

Summary and Implications

5Th PCB Workshop

Iowa City, Iowa

May 18-21, 2008

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Major Change from 2004

- ½ of sessions dealt with environmental sources, fate and transport, transformation
- Decreased emphasis on toxicology – except for developmental neurotoxicity
- Epidemiology focus on Anniston – less discussion on Slovak population
 - Current PCB levels higher in Slovakia
- Less focus on endocrine disrupting effects of PCBs
- Site Visit of University of Iowa Superfund Basic Research Program

Common Findings to 2004

- Chirality as a tracer of biological processes
- Most PCBs ever made are still present in environment
- Microbial remediation still needs work
- Congener information key to sources and mechanisms
- Lighter congeners in air

What am I going to try to do?

- Personal Summation
- Focus on New and Novel Findings
- Identify Data Gaps/Research Needs
- Identify Issues for Future Discussion

- “Our job as scientists to look into the future-
→prevent negative health consequences ”
- Who’s exposed? How much? How often? – want real time measures of personal exposure in order to link exposure with disease
- PCBs are mixtures – need better tools to make RA more dynamic and understandable and appreciated
- 209 congeners with dif PC properties, dif movement, persistence, and accumulation dif biological properties
- Current absence does NOT preclude historic exposures
- Remember old data! It still has utility
- intermittent exposures happen – will only see them if look at episodic congeners-

1. Emissions and transport of PCBs in Natural and Urban Settings

- Soil contamination occurs near buildings with contaminated sealants
- indoor contamination contributes to human exposure
- As dietary contamination decreases, dust may become more important
- Surficial sediments are major source to ambient air
- Higher air conc in summer than winter
- Atmospheric contamination coming from urban areas
- Air data - lots of low chlorinated PCBs (opposite of food patterns)
 - Accumulation may not be as important as exposure

1. Emissions and transport of PCBs in Natural and Urban Settings (con)

- Lower chlorinated PCBs rapidly metabolized and eliminated
- When see something that doesn't fit the pattern – something else is going on
- Hot spots (sources) are highly localized
- Assess internal doses of chemicals
- Lower chlorinated PCBs are higher in 12-19, but go down with age
- Higher chlorinated increase with age, and levels out by 60+
- Patterns vary with age
- PCB levels are decreasing over time

2. Chiral Aspects of PCB Transport, Metabolism and Distribution

- Enzymatic metabolism can favor specific enantiomers
- 19/209 congeners containing chiral centers
- Changes in enantiomeric fractions with seasons
- Chiral techniques can afford unexpected insights into environmental processes
- PCB biodegradation – dechlorination
- Enantiomers mark biological processes

2. Chiral Aspects of PCB Transport, Metabolism and Distribution (con)

- Different biological effects of enantiomers
 - Enantioselective inductive of CYPs
 - Blood brain barrier may be highly enantiomer selective
- Chiral PCBs, all have multiple ortho-chlorine substituents – are they a human health concern?
 - Chiral PCBs are episodic
 - Chiral PCBs have greatest effect on calcium release (RyR)
- What are the human health implications of enantiomeric enrichment of toxic PCB congeners?

3. New Aspects of Environmental Metabolism of PCBs: From Microbes to Plants to Animals

- Anaerobic Dechlorination can go all the way to mass loss
- Aerobic Dechlorination - biostimulate PCB degradation by adding biphenyl which leads to co-metabolism
- identify effective plant species to enhance aerobic PCB degradation
- Exposure to different PCB congeners modifies the structure of the microbial community, resulting in higher numbers of bacteria belonging to phyla involving "PCB degraders"
- Potential for phytoremediation at hot spots

3. New Aspects of Environmental Metabolism of PCBs: From Microbes to Plants to Animals (con)

- People who eat fish and shellfish often have higher BB of PCBs than those who don't – esp., contaminated fish
- Are metabolites passing up the food chain?
- Phase II metabolism – some species differences in glucuronidation and sulfation
- Depending on state of oxidation, some substrates can switch from inhibitor to substrate → what happens under oxidative stress?

4. Reproductive, Developmental and Cardiovascular Effects of PCBs – AHR Mediated

- PCBs-inflammation trigger thru toll-like receptors
 - Inflammatory signals – anti pregnancy
 - IL10 KO mice – model human PCB epi studies ~ Preterm birth, reduced litter size, DNT with A1254
- PCBs inhibit angiogenic processes
- Cardiovascular effects – reported as result of PCBs
 - Only Coplanar PCBs disrupt endothelial barrier function
 - Mechanism? Oxidative stress-→NFkB-→inflammation-→endothelial cell dysfunction
- interaction of dietary fat and PCB77
 - Modulate levels of PCB77-induced NFkB activation
 - PCB77 upregulates genes involved in oxidative stress

4. Reproductive, Developmental and Cardiovascular Effects of PCBs – AHR Mediated (con)

- Direct correlation between DL-PCBs and obesity (Not NDL-PCBs)
 - Obesity promotes inflammation
 - Coplanar PCBs promote inflammation in endothelial cells
 - PCB77 promotes differentiation of adipocytes, hypertrophy and proinflammatory adipokine expression
- Sustained AHR activation-→
 - hypertension and coronary heart disease in humans
 - animals models of atherosclerosis, hypertension, and CVD
 - associated with oxidative stress
 - contribute to hypertension
- Have adverse effects at levels to which people are actually exposed

5. Anniston: The Most Severe US PCB Community Exposure

- Lawsuits divided community
- Anniston is really a "dioxin" exposure
 - Adult levels are elevated ~4X, but much higher relative to DL-PCBs
 - Parallels to Yusho/Yucheng?
- Differences in levels between AA and whites
 - ~3X
- More AA ate locally raised livestock, local fish, clay
- Age is the biggest determinant
- Living in Contaminated Area plays a role
- Middle School Kids levels are not elevated

5. Anniston: The Most Severe US PCB Community Exposure (con)

- Child IQ appears to be related to parent PCB level, not their own
 - Perinatal exposure
 - No way to estimate episodic PCB exposure during critical windows
- Child IQ scores appeared to be affected by lead levels that were below the level that requires treatment
- Parent IQ and working memory related to their PCB level
- 2/3 of people think they have been highly exposed, and 2/3 of them say they've had severe negative health effects from their PCB exposure
- PCB exposure related to risk behaviors
- Diabetes at younger age in association with elevated PCBs
 - more associated with TEQ
- Heart disease reported in higher PCB quartiles – also TEQ?

6. TEFs: New&Novel Approaches; Implications for Risk Assessment

- Mixtures – not just DL+NDL-PCBs
 - PBDEs~NDL-PCBs
- Developmental Neurotoxicity at Low Doses from NDL-PCBs
 - Cognitive and behavioral deficits
 - *in vitro* effects at nM conc
 - Potential mechanisms
 - Thyroid, Estrogen, Dopamine, Calcium, RyR
- Deficits in spatial learning at **low** doses ~ neuronal connectivity ~ dendritic growth ~ Ca^{++} ~RyR
 - Episodic, ortho PCBs – chirality matters
- Reductions in Dopamine via Inhibition of Transport
 - 95>153>DL-PCBs
 - A1016 and A1260 in primates decrease dopamine
- Dioxin-like PCBs Also Alter Behavior and Neurochemical Function

6. TEFs: New&Novel Approaches; Implications Risk Assessment (con)

- Oxidative Stress?
 - 95-→ROS-→Neuronal Cell Death
- Mitochondrial Dysfuncton
- QSARs for ryanodine binding, inhibition of GJIC, dopamine uptake as well as Phys-chem properties
- Steady State level vs. Number of Excursions over a threshold
- PCB "TEFs" based on Neurotoxicity

- Outliers tell you a lot
- “Total” or “Indicator” PCB Measures have utility
 - Screening and Prioritization
- Its not only What you measure, but When
- Why measure specific congeners?
 - Sources?
 - Pathways?
 - Mechanisms?

- It's NOT just AhR, CAR/PXR, RyR, Thyroid, Estrogen, ...
- It's NOT just DNT, adult neurotoxicity, endocrine disruption, reproductive effects, immun dysregulation, skin/teeth/bone/nails, liver, kidney, cardiovascular, diabetes, obesity, cancer
- It's NOT just PCB 3 or 52 or 95 or 77 or 153 or 180 or 126 or...
 - Be careful of Nomenclature
- It's NOT just PCBs!!!
 - Other OCs, PBDEs, PFCs, metals, solvents, pharmaceuticals/PCPs

- Design Targeted Studies to answer key uncertainties for Risk Assessment
- Canadian Approach – make a mixture that resembles actual exposures
- Need Dose/Response Studies
 - Non-Monotonic Responses are Real
- Need comparisons of “Body Burden” between animals and humans

- Do Lower Chlorinated PCBs have Effects at Relevant Doses?
- Are Metabolites Causing Effects?
- Don't Use PCB77 (or PCB66) if you're doing mechanistic studies
- Take off your own Research Blinders
 - Its not just one Health Effect
- If Risk Assessment is based on TEQ, will it be Protective of All PCB Effects?

HEALTH RISK ASSESSMENT

