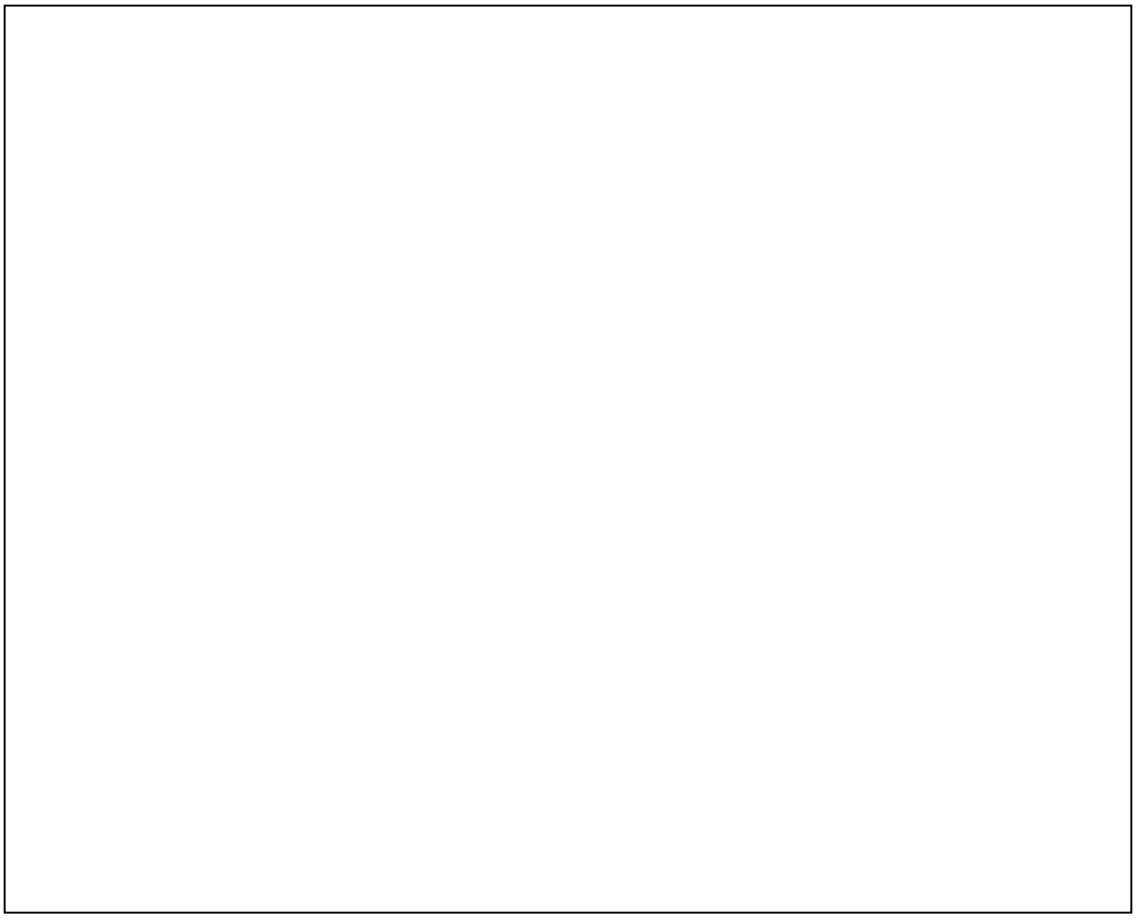
Developmental Effects of Prenatal Exposure to PCBs

Polychlorinated Biphenyls (PCBs)

- 209 different chemicals
- Use 1930's-1977
- Lipophilic & slowly metabolized
- Health effects

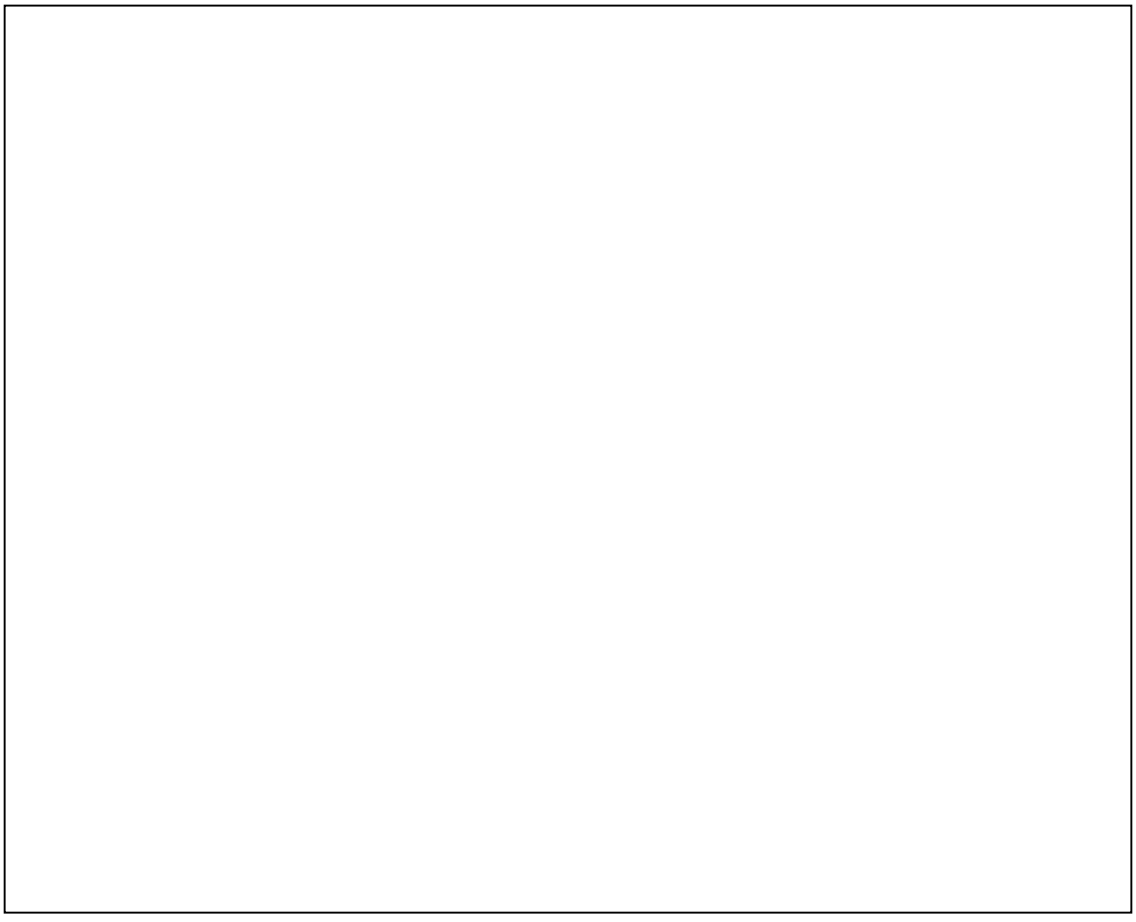
  Probable human carcinogen
  Structural teratogen
  Functional teratogens
  Growth & maturational impairment

A-2



Background:
PCBs and Child Development

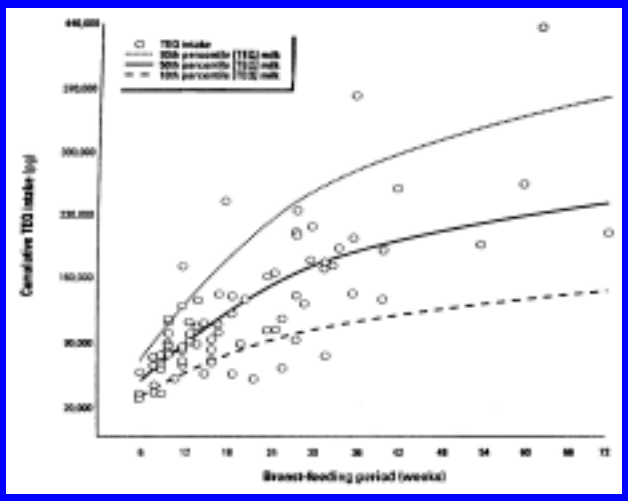
- Accidental poisonings
  (1968; 1979)
- Population-based studies
  (b. 1978-01)
- Occupational cohorts (1980's)



PCBs and Child Development: Accidental Poisonings

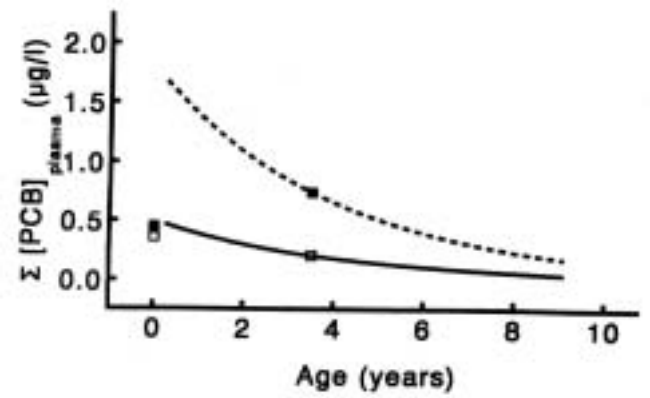
- PCB-tainted cooking oil (Japan 1968; Taiwan 1979)
- Newborn: IUGR, pigmentation, hyperbilirubinemia
- School age: diminished IQ, psychomotor & behavioral impairment
- Other etiology (dibenzofurans or dibenzodioxins)

Intake of TEQs as a Function of Breast-feeding



Source: S Patindin, Environ Health Perspect 1999.

Estimated PCB Levels for Children Breast-Fed As Infants

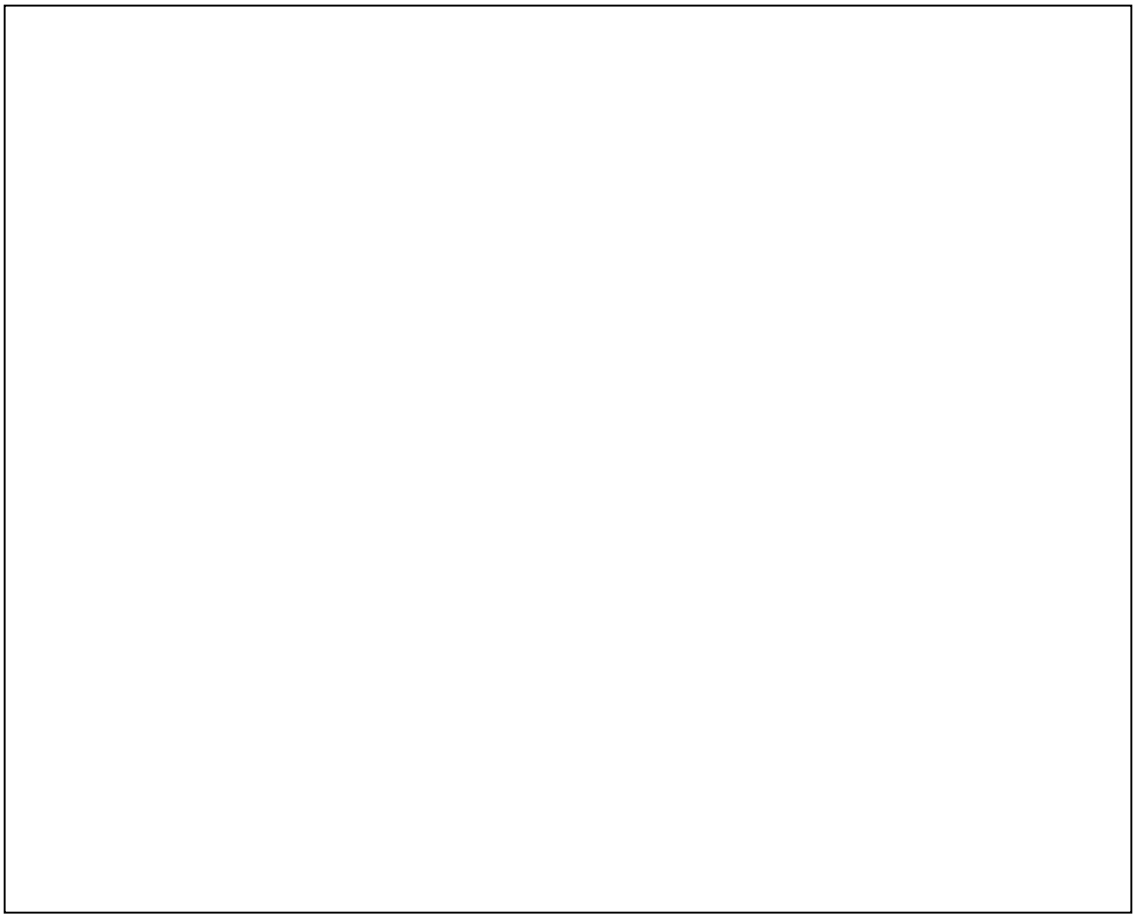


Note. Estimated PCB values are calculated from measured PCB values at 3.5 years of age and based on the assumption that the half-life of PCBs is 2.8 years. The dashed line represents estimated values for children from the breast-fed group, and the solid line, estimated values for children from the formula-fed group. Measured values have been marked with closed squares (breast-fed group) and open squares (formula-fed group).

Source:S Patandin et al, Am J Public Health 1997.

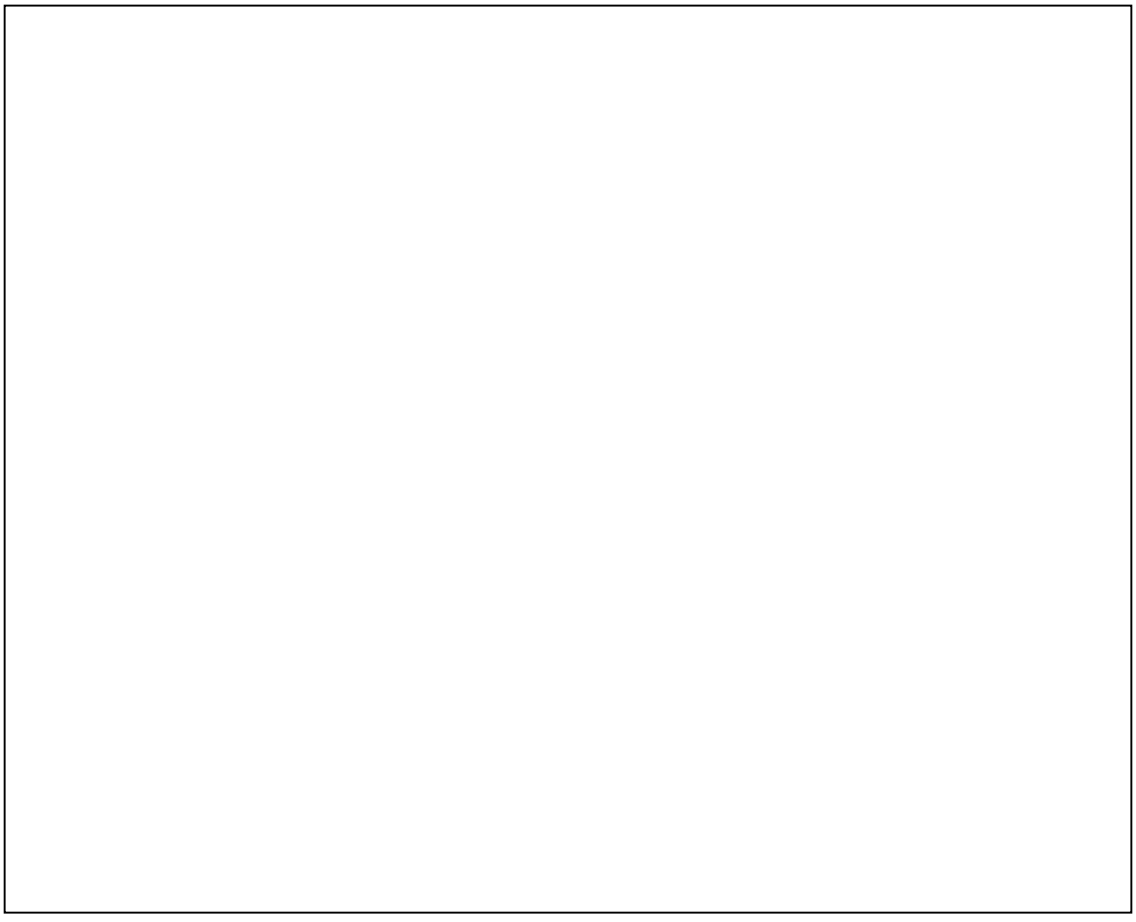
Cohort Studies of PCBs and Neurodevelopment

Reference	Population	N	Birth Years
Rogan et al., 1986	N.Carolina	931	1978-82
Jacobson et al., 1984	Michigan	313	1980-81
Grandjean et al., 1997	Faroe Islands	1,022	1986-87
Steuerwald et al., 2000	Faroe Islands	182	1994-95
Sauer et al., 1994	Netherlands	418	1990-92
Lonky et al., 1996	New York	316	1991-94
Winneke et al., 1998	Germany	171	1993-95
Korrick et al., 2000	Massachusetts	788	1993-98
Muckle et al., 2001	Canada/Greenland	300	1996-01
Longnecker, 2000	CPP (U.S.)	1,000	1959-66
James, 2002	CHDS (CA)	400	1964-67



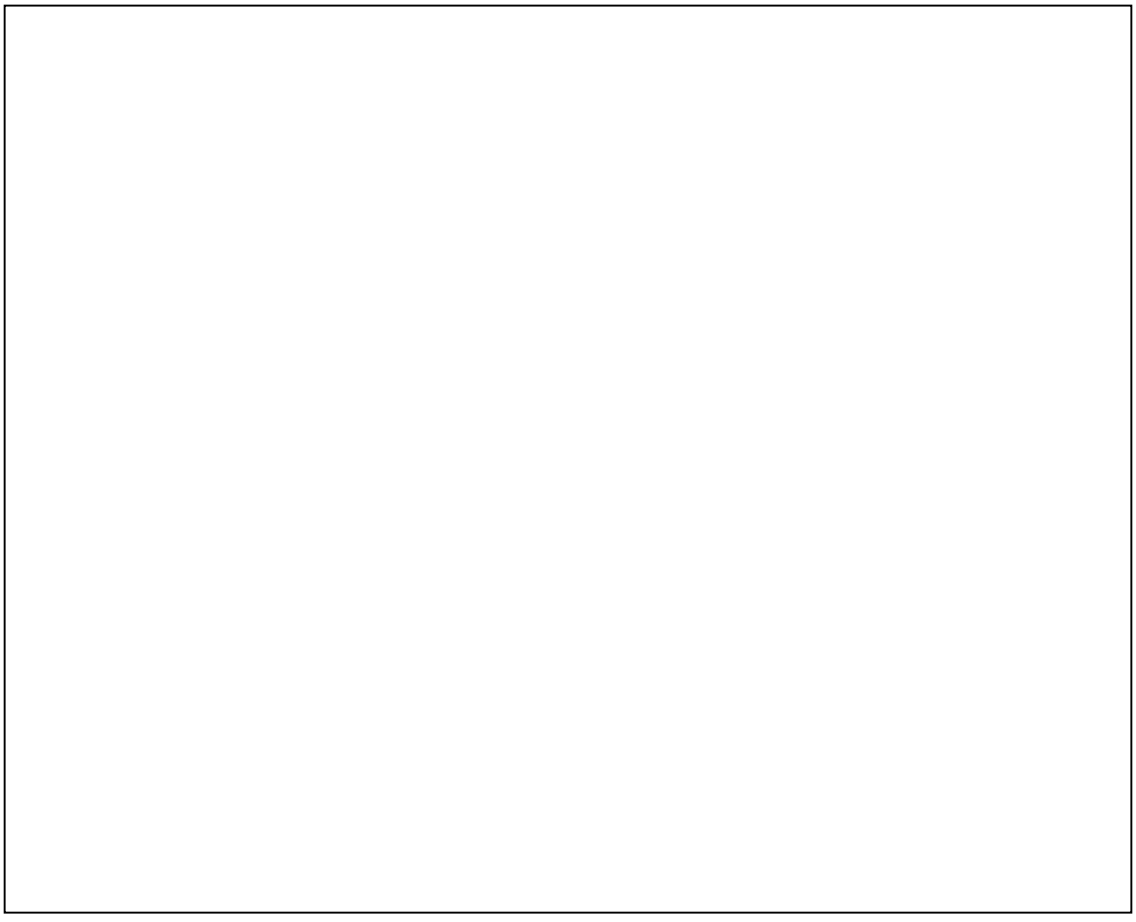
North Carolina Study
(Rogan et al., 1986)

Population	Exposure	Development
915 infants	PCBs & DDE:	0 – 16 years:
b. 1978-82	serum	NBAS
Raleigh-Durham	milk	Bayley
	Breastfeeding	McCarthy
		grades
		Tanner
		ht/wt



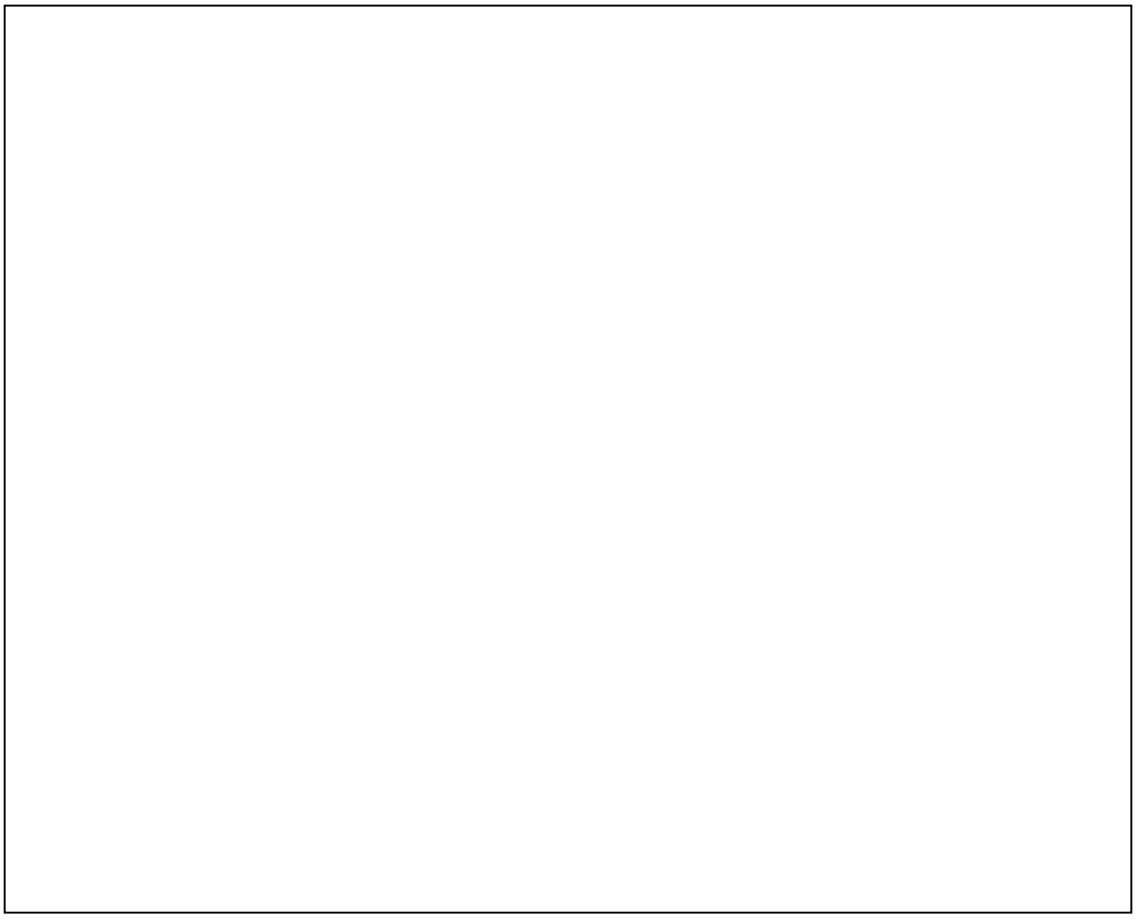
Michigan Study
(Jacobson et al., 1984)

Population	Exposure	Development
313 infants	PCBs:	0 – 11 years:
b. 1980-81	serum	NBAS
Fish & non-fish	milk	Bayley
eaters	L. Mich. Fish	Fagan
	Breastfeeding	McCarthy
		WISC-R
		Achievement



The Netherlands Cohort (Sauer et al., 1994)

Population	Exposure	Development
418 infants b. 1990-92 Groningen & Rotterdam	PCBs & dioxins: plasma milk Breastfeeding	0 – 7 years: NOS Bayley KaufmanABC Reynell DLS McCarthy



The Faroe Islands Cohorts
(Grandjean et al., 1997; Steuerwald et al., 2000)

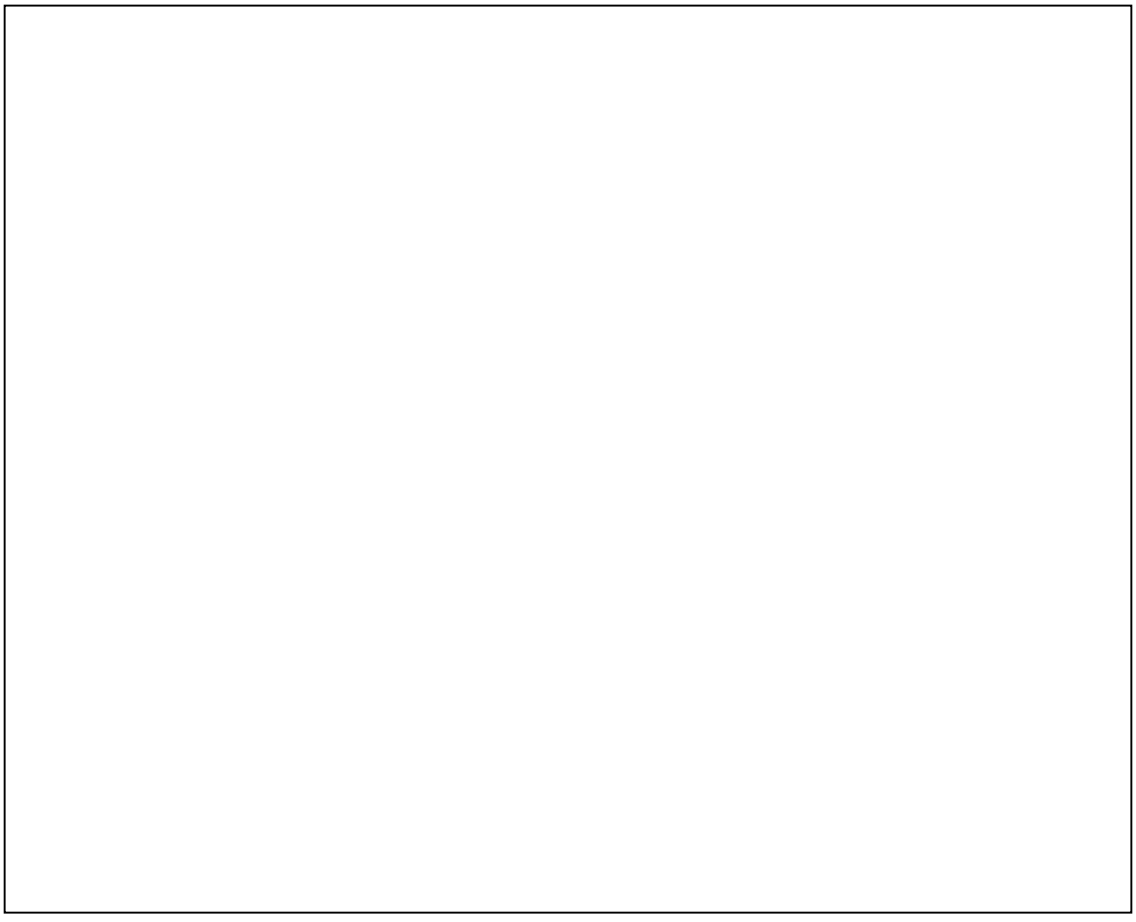
Population	Exposure	Development
1,022 infants (i)	MeHg & PCBs:	0 – 7 years:
182 infants (ii)	(i) cord blood	NOS
b. 1986-87 (i)	cord tissue	WISC-R
b. 1994-95 (ii)	mat. hair	CVLT-C
	(ii) cord blood	NES2 CPT
	mat.hair	Boston nm.
	mat. serum	etc.
	milk	

The Germany Cohort (Winneke et al., 1998)

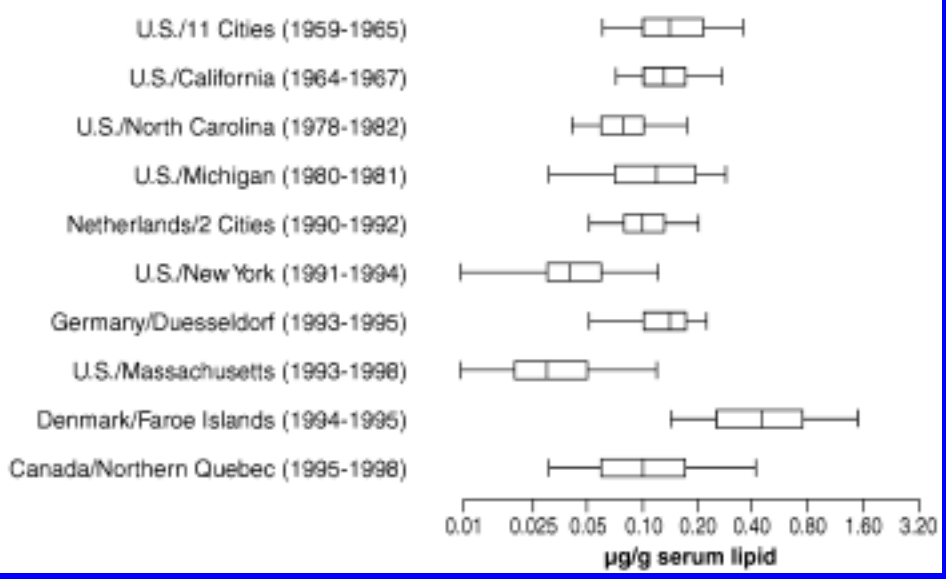
Population	Exposure	Development
171 infants	PCBs:	0 – 42 months:
b. 1993-95	plasma	Fagan
Dusseldorf	milk	Bayley II
	Breastfeeding	Kaufman-ABC

The Oswego, NY Cohort (Stewart et al., 2000)

Population	Exposure	Development
316 infants b. 1991-94 Fish & non-fish eaters	PCBs, DDE, Pb & Hg: cord blood mat. hair mat. milk Lake Ontario fish	0 - 12 months NBAS Fagan

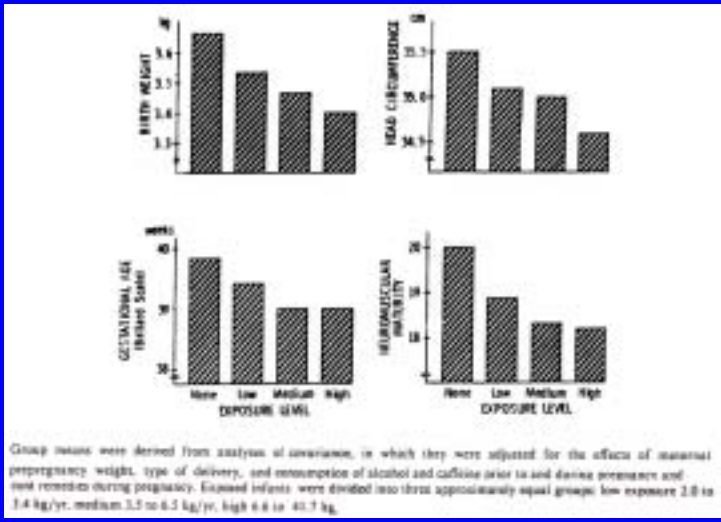


Distribution of PCB 153 concentration in serum, 10 studies



Source: Longnecker et al., Environ. Health Perspect. (in press)

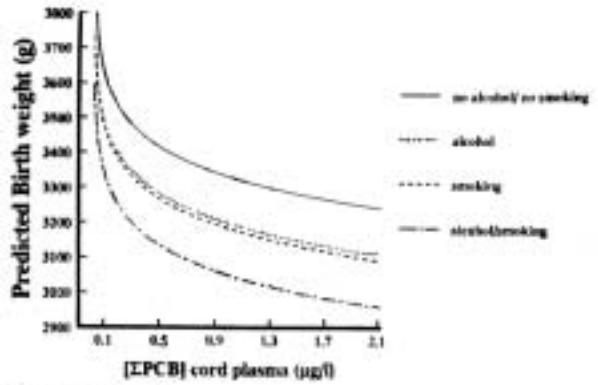
Relationship of Birth Size, Gestational Age and Neuromuscular Maturity with Fish Consumption



Group means were derived from analysis of covariance, in which they were adjusted for the effects of maternal prepregnancy weight, type of delivery, and consumption of alcohol and caffeine prior to and during pregnancy and over remedies during pregnancy. Exposed infants were divided into three approximately equal groups: low exposure 2.0 to 3.4 kg/yr, medium 3.5 to 6.3 kg/yr, high 6.6 to 41.7 kg.

Source:GG Fein et al, J Pediatr 1984.

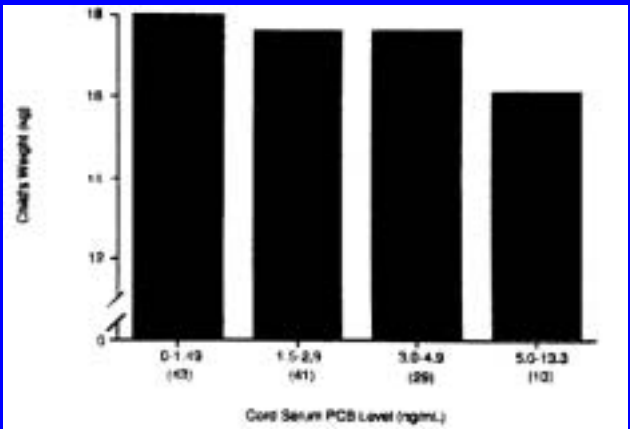
Birth Weight in Relation to Cord PCB Levels



Prediction is given for birth weight when gestational age is 40.1 wk (mean value), TH is 178.8 cm (mean value), parity is zero (first born). ΣPCBcord = the sum of PCB congeners 118, 138, 153, and 180 in cord blood.

Source: S Patandin et al, Pediatr Res 1998.

Child's Weight at 4 Years By Cord Serum PCB Level



(adjusted for child's sex, maternal and paternal weight and height, maternal age, gravidity, and examiner)

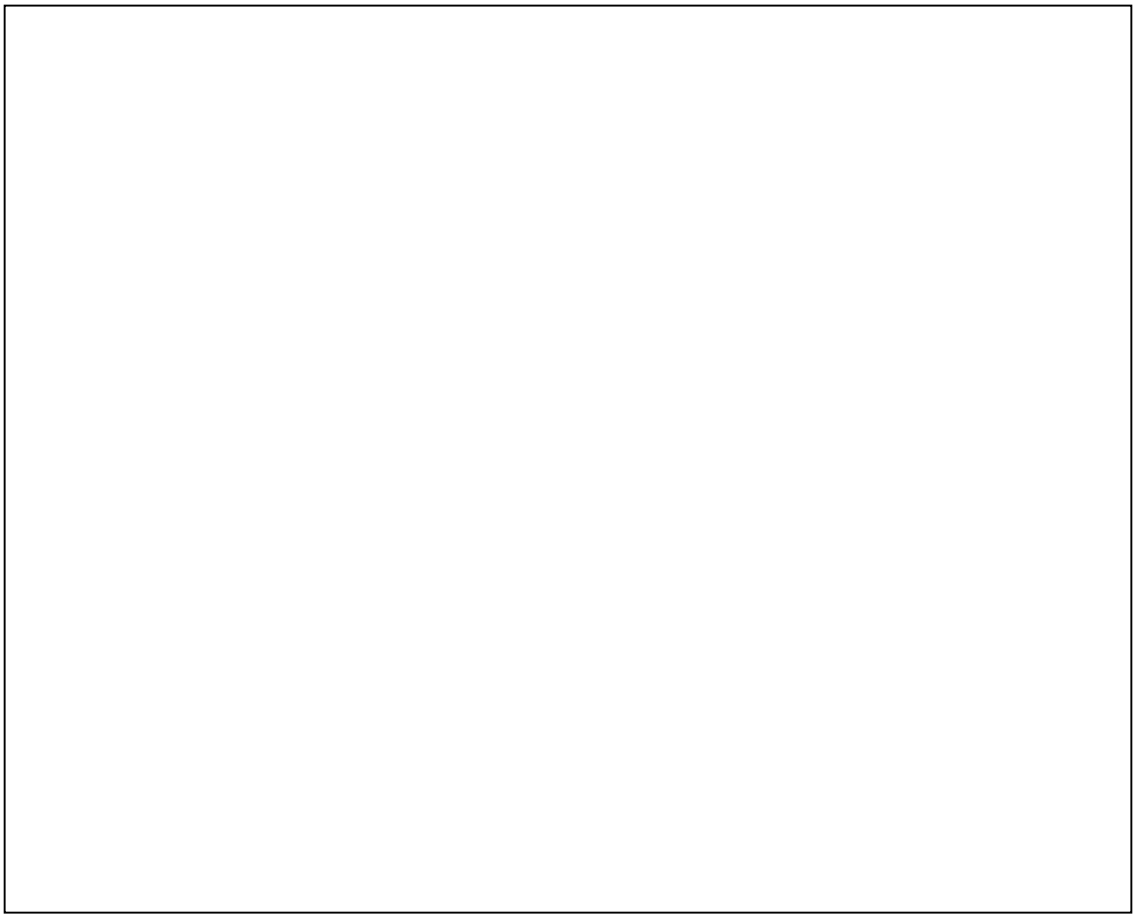
Source:JL Jacobson et al, Neurotoxicol Teratol 1990.

Summary of Findings Relating PCBs to Growth

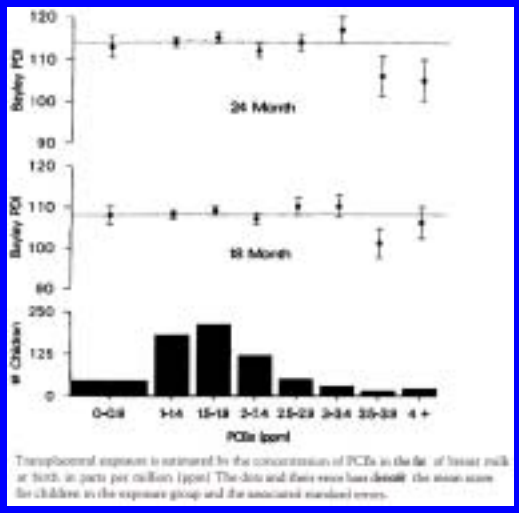
Age	Study	PCB Measure	Effect
Newborn	Michigan	Cord serum	↓birth wt.
	N. Carolina	Milk	no Δ
	Netherlands	Plasma	↓birth wt.
	Oswego, NY	Fish intake	no Δ
	Faroe Islands	Maternal serum	no Δ
0-3 months	Netherlands	Plasma (formula fed)	↓growth
4 years	Michigan	Cord serum	↓weight
14 years	N. Carolina	Milk	↑wt. (white)

Summary of Findings Relating PCBs to Neonatal Neurological Development

Study	Exam Age	Reflexes	Tone
Michigan	3 days	↓ (fish)	no Δ
N. Carolina	1 week	↓	↓
Netherlands	2 weeks	no Δ	↓ (breastfed)
Oswego, NY	2 weeks	↓↑ (fish)	no Δ
Faroe Islands	1-2 days	no Δ	no Δ

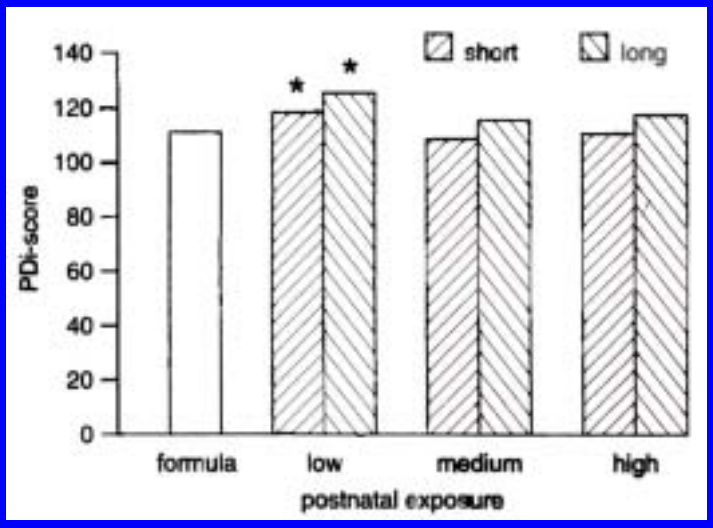


Psychomotor Development Index (PDI) at 18 and 24 Months by Prenatal PCB Exposure



Source: WJ Rogan and BC Gladen, Ann Epidemiol 1991.

Psychomotor Development at 7 Months in Relation to TEQ Level and Breast-Feeding



Source: C Koopman-Esseboom et al, Pediatrics 1996.

Findings Relating PCBs to Infant and Todler Bayley Assessments

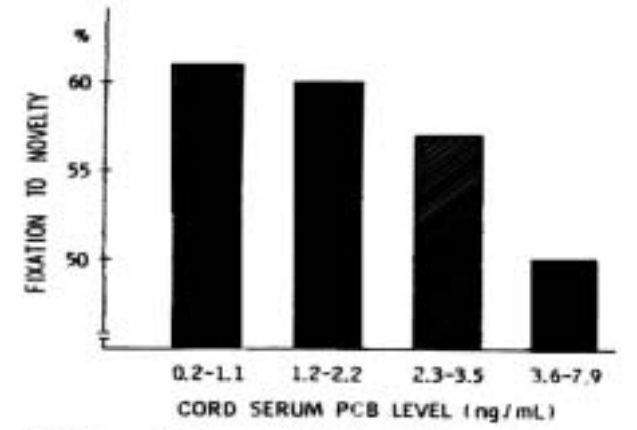
Study	Exam age (months)	MDI	PDI
Michigan	5	No Δ	No Δ
N. Carolina	6, 12, 24	No Δ	↓
Netherlands	3, 7	No Δ	↓(mlk, 7)
Netherlands	18	No Δ	No Δ
Germany	7, 18	No Δ	↓ (mlk, 18)
Germany	30	↓ (mlk)	↓ (mlk)

Fagan Test of Infant Intelligence

- Assess infant's preference for novel images
- Short-term visual memory indicator
- Predictive of later cognitive function

Source: New Bedford Standard Times 1996.
(reproduced with permission)

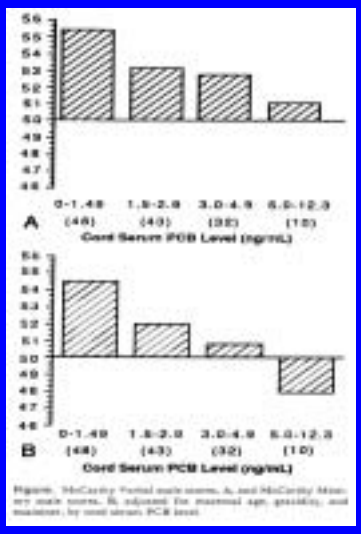
Relationship of Visual Recognition Memory with Cord Serum PCB Level



$F(3,74) = 3.90$, $p = .01$. Group N's are 20, 21, 20, and 20, respectively.

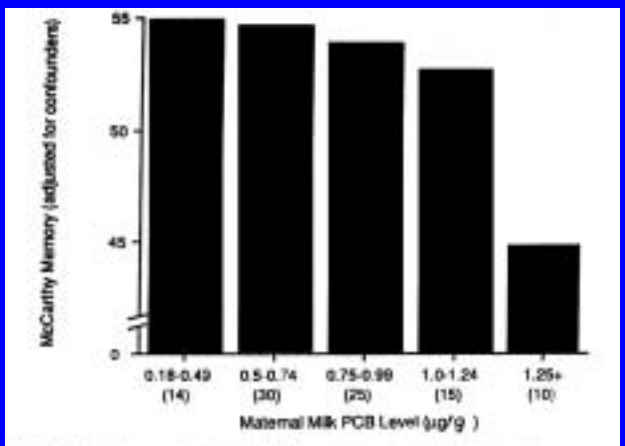
Source:SW Jacobson et al, Child Development 1985.

McCarthy Scores By Cord Serum PCB Level



Source:JL Jacobson et al, J Pediatr 1990

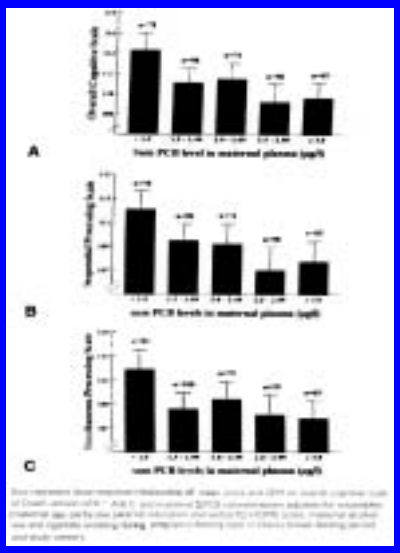
Relation of Milk PCB Level with 4-Year McCarthy Memory Scale Scores



(adjusted for socioeconomic status; HOME Inventory; maternal PPVT-R vocabulary score, employment, alcohol consumption before pregnancy, smoking before and during pregnancy, and milk PBB level; and child's four-year blood DDT and lead levels)

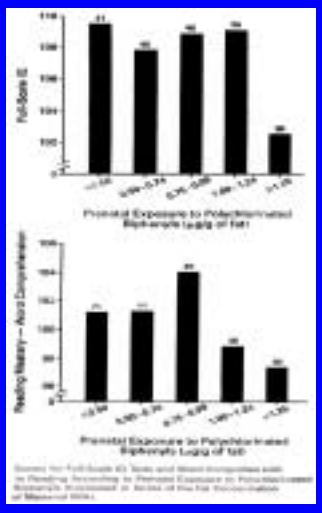
Source: JL Jacobson & SW Jacobson, Toxicology and Industrial Health 1996.

Kaufman Assessment Battery for Children and Maternal PCB Levels



Source: S Patandin et al, J Pediatr 1999.

IQ and Word Comprehension in Relation to PCB Levels



Source:JL Jacobson & SW Jacobson, N Engl J Med 1996.

Summary of Findings Relating PCBs to Childhood Cognitive Function

Study	Exam Age	Finding
Michigan	7 months	↓FTII
	4 years	↓McCarthy
	11 years	↓IQ
N. Carolina	3, 4, 5 years	Null (McCarthy)
	7-10 years	Null (grades)
Faroe Islands	7 years	Null (multiple)
Netherlands	3.5 years	↓K-ABC/RDLS
	7 years	↓McCarthy (subgrp)
Germany	3.5 years	↓K-ABC (postnatal)
Oswego, NY	6, 12 months	↓FTII

The Massachusetts Cohort (Korrick et al., 2000)

Population	Exposure	Development
788 infants b. 1993-98 New Bedford (Superfund site)	PCBs & DDE: serum milk Breastfeeding	0 – 8 years Fagan WISC-III WRAML CVLT-C etc.

Study Goals

- Evaluate relationship of low level *in utero* PCB and DDE exposure with growth and neurodevelopment at birth and early infancy

- Evaluate relationship of low level *in utero* PCB and DDE exposure with growth and neurodevelopment in later childhood

History of New Bedford Study Site

- 1940s-70s: Discharge of PCB-laden waste
- 1970s: Contamination discovered in Harbor
- 1977: PCB production banned in U.S.
- 1979: Harbor closed to fishing
- 1982: Harbor on EPA's National Priority List

New Bedford Harbor Water Front

Prosperous 19th c. whaling port

Manufacturing industry in 20th c.

Continued fishing industry

Photo: J Shine

A-33

New Bedford Water Front Industry

Photos: J Shine

PCB “Hot Spot”, New Bedford Harbor

WARNING Hazardous Waste : No wading, fishing, shellfishing per order U.S. EPA.

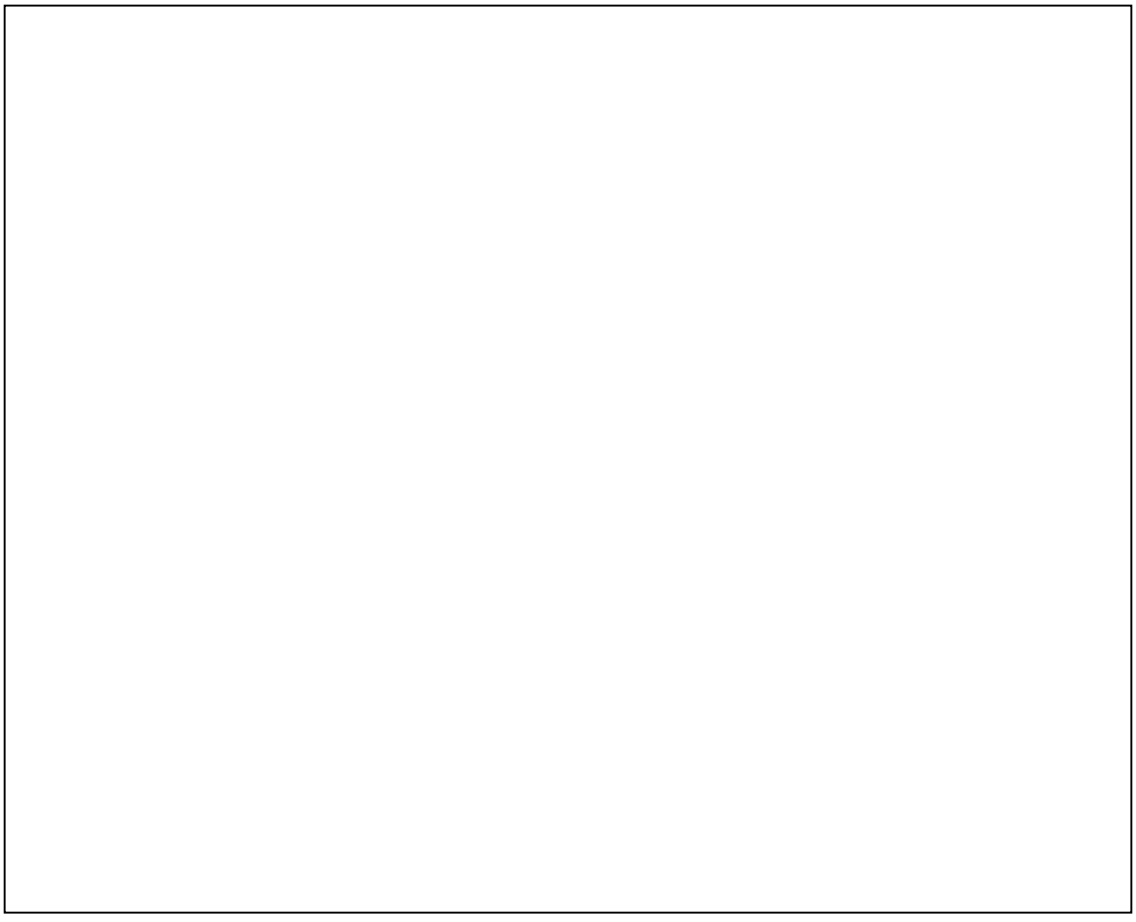
Photo: S. Korrick, 1998

Current Status of New Bedford Study

- Completed assessments from birth to 6 months.
  - Final results not yet available.
- School age (8 years) assessments underway.
  - Broad & focused cognitive tests
  - Behavioral assessments
  - Measures of attention
  - Anthropometry

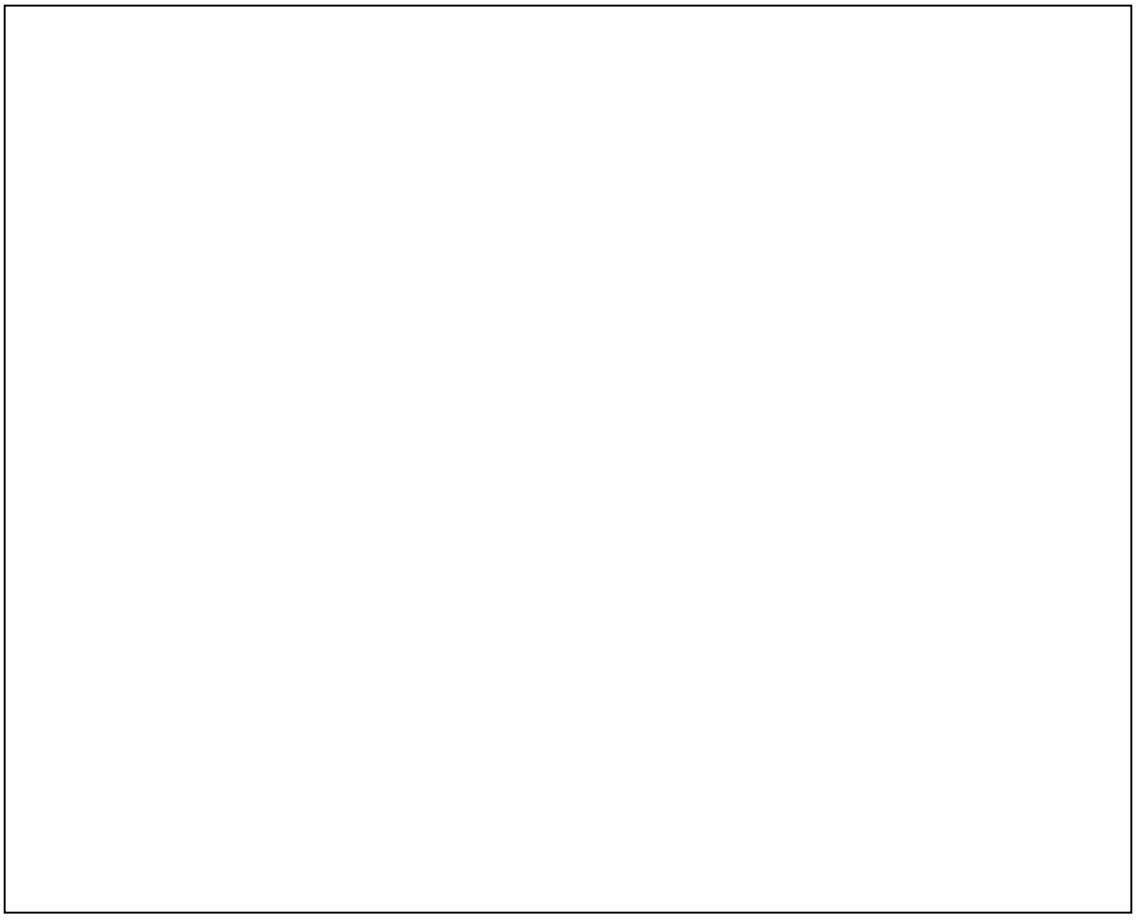
The Collaborative Perinatal Project (CPP) (Gray et al., 2000)

Population	Exposure	Development
1,000 infants	PCBs & DDE:	0 – 7 years:
b. 1959-66	serum (archived)	Bayley
Nat'l sample		WISC
(n=50,000+)		etc.



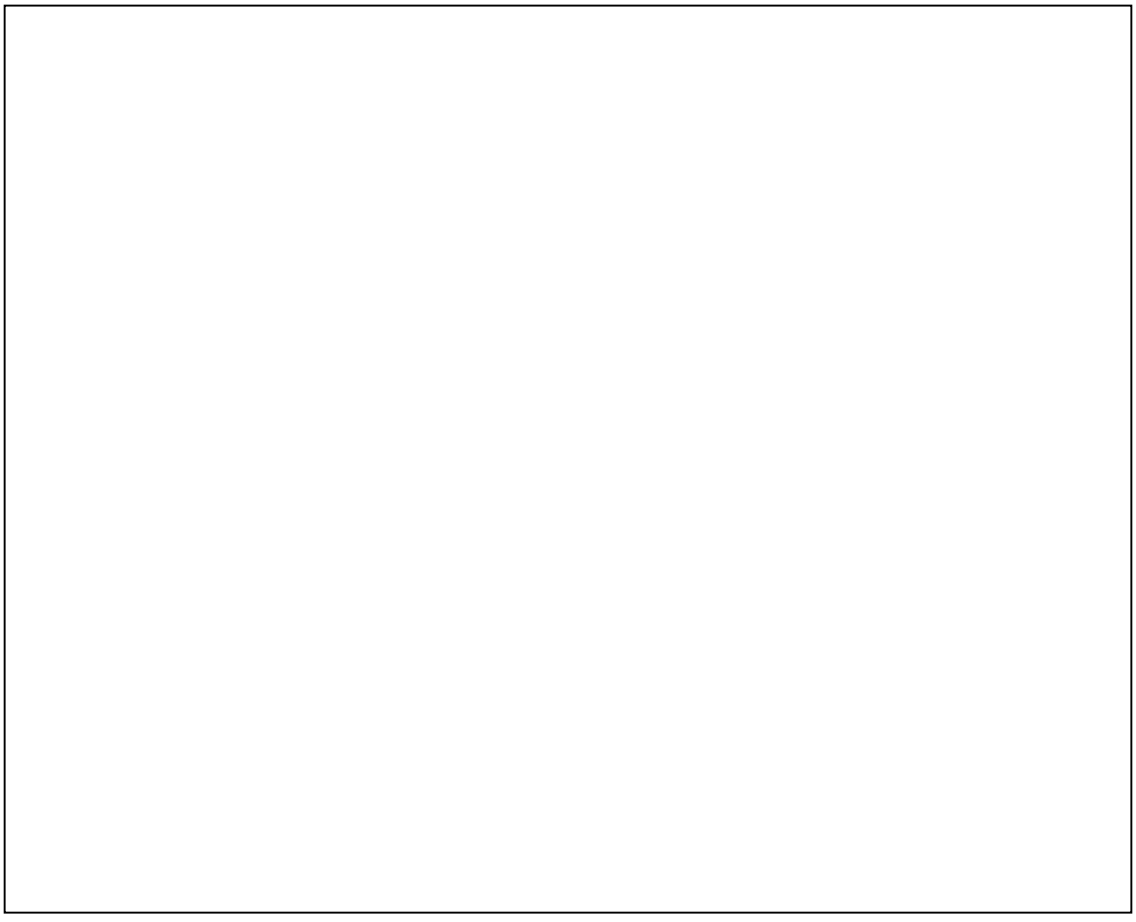
The Childhood Health and Development Study Cohort (CHDS) (James et al., 2002)

Population	Exposure	Development
400 infants	PCBs & DDT:	0 – 5+ years:
b. 1964-67	serum (archived)	5, 10, 15+ yrs.
Calif. Sample		hearing/vision
(n=20,000)		anthropometry



Nunavik Inuit Cohort (Quebec, Canada) (Muckle et al., 2001)

Population	Exposure	Development
200+ infants	PCBs, MeHg	(in progress)
b. 1996-01	Pb, OC pesticides	
	Se, n3-PUFA:	
	blood	
	serum	
	milk	
	hair	

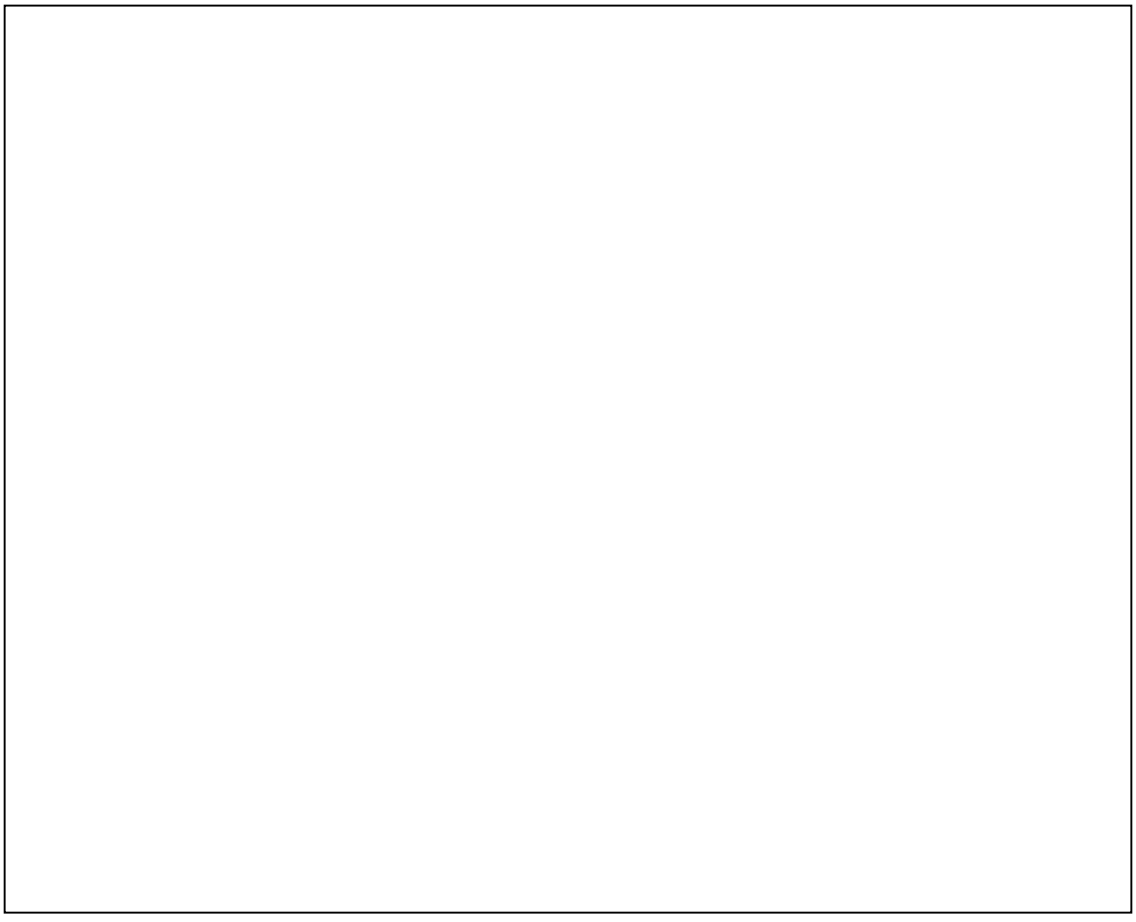


Summary: Associations of Early Life PCB Exposure with Neurodevelopment

Some evidence for:

- decrements in fetal and early postnatal growth
- deleterious effects on early (0 – 24 mos.) neuromuscular development
- declines in preschool cognitive function
- declines in later cognitive function

No consistent postnatal exposure (via breastfeeding) effects



Summary: Associations of Early Life PCB Exposure with Neurodevelopment (cont'd)

However, evidence for adverse associations:

- not consistent across populations
- not consistent over time
- not consistent across domains of function (although comparable domains not always assessed)

Possible Sources of Inconsistency Among Epidemiologic Studies of PCBs & Neurodevelopment

Study population

differential susceptibility

Exposure

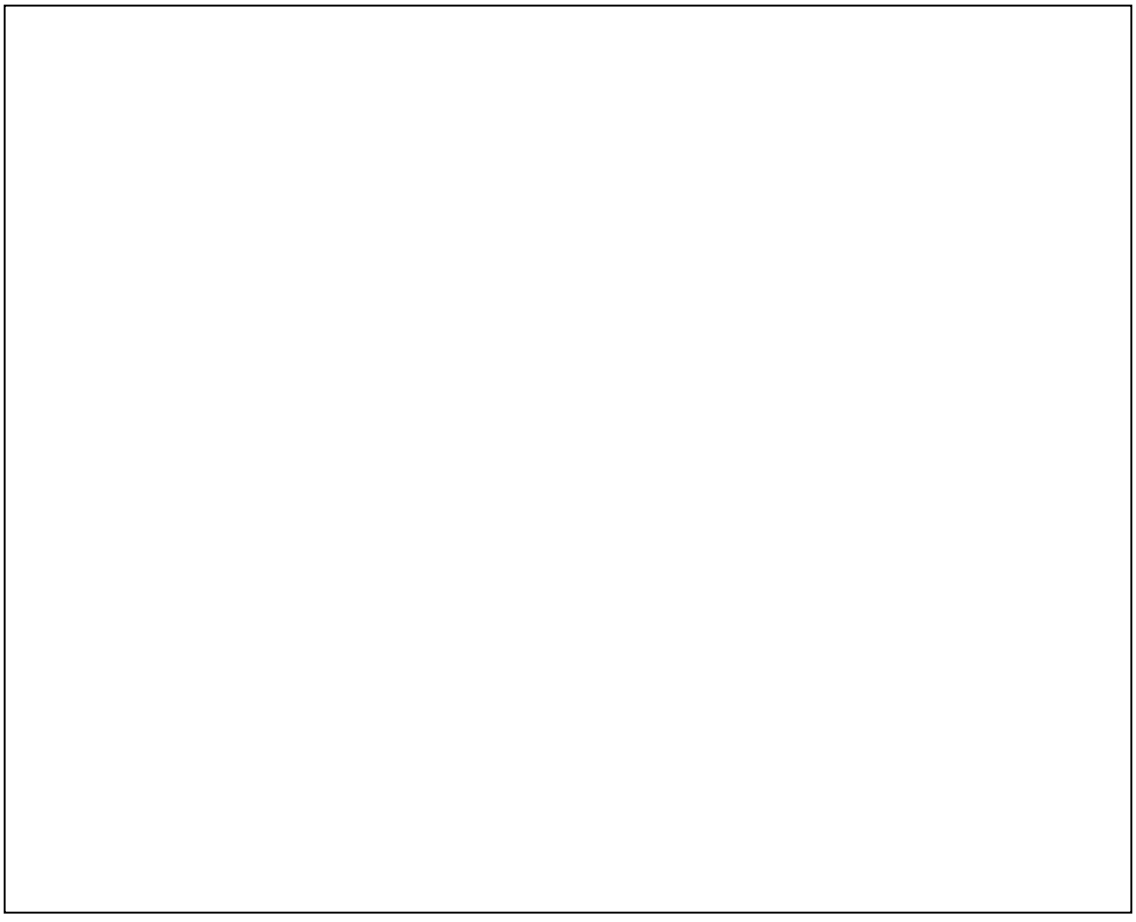
concentration, rate, congener mix

Outcome

choice, age

Confounding

Dose-Response Modeling



The Future

Definitive conclusions & interpretations not yet possible

Results from ongoing prospective epidemiologic studies are pending

Mechanistic studies

Heller's view

Source: The Boston Globe 2000.

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Uterine Muscle as a Target of Polychlorinated Biphenyls

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B-1

Childbirth

B-2

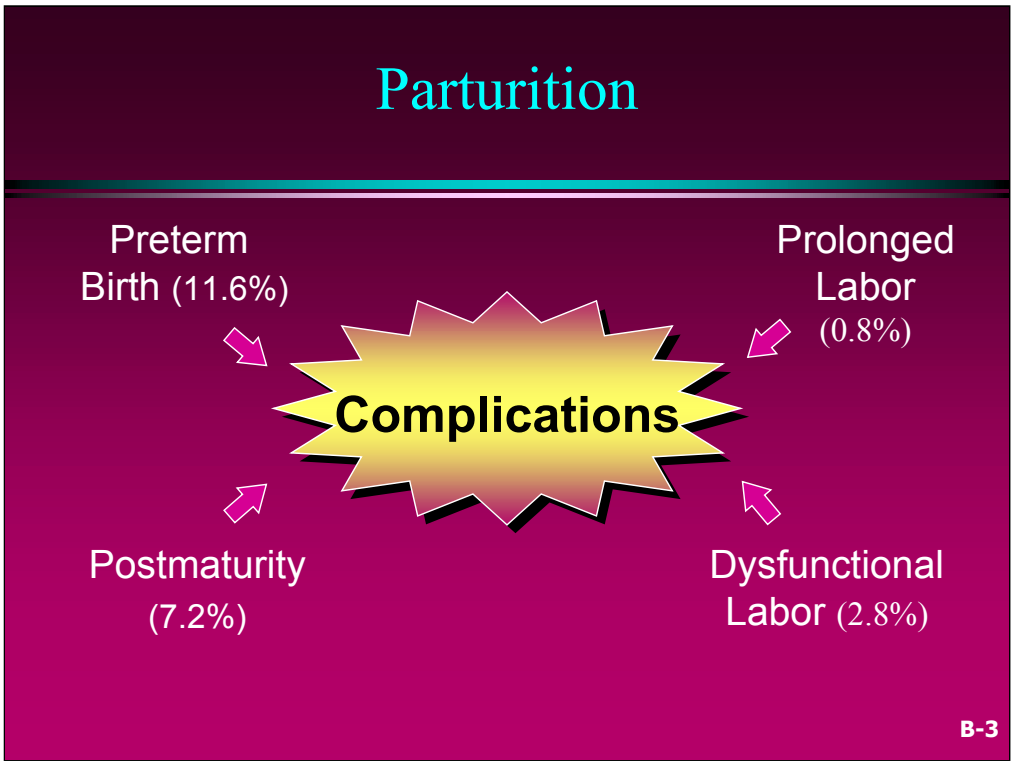
The birth of healthy children is an imperative mandate of public health.

Parturition (childbirth) is the final necessary event of pregnancy. Consequently, in order for pregnancy to be successful, parturition must be successful, also.

Parturition must initiate at the proper time and progress in a timely and effective manner to ensure the health of the child and the mother.

However, parturition is complicated and incompletely understood in women.

•Ability to medically intervene is limited, particularly for preterm labor.



Preterm birth (<37 weeks gestation)

•In 2000, the most recent year for which CDC birth statistics are avaiable, the preterm birth rate declined from 11.8 % to 11.6 % of all births. This is the first decline since 1992.

•Low birthweight rate (7.6 %) did not improve in 2000.

•The preterm rate has risen fairly steadily over the past two decades, from 9.4 % in 1981, and 10.6 % in 1990.

•The **very preterm birth rate** (gestational age of under 32 completed weeks) was 1.93 percent for 2000, compared with 1.96 percent for 1999. The proportion of infants born at these earlier, more vulnerable gestational ages is essentially unchanged from that reported for 1990 (1.92 percent), but has increased from 1.81 percent since 1981.

•Preterm birth is highest for non-hispanic black women at 17.3%, similar to that reported for the early 1980s. The preterm birth rate for black mothers has been slowly declining since peaking at 18.9 % in 1991. The very preterm rate for black infants, 4.04%, is the lowest since 1981 (when comparable data are first available).

Prolonged labor (>20 h)

Rates of dysfunctional labor were highest for Chinese (45.7 per 1,000) and Cuban (40.4) mothers.

Rates of cesarean deliveries

Increased 11% between 1996 and 2000 to 22.9%

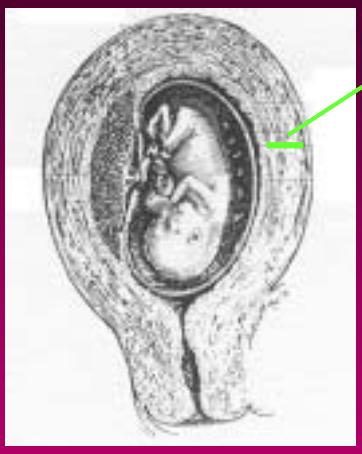
Currently the highest rate reported since data became available on birth certificates in 1989

35.7% of women in prolonged labor delivered by cesarean

66.7% of women with dysfunctional labor delivered by cesarean

Reference: J.A. Martin, B.E. Hamilton, S.J. Ventura, F. Menacker, and M.M. Park. Births: Final Data for 2000. Natl. Vital Stat. Rep. 50(5):1-104, 2002.
(http://www.cdc.gov/nchs/releases/02news/womenbirths.htm)

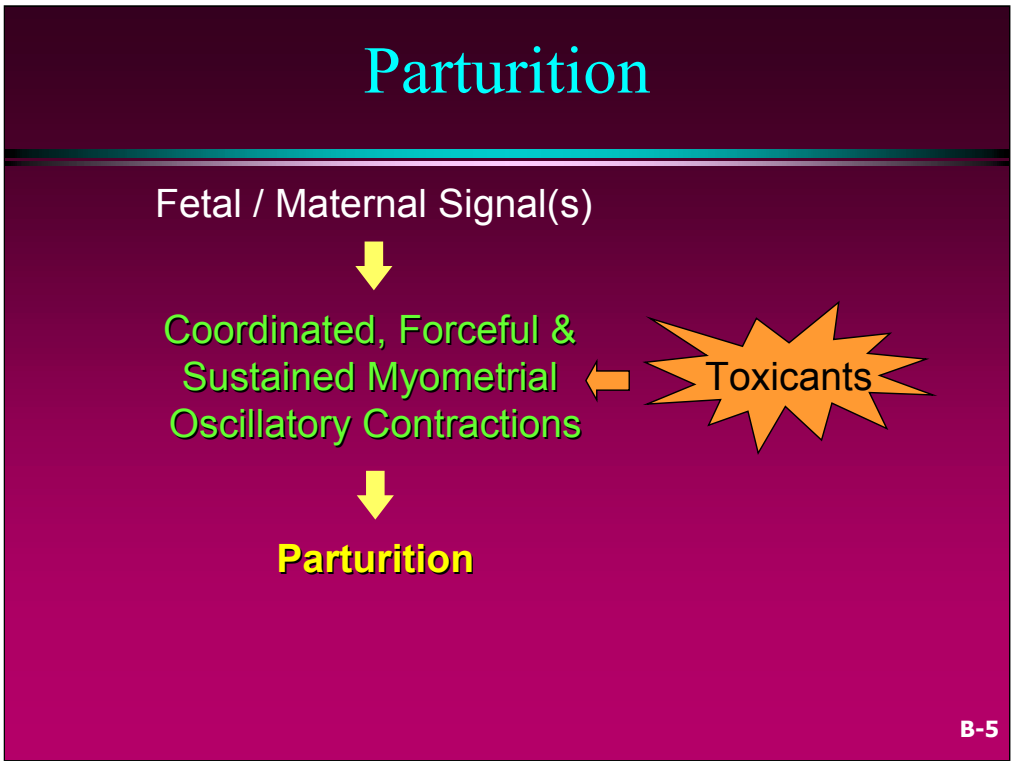
Human Pregnancy



Drawing by M. Brodel, from Williams, Am. J. Obstet. Gynecol, 13:1, 1927

B-4

Regulation of myometrial contractility is necessary for successful pregnancy

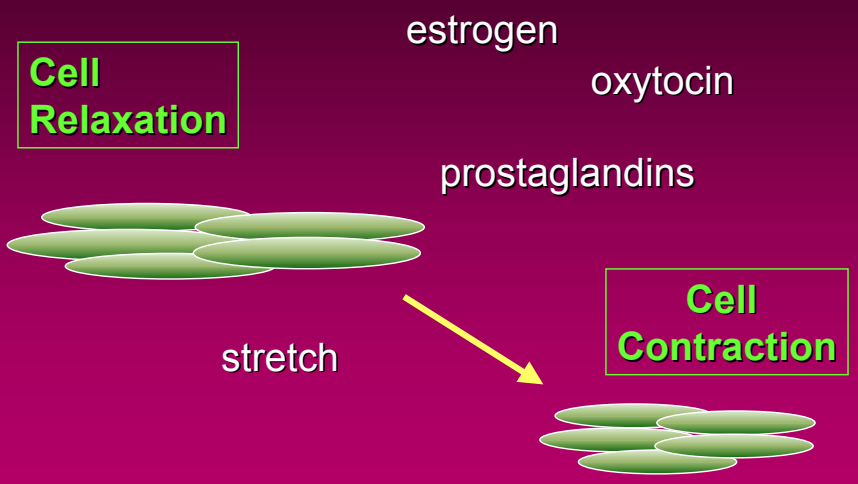


Species differences exist at the level of maternal and fetal signals

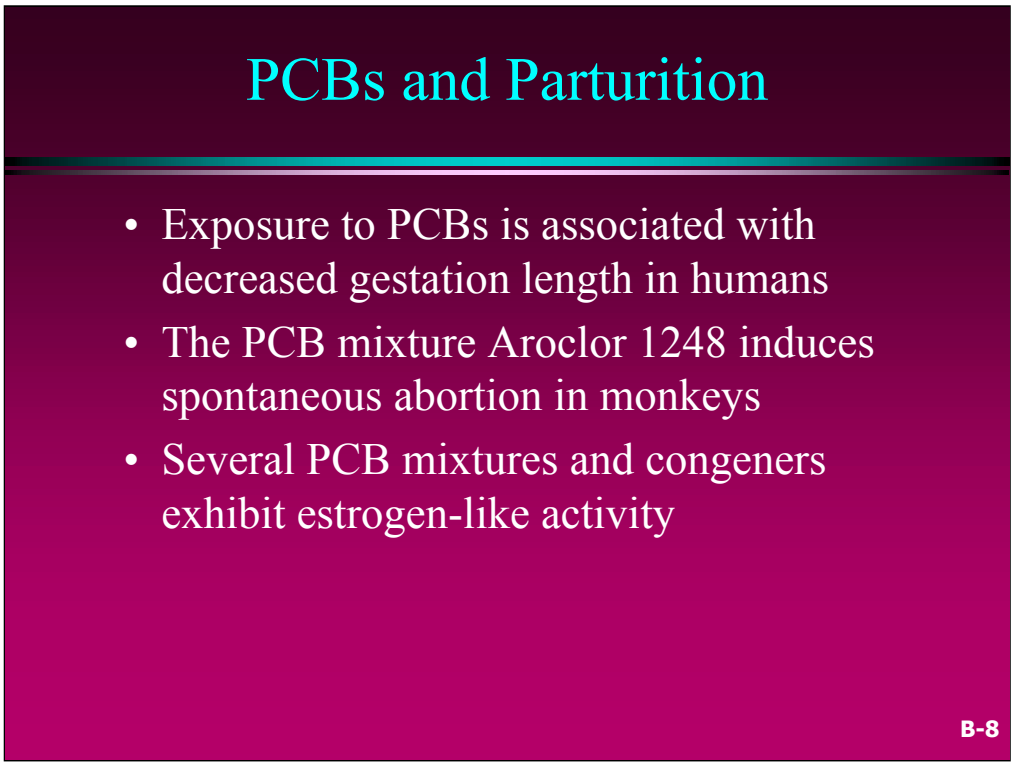
Mechanisms converge at the level of the uterine muscle or myometrium

By taking a mechanistic approach to the study of chemical modification of uterine muscle, we will increase our knowledge of chemical risks to pregnant women and we may also learn about strategies to improve labor management.

Contraction-Promoting Signals



B-7



The PCB mixture Aroclor 1254 and the PCB congeners 2,2'-DCB and 3,4,3',4'-TCB increase gestation length in rats

PCB Residues in Tissues Sampled From Women During Parturition

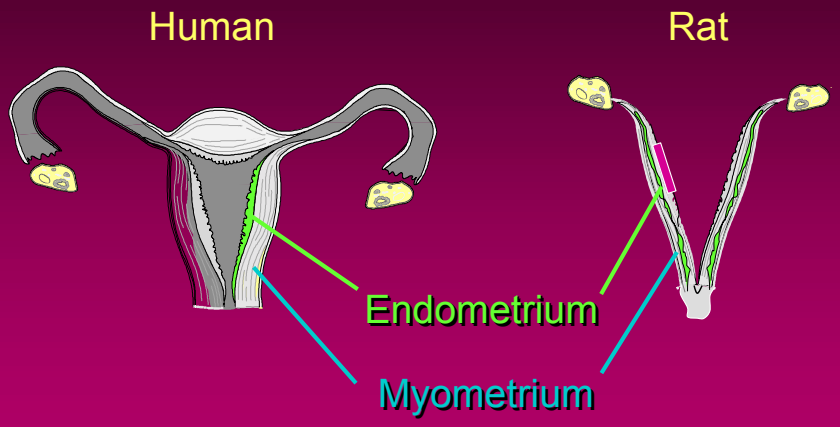
ADIPOSE	BLOOD	UTERUS
1.21	2.80	14.1

Data are expressed as ppm of extracted lipids.

From Polishuk *et al., Environ. Res.* 13:278, 1977.

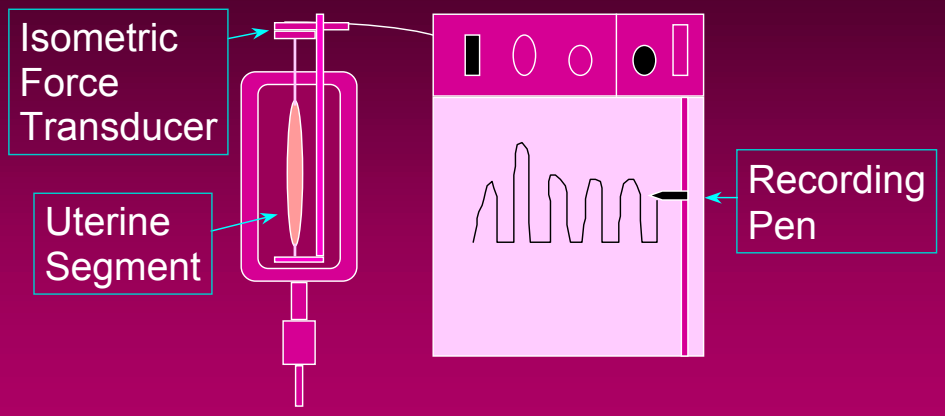
B-9

Uterine Anatomy



B-10

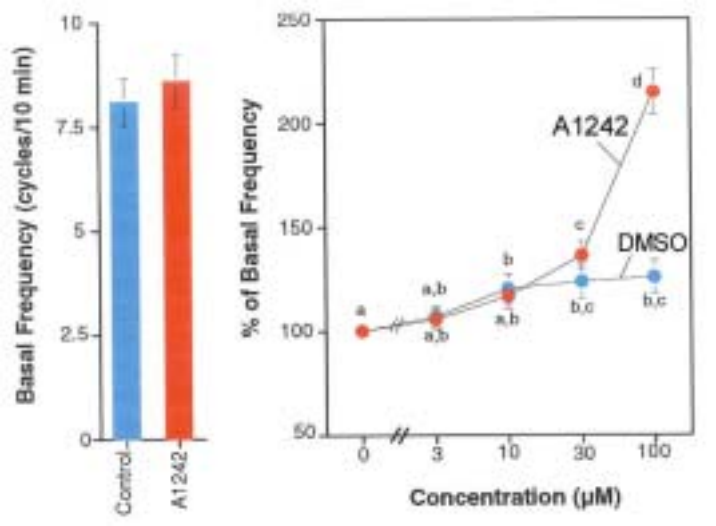
Uterine Contractility Measurement



Organ Bath Polygraph

B-11

Aroclor 1242 Stimulates Uterine Contraction

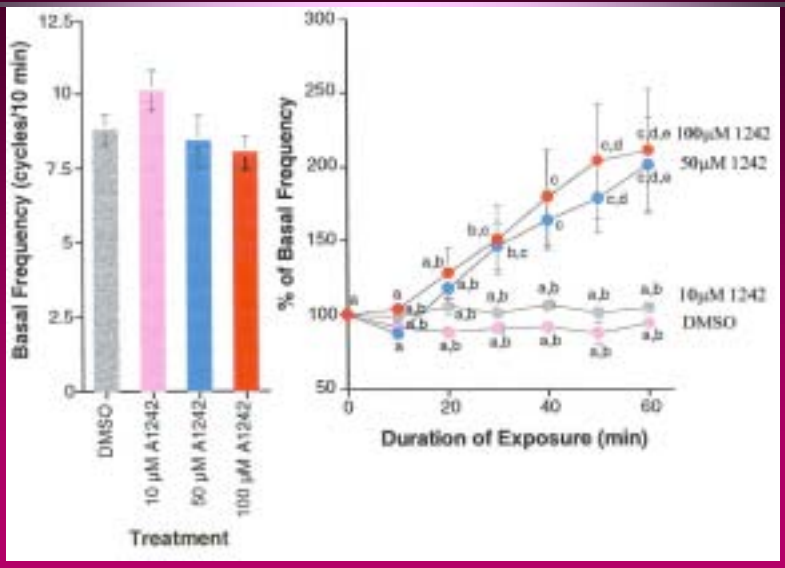


Bae, J. et al. Environ. Health Perspect. 109:275, 2001

B-12

Cumulative concentration response curves.

Aroclor 1242 Stimulates Uterine Contraction



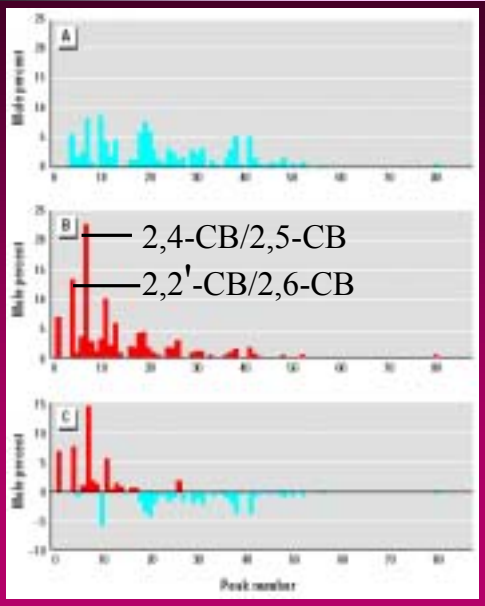
B-13

PCB stimulation increases with duration of exposure up to 1 h.

PCB stimulation may be saturable because the response was similar to 50 and 100 uM.

PCB stimulation is not readily reversible.

Microbial Dechlorination of Aroclor 1242



Auto1242 (control)

HR1242 (incubated with microbes)

Difference between Auto1242 and HR1242

B-14

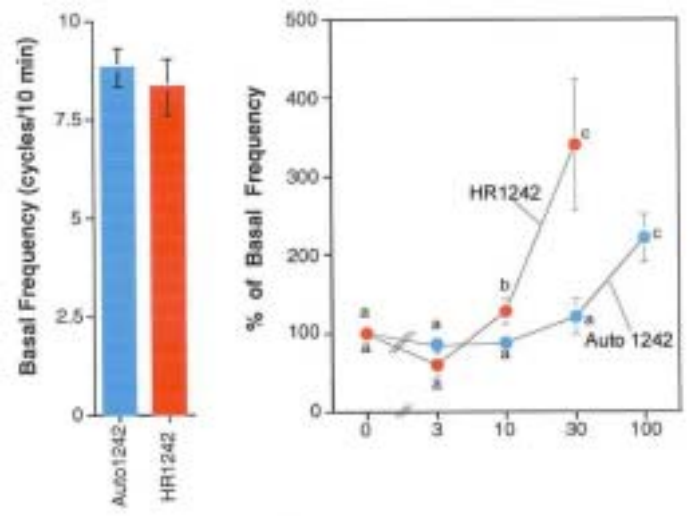
Microbes were isolated from the PCB contaminated Hudson River and incubated with Aroclor 1242 under anaerobic conditions for 20 months.

As a control, bacteria isolated from the Hudson River were autoclaved prior to incubation with Aroclor 1242.

Dechlorination was primarily from the meta position with modest dechlorination from the para position. There was no dechlorination from the ortho position.

Overall, 35% of chlorines were removed.

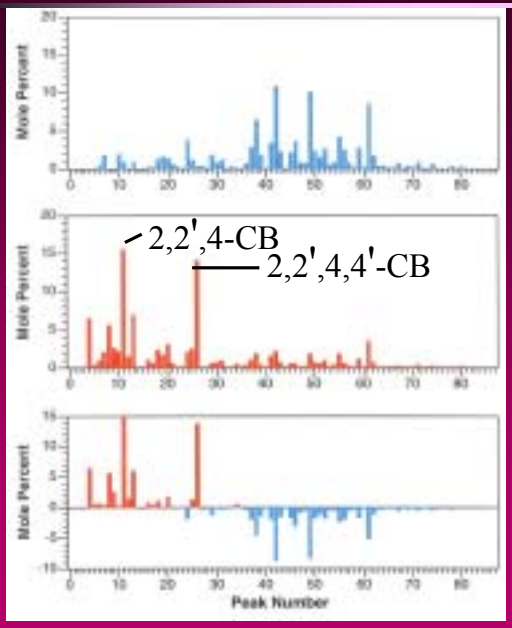
Microbial Dechlorination Increases Uterotonicity of Aroclor 1242



Bae, J. et al. Environ. Health Perspect. 109:275, 2001

B-15

Microbial Dechlorination of Aroclor 1254



Auto1242 (control)

HR1242 (incubated with microbes)

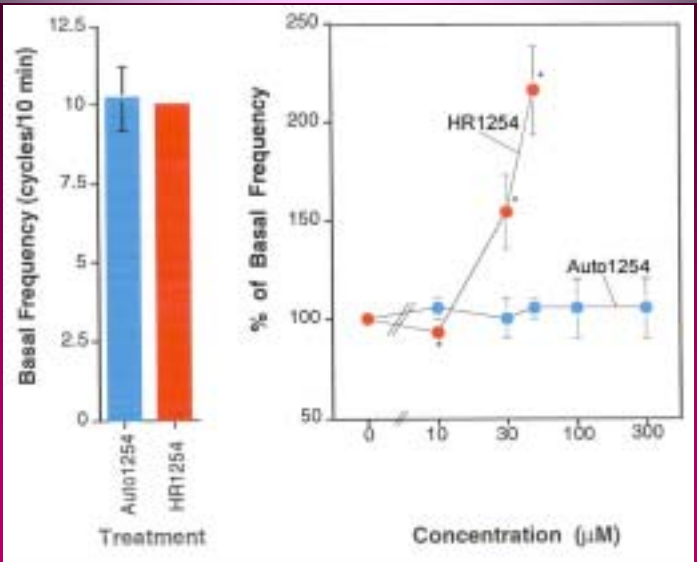
Difference between Auto1242 and HR1242

B-16

Overall, 40 % of chlorines were removed.

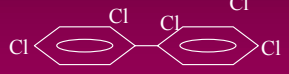
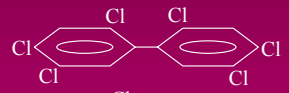
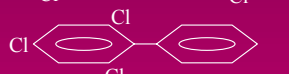
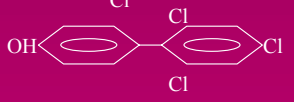
Dechlorination was primarily from the meta position with modest dechlorination from the para position. There was no dechlorination from the ortho position.

Microbial Dechlorination Increases Uterotonicity of Aroclor 1254



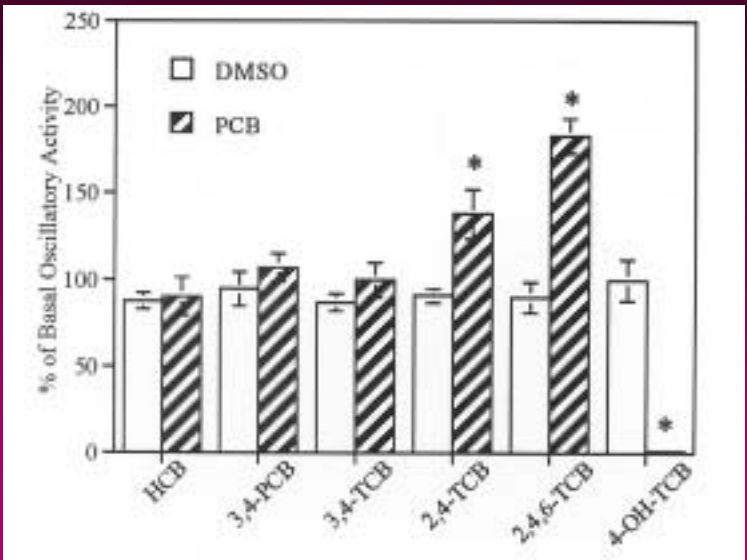
Bae, J. et al. Environ. Health Perspect. 109:275, 2001

B-17

Structure	PCB	Abbreviation
	3,3',4,4'-CB	3,4-TCB
	3,3',4,4',5'-CB	3,4-PCB
	2,2',4,4'-CB	2,4-TCB
	2,2',4,4',5,5'-CB	HCB
	2,4,6-CB	2,4,6-TCB
	4-OH-2',4',6'-CB	4-OH-TCB

B-18

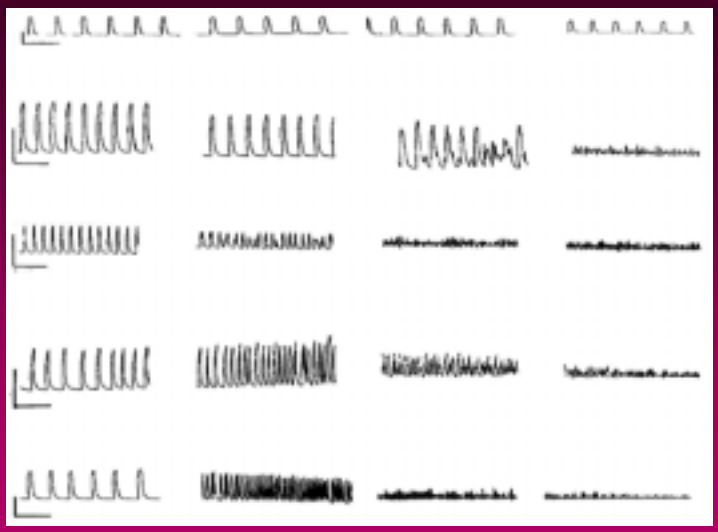
PCB Congener Uterotonicity



Tsai, Webb, and Loch-Caruso. Reprod. Toxicol. 10:21-28, 1996.

B-19

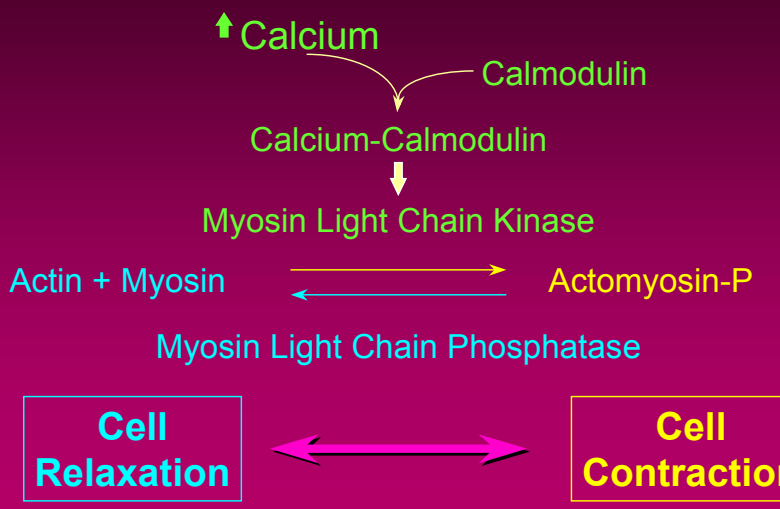
Ortho- and *Para*-Substituted PCB Congeners



Tsuneto et al., unpublished

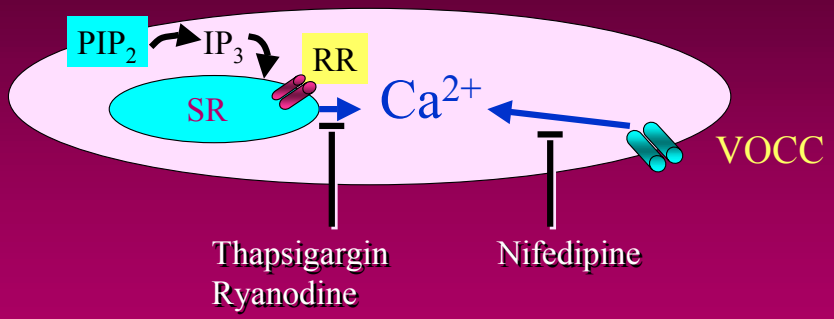
B-20

Intracellular Calcium Increases Stimulate Uterine Muscle Cell Contraction



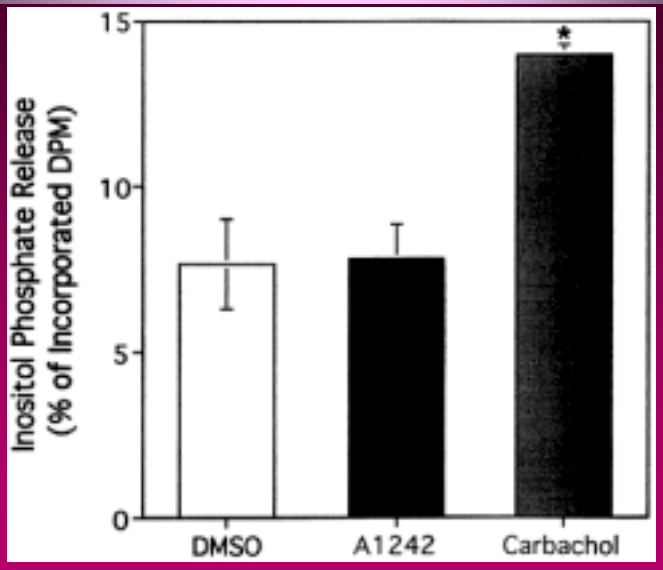
B-21

Mechanisms of Intracellular Calcium Increase



B-22

Aroclor 1242 Does Not Increase Inositol Phosphate Release



B-23

Cells were incubated with myo-[3]H-inosito for 60-72 hours prior to treatment.

Total inositol phosphates were measured after a 60 minute exposure to Aroclor 1242, carbachol or DMSO (solvent controls).

Aroclor 1242 Increases Intracellular Calcium

Treatment	Ca^{2+}	No. Cells	% Basal $[Ca^{2+}]_i$
Control	+	6	102.8±1.0
Control	-	6	99.1±0.8
A1242	+	7	777.8±232.2
A1242	-	8	92.5±5.3
A1242 + Nifedipine	+	7	111.8±21.2

Bae et al. Toxicol. Appl. Pharmacol. 155:261, 1999

B-24

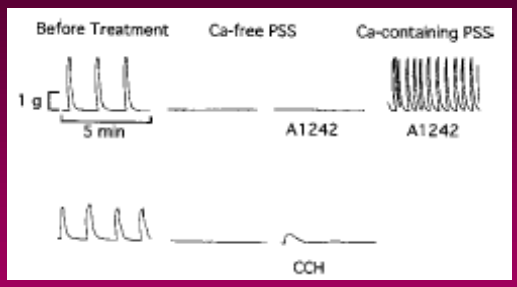
Myometrial cells in culture were exposed to 100 uM Aroclor 1242 for 15-20 minutes.

The treatment with nifedipine (10 uM) was 42-3 minutes prior to petition of Aroclor to 42.

Aroclor 1242 Requires Calcium for Uterotonicity

Aroclor 1242 (A1242)

Carbachol (CCH)



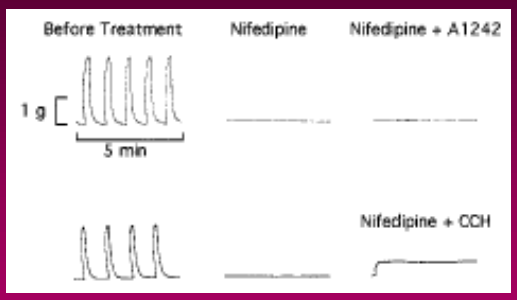
B-25

Longitudinal uterine strips were exposed and muscle baths to 50 uM Aroclor 1242 or to 5 uM carbachol in calcium free buffer.

Inhibition of Voltage-Operated Calcium Channels Prevents Aroclor 1242 Stimulation

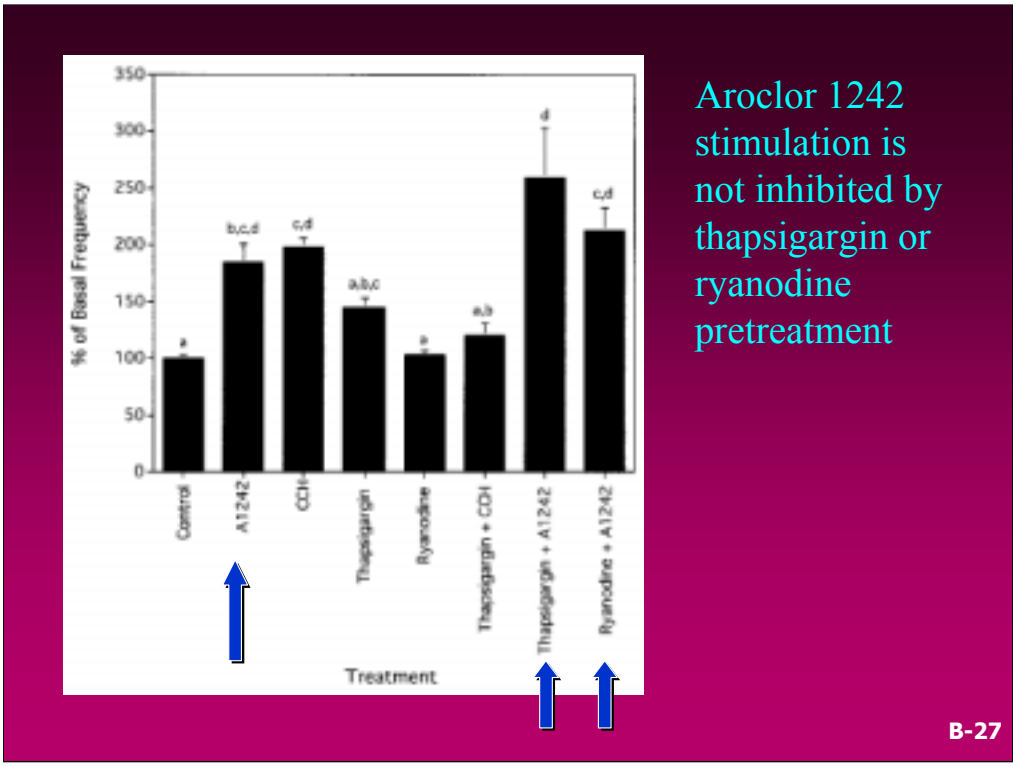
Aroclor 1242 (A1242)

Carbachol (CCH)



B-26

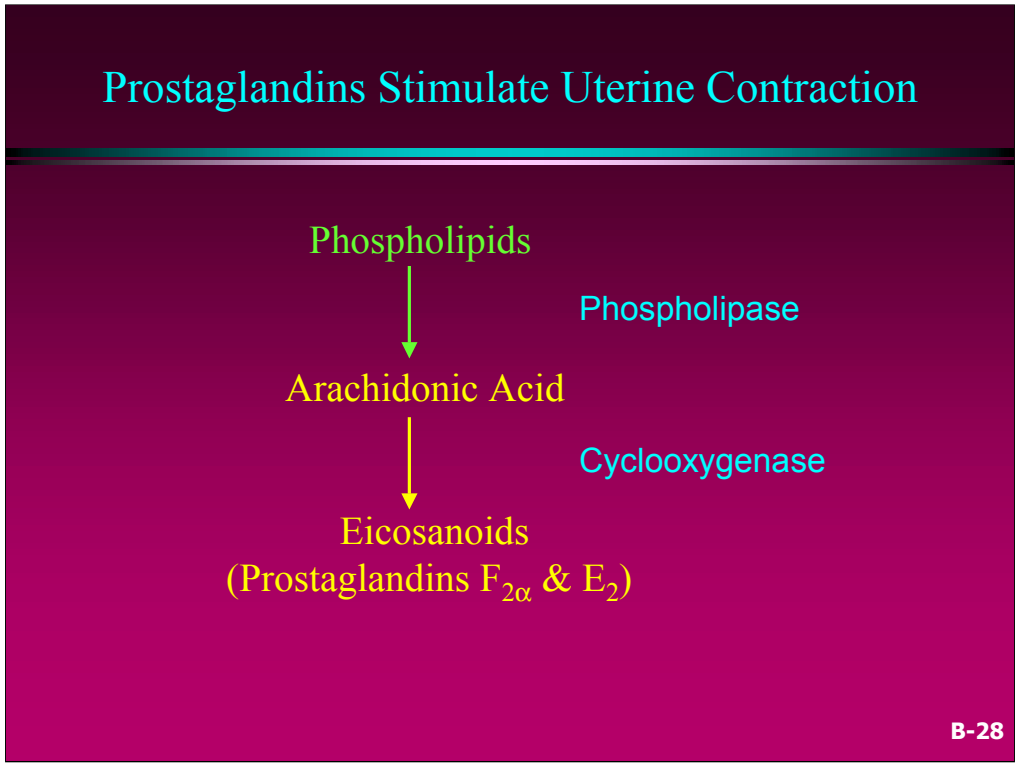
Longitudinal uterine muscle strips were pretreated with 10 uM nifedipine, then exposed to 100 uM Aroclor 1242 or to 10 uM carbachol in calcium containing buffer.



Longitudinal uterine strips were pretreated with 1 uM thapsigargin or 5 uM ryanodine for 20 minutes, exposures previously shown by us to be effective in depleting IP3-sensitive and ryandine-sensitive intracellular calcium stores of myometrial cells (Criswell et al., 1994).

Thapsigargin inhibits the sarcoplasmic reticulum calcium-ATPase. It empties the IP3-sensitive intracellular calcium stores by preventing calcium uptake.

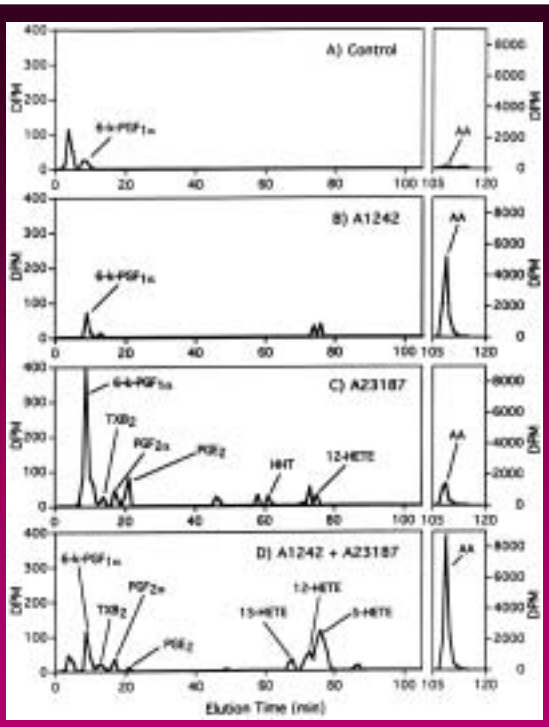
Ryanodine locks open ryandine-sensitive calcium channels to deplete calcium induced calcium release intracellular (IICR) calcium stores.



Release of arachidonic acid is considered by many to be the rate limiting step for the production of prostaglandins.

Phospholipases that release arachidonic acid from membrane glycerol phospholipids include phospholipase A2, which releases arachidonic acid directly, and phospholipases C and D. which convert diacylglycerol to arachidonic acid.

In addition to cyclooxygenase (of which there are two isoforms), lipoxygenases and P450s generate eocosanoids.



- Aroclor 1242 releases large amounts of arachidonic acid that is not significantly metabolized
- Aroclor 1242 inhibits prostaglandin synthesis

B-29

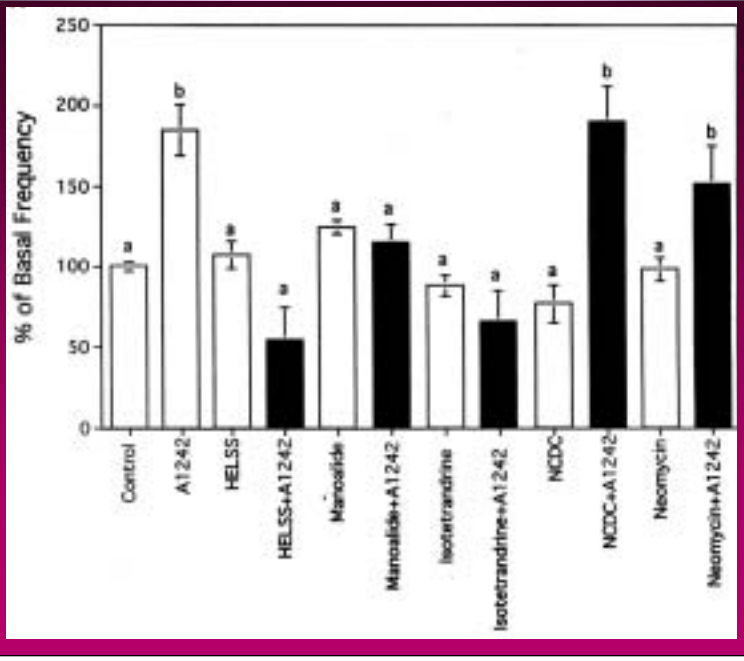
Myometrial cells in culture are capable of prostaglandin synthesis.

6-keto-PGF2a is the stable metabolite of prostacyclin.

6-keto-PGF2a and PGE2 were decreased in cells co-treated with Aroclor 1242 and A23187, even the the amount of arachidonic acid released increased substantially. 5-HETE production was also increased, suggesting stimulation of 5-lipoxygenase.

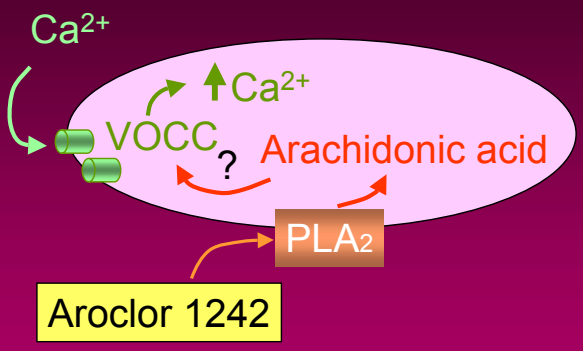
Inhibitors to cyclooxygenase and lipoxygenase abolished spontaneous uterine contractions, so we were unable to test whether Aroclor 1242 stimulation required prostaglandin synthesis through these pathways.

PLA2 Inhibitors Prevent Aroclor 1242 Uterotonicity



B-30

Aroclor 1242 Mechanism

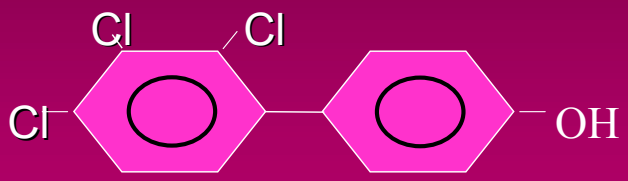


VOCC: Voltage operated Ca^{2+} channels
PLA_2: Phospholipase A_2

B-31

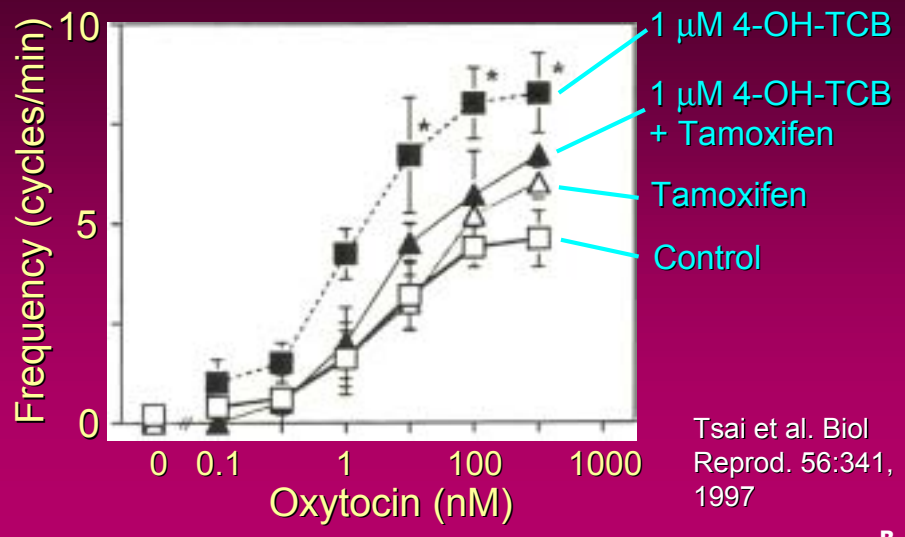
Hypothesis:

Long-term exposure to estrogenic PCBs promotes uterine contraction by an estrogen receptor-mediated mechanism.



B-32

4-Hydroxy-2',4',6'-Trichlorobiphenyl Increases Oxytocin-induced Contraction Frequency



Tsai et al. Biol Reprod. 56:341, 1997

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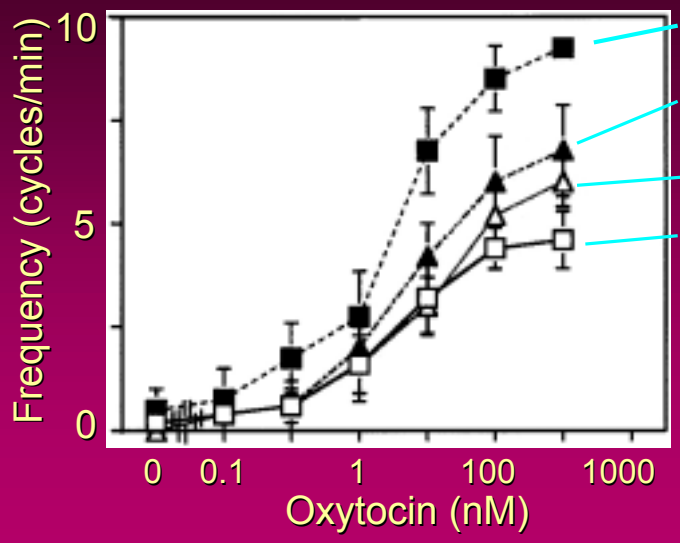
17β-Estradiol Increases Oxytocin-induced Contraction Frequency



Tsai et al. Biol Reprod. 56:341, 1997

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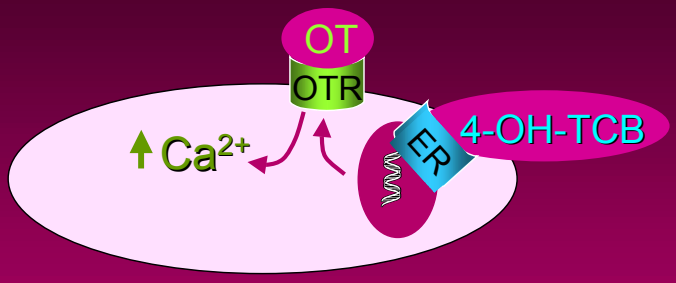
4-OH-2',4',6'-TCB Mechanism



4-OH-TCB: 4-hydroxy-2',4',6'-trichlorobiphenyl
ER: Estrogen receptor
OT: Oxytocin
OTR: Oxytocin Receptor

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