The Health Effects of Polychlorinated Biphenyls

or

“How I learned to stop worrying and love the ban”

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Outline

I. What are PCBs and why should we care?
II. Molecular mechanisms as a predictor of toxicity/carcinogenicity
   A. Activation of the Aryl Hydrocarbon Receptor (AhR)
   B. Activation of the Pregnone X (PXR) and Constitutive Androstone (CAR) receptors.
III. Some specific examples of PCB exposure health effects
   A. Endocrine/Reproductive disruption
   B. Neurotoxicity
   C. Immunotoxicity
   D. Carcinogenicity
IV. Helpful links
What Are PCBs?

**STRUCTURE OF POLYCHLORINATED BIPHENYLS (PCBs)**

PCBs are structurally distinct and have more than one mechanism of action:

- **Coplanar PCBs**
  - meta, para substituted
  - Bind with high affinity to the Ah receptor
  - Mediate many effects through changes in gene transcription

- **Noncoplanar PCBs**
  - ortho substituted
  - Are not good ligands for the Ah receptor
  - Mechanisms of action are unknown but initiated by changes in cell signaling

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Co-Planar (Flat) PCBs Look Like Dioxin

Co-Planar PCBs

Dioxin
Planar PCBs and Dioxin Act Through a Protein Receptor (The AhR)

Co-planar PCB

AhR Binding Sites

AhRE

DNA

>50 genes

Growth, death, migration, hormone production, red blood cell development, blood clotting, heart development, immune system function, inflammation, neurologic function, reproduction…
Non-Planar PCBs Intercalate into the Cell Membrane
Non-Co-Planar PCBs Activate the Constitutive Adrostone Receptor (CAR) and the (PXR) and the Pregnane X Receptor
PCBs and Endocrine and Reproductive Systems

- Altered thyroid gland structure (animals)
- Reduced thyroid hormone levels (animals and humans) (both co-planar and non-co-planar PCBs)
- Children born to mothers exposed to PCBs exhibit decreased gestational age and decreased birth weight.
- Reduced conception rates and live birth rates (non-human primates and other species)
- Reduced sperm counts (Rats)
- Reduced testosterone production in boys (which may result in delayed puberty)
PCBs and Neurotoxicity

- Hyperactivity (non-human primates and humans)
- Impaired learning ability (non-human primates and humans)
- Decreased visual acuity (humans)
- Decreased verbal and memory test scores at 4 years old (human)
- Lower cognitive and attention scores (humans)
- Psychomotor development at 6, 12, and 24 months of age (human)
- Possible increased risk of Parkinson’s Disease
PCBs and Immunity

- Co-planar PCBs activate the AhR which is critical to development of the entire gut immune system and contributes significantly to inflammation and defense against cancerous cells.
- Decreased thymus size (infant monkeys). (The thymus generates T lymphocytes)
- Reduced ability of children to generate protective antibody responses following vaccination with standard childhood vaccine (i.e., tetanus and diphtheria toxoids)
- Decreased resistance to Epstein-Barr virus and other infections (rodents)

- Overall end result: Immunosuppression
PCBs and Cancer

- Co-planar PCBs activate the AhR which has been implicated in several cancers.
- Every commercial mixture of PCBs (Aroclors 1016, 1242, and 1254) causes cancer in the 2 year rat bioassay.
- Human epidemiological studies implicate PCBs in melanomas, liver cancer, gall bladder cancer, biliary tract cancer, gastrointestinal tract cancer, non-Hodgkin’s lymphoma and brain cancer.
- PCBs that accumulate in sediment and bioaccumulate, for example, in fish are likely to be the most carcinogenic.
- Conclusion: Both co-planar and non-co-planar PCBs are human carcinogen.

1. U.S. EPA
2. International Agency for Research on Cancer (IARC)
3. National Toxicology Program/NIEHS (NTP)
4. National Institute of Occupational Health (NIOSH)
5. American Toxic Substances Disease Registry (ATSDR)
Helpful Links

• EPA website on PCBs: http://www.epa.gov/epawaste/hazard/tsd/pccbs/
• IARC upgrades PCBs to “known carcinogens”: http://www.carexcanada.ca/en/announcements/PCBs_IARC_upgrade/
• PCBs and hypothyroidism: http://www.bio.umass.edu/biology/zoeller/pdf/chap33.pdf
• PCBs and decreased responses to childhood vaccines: http://www.nytimes.com/2006/09/05/science/05immu.html?_r=0
• PCBs and neurotoxicity: http://www.ncbi.nlm.nih.gov/pubmed/8725628
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