prenatal PCBs 0.89, 0.65-1.23 Current child PCBs 1.27, 0.61-2.64		History of 6 or more ear infections	Multiple logistic analysis: odds ratios per unit increase in PCB concentration	Prenatal PCBs 1.37, 0.87-2.17 Current child PCBs 3.06, 1.17-7.98
History of pneumonia	Prenatal PCBs 0.41, 0.10-1.63 Current child PCBs 0.01, 0.01-0.37					
(Karmaus and others 2001), Hamburg, Germany	Cross-sectional	Second-grade children in schools in 18 townships	343 children age 7-10; serum IgE levels, physician-diagnosed middle ear infections, whooping cough and pneumonia	Measured whole blood levels of DDE, HCB, β -HCH, γ -HCH, PCBs (101, 118, 138, 153, 170, 180, 183, 187)	Median, 95 th and maximum blood levels (μ g/L): PCBs – 0.5, 1.5, 4.5; HCB – 0.2, 0.5, 2.5; DDE – 0.3, 1.0, 4.0; β -HCH – 0.06, 0.3, 4.5; γ -HCH – 0.02, 0.06, 0.2	Sex, age, breast-feeding; note-excluded ETS as effect was minimal in logistic model
Middle ear infections	Logistic regression analysis: odds ratios for whole blood PCB >0.48 vs \leq 0.48 μ g/L within DDE strata	DDE <0.3 μ g/L 0.85, 0.40-1.80 DDE \geq 0.3 μ g/L 3.70, 1.64-8.34		Pneumonia	Logistic regression analysis: odds ratios for whole blood PCB >0.48 vs \leq 0.48 μ g/L within DDE strata	DDE <0.3 μ g/L 1.24, 0.53-2.92 DDE \geq 0.3 μ g/L 0.68, 0.26-1.76
(Weisglas-Kuperus and others 2004),	Birth cohort; parent-reported	207 mother-infant pairs recruited in	Examined 167 children at age 7-8	Prenatal exposure based on maternal and	Medians and ranges: maternal plasma	Breast/formula feeding, duration of

Rotterdam, The Netherlands	history of infectious diseases and allergies	1990-92, 1 st or 2 nd born term infants, half breastfed, half formula fed		cord plasma – 4 non-coplanar PCBs (118, 138, 153, 180); postnatal exposure based on breastfeeding duration and breast milk levels of 6 dioxin-like (77, 105, 118, 126, 156, 169), 20 non-dioxin-like PCBs and 17 PCDDs and PCDFs	PCBs – 2.1, 0.7-5.1 µg/L; cord plasma PCBs – 0.4, 0.1-2.0 µg/L; breast milk PCBs – 390, 174-805 ng/g lipid; breast milk total PCB and PCDD/PCDF TEQ – 68, 28-135 pg/g lipid	breast feeding, parity, maternal education, paternal occupational class, parental smoking, family history of allergy, day care attendance, child sex, age at examination
Recurrent middle ear infections, age 3-7	Multiple logistic analysis, odds ratio per unit increase of prenatal maternal plasma PCB	Prenatal exposure 0.98, 0.53-1.80		Recurrent middle ear infections, age 3-7	Multiple logistic analysis, odds ratio per unit increase of cumulative lactational PCB exposure (µg/g lipid in milk times weeks of breastfeeding)	Lactational exposure 1.19, 1.01-1.41
(Dallaire and others 2004), Nunavik, Canada	Birth cohort	Inuit infants born in 3 communities during 1995-2001	199 mother-infant pairs; trained nurses extracted medical chart information on health problems during first year of life	Measured 14 PCB congeners (28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 170, 180, 183, 187) and DDE in maternal, cord and infant plasma (at about age 7 mos); used PCB-153 ^f as proxy for total PCBs	Geometric mean maternal plasma levels: PCBs – 308, range 60-1951 µg/kg lipid); DDE – 294, range 54-2269 µg/kg lipid; strong correlation between plasma PCB-153 and DDE (r=0.94)	Maternal age, season of birth, year of birth, breast feeding duration, sex, SES of caregiver, prenatal smoking, village, number of children in household
Lower respiratory tract infection in first	Poisson regression	1.18, 0.68-2.04 p-trend=.38		Lower respiratory tract infection in first	Poisson regression analysis, relative	1.03, 0.72-1.48 p-trend=.36

^f PCB-153 is the most abundant congener and its concentration is strongly correlated with all the moderate to heavily chlorinated PCB congeners.

6 months	analysis, relative risks, 4 th vs 1 st quartile of prenatal maternal plasma PCB-153			12 months	risks, 4 th vs 1 st quartile of prenatal maternal plasma PCB-153	
Middle ear infection during first 6 mos	Poisson regression analysis, relative risks, 4 th vs 1 st quartile of prenatal maternal plasma PCB-153	1.39, 0.82-2.35 p-trend=.17		Middle ear infection during first 12 mos	Poisson regression analysis, relative risks, 4 th vs 1 st quartile of prenatal maternal plasma PCB-153	0.97, 0.73-1.28 p-trend=.89
(Dallaire and others 2006), Nunavik	Birth cohort	Recruited 1993-96	491 mother-infant pairs; trained medical students extracted medical chart information on health problems up to age 5 yr	Measured cord blood PCB (used PCB-153 [§] as proxy for total PCBs) and metals		Adjusted for mat age, parity; showed that prenatal smoking, infant sex, chart reviewer and gestation length were not confounders
History of infection vs cord blood PCB-153, relative risk per log increment	Acute otitis media 1.12, 1.05-1.20	Lower resp tract infections 1.14, 1.04-1.24	History of infection vs cord blood PCB-153, relative risk 4 th vs 1 st quartile	Acute otitis media 1.37, 1.20-1.55	Lower resp tract infections 1.44, 1.20-1.72	

Summary: Childhood respiratory tract infections

Lung infections

High-level maternal PCB/PCDF exposure, limited evidence

A retrospective cohort study of Yucheng children age 6 revealed a substantially increased prevalence of a history of bronchitis or pneumonia by age 6 months (exposed vs comparison children, OR=7.02, 95% CI 2.74-21.0; calculated from data in paper) (Rogan and others 1988). A WHO expert group concluded that high-level maternal PCB/PCDF exposure was associated with increased risk of bronchitis among infants (Brouwer and others 1998).

[§] PCB-153 is the most abundant congener and its concentration is strongly correlated with all the moderate to heavily chlorinated PCB congeners.

Background maternal PCB exposure, inadequate evidence

Reviews of epidemiologic studies published up to the mid-1990's found inadequate evidence for an association between risk of infections during infancy and background maternal PCB exposure levels (Longnecker and others 1997; Tryphonas 1998). A multicentre Dutch birth cohort study reported no association between a history of pneumonia by age 42 months and maternal plasma PCB (per natural log increment of maternal plasma PCB, OR=0.41, 95% CI 0.10-1.63, adjusted for breastfeeding history and duration) (Weisglas-Kuperus and others 2000). Among Inuit women and infants in northern Quebec, a history of clinically confirmed lower respiratory tract infection by age 12 months was not associated with maternal plasma PCB-153 levels (4th vs 1st quartile plasma PCB-153, OR=1.03, 95% CI 0.72-1.48, p-trend=.36) (Dallaire and others 2004). In a similar study, a clinically confirmed history of lower respiratory tract infection by age 5 was associated with cord plasma PCB-153 (4th vs 1st quartile, OR=1.44, 95% CI 1.20-1.72) with evidence of a dose-response relationship (per log cord plasma PCB-153 increment, OR=1.14, 95% CI 1.04-1.24) (Dallaire and others 2006).

Lactational PCB exposure, inadequate evidence

The Dutch birth cohort study revealed an inverse association between a history of pneumonia by age 42 months and current child plasma PCB, an index of lactational exposure (per natural log increment of child plasma PCB ($\mu\text{g/L}$), OR=0.01, 95% CI 0.01-0.37, adjusted for breastfeeding vs formula feeding and duration of breastfeeding) (Weisglas-Kuperus and others 2000). In a German cross-sectional study of children age 7-10, a history of physician-diagnosed pneumonia was not associated with whole blood PCB levels stratified by whole blood DDE levels (for DDE $<0.3 \mu\text{g/L}$, PCB >0.48 vs $\leq 0.48 \mu\text{g/L}$, OR=1.24, 95% CI 0.53-2.92; for DDE $\geq 0.3 \mu\text{g/L}$, PCB >0.48 vs $\leq 0.48 \mu\text{g/L}$, OR=0.68, 95% CI 0.26-1.76) (Karmaus and others 2001).

Middle ear infections

High-level maternal PCB/PCDF exposure, inadequate evidence

Yucheng children age 8-16 had a statistically non-significant increased risk of parent-reported ear infections during the 6 months before their 1995 examination (mean frequency, exposed vs unexposed, 0.67 ± 3.88 vs 0.03 ± 0.22 , $p > .05$) (Yu and others 1998). However, Yucheng children had an increased risk of otolaryngologically-confirmed chronic otitis media compared to unexposed children (OR=3.23, 95% CI 1.70-6.23) (Chao and others 1997). This study revealed associations between chronic otitis media and current serum PCDF levels (cases vs controls, proportion with serum PCDF $\geq 400 \text{ ng/kg lipid}$, 5/15 vs 0/15, $p = .04$) but not current serum PCB levels (cases vs controls, proportion with serum PCB $\geq 4 \text{ mg/kg lipid}$, 5/15 vs 4/15, $p = .86$).

Background maternal PCB exposure, inadequate evidence

In the Dutch birth cohort, a history of at least 6 ear infections by age 42 months was weakly associated with maternal plasma levels of 4 non-coplanar PCBs (per natural log increment, OR=1.37, 95% CI 0.87-2.17, adjusted for breastfeeding history and duration) (Weisglas-Kuperus and others 2000). Further follow-up of this cohort showed that a history of recurrent otitis media at age 3-7 years was not associated with maternal plasma PCB (per natural log increment of plasma PCB ($\mu\text{g/L}$), OR=0.98, 95% CI 0.53-1.80) (Weisglas-Kuperus and others 2004). In a cohort of Inuit infants, a history of otitis media by age 1 was not associated with prenatal plasma PCB-153 levels (4th vs 1st quartile, OR=0.97, 95% CI 0.73-1.28, p-trend=.89) (Dallaire and others 2004). In a similar study, a clinically confirmed history of acute otitis media by age 5 was associated with cord plasma PCB-153 (4th vs 1st quartile, OR=1.37, 95% CI 1.20-1.55) with evidence of a dose-response relationship (per log cord plasma PCB-153 increment ($\mu\text{g/g lipid}$), OR=1.12, 95% CI 1.05-1.20) (Dallaire and others 2006).

Lactational PCB exposure, limited evidence

In the North Carolina birth cohort study, the prevalence of a history of ear infections before age 1 was lower (47%) among those in the highest cumulative lactational PCB dose category than that for formula-fed infants (58%) or those in the lowest cumulative lactational PCB dose category (50%); the authors did not include a statistical measure of the trend of prevalence vs PCB dose (Rogan and others 1987). Among breastfed Quebec Inuit infants in the highest tertile of breast milk PCB levels, there were statistically non-significant elevated risks of otitis media (at least once before age 12 months, 3rd vs 1st tertile, OR=1.28, 95% CI 0.92-1.77; at least 3 occurrences before age 1, OR=1.65, 95% CI 0.49-5.57) (Dewailly and others 2000). In the Dutch birth cohort, a history of 1 or more ear infections by age 42 months was not associated with current child plasma PCB levels (per natural log plasma PCB increment, OR=1.27, 95% CI 0.61-2.64, adjusted for breastfeeding history and duration) but there was an association for the occurrence of at least 6 ear infections by age 42 months (per natural log plasma PCB increment, OR=3.06, 95% CI 1.17-7.98) (Weisglas-Kuperus and others 2000). This study also showed that recurrent otitis media was inversely associated with short lactational exposure (6-16 vs \geq 16 weeks, OR=0.12, 95% CI 0.01-1.07) (Weisglas-Kuperus and others 2000). Plasma PCB levels at age 3-4 years are 4-5 times higher among breast-fed compared to formula-fed children; thus plasma PCB levels in young children are a proxy for lactational exposure (Lanting and others 1998a). Further follow-up of the Dutch birth cohort revealed that a history of recurrent otitis media at age 3-7 years was associated with cumulative lactational PCB dose based on breast milk PCB levels times weeks of lactation (per natural log increment of lactational PCB dose ($\mu\text{g-week/g lipid}$), OR=1.19, 95% CI 1.01-1.41) (Weisglas-Kuperus and others 2004). Among German children age 7-10, a history of physician-diagnosed ear infections was associated with whole blood PCB levels among the subgroup of children with above-median whole blood DDE levels (whole blood PCB >0.48 vs ≤ 0.48 $\mu\text{g/L}$, OR=3.70, 95% CI 1.64-8.34) but not among children with below-median DDE levels, suggesting a possible interaction between these 2 exposures (Karmaus and others 2001).

13. Childhood asthma

Original studies

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Weisglas-Kuperus and others 2000), Rotterdam, The Netherlands	Birth cohort; parent-reported history of infectious diseases and allergies	207 mother-infant pairs recruited in 1990-92, 1 st or 2 nd born term infants, half breastfed, half formula fed	Parent-reported history of illness up to age 42 mos	Prenatal exposure based on maternal and cord plasma – 4 non-coplanar PCBs (118, 138, 153, 180); postnatal exposure based on breastfeeding duration and breast milk levels of 6 dioxin-like (77, 105, 118, 126, 156, 169), 20 non-dioxin-like PCBs and 17 PCDDs and PCDFs	Medians and ranges: maternal plasma PCBs – 2.1, 0.7-5.1 µg/L; cord plasma PCBs – 0.4, 0.1-2.0 µg/L; breast milk PCBs – 390, 174-805 ng/g lipid; breast milk total PCB and PCDD/PCDF TEQ – 68, 28-135 pg/g lipid	Breast/formula feeding, duration of breast feeding, parity, maternal education, parental occupational class, parental smoking, family history of allergy, day care attendance, child sex
History of dyspnea with wheezing, age 3	Multiple logistic analysis, odds ratio per unit increase of prenatal maternal plasma PCB	Prenatal exposure 0.44, 0.18-0.99		History of dyspnea with wheezing, age 3	Multiple logistic analysis, odds ratio per unit increase of cumulative lactational PCB exposure (µg/g lipid in milk times weeks of breastfeeding)	Lactational exposure 0.34, 0.02-4.49
(Karmaus and others 2001), Hamburg, Germany	Cross-sectional	Second-grade children in schools in 18 townships	343 children age 7-10; serum IgE levels, physician-diagnosed	Measured whole blood levels of DDE, HCB, β-HCH, γ-HCH, PCBs (101, 118, 138, 153, 170, 180, 183, 187)	Median, 95 th and maximum blood levels (µg/L): PCBs – 0.5, 1.5, 4.5; HCB – 0.2, 0.5, 2.5; DDE – 0.3, 1.0, 4.0; β-	Sex, age, breast-feeding; note-excluded ETS as effect was minimal in logistic model

			middle ear infections, whooping cough and pneumonia		HCH – 0.06, 0.3, 4.5; γ -HCH – 0.02, 0.06, 0.2	
History of asthma	Logistic regression analysis: odds ratios for whole blood PCB >0.48 vs \leq 0.48 $\mu\text{g/L}$ within DDE strata	DDE <0.3 $\mu\text{g/L}$ Only 4 cases DDE \geq 0.3 $\mu\text{g/L}$ 0.56, 0.13-2.52				
(Ten Tusscher and others 2003), The Netherlands	Birth cohort		27 children breast-fed for at least 2 mos; at age 8 yr, assessed medical history and conducted white blood cell flow cytometry	Measured breast milk dioxin-TEQ levels at baseline and estimated total lactational exposure (excluded dioxin-like PCBs)	mean breast milk dioxin-TEQ was 28 pg/g lipid (range 8.7-47); mean lactational exposure was 43 ng (range 4.3-124); also measured urinary mercury and blood lead	Adj for mat prenatal or current smoking did not change results (stated without supporting data)
History of asthma at age 8 (yes/no) vs TCDD-TEQ in breast milk PCDDs shortly after birth (index of prenatal exposure)	Binary logistic slope = -0.038, CI 0.88-1.06, p=.44	History of asthma at age 8 (yes/no) vs cumulative lactational exposure to TCDD-TEQ in breast milk PCDDs (postnatal exposure)	Binary logistic slope = 0.008, CI 0.98-1.04, p=.58			
(Weisglas-Kuperus and others 2004), Rotterdam, The	Birth cohort; parent-reported history of	207 mother-infant pairs recruited in 1990-92, 1 st or 2 nd	Examined 167 children at age 7-8	Prenatal exposure based on maternal and cord plasma – 4 non-	Medians and ranges: maternal plasma PCBs – 2.1, 0.7-5.1	Breast/formula feeding, duration of breast feeding,

Netherlands	infectious diseases and allergies	born term infants, half breastfed, half formula fed		coplanar PCBs (118, 138, 153, 180); postnatal exposure based on breastfeeding duration and breast milk levels of 6 dioxin-like (77, 105, 118, 126, 156, 169), 20 non-dioxin-like PCBs and 17 PCDDs and PCDFs	µg/L; cord plasma PCBs – 0.4, 0.1-2.0 µg/L; breast milk PCBs – 390, 174-805 ng/g lipid; breast milk total PCB and PCDD/PCDF TEQ – 68, 28-135 pg/g lipid	parity, maternal education, paternal occupational class, parental smoking, family history of allergy, day care attendance, child sex, age at examination
History of dyspnea with wheezing, age 3-7	Multiple logistic analysis, odds ratio per unit increase of prenatal maternal plasma PCB	Prenatal exposure 0.59, 0.36-0.97		History of dyspnea with wheezing, age 3-7	Multiple logistic analysis, odds ratio per unit increase of cumulative lactational PCB exposure (µg/g lipid in milk times weeks of breastfeeding)	Lactational exposure 0.93, 0.80-1.08

Summary: Asthma

Background maternal PCB exposure, inadequate evidence

In the Rotterdam component of the Dutch cohort, a history of asthma symptoms by age 3 was inversely associated with maternal plasma PCB level (per natural log increment of maternal plasma PCB, OR=0.44, 95% CI 0.18-0.99) (Weisglas-Kuperus and others 2000). Further follow-up revealed an inverse association between a history of asthma symptoms at age 3-7 years and maternal plasma levels of 4 non-coplanar PCBs (per natural log increment of maternal plasma PCB, OR=0.59, 95% CI 0.36-0.97) (Weisglas-Kuperus and others 2004). In a German cross-sectional study of children age 7-10, a history of physician-diagnosed asthma was not associated with whole blood PCB levels stratified by whole blood DDE levels (for DDE <0.3 µg/L, only 4 cases; for DDE ≥0.3 µg/L, PCB >0.48 vs ≤0.48 µg/L, OR=0.56, 95% CI 0.13-2.52) (Karmaus and others 2001). Among breastfed children in the Dutch cohort, a history of asthma by age 8 was not associated with breast milk PCDD-TEQ level (logistic slope =-0.038, p=.44) (Ten Tusscher and others 2003).

Lactational PCB exposure, inadequate evidence

In the Rotterdam component of the Dutch cohort, a history of asthma symptoms by age 3 was not associated with lactational PCB dose (per natural log increment of cumulative lactational PCB dose, OR=0.34, 95% CI 0.02-4.49) (Weisglas-Kuperus and others 2000). Further follow-up revealed no association between a history of asthma symptoms at age 3-7 years and cumulative lactational PCB dose (per natural log increment of cumulative lactational PCB dose, OR=0.93, 95% CI 0.80-1.08) (Weisglas-Kuperus and others 2004). Among breastfed children in the Dutch cohort, a history of asthma by age 8 was not associated with cumulative breast milk PCDD-TEQ dose (logistic slope =0.008, p=.58) (Ten Tusscher and others 2003).

14. Childhood allergies

Original studies

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Weisglas-Kuperus and others 2000), Rotterdam, The Netherlands	Birth cohort; parent-reported history of infectious diseases and allergies	207 mother-infant pairs recruited in 1990-92, 1 st or 2 nd born term infants, half breastfed, half formula fed	Parent-reported history of illness up to age 42 mos	Prenatal exposure based on maternal and cord plasma – 4 non-coplanar PCBs (118, 138, 153, 180); postnatal exposure based on breastfeeding duration and breast milk levels of 6 dioxin-like (77, 105, 118, 126, 156, 169), 20 non-dioxin-like PCBs and 17 PCDDs and PCDFs	Medians and ranges: maternal plasma PCBs – 2.1, 0.7-5.1 µg/L; cord plasma PCBs – 0.4, 0.1-2.0 µg/L; breast milk PCBs – 390, 174-805 ng/g lipid; breast milk total PCB and PCDD/PCDF TEQ – 68, 28-135 pg/g lipid	Breast/formula feeding, duration of breast feeding, parity, maternal education, parental occupational class, parental smoking, family history of allergy, day care attendance, child sex
Allergic reaction to food, pollen, dust and/or hhld pets, age 3	Multiple logistic analysis, odds ratio per unit increase of prenatal maternal plasma PCB	Prenatal exposure 0.62, 0.29-1.32		Allergic reaction to food, pollen, dust and/or hhld pets, age 3	Multiple logistic analysis, odds ratio per unit increase of cumulative lactational PCB exposure (µg/g lipid in milk times weeks of breastfeeding)	Lactational exposure 0.01, 0.01-0.37
(Ten Tusscher and others 2003), The Netherlands	Birth cohort		27 children breast-fed for at least 2 mos; at age 8 yr, assessed	Measured breast milk dioxin-TEQ levels at baseline and estimated total lactational exposure (excluded dioxin-like PCBs)	Mean breast milk dioxin-TEQ was 28 pg/g lipid (range 8.7-47); mean lactational exposure was 43 ng (range 4.3-124); also	Adj for mat prenatal or current smoking did not change results (stated without supporting data)

			medical history		measured urinary mercury and blood lead	
History of allergies to milk, chicken products, animals or house dust mites at age 8 (yes/no) vs TCDD-TEQ in breast milk PCDDs shortly after birth (index of prenatal exposure)	Binary logistic slope = -0.141, CI 0.77-0.98, p=.02	History of allergies to milk, chicken products, animals or house dust mites at age 8 vs cumulative lactational exposure to TCDD-TEQ in breast milk PCDDs (postnatal exposure)	Binary logistic slope = -0.06, CI 0.89-0.99, p=.03			
(Weisglas-Kuperus and others 2004), Rotterdam, The Netherlands	Birth cohort; parent-reported history of infectious diseases and allergies	207 mother-infant pairs recruited in 1990-92, 1 st or 2 nd born term infants, half breastfed, half formula fed	Examined 167 children at age 7-8	Prenatal exposure based on maternal and cord plasma – 4 non-coplanar PCBs (118, 138, 153, 180); postnatal exposure based on breastfeeding duration and breast milk levels of 6 dioxin-like (77, 105, 118, 126, 156, 169), 20 non-dioxin-like PCBs and 17 PCDDs and PCDFs	Medians and ranges: maternal plasma PCBs – 2.1, 0.7-5.1 µg/L; cord plasma PCBs – 0.4, 0.1-2.0 µg/L; breast milk PCBs – 390, 174-805 ng/g lipid; breast milk total PCB and PCDD/PCDF TEQ – 68, 28-135 pg/g lipid	Breast/formula feeding, duration of breast feeding, parity, maternal education, paternal occupational class, parental smoking, family history of allergy, day care attendance, child sex, age at examination
Allergic reaction to food, pollen, dust and/or hhld pets, age 3-7	Multiple logistic analysis, odds ratio per unit increase of prenatal maternal plasma PCB	Prenatal exposure 0.95, 0.59-1.52		Allergic reaction to food, pollen, dust and/or hhld pets, age 3-7	Multiple logistic analysis, odds ratio per unit increase of cumulative lactational PCB exposure (µg/g lipid in milk times weeks of breastfeeding)	Lactational exposure 1.09, 0.97-1.22

Summary: Allergies

Background maternal PCB exposure, inadequate evidence

In the Rotterdam component of the Dutch cohort, a history of allergic reaction to food, pollen, dust or household pets by age 3 was not associated with maternal plasma PCB level (per natural log increment of maternal plasma PCB, OR=0.62, 95% CI 0.29-1.32) (Weisglas-Kuperus and others 2000). Further follow-up revealed no association between a history of allergic reaction to food, pollen, dust or household pets at age 3-7 years and maternal plasma levels of 4 non-coplanar PCBs (per natural log increment of maternal plasma PCB, OR=0.95, 95% CI 0.59-1.52) (Weisglas-Kuperus and others 2004). Among breastfed children in the Dutch cohort, a history of allergies to milk, chicken products, animals or house dust mites at age 8 was inversely associated with breast milk PCDD-TEQ level (logistic slope=-0.141, p=.02) (Ten Tusscher and others 2003).

Lactational PCB exposure, inadequate evidence

In the Rotterdam component of the Dutch cohort, a history of allergic reaction to food, pollen, dust or household pets by age 3 was inversely associated with lactational PCB dose (per natural log increment of cumulative lactational PCB dose, OR=0.01, 95% CI 0.01-0.37) (Weisglas-Kuperus and others 2000). Further follow-up revealed a small and statistically non-significant increased risk of a history of allergic reaction to food, pollen, dust or household pets at age 3-7 years related to cumulative lactational PCB dose (per natural log increment of lactational PCB dose, OR=1.09, 95% CI 0.97-1.22) (Weisglas-Kuperus and others 2004). Among breastfed children in the Dutch cohort, a history of allergies to milk, chicken products, animals or house dust mites at age 8 was inversely associated with cumulative lactational PCDD-TEQ dose (logistic slope=-0.06, p=.03) (Ten Tusscher and others 2003).

15. Selected citations on exposure levels

Reference/Outcome	Design/Stratum	Exposure
(Kashimoto and others 1981), Taiwan	Case series, 15 students poisoned by consuming contaminated cooking oil	Ratios of mean PCBs, PCDFs and PCQs in blood were 1:160:500; blood PCB levels were 54-136 µg/L. Concluded that PCDFs were the main cause of Yusho: (1) severity of Yusho was disproportionate to the observed blood PCB levels, (2) PCDFs accumulate in liver, possibly explaining the frequent jaundice and other abdominal symptoms in Yusho and (3) PCDFs are up to 10 ⁴ times more toxic in experimental animals than PCBs or PCQs.
(Anderson and others 1998), USA	Cross-sectional study, 31 persons who consumed an avg of 49 Great Lakes sport fish meals per yr for an avg of 33 yr; historical comparison group of 70 persons from Jacksonville, Arkansas, and 41 non-Great Lakes fish consumers	Measured 8 PCDD, 10 PCDF and 32 PCB congeners and 11 organochlorine pesticides. Great Lakes fish consumers had mean serum PCDD, PCDF and coplanar PCB dioxin-TEQ levels, respectively, about 1.8, 2.4 and 9.6 times those of the comparison group.
(Longnecker and others 2003), USA	Review of PCB levels in 10 epidemiological studies of neurodevelopment	Range of median maternal serum PCB-153 levels in the 10 studies was 30-450 ng/g lipid; the median level in the Faroe Islands study (450 ng/g lipid) was 3-4 times those in most other studies. Levels in the 2 recent US studies were about 10% of those in the Faroe Islands study and a third of those in 4 earlier US or recent studies in The Netherlands, Germany and northern Quebec.

^a + means that a statistically significant association or dose-response relationship was demonstrated

16. Dioxin-like activity of PCBs, PCDDs, PCDFs and related compounds

Reviewers	Scope	Conclusions
(Ahlborg and others 1994)	Joint WHO/IPCS project to determine toxic equivalency factors (TEFs) for dioxin-like PCBs	Identified 13 of the 209 PCB congeners (77, 105, 114, 118, 123, 126, 156, 157, 167, 169, 170, 180) as having dioxin-like activity ^h and recommended TCDD-TEFs for each. Order-of-magnitude TEFs were assigned based on: published values, estimation from dose-response curves, ratios of ED ₅₀ , LD ₅₀ , ED ₅₀ , ED ₂₅ or ED ₁₂ values or ratios of NOAELs or LOAELs or minimum detectable concentration values or from ratios of tumour promotion indices, maximum induction levels (mainly CYP1A1-related), ≥80% effect levels or K _d values for AhR binding. In human breast milk, most of the PCB-TEQ (TEF times PCB congener concentration in pg/g lipid) comes from PCBs 118, 126 and 156.
(Van den Berg and others 1998)	WHO expert meeting to derive consensus TEFs for PCDDs, PCDFs and dioxin-like PCBs for human and wildlife risk assessment.	A few mammalian WHO-TEFs were revised, including PCB 77. Found insufficient <i>in vivo</i> evidence for continued use of TEFs for PCBs 170 and 180. Added a TEF for PCB 81. Uncertainties about TEFs include non-additive interactions, different dose-response curves and species responsiveness. Based on mammalian systems, PCBs 126 and 169 had the highest TEFs
(van Birgelen and van den Berg 2000), USA	Review of toxicokinetics of TCDD and related chemicals	Tissue concentrations of TCDD and related chemicals depend on their lipophilicity, metabolism and binding to hepatic CYP1A2. Lipophilicity increases with more chlorination and controls absorption and tissue partitioning. Induction of CYP1A2 increases hepatic sequestration of TCDD.
(Guo and others 2004), Taiwan	Review of health effects among the cohort of persons exposed to food cooked in oil contaminated by PCBs, PCDFs, PCTs and PCQs during the 1979 Yucheng incident	On average, Yucheng adults were exposed over a period of 9 mos to 1000 mg of PCBs and 3.8 mg of PCDFs; among pregnant women, the median serum PCB level near the end of pregnancy was 27 µg/L. In 1992, prenatally exposed Yucheng women had these serum concentrations: 2,3,4,7,8-pentaCDF 1090 pg/g lipid, 1,2,3,4,7,8-hexaCDF 2560 pg/g lipid, total PCBs 2820 pg/g lipid. Prenatally exposed Yucheng children had these serum concentrations: 2,3,4,7,8-pentaCDF – 89 pg/g lipid; 1,2,3,4,7,8-hexaCDF – 180 pg/g lipid; total PCBs – 1 µg/L. A comparison group of unexposed children had these serum concentrations: 2,3,4,7,8-pentaCDF – 19 pg/g lipid; 1,2,3,4,7,8-hexaCDF – 23 pg/g lipid;

^h Inclusion criteria: structural relationship to PCDDs and PCDFs, binds to AhR, elicits dioxin-specific biochemical and toxic responses and is persistent and accumulates in the food chain.

		total PCBs – 0.5 µg/L.
(Haws and others 2006), USA	Review of 1998 WHO TEFs based on updated database of mammalian relative potencies for dioxin-like compounds	Among 7 PCB congeners evaluated, PCBs 126 and 169 had the highest TEQs in mammalian <i>in vivo</i> and <i>in vitro</i> systems.

17. Notes on PCB congeners

Dioxin-likeⁱ PCB congeners

PCB Number	TEF ^j	Most frequently detected NHANES ^k , age ≥ 12 yr	Serum levels (95 th percentile, pg/g lipid)	Human breast milk levels, Canada ^l (median, pg/g lipid)	Human breast milk levels, Canada ^m (median, ng/g lipid)	Plasma levels in Arctic Quebec ⁿ (mean, ng/g lipid)	Plasma levels in southern Quebec ^f (mean, ng/g lipid)
77	0.0001					< 100	29.3
81	0.0001		< LOD ^o				
105	0.0001	+	< LOD	4.3			
114	0.0005						
118	0.0001	+	40.3	14.2			
123	0.0001						
126	0.1	+	80.5		36	220	49.3
156	0.0005	+	16.5	5.3			
157	0.0005		< LOD	0.8			
167	0.00001		< LOD				
169	0.01	+	44.5			419	29.0
189	0.0001			< LOD			

ⁱ Congeners that are coplanar or mono-ortho-chlorine-substituted (have 0 or 1 chlorine atoms at the 2,2', 6 and 6' positions), have at least 4 chlorine atoms, have both para positions (4, 4') chlorinated and have at least 2 meta positions (3,3', 5, 5') chlorinated.

^j 1997 WHO TEF for humans and other mammals (TEF = toxic equivalency factor, i.e., toxicity relative to 2,3,7,8-TCDD which is assigned a TEF of 1.0).

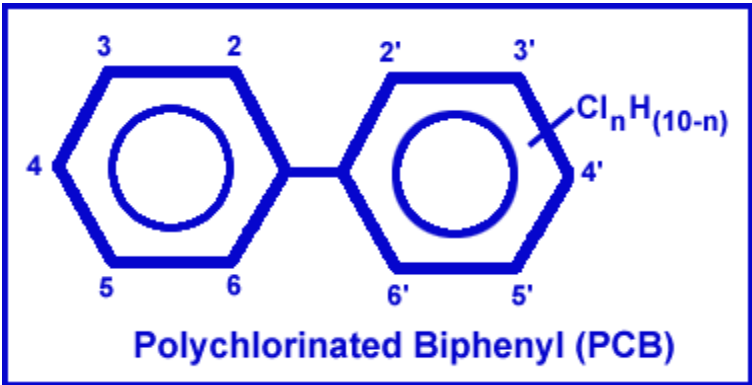
^k NHANES 1999-2000, CDC

^l Newsome WH, Davies D, Doucet J. 1995. PCB and organochlorine pesticides in Canadian human milk--1992. *Chemosphere* 30(11):2143-53.

^m Newsome WH, Ryan JJ. 1999. Toxaphene and other chlorinated compounds in human milk from northern and southern Canada: a comparison. *Chemosphere* 39(3):519-26.

ⁿ Ayotte P, Dewailly E, Ryan JJ, Bruneau S, Lebel G. 1997. PCBs and dioxin-like compounds in plasma of adult Inuit living in Nunavik (Arctic Quebec). *Chemosphere* 34(5-7):1459-68.

^o LOD = Limit of detection



Source: US EPA <http://www.epa.gov/toxteam/pcb/defs.htm>

Non-coplanar PCBs

Congener number	Serum levels in German Environmental Survey ^p (median, µg/L)	Maternal plasma levels in Dutch birth cohort ^q (median, µg/L)	Human breast milk levels, Canada ^r (median, ng/g lipid)	Plasma levels in Arctic Quebec ^s (mean, ng/g lipid)	Plasma levels in southern Quebec ⁴ (mean, ng/g lipid)
118	-	0.15	14.2	160	9
138	0.45	0.56	24.2	650	29
153	0.72	0.84	33.4	1270	33
180	0.48	0.50	17.9	680	22

^p Source: <http://www.umweltbundesamt.de/survey-e/us98/organo.htm#tab4>

^q Source: Huisman M, Koopman-Esseboom C, Fidler V, Hadders-Algra M, van der Paauw CG, Tuinstra LG, Weisglas-Kuperus N, Sauer PJ, Touwen BC, Boersma ER. 1995. Perinatal exposure to polychlorinated biphenyls and dioxins and its effect on neonatal neurological development. *Early Hum Dev* 41(2):111-27.

^r Newsome WH, Davies D, Doucet J. 1995. PCB and organochlorine pesticides in Canadian human milk--1992. *Chemosphere* 30(11):2143-53.

^s Ayotte P, Dewailly E, Ryan JJ, Bruneau S, Lebel G. 1997. PCBs and dioxin-like compounds in plasma of adult Inuit living in Nunavik (Arctic Quebec). *Chemosphere* 34(5-7):1459-68.

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