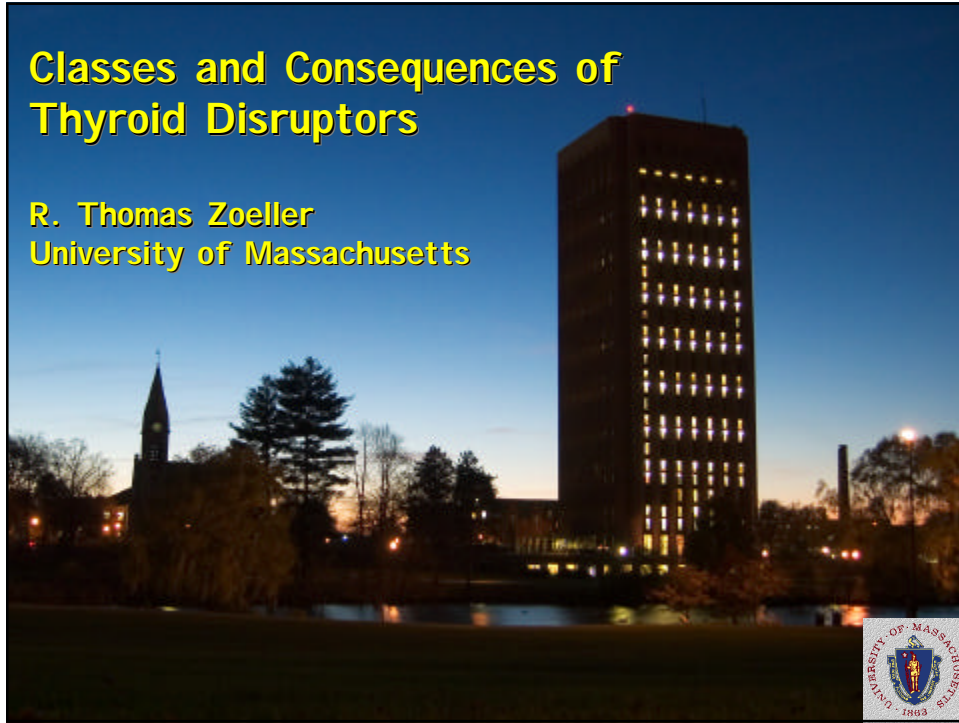


Classes and Consequences of Thyroid Disruptors

R. Thomas Zoeller
University of Massachusetts



The Hypothalamic-Pituitary-Thyroid "Axis"

Serum Thyroid Hormone levels are controlled by a complex interaction between the brain, the pituitary gland, and the thyroid.

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.



The Hypothalamic-Pituitary-Thyroid "Axis"

Various disease states show that the distribution of the active form of thyroid hormone is an active process that can be "disrupted".

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.



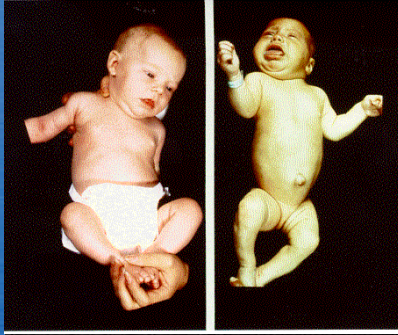
The Problem

Pregnancy represents a significant demand on the mother's thyroid gland.

The fetus does not produce its own thyroid hormone until the second trimester



Normal development requires thyroid hormone

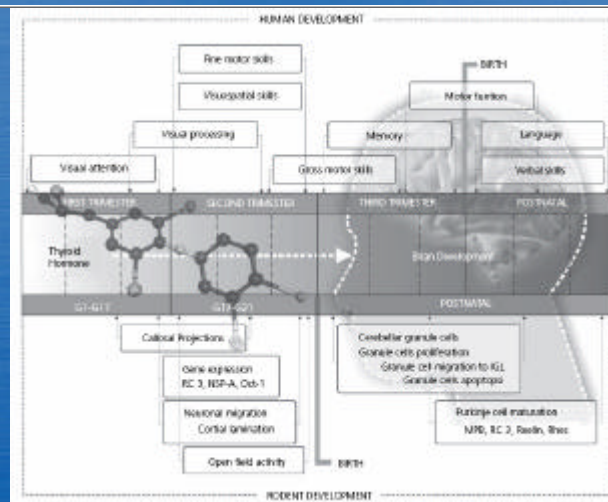


The "critical period" of thyroid hormone action in brain development was defined as that period after birth when TH therapy must be initiated to rescue the infant from cretinism.

Brown AW *et al.* (1939) Hypothyroidism and cretinism in childhood. VI. Influence of thyroid therapy on mental growth. *Amer J Dis Child* 57:517-523.



The Effects of Development TH Insufficiency Depend on Severity and Timing

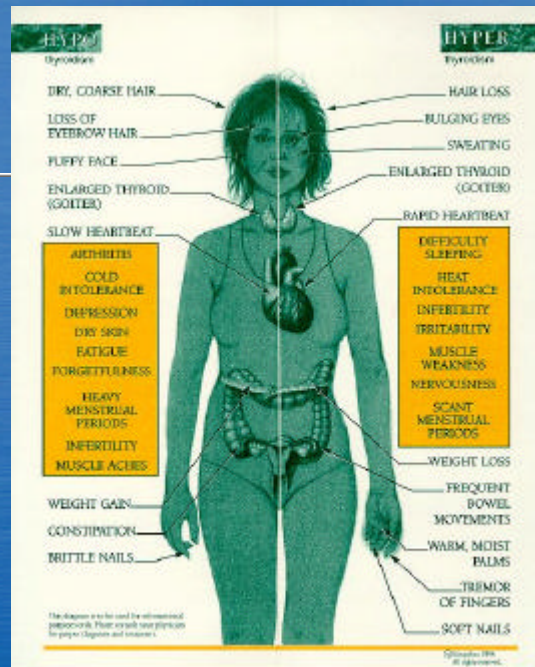


Zoeller et al. *Journal of Neuroendocrinology*, 2004



TH Insufficiency

- Mild TH insufficiency is associated with cognitive deficits in the absence of physical (somatic) symptoms
- There may be genetic predispositions to specific modes of actions of environmental chemicals.

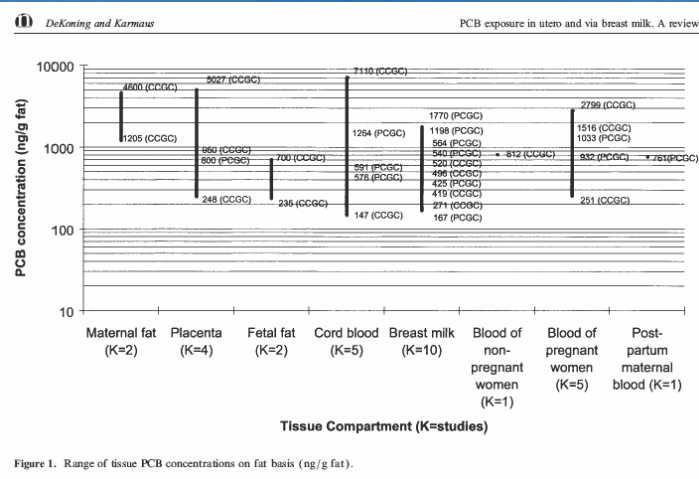


"Classification" of Thyroid Disruptors

- Effects on Thyroid
 - Perchlorate/
 - Thiocyanates
- Effect on "Clearance" (Liver)
 - Phenobarbital
 - Linuron
 - PCBs
 - PBDEs
- Effect on TH Receptors
 - PCBs, PBDEs, Triclosan

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.

Polychlorinated Biphenyls





Polychlorinated Biphenyls

Breast milk levels:

Low: 1.28 µg/mL (3.52 µM)

High: 13.2 µg/mL (36.3 µM)

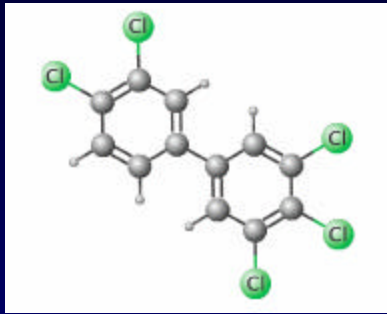


Polychlorinated Biphenyls

Table 3. Neuropsychological outcomes of human PCB studies.*

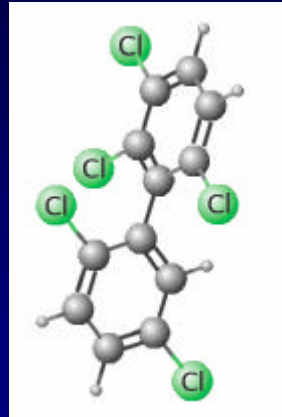
Test	Age	Outcome	Exposure variable	References
Congener-specific studies				
Oswego cohort				
NBAS	Birth	↓ Autonomic ↓ Habituation	7-9 chlorinated PCBs	Stewart et al. (2000)
Fagan	6 months 12 months	↓ Fixation time ↓ Fixation time	Cord blood PCBs, 7-9 chlorinated PCBs Cord blood PCBs	Darvill et al. (2000) Darvill et al. (2000)
German cohort				
Fagan	7 months	No effect	In ΣPCBs (138, 153, and 180) breast milk	Winnike et al. (1998)
Bayley scales	7 months	↓ MDI	In ΣPCBs (138, 153, and 180) breast milk	Winnike et al. (1998)
Fagan	18 months	No effect	In ΣPCBs (138, 153, and 180) breast milk	Walkowiak et al. (2001)
Bayley scales	30 months	↓ MDI	In ΣPCBs (138, 153, and 180) breast milk	Walkowiak et al. (2001)
Kaufman ABC	42 months	↓ Mental processing composite index	In ΣPCBs (138, 153, and 180) breast milk	Walkowiak et al. (2001)
Faroe Islands cohort				
Boston Naming Test		↓ Performance	Cord blood PCBs	Grandjean et al. (2001)
Auditory function		↑ Auditory thresholds	Cord blood PCBs	Grandjean et al. (2001)
Noncongener-specific studies				
Michigan cohort				
Birth size/growth	Birth	↓ Birth weight ↓ Head circumference ↓ Gestational age ↓ Body weight	Cord blood PCBs Cord blood PCBs Cord blood PCBs Cord blood PCBs	Fein et al. (1984)
Bayley scales	5 months	No effect	Cord blood PCBs	Jacobson and Jacobson (1988)
Fagan	7 months	↓ Fixation time	Cord blood PCBs	Jacobson and Jacobson (1988)
McCarthy scales	4 years	↓ Verbal memory ↓ Numerical memory ↓ Visual discrimination	Cord blood PCBs, breast milk PCBs Cord blood PCBs, breast milk PCBs Breast milk PCBs	Jacobson et al. (1990a) Jacobson et al. (1990a) Jacobson et al. (1992)
Birth size/growth	4 years	↓ Short term memory ↓ Body weight ↓ Activity	Cord blood PCBs Total cord PCBs Child's total PCBs	Jacobson et al. (1990b)
WISC-R	11 years	↓ Full-scale IQ ↓ Verbal IQ	Prenatal PCBs Prenatal PCBs	Jacobson and Jacobson (1996)
North Carolina cohort				
NBAS	Birth	↓ Muscle tone ↓ Activity ↓ Reflexes	Breast milk PCBs Breast milk PCBs Breast milk PCBs	Rogan et al. (1986b)
Bayley scales	6 months	↓ PDI	Breast milk PCBs	Gladen et al. (1988)
	12 months	↓ PDI	Breast milk PCBs	Gladen et al. (1988)
	18 months	No effect	Breast milk PCBs	Rogan and Gladen (1991)
	24 months	↓ PDI	Breast milk PCBs	Rogan and Gladen (1991)
McCarthy scales	3-5 years	No effect	Breast milk PCBs	Gladen and Rogan (1991)

Abbreviations: ↓, decrease; ↑, increase; Bayley scales, Bayley Scales of Infant Development; Fagan, Fagan Test of Infant Intelligence; Kaufman ABC, Kaufman Assessment Battery for Children; McCarthy scales, McCarthy Scales of Children's Abilities; NBAS, Brazelton Neonatal Behavioral Assessment Scale; Wisc-R, Wechsler Intelligence Scales for Children-Revised. *Dutch cohort is summarized in Table 2.



PCB 77 is "co-planar"

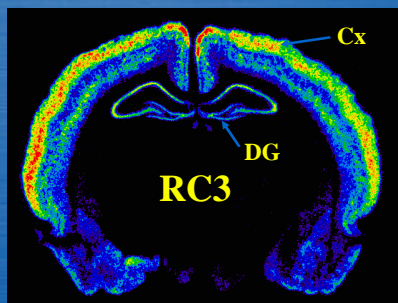
Polychlorinated Biphenyls



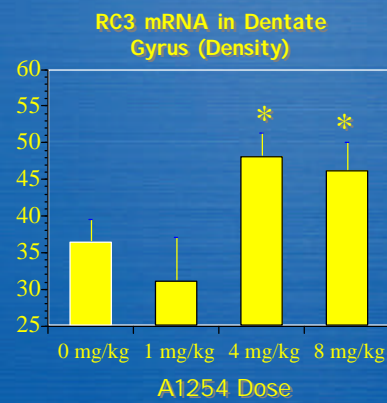
PCB 95 is non coplanar



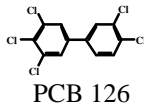
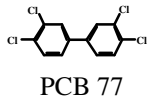
Effect of PCB Exposure on RC3/Neurogranin



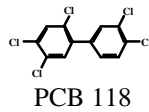
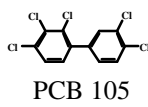
Pseudocolor image of Autoradiogram following in situ hybridization for RC3 mRNA



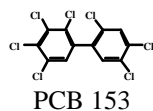
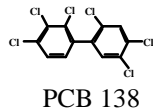
Non-ortho chlorinated PCBs



Mono-ortho chlorinated PCBs



Di-ortho chlorinated PCBs



To identify specific PCB congeners that may act as TR agonists, we developed a mixture of 6 PCBs that represent three classes.

PCB 118 and 105 are "activated" to form TR agonists by CYP1A1 in GH3 cells

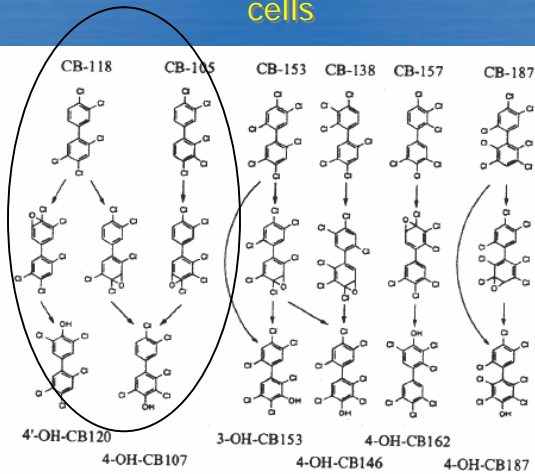
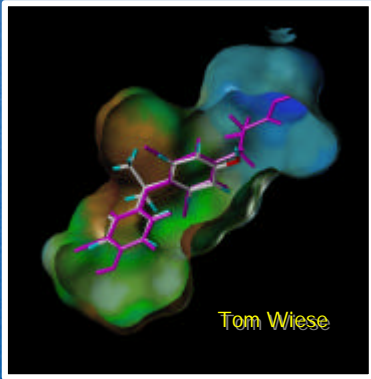
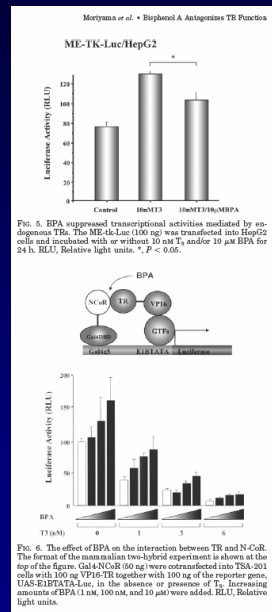
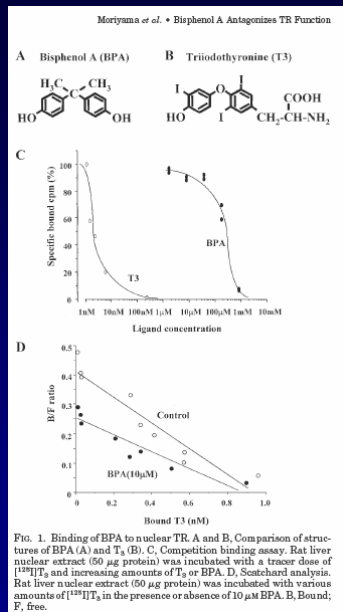


Figure 1. OH-PCBs identified in rat plasma after exposure to individual PCB congeners. Possible metabolic routes are indicated.

Bisphenol A

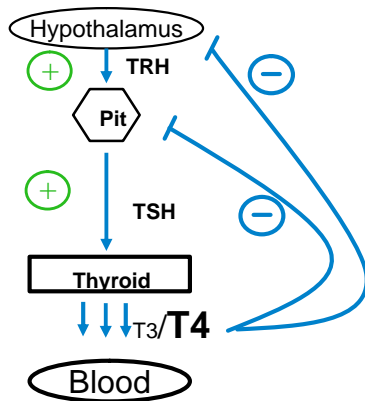


- Component of plastic
- Polycarbonates
- Dental sealants
- Can linings

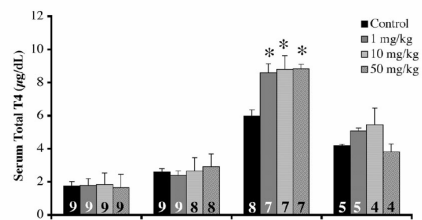


Moriyama et al., JCEM 2002 87(11):5185.

BPA antagonizes TR- β mediated negative feedback *in vivo*



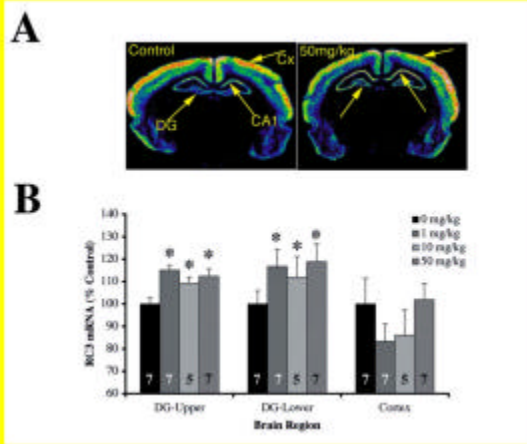
Negative feedback in the rat is not functional for the first week.



Zoeller et. al. (2004) *Endocrinology* 146:607

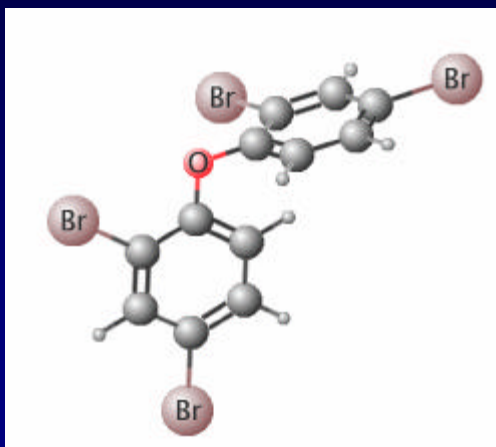
Elevated levels of TH increase RC3/Neurogranin expression on P15

•BPA may be a TR β selective antagonist.



Endocrinology 146(2): 607-612

Polybrominated Diphenyl Ethers



PBDEs are found in human tissues in the US at 10x the level found in Europe. Very high levels in house pets (infants/children?)

Polybrominated Diphenyl Ethers

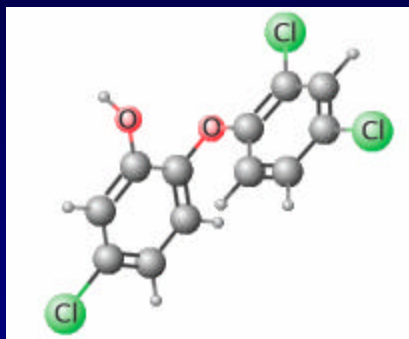
Table 1.

Receptor binding (IC_{50})	THR- α (nM)	THR- β (nM)
T ₃	0.39	0.29
T ₄	1.3	3.6
Triac	0.13	0.037
4-hydroxydiphenyl ether	$B_{min} > Ref B_{min}$	8800
4'-hydroxy-1,3,5-tribromodiphenyl ether (III)	>1000	>1000
4'-hydroxy-1,3,3',5-tetrabromodiphenyl ether (IV)	198.9	41.1
4'-hydroxy-1,3,3',5,5'-pentabromodiphenyl ether (V)	543.7	181.3

¹ To facilitate the comparison between the structures of the hydroxybromodiphenyl ethers synthesized in the present study and the thyroid hormones, the numbering system used for the thyroid hormones are used.

Marsh, Bergman et al., 1998, Organohalogen Compounds 37:305.

Triclosan



Triclosan is a bacteriocidal agent found in soaps, toothpaste, etc.



Conclusions

- It is becoming clear that common contaminants in human tissues (fetus, pregnant/lactating women, adults) can exert direct actions on the thyroid system.
- EPA is currently developing an EDSP that incorporates NO measures of TH action.

