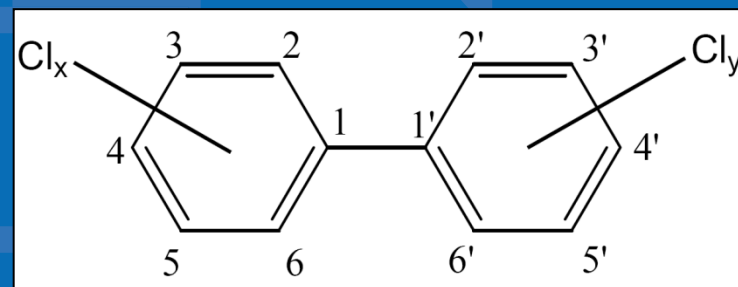


Scoping and Problem Formulation for the IRIS Toxicological Review of Polychlorinated Biphenyls (PCBs): Effects Other Than Cancer

Geniece M. Lehmann, PhD
Assessment Manager



Overview

- Background & Scoping
- Problem Formulation
 - Health Outcomes
 - Key Science Topics

Polychlorinated Biphenyls (PCBs)

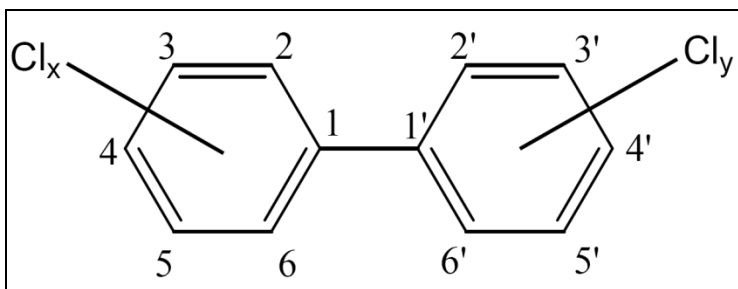
U.S. Manufacture and Production:

- Manufactured as Aroclors from 1929 to 1977
- Total U.S. production >600 million kg

Some Uses:

- Dielectric fluid in transformers
- Oil used in motors and hydraulic systems
- Electrical devices/appliances containing PCB capacitors
- Fluorescent light ballast capacitors
- Adhesives and tapes
- Oil-based paints
- Plasticizer in caulk and window glazing

Humans are exposed to PCBs as diverse mixtures of congeners.



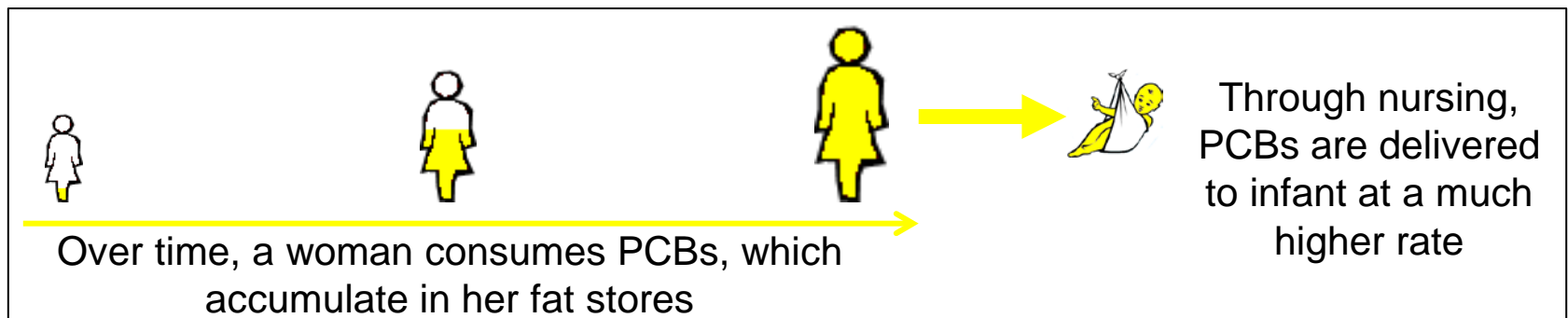
Congeners vary in structure, stability, toxicity and MOA: these properties are determined by chlorine number and position

Human Exposure Pathways

- Oral
 - Dietary
 - Incidental ingestion of soil or dust
- Inhalation
 - May be an important exposure pathway in buildings containing PCB sources (e.g., PCB-containing fluorescent light ballasts or caulk); most likely in buildings built or renovated between 1950 and 1979
- Dermal
 - Contact with soil, dust, etc.

Susceptible Populations and Life Stages

- Consumers of PCB-contaminated fish
 - Recreational, subsistence and traditional fishing populations
- Occupants of PCB-contaminated buildings
 - Students, teachers, and other occupants of PCB-contaminated schools
- Breastfed infants



PCB Regulations	Current IRIS Reference Values for PCBs	Scope of the New Assessment
<p>TSCA (40 CFR 761) CWA SDWA RCRA</p> <p><i>Human exposure continues</i></p>	<p>RfDs Aroclor 1016 Aroclor 1254</p> <p>Cancer slope factors Environmental PCB mixtures tiered by exposure source/route</p> <p><u>NO RfD</u> for general PCB mixtures</p> <p><u>NO RfC</u></p>	<p>Hazard Identification Non-cancer Oral and inhalation routes</p> <p>Dose-Response Assessment For exposure routes and health outcomes with adequate supporting data</p>

Preliminary Literature Survey for PCBs

Health Effect Categories	Human Studies	Animal Studies (oral)	Animal Studies (inhalation)	Health Effect Categories	Human Studies	Animal Studies (oral)	Animal Studies (inhalation)
Cardiovascular	✓	✓		Immunological	✓	✓	✓
Dermal & Ocular	✓	✓		Metabolic Disease	✓	✓	
Effects on Growth & Maturation	✓	✓	✓	Musculoskeletal	✓	✓	
Endocrine	✓	✓	✓	Neurological & Sensory	✓	✓	✓
Gastrointestinal	✓	✓		Renal	✓	✓	✓
Hematological	✓	✓	✓	Reproductive	✓	✓	
Hepatic	✓	✓	✓	Respiratory	✓	✓	✓

Health Effect Categories to Consider for Systematic Review

- Neurological
- Immunological
- Endocrine (thyroid)
- Reproductive (male & female)
- Developmental (effects on growth & maturation)
- Hepatic
- Cardiovascular
- Dermal and Ocular
- Gastrointestinal
- Hematological
- Metabolic Disease

Key Science Topics

1. Impact of congener profile on the toxicity of PCB mixtures
2. Evaluation of epidemiological studies for PCB dose-response assessment
3. Potential for hazard identification and dose-response assessment for PCB exposure via inhalation
4. Suitability of available toxicokinetic models for reliable route-to-route, interspecies, and/or intraspecies extrapolation
5. Potential toxicokinetic models or methods to estimate the relationship between continuous daily maternal PCB intake and milk PCB concentrations in humans
6. Putative mechanisms of PCB toxicity
7. Factors influencing human susceptibility

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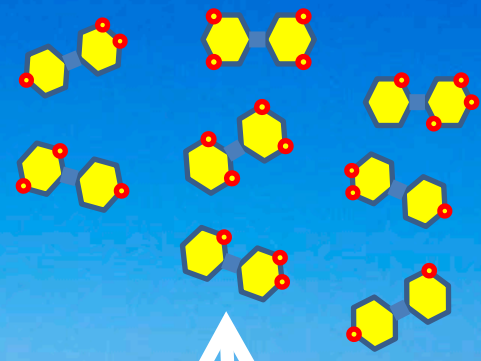
Key Science Topics

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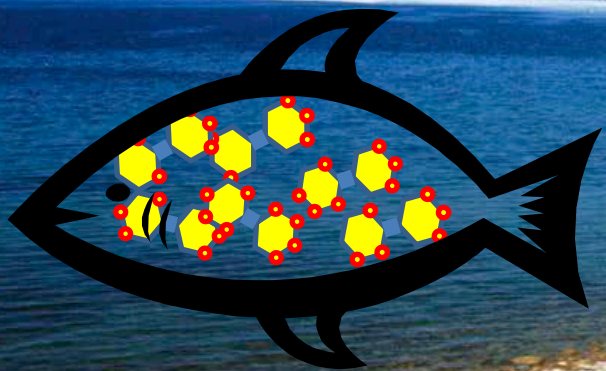
Science Topic 1: Congener Profile and Toxicity

- PCB congener profiles are highly variable across exposure media.

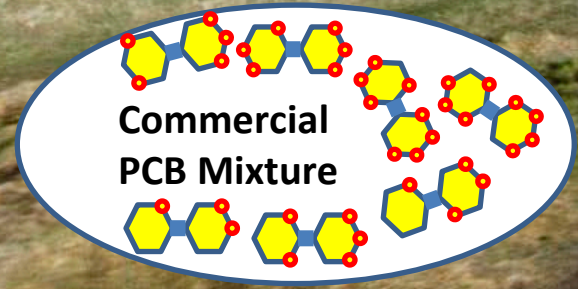
Lower-chlorinated congeners tend to be more volatile



Higher-chlorinated congeners tend to be resistant to metabolism & bioconcentrate in the food chain



Commercial PCB Mixture

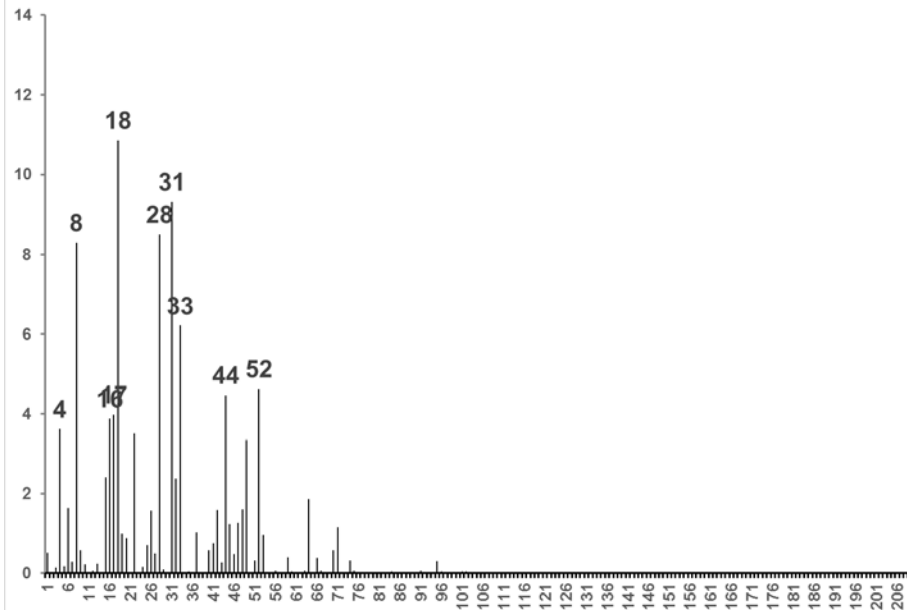


Science Topic 1: Congener Profile and Toxicity

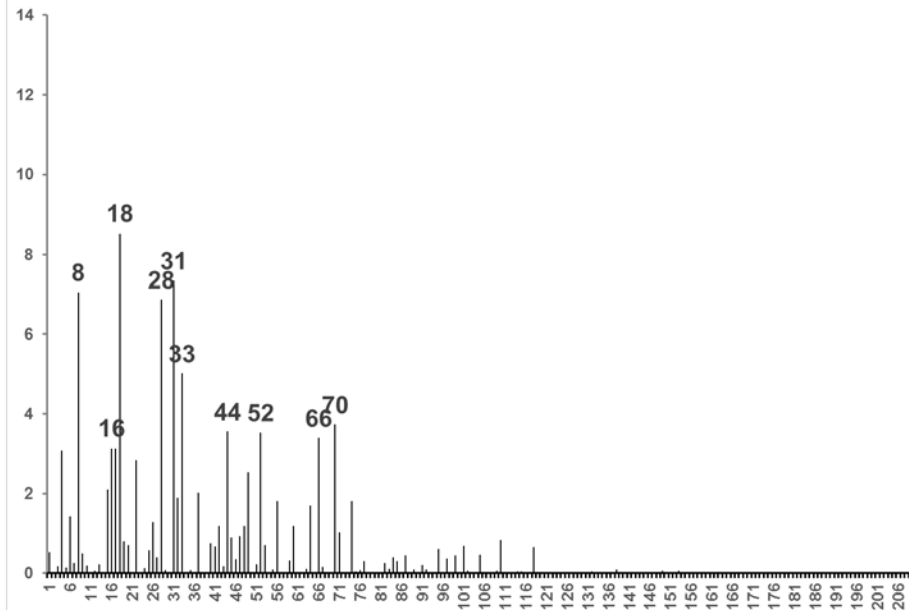
- PCB congener profiles are highly variable across exposure media.
- PCB mixtures used in animal studies often do not contain the same congeners in the same proportions as PCB mixtures found in the environment.



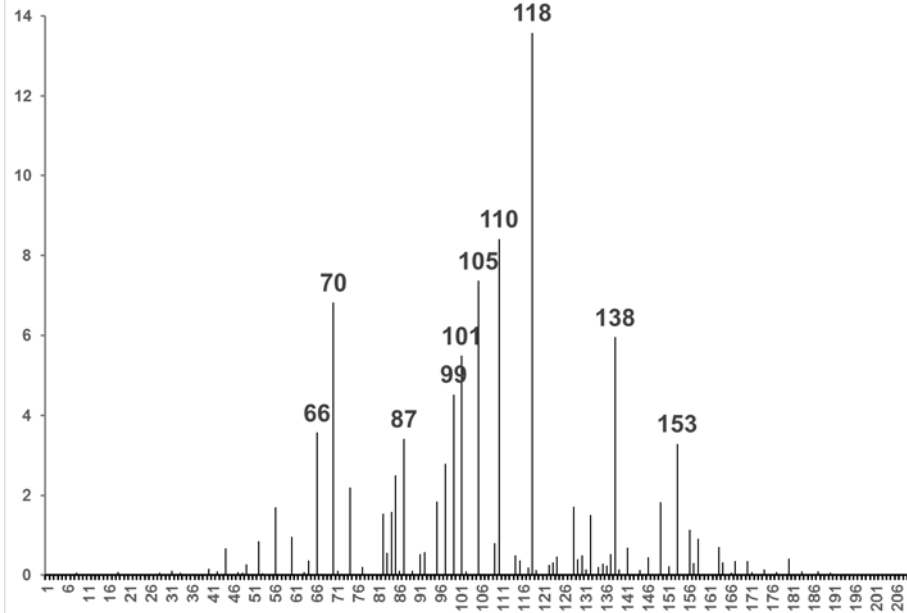
Aroclor 1016



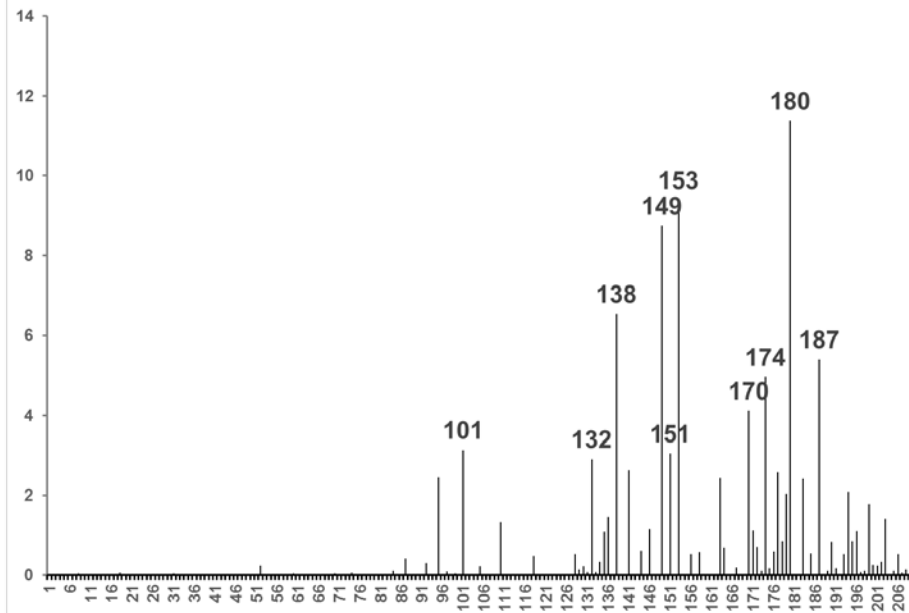
Aroclor 1242



Aroclor 1254



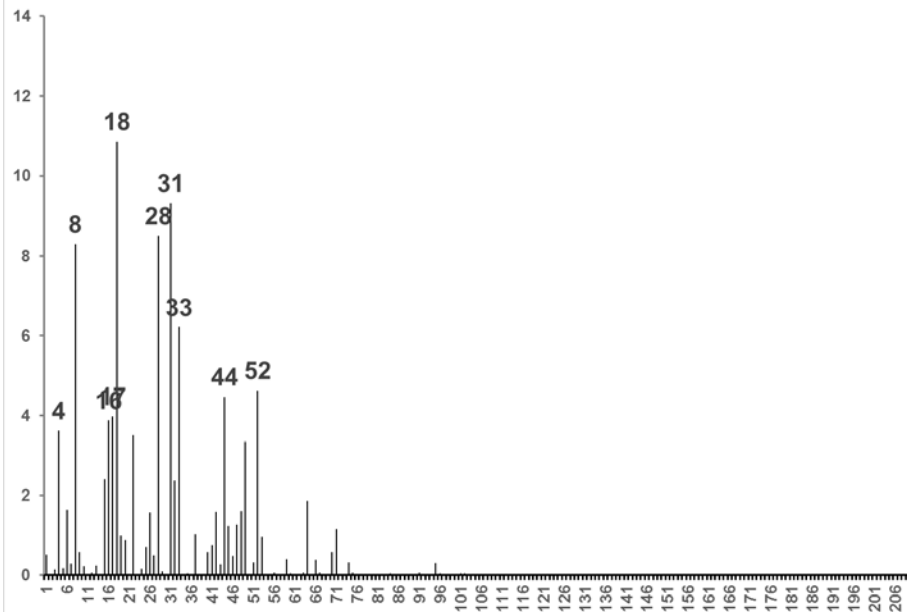
Aroclor 1260



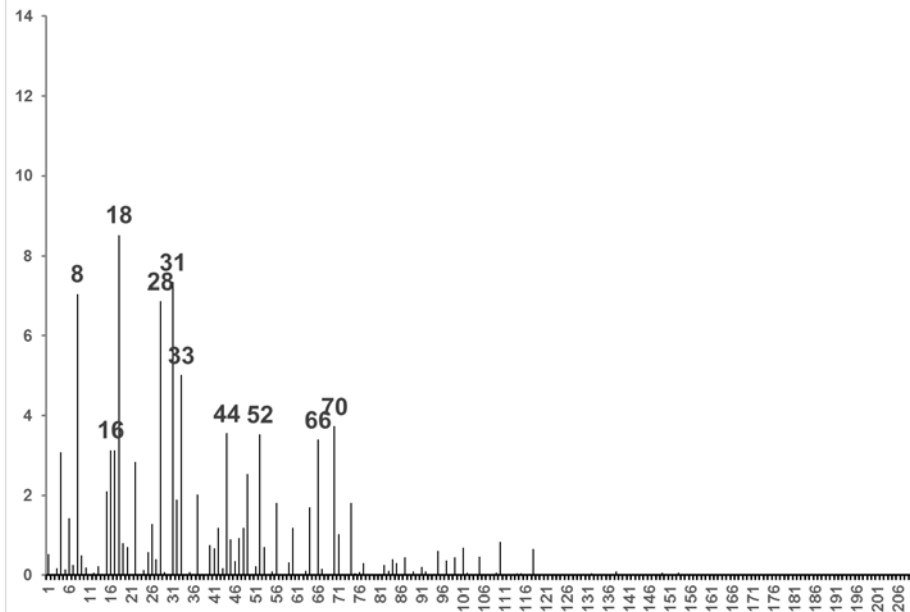
Congener Number (increasing 1 to 209)



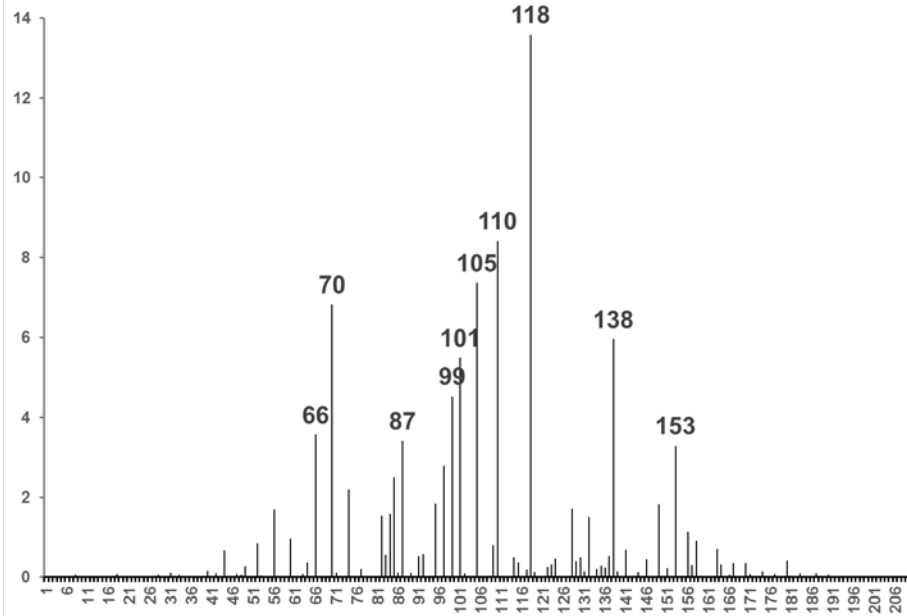
Aroclor 1016



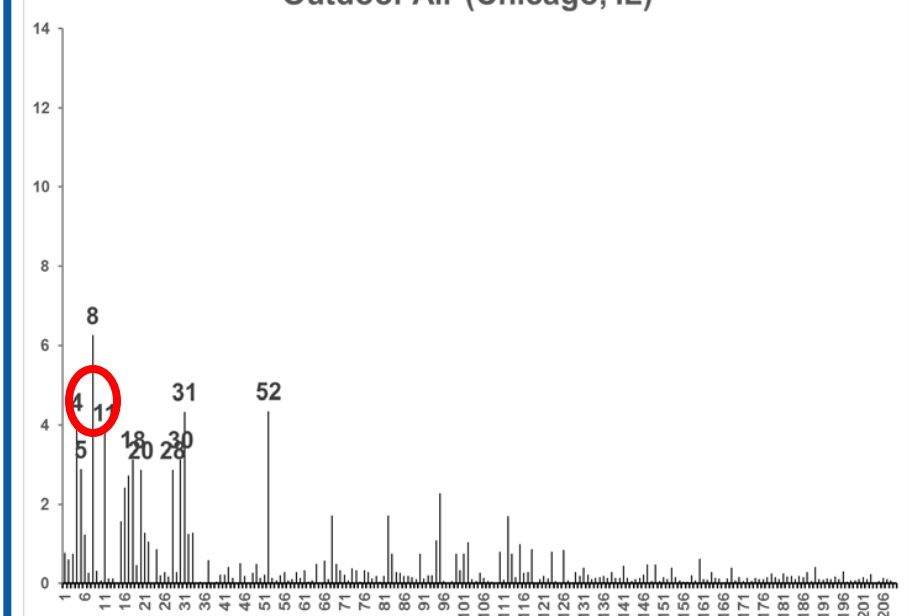
Aroclor 1242



Aroclor 1254



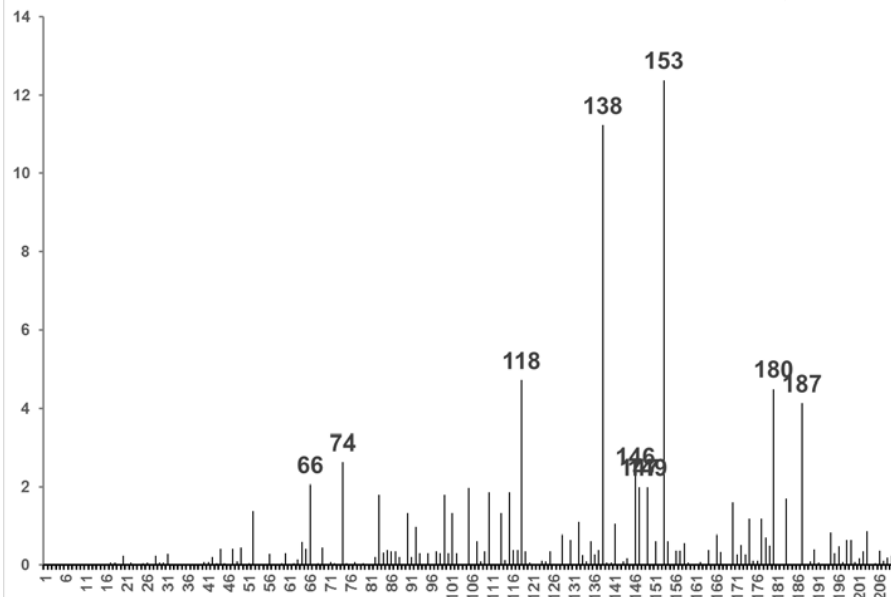
Outdoor Air (Chicago, IL)



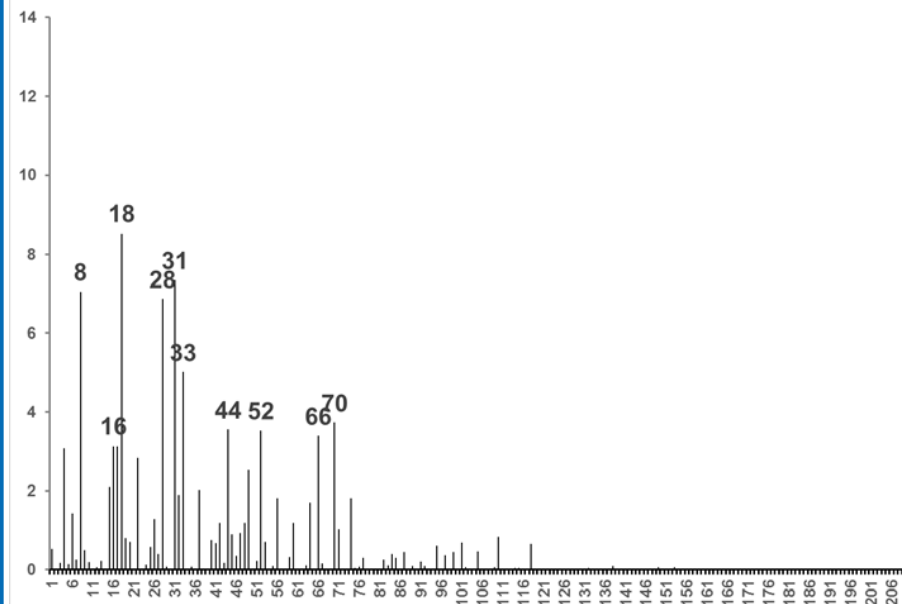
Congener Number (increasing 1 to 209)



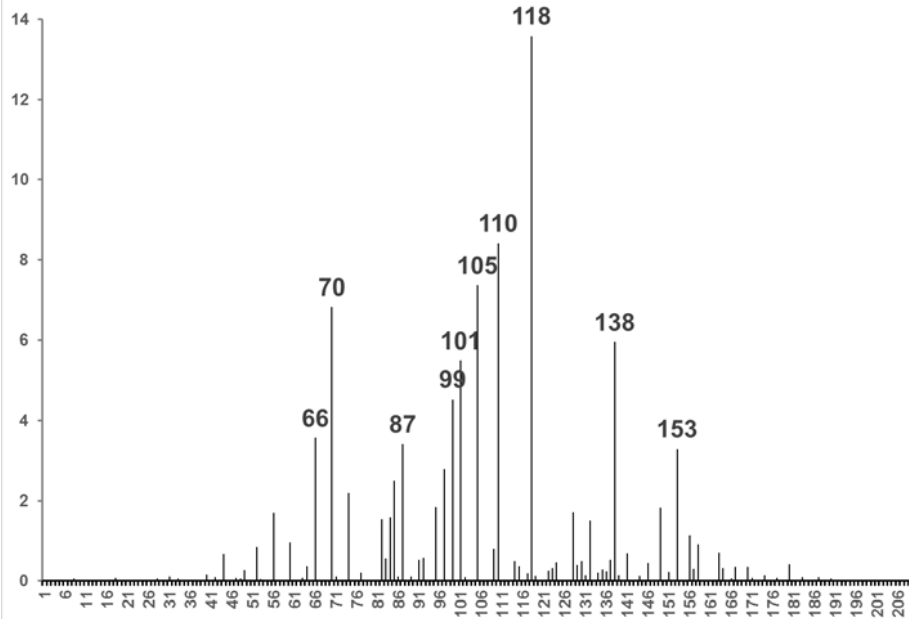
Great Lakes Human Health Fish Tissue Study



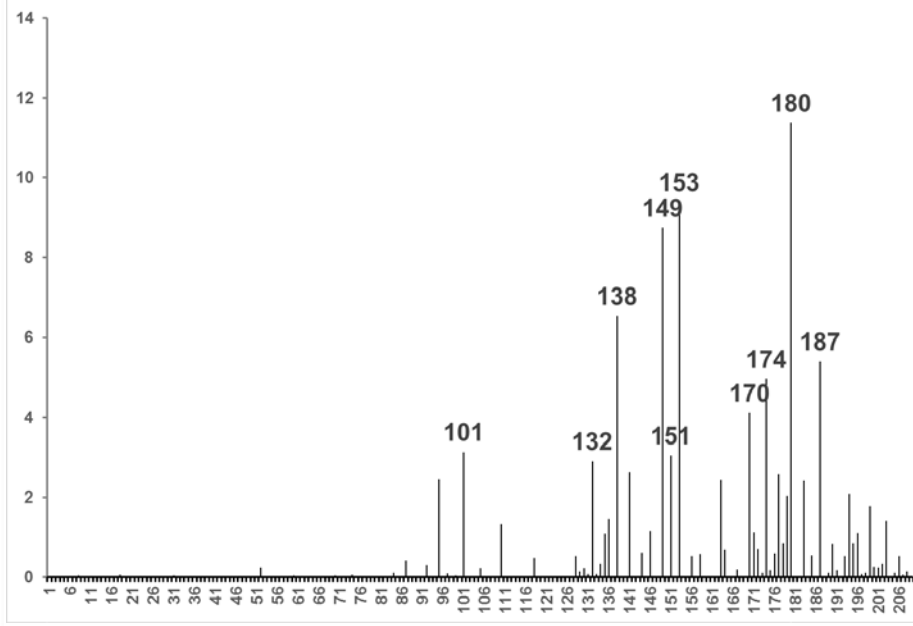
Aroclor 1242



Aroclor 1254



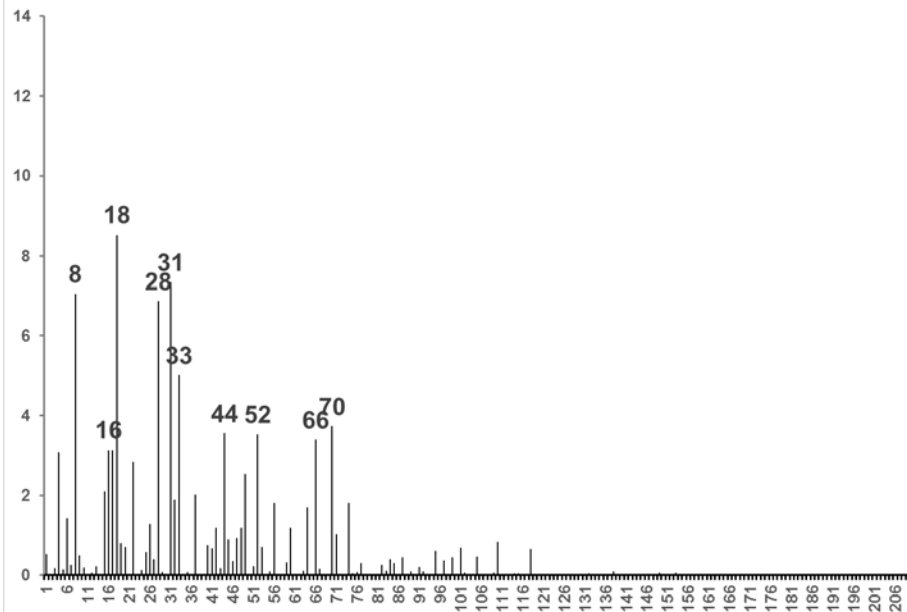
Aroclor 1260



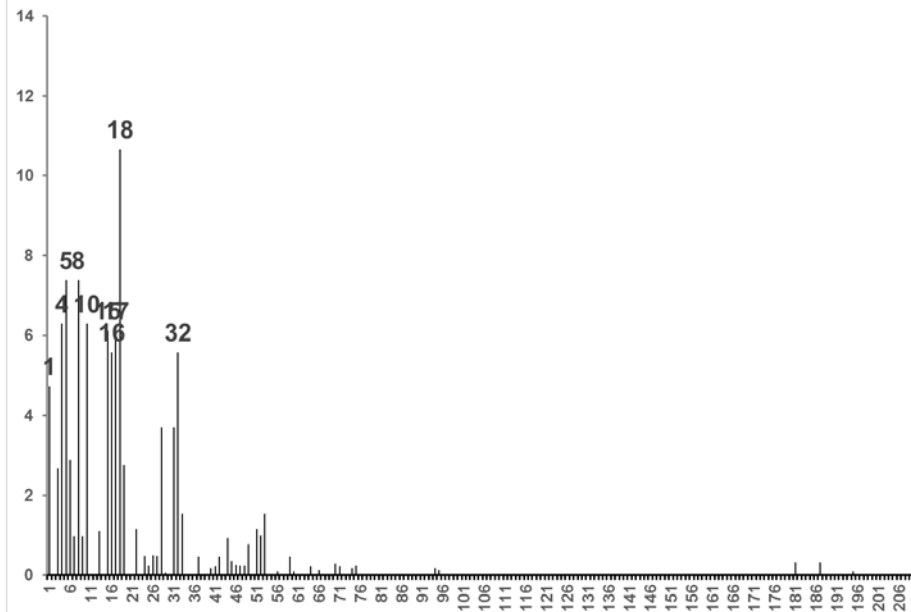
Congener Number (increasing 1 to 209)



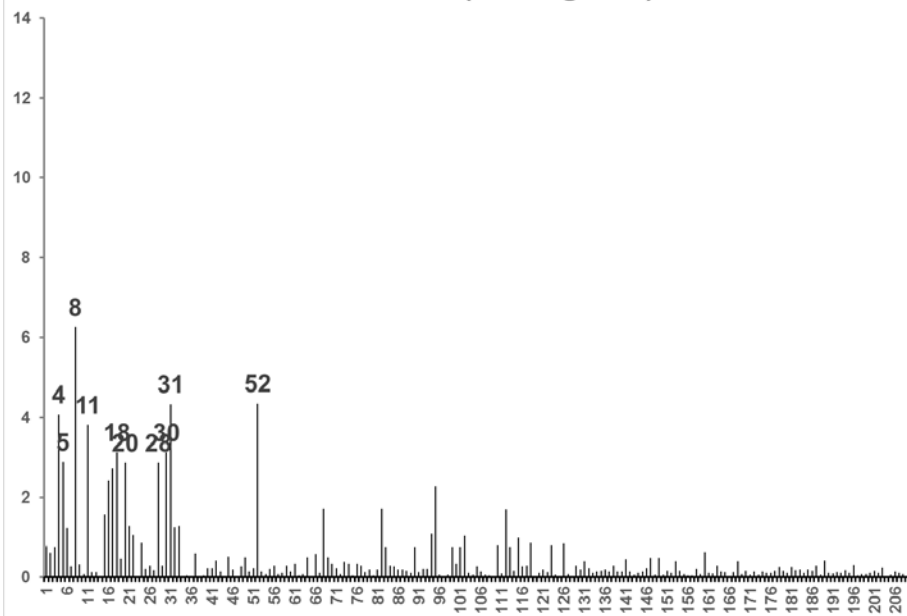
Aroclor 1242



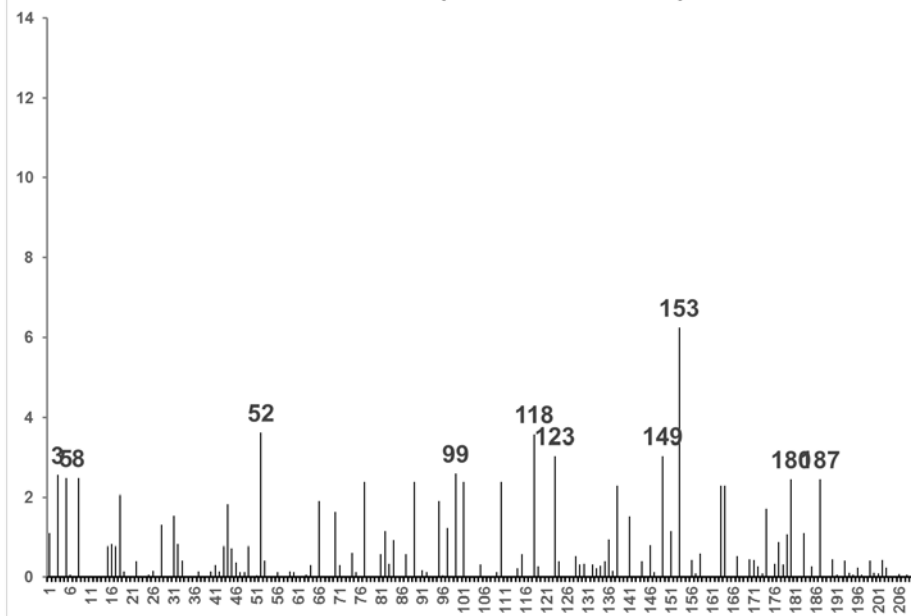
Aroclor 1242 (Vapor)



Outdoor Air (Chicago, IL)



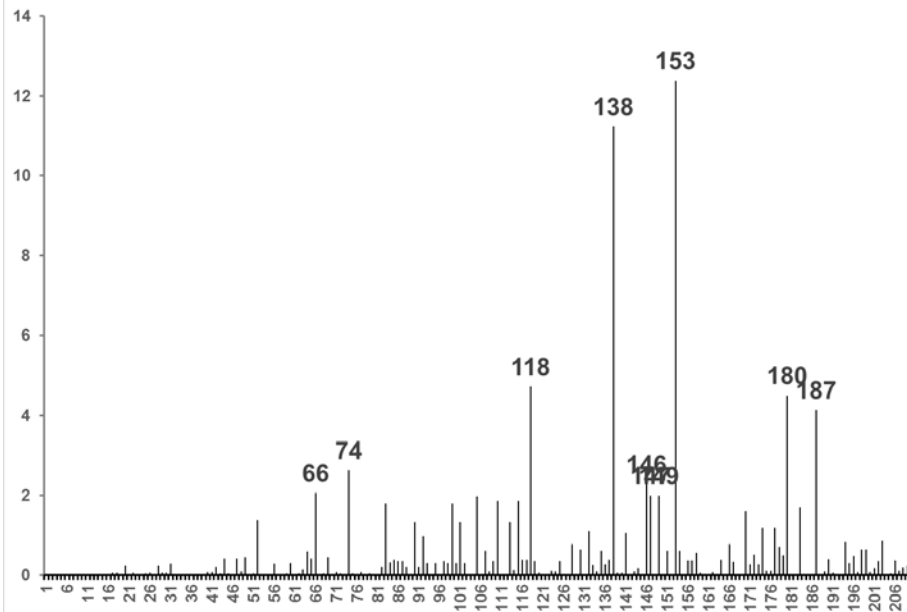
Outdoor Air (Rice Creek, NY)



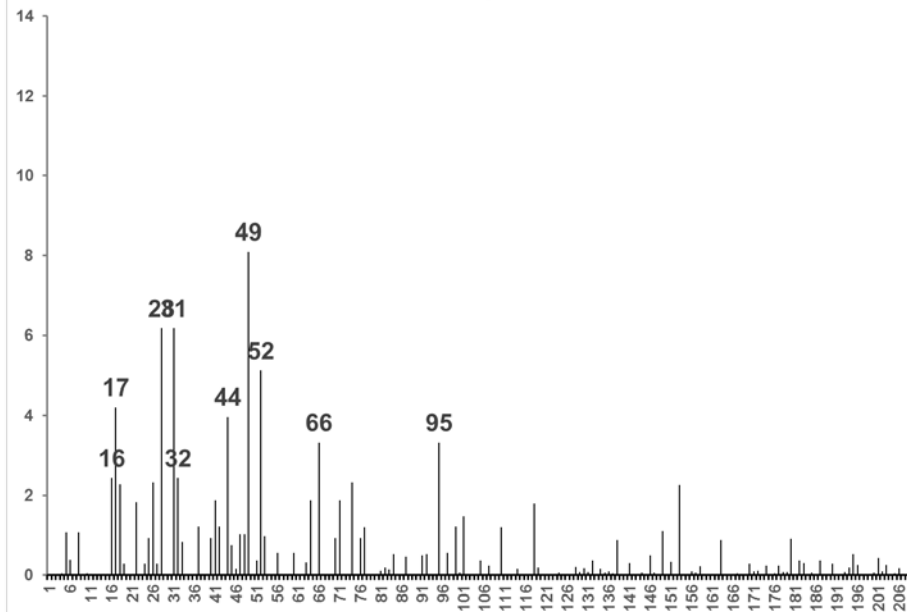
Congener Number (increasing 1 to 209)



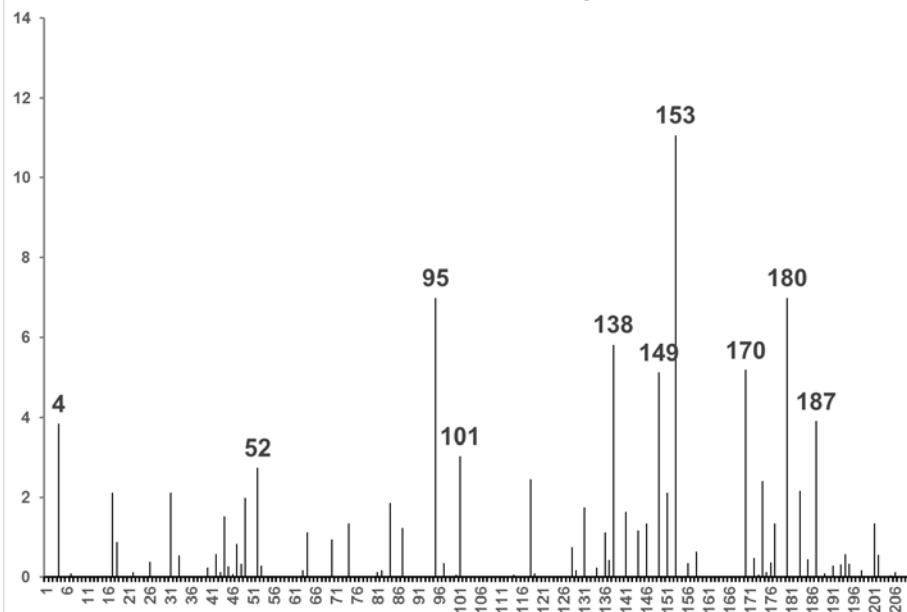
Great Lakes Human Health Fish Tissue Study



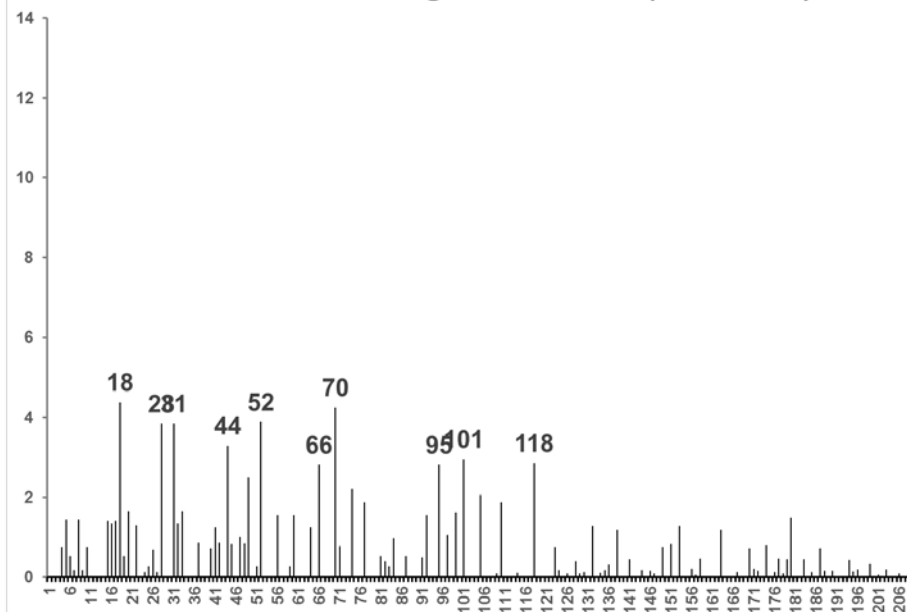
Lake Michigan Carp



Detroit River Carp



Simulated Fish Congener Mixture (Fox River)

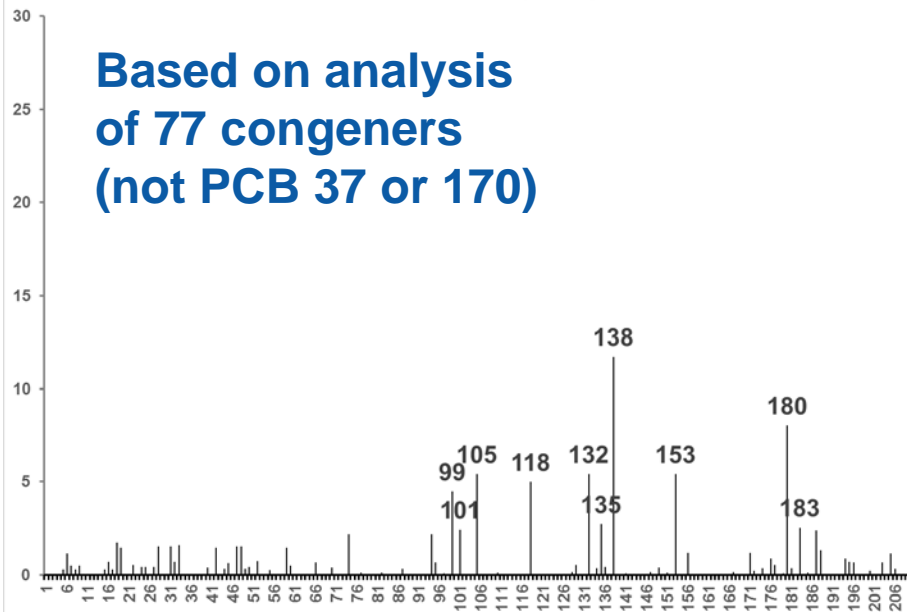


Congener Number (increasing 1 to 209)



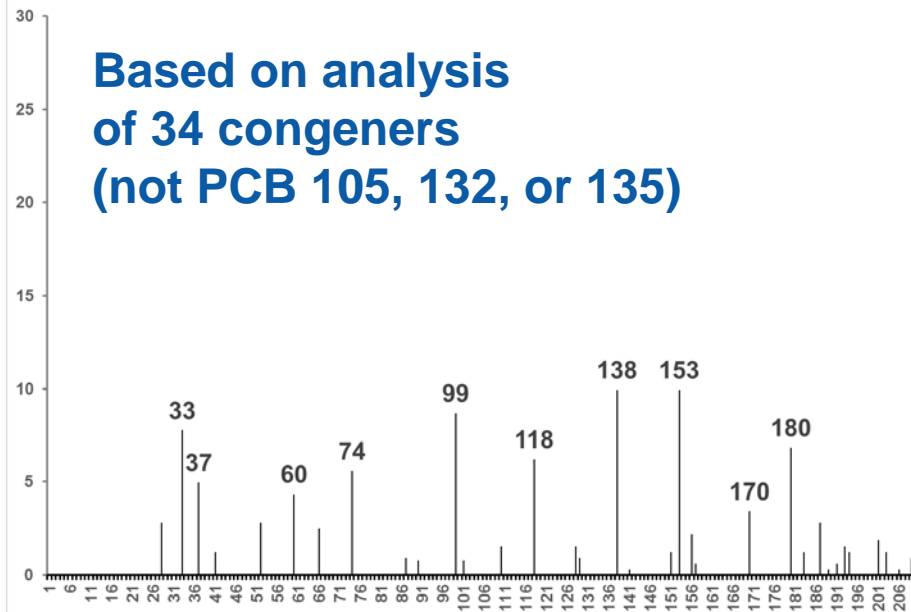
Human Milk (U.S.)

Based on analysis
of 77 congeners
(not PCB 37 or 170)



Human Milk (Canada)

Based on analysis
of 34 congeners
(not PCB 105, 132, or 135)

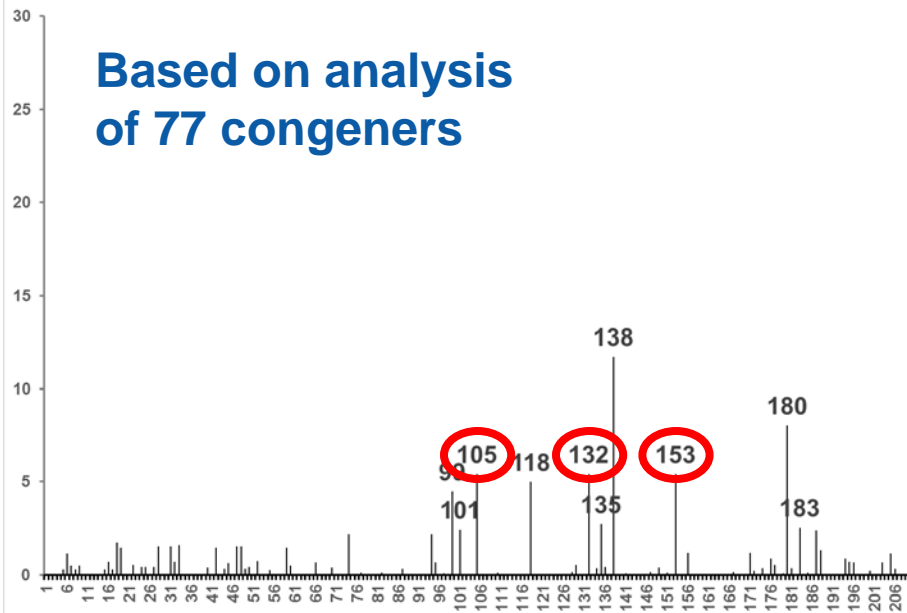


Congener Number (increasing 1 to 209)



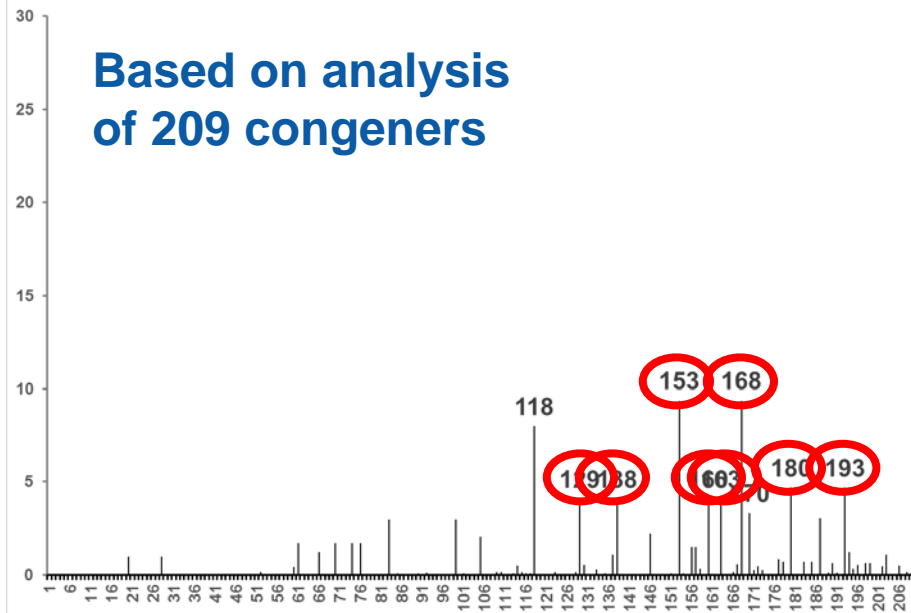
Human Milk (U.S.)

Based on analysis of 77 congeners



Human Milk (U.S.)

Based on analysis of 209 congeners



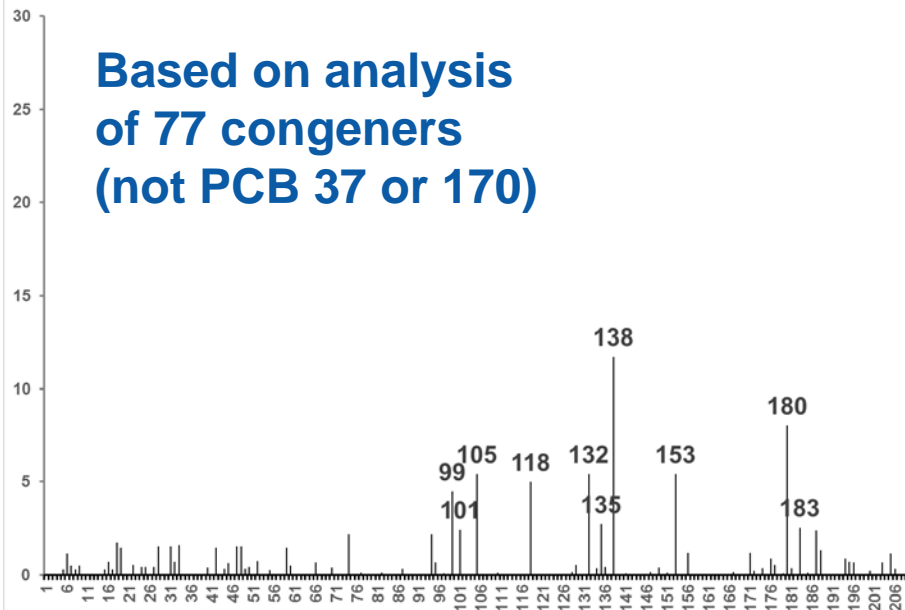
Percentage of Congener Mixture (up to 30%)

Congener Number (increasing 1 to 209)



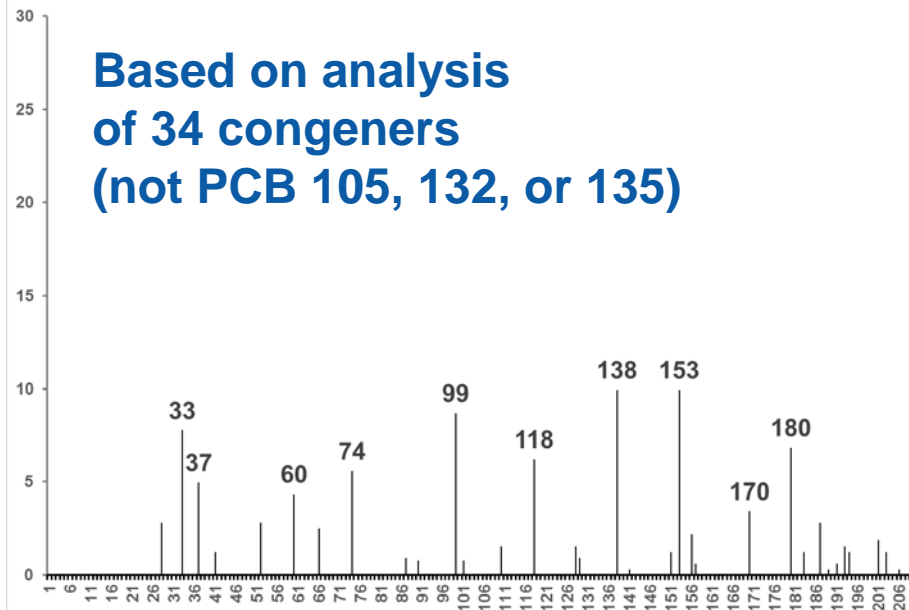
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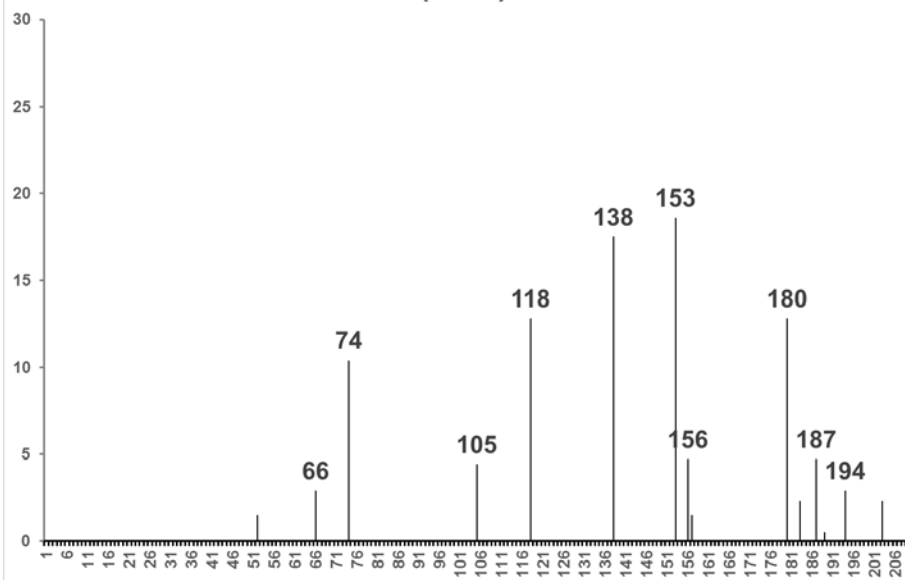


Human Milk (Canada)

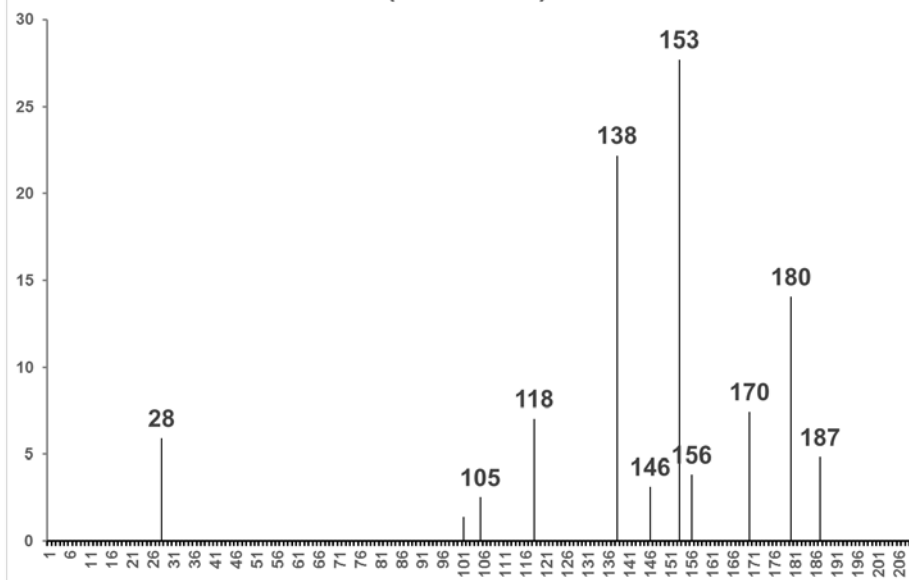
Based on analysis
of 34 congeners
(not PCB 105, 132, or 135)



Simulated Human Milk Congener Mixture
(Rice)



Simulated Human Milk Congener Mixture
(Lilienthal)

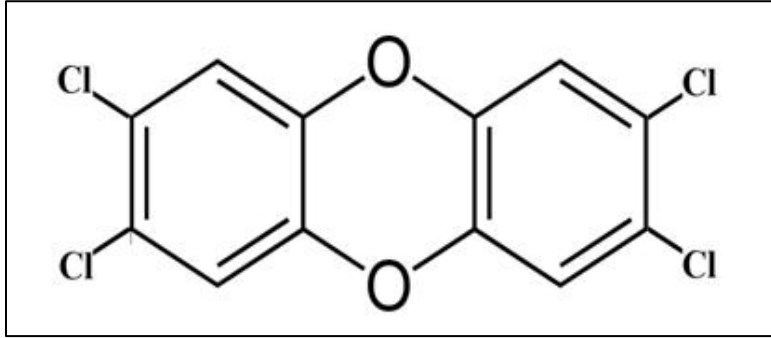


Congener Number (increasing 1 to 209)

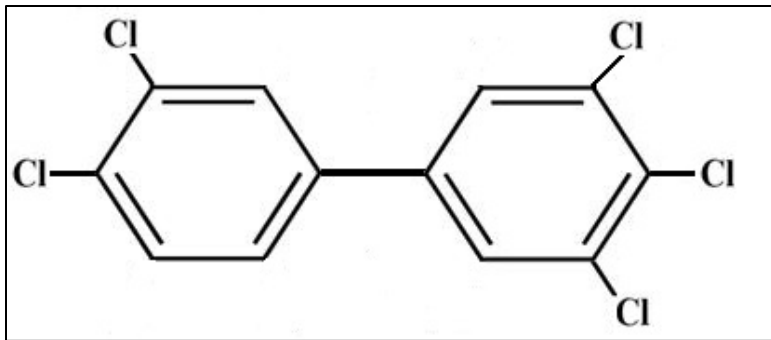
Science Topic 1: Congener Profile and Toxicity

- PCB congener profiles are highly variable across exposure media.
- PCB mixtures used in animal studies often do not contain the same congeners in the same proportions as PCB mixtures found in the environment.
- The relationship between PCB congener profile and non-cancer toxicity is complex.

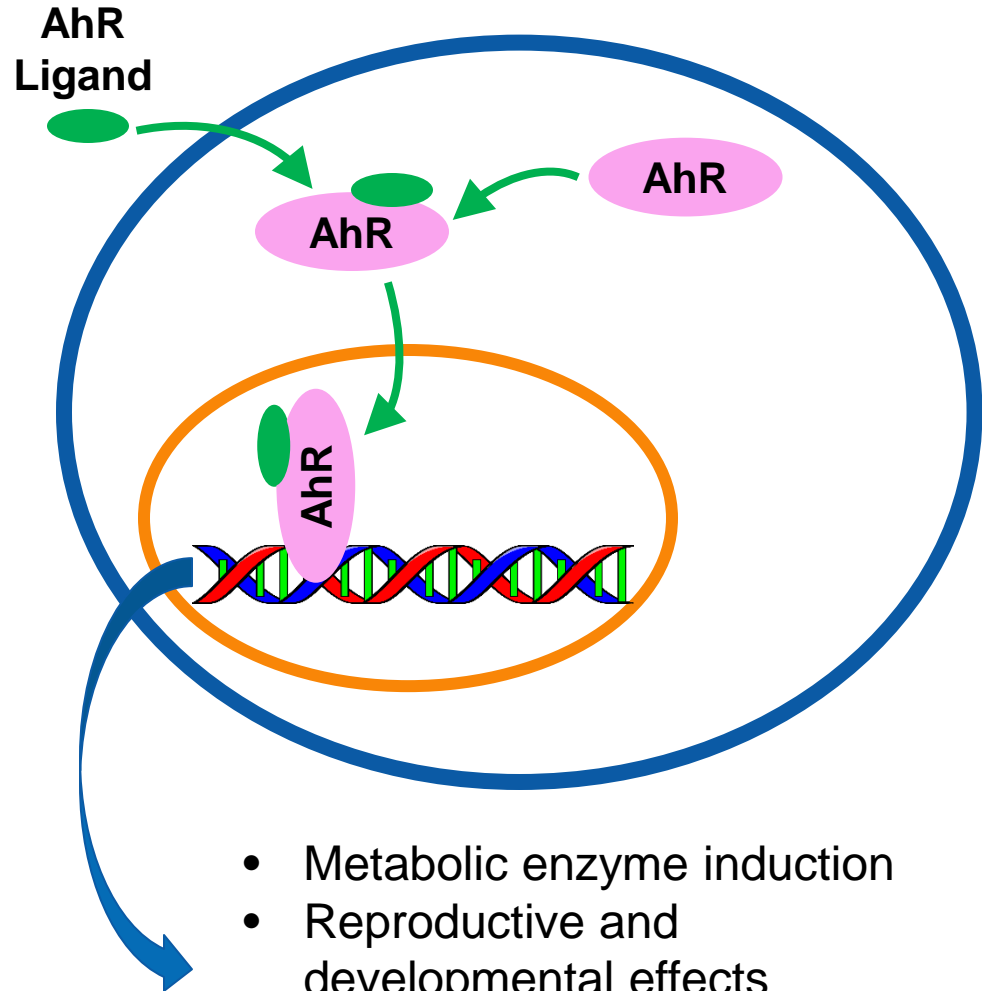
Science Topic 6: MOA



**2,3,7,8 -Tetrachlorodibenzo-p-dioxin
(TCDD, "dioxin")**



PCB 126



- Metabolic enzyme induction
- Reproductive and developmental effects
- Immunotoxicity
- Endocrine disruption

Dioxin-like Compounds	TEF	Dioxin-like Compounds	TEF
TCDD	1		
PCB 77	0.0001	PCB 126	0.1
PCB 81	0.0003	PCB 156	0.00003
PCB 105	0.00003	PCB 157	0.00003
PCB 114	0.00003	PCB 167	0.00003
PCB 118	0.00003	PCB 169	0.03
PCB 123	0.00003	PCB 189	0.00003

TCDD RfD: 7×10^{-10} mg/kg-day

Using TEQ approach:

- PCB 126: 7×10^{-9} mg/kg-day
- PCB 77: 7×10^{-6} mg/kg-day
- PCB 118: 2×10^{-5} mg/kg-day

$$TEQ = \sum_{i=1}^n (C_i \times TEF_i)$$

TEF = toxic equivalency factor; derived using comparisons of potency in *in vitro* and *in vivo* assays

TEQ = toxic equivalence; calculated for a mixture using the concentration of each dioxin-like compound (C_i) and the compound-specific TEFs (TEF_i)

- Some non-cancer health effects of PCBs likely result from a dioxin-like MOA:
 - CYP1A induction
 - Some hepatic effects (e.g., porphyria)
 - Decreased T cell-dependent antibody responses
 - Thyroid hormone disruption via induction of uridine-5-diphosphoglucuronosyltransferase (UDP-GT)
 - Neurodevelopmental and reproductive effects resulting from thyroid hormone disruption

- Other non-cancer health effects may result from non-dioxin-like MOAs:
 - CYP2B1, CYP2B2, and CYP3A induction
 - Decreased T cell-dependent antibody responses
 - Thyroid hormone disruption via decreased binding to transthyretin
 - Neurological effects via reduction of dopamine levels and/or disruption of intracellular Ca^{2+} homeostasis
 - Reproductive effects resulting from estrogenic or anti-estrogenic activity

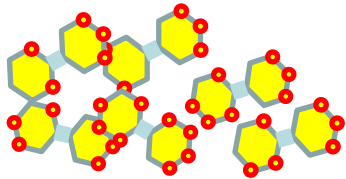
“Neurotoxic Equivalence” (NEQ) scheme

Simon et al. (2007) *Regul Toxicol Pharmacol* 48: 148-170

PCB	NEQ	Results of <i>in vivo</i> tests
95	0.991	Less potent than PCBs 118 (NEQ = 0.293) and 28 (NEQ = 0.298): impairing spatial delayed alternation performance in rats
52	0.699	Less potent than PCBs 138 (NEQ = 0.115), 153 (NEQ = 0.091) and 180 (NEQ = 0.36): decreasing activity levels in rats
47	0.497	Less potent than PCB 77 (NEQ = 0): inducing latency to movement in catalepsy test and latency in passive avoidance task in rats
105 156	0.487 0.363	Less potent than PCBs 28 (NEQ = 0.298) and 126 (NEQ = 0) at altering spontaneous behavior in mice; less potent than PCB 126 (NEQ = 0) at altering Morris water maze performance in mice
28 118	0.298 0.293	Less potent than PCB 126 (NEQ = 0): altering Morris water maze performance in mice
153	0.091	Less potent than PCB 126 (NEQ = 0): altering spontaneous behavior in mice

Science Topic 1: Congener Profile and Toxicity

Higher-chlorinated
PCB congeners



“Dioxin-like” congeners

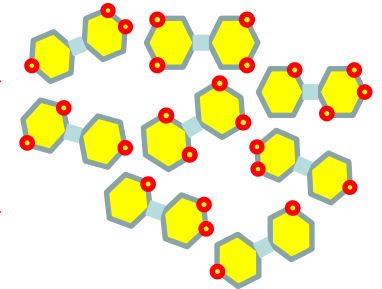
PCB 77	PCB 126
PCB 81	PCB 156
PCB 105	PCB 157
PCB 114	PCB 167
PCB 118	PCB 169
PCB 123	PCB 189

Health effects of
PCB exposure*:

Hepatotoxicity
Thyroid effects

Immunotoxicity
Neurotoxicity

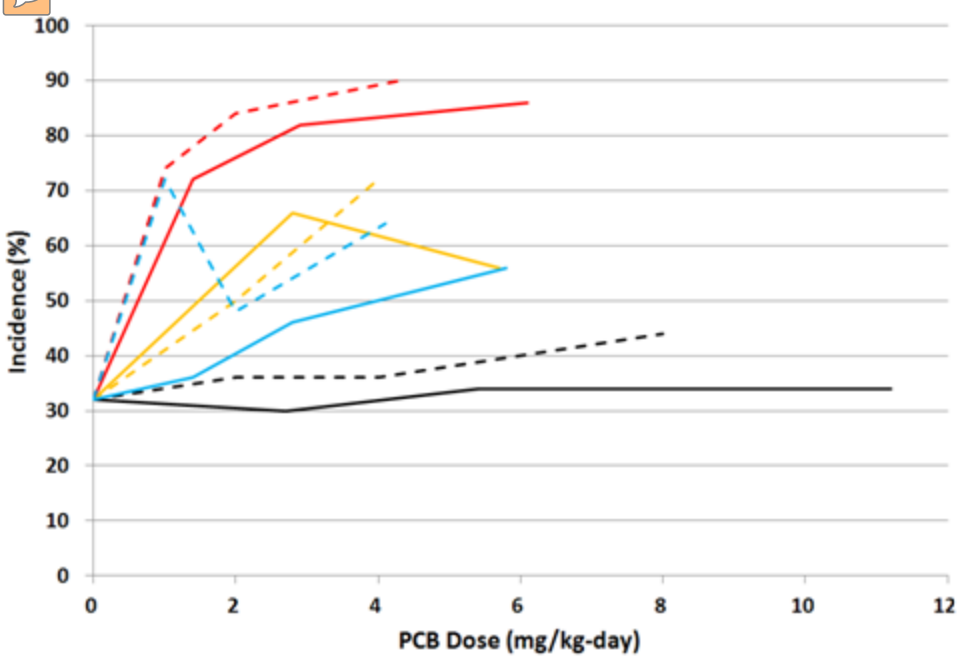
Lower-chlorinated
PCB congeners



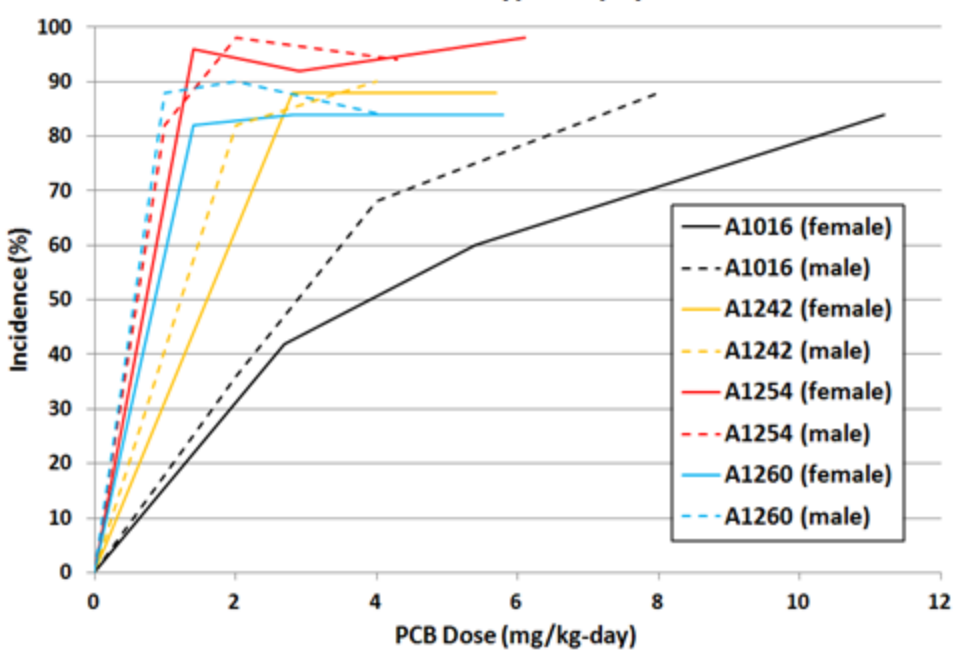
*observed in animal studies



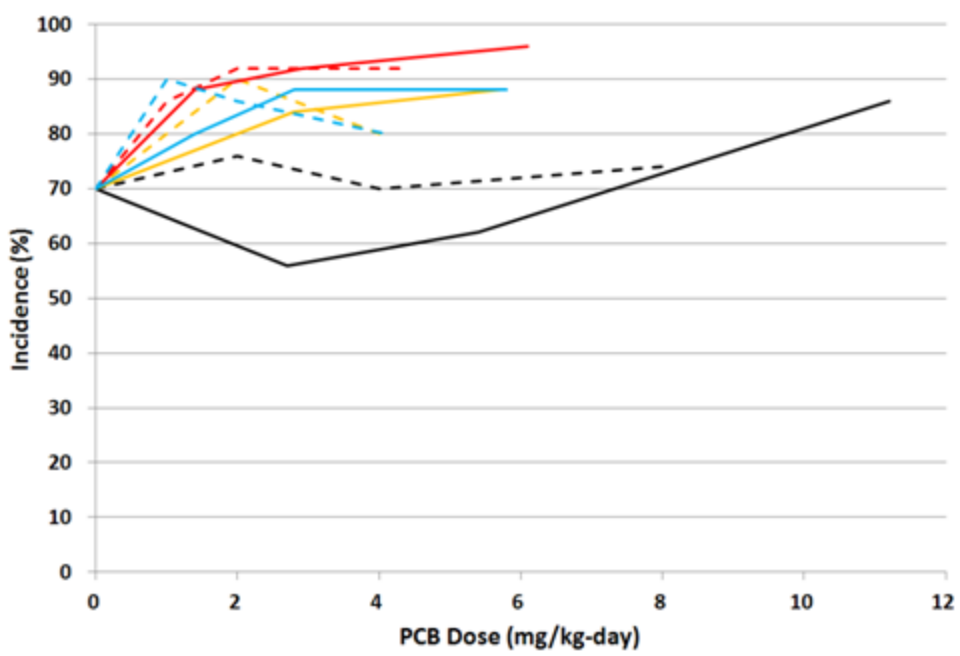
Hepatocytic Vacuolization



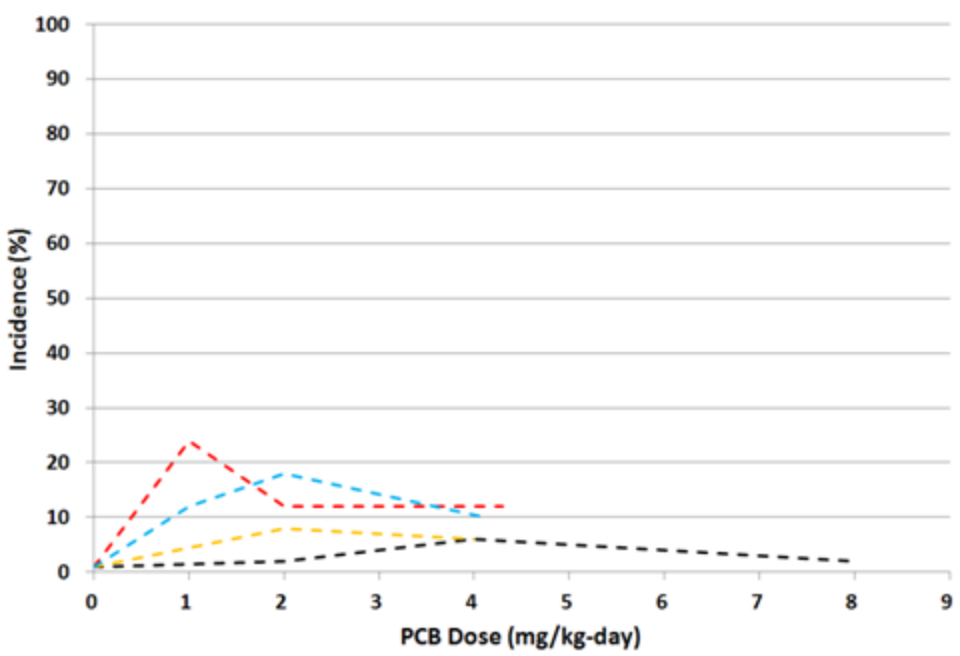
Centrilobular Hypertrophy



Bile Duct Hyperplasia

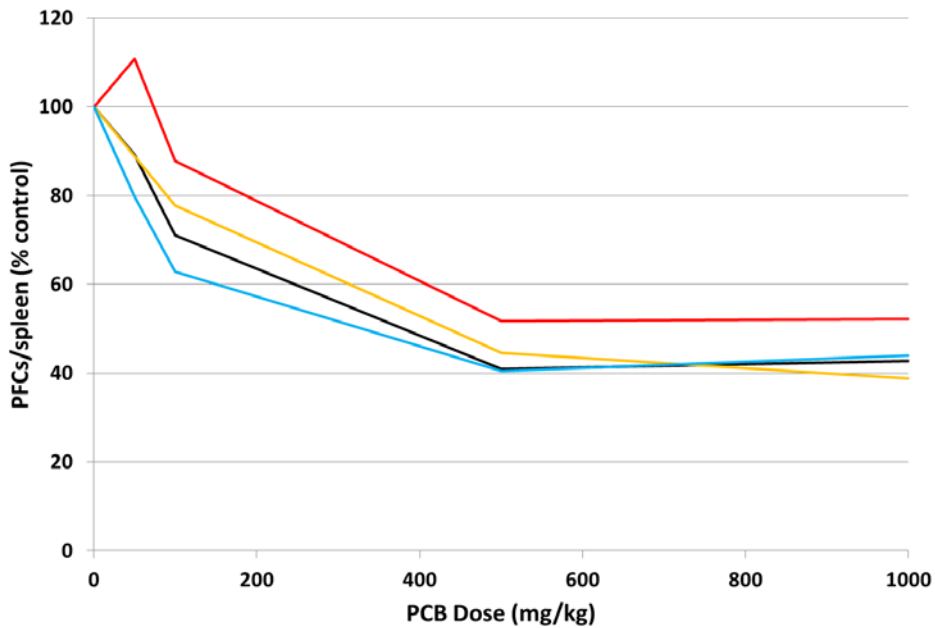


Thyroid Follicular Cell Hyperplasia

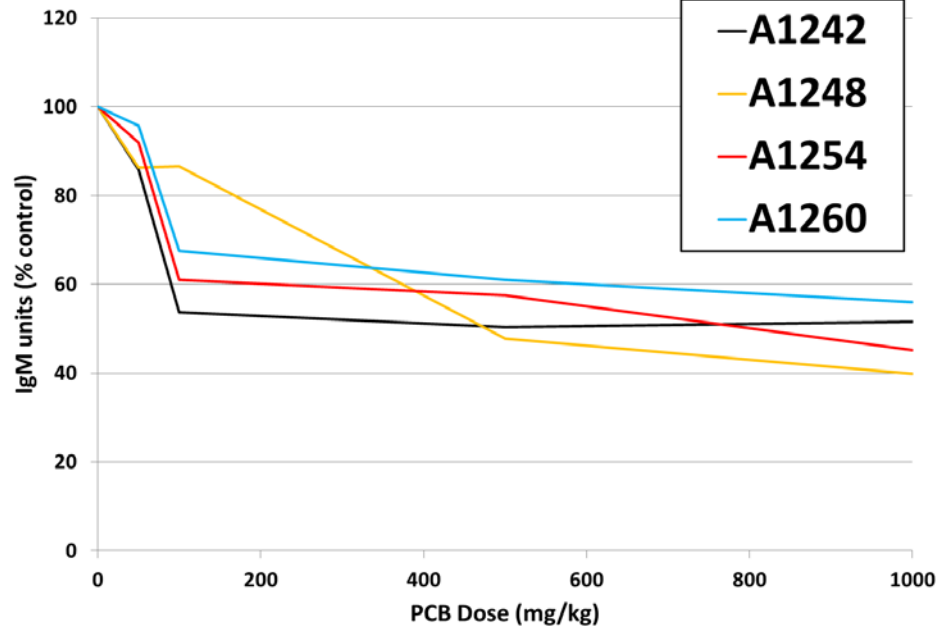




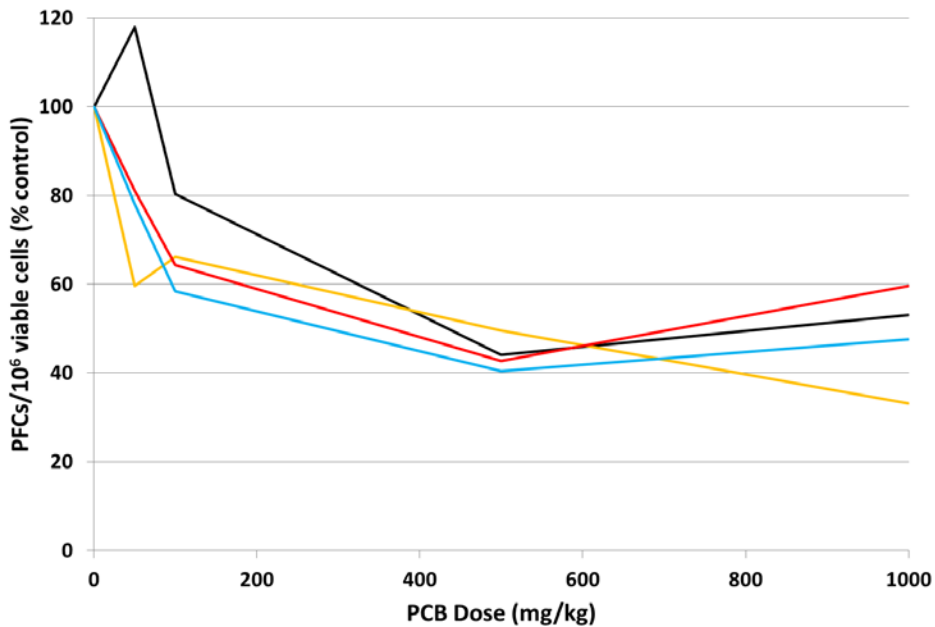
Splenic PFC Response to TNP



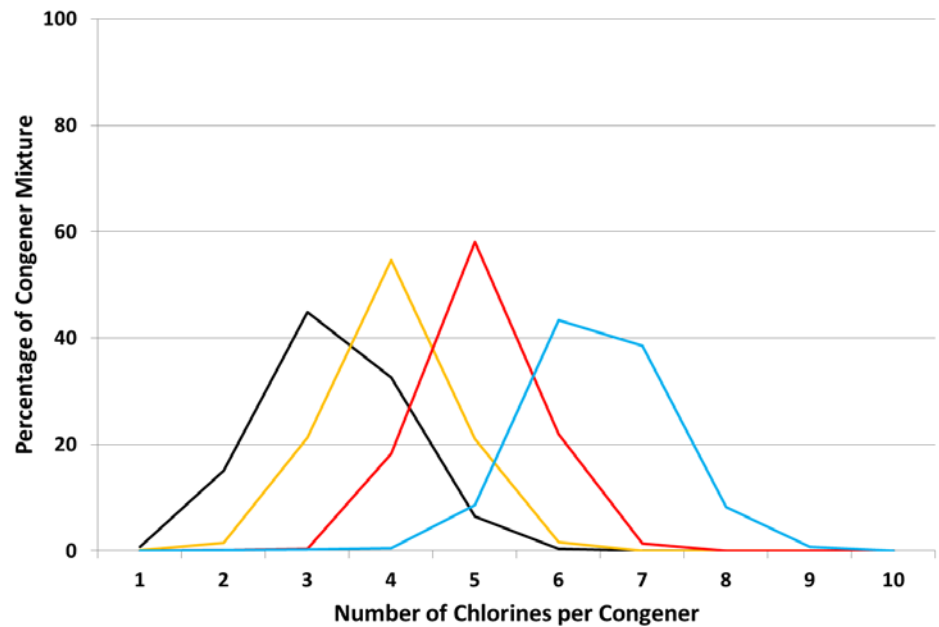
Anti-TNP Antibody Titers



Splenic PFC Response to TNP

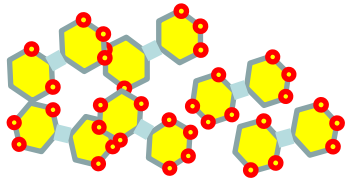


Aroclor Compositions by Homolog



Science Topic 1: Congener Profile and Toxicity

Higher-chlorinated
PCB congeners



“Dioxin-like” congeners

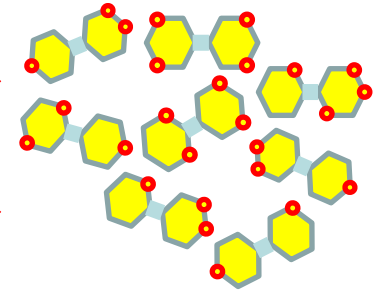
PCB 77	PCB 126
PCB 81	PCB 156
PCB 105	PCB 157
PCB 114	PCB 167
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PCB 123	PCB 189

Health effects of
PCB exposure*:

Hepatotoxicity
Thyroid effects

Immunotoxicity
Neurotoxicity

Lower-chlorinated
PCB congeners



*observed in animal studies

Science Topic 1: Congener Profile and Toxicity

- PCB congener profiles are highly variable across exposure media.
- PCB mixtures used in animal studies often do not contain the same congeners in the same proportions as PCB mixtures found in the environment.
- The relationship between PCB congener profile and non-cancer toxicity is complex.
- *Determine how toxicological data for specific PCB mixtures may best be used to assess risk in the context of human exposure to PCBs in the environment*