The Fifth PCB Workshop
New Knowledge Gained from Old Pollutants

Book of Abstracts

Iowa City, Iowa
May 18-22, 2008

Editor: Larry W. Robertson

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Sunday, May 18th

18:30 Evening Welcoming Reception with Guest Lectures

19:30 – 19:40 **Thomas R. Sharpe** (Associate Vice President for Economic Development) Special Welcome to the Participants

19:40 – 19:45 **Larry Robertson** (University of Iowa) Thanks to the Supporters & Sponsors

19:45 – 20:15 **William Suk** (NIEHS) Strategies for Addressing Environmental Health Needs and Disease Outcomes

20:15 – 20:25 **Rich Seegal** (University of Albany) Introduction of the Honorary Lecturer

20:25 – 20:55 **Larry Hansen** (University of Illinois) Honorary Lecture: Forty Years of PCBs—More or Lessons?

STRATEGIES FOR ADDRESSING ENVIRONMENTAL HEALTH NEEDS AND DISEASE OUTCOMES

William A. Suk, Ph.D., M.P.H.

Acting Deputy Director, National Institute of Environmental Health Sciences

The prevalence of common diseases is increasing. Led by cardiovascular disease and followed by cancer, chronic lung diseases, and diabetes mellitus, major diseases confronting us today are chronic and disabling conditions, complex and multifactorial in nature. Detailed knowledge of the etiology of these diseases has spurred many mechanistic studies to understand their pathogenesis, and this knowledge is beginning to be translated to preventive interventions in high-risk populations. It is becoming increasingly clear that environmental factors play a huge role in common disease susceptibility. Associations between environmental factors and health outcomes are, however, complex and poorly differentiated. Levels of exposure, for example, are often difficult to ascertain, owing to a lack of detailed biomonitoring as well as to inevitable variations within any population. The advent and maturation of high-throughput techniques has steadily shifted the biomedical sciences to a more comprehensive global approach focused on understanding the diverse and complex responses underlying the development of disease. Coupled with increases in computational power and sophisticated informatics tools for data integration and modeling, researchers have developed quantitative models to support predictive toxicity assessment, helped to determine the uncertainty of risk, and improved our understanding of biological processes. The long-range goal is rational prevention of environmentally induced diseases. This goal is fundamental: to translate the discoveries into interventions that improve health and prevent disease by the conversion of research findings into information, resources, and/or tools used by public health and medical professionals and by the public to improve overall health and well-being, especially in vulnerable populations.

FORTY YEARS OF PCBS–MORE OR LESSONS?

Larry G. Hansen

Prof. Emeritus, University of Illinois at Urbana-Champaign

There was a time (46-50 years ago) when there was much concern about PCBs but barely any literature available to the public. Interested scientists and regulators began the "PCB Newsletter" to quickly share new information. By the 1980s and 90s, the PCB literature became overwhelming and some important misconceptions developed. The most troublesome, exclusive of health effects, regarded PCB mixture composition, disposition, exposure sources and the extent of human as well as environmental burdens. We now have a much better understanding because of landmark work made possible by advances in analytical and synthetic chemistry. No less important was the next step of developing methods to digest and interpret the wealth of information present in more complete analytical profiles.

Health effects were also somewhat vague and confusing. Hepatic and dermatological effects had been known since the 1930s and 40s. Endocrine effects such as estrogenicity and thyroid hormone disruption were demonstrated by the early 1970s. The greatest effort was focused on enzyme (especially cytochrome P-450) effects since these were easily measured, always yielded "results" and were linked to types of congener toxicities and endogenous substrate perturbations. Effects on neuro-development were clearly demonstrated, but strongly resisted for 2 decades. The earlier critical discovery and development of the AhR concepts provided a unifying mechanism to describe the toxicities of some of the most potent (but less abundant) PCB congeners. We now have other unifying, congener-specific mechanisms which also disrupt very basic and far-reaching endogenous processes. All of this helps to explain why there is no single specific syndrome that can be linked to PCB exposures–not just because there are so many similar but unique-acting congeners present, but because each congener may disrupt several very basic functions.

I had nothing to do with the planning of this PCB Workshop, but it appears to have remained faithful to our initial goals of updating and correcting with simultaneous inputs from all the critical disciplines. Although becoming ever more complex, we should emerge from this PCB Workshop with a better understanding of PCB health effects.

Monday, May 19th

Session 1
Emissions and transport of PCBs in Natural and Urban systems

Session Chairs Keri Hornbuckle (University Iowa) and Stuart Harrad (University Birmingham)

8:30 – 9:00 **Bob Herrick** (Harvard University) PCB Exposures from Building Materials

9:00 – 9:30 **Stuart Harrad** (University of Birmingham) Household dust ingestion as a pathway of human exposure to PCBs in Canada and the UK

9:30 – 10:00 **Keri Hornbuckle** (University of Iowa) Spatial Distribution and Sources of Atmospheric PCBs in the Chicago Urban Industrial Region

10:00 – 10:30 COFFEE BREAK & POSTER VIEWING

10:30 – 11:00 **Karin Norström** (Stockholm University) Do PCB congener profiles differ in humans depending on the route of exposure? - A model assessment using ACC-HUMAN

11:00 – 11:30 **Lisa Rodenburg** (Rutgers University) Investigating Atmospheric PCB Source Types, Locations, and Magnitudes in Urban Areas of New Jersey

11:30 – 12:00 **Don Patterson** (CDC) A U.S. National Reference Range for PCB congeners and Total PCBs from the NHANES 2003-2004 Survey

12:00 – 14:00 LUNCH & POSTER VIEWING

PCB EXPOSURES FROM BUILDING MATERIALS

Robert F Herrick, Russ Hauser, Larisa Altshul (Harvard School of Public Health), John D Meeker (University of Michigan School of Public Health), George A Weymouth (International Union of Bricklayers and Allied Craft Workers, Local 3, Retired), Daniel J Lefkowitz (Pcbinschools.org, Yorktown, NY)

Background: The presence of PCB in caulking (sealant) material found in masonry buildings has been well-documented in several countries. Elevated PCB levels have been found in soil around buildings from which caulking has been removed, but natural weathering and deterioration of the caulking may have also been a source. The workers removing caulking material have been shown to have elevated serum PCB levels.

Methods: We measured PCB levels in soil surrounding buildings where undisturbed PCB-containing caulk was still in place, and evaluated the mobility of the PCB from caulking by the Toxicity Characteristic Leaching Procedure (EPA Method 1311). We also compared serum PCB levels among workers removing PCB-containing caulking material from buildings with reference serum PCB levels from 358 men living in the same area. Soil and serum PCB levels were measured in the same laboratory by liquid-liquid extraction, column chromatography clean-up and dual capillary column GC/microECD analysis.

Results: We found soil PCB contamination ranging from 3.3 to 34 mg/kg around buildings containing undisturbed caulking with PCB contents ranging from 10,000 to 36,200 mg/kg. The results of the Toxicity Characteristic Leaching Procedure (leachate concentrations 76-288 mg PCB/L) suggest that PCB in caulking can be mobilized, apparently as complexes with dissolved organic matter that also leached off the caulking material.

Among construction workers removing this caulk, the serum congener profiles were very different compared to the referents. Serum levels of the more volatile, lighter PCBs (di-, tri-and tetrachloro, sum of IUPAC# 6-74) were substantially higher among the construction workers. One of the youngest workers had the lowest total serum PCB levels (sum of 57 congeners), but the contribution of more volatile (less chlorinated) PCB congeners (#16, 26, 28, 33, 74, 66, and 60) was markedly higher than in the other 5 workers, and the reference men. Only this worker was working on a job that involved removing PCB caulking at the time of the blood sampling.

Conclusion PCB-containing caulk in these buildings is deteriorating, and releasing PCB into the environment. A likely cause of the soil contamination found around these PCB-containing buildings is natural weathering. Serum PCB levels among construction workers removing deteriorated PCB caulk exceed age-matched referents. Comparison of the serum congener profiles suggests that there are substantial differences between the construction workers and the general population samples. Occupational contact with caulking material can be a major source of PCB exposure for construction workers.

Keywords:
caulk, environmental exposure, leachability, PCB, soil, congener profile

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HOUSEHOLD DUST INGESTION AS A PATHWAY OF HUMAN EXPOSURE TO PCBS IN CANADA AND THE UK

Stuart Harrad, School of Geography, Earth, and Environmental Sciences, University of Birmingham, Birmingham, UK, Miriam Diamond, Lisa Melymuk, and Matt Robson, Department of Geography, University of Toronto, Canada; Catalina Ibarra, School of Geography, Earth, and Environmental Sciences, University of Birmingham, Birmingham, UK

Recently, much attention has focused on the significance of ingestion of household dust as a pathway of human exposure to brominated flame retardants. Given recent evidence of the continuing substantial contamination of indoor atmospheres with PCBs, this study examines the extent to which this pathway contributes to human exposure to PCBs in both Canada and the UK. Concentrations of tri- through heptachlorinated PCBs (sum PCBs) were measured in samples of household dust taken in 2006 from Toronto, Canada (n=10) and Birmingham, UK (n=20). Average and median concentrations were respectively 110 and 48 ng/g (UK), and 290 and 260 ng/g (Canada). A t-test of this limited dataset revealed significantly higher ($p<0.05$) concentrations in the Canadian homes studied. These data are used to derive a range of dust ingestion exposure scenarios for both toddlers and adults, which are compared with Canadian and British government dietary exposure estimates. In summary, while for many individuals, diet is considerably more important than dust ingestion, toddlers ingesting 200 mg/d of dust contaminated at the 95th percentile concentration, are exposed to 144 ng/d (Canada) and 54 ng/d (UK). This constitutes 66% (Canada) and 23% (UK) of the sum of dust and dietary exposure. More detailed study of this issue appears warranted.

Keywords:
Indoor contamination

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SPATIAL DISTRIBUTION AND SOURCES OF ATMOSPHERIC PCBS IN THE CHICAGO URBAN INDUSTRIAL REGION

Keri Hornbuckle1, Dingfei Hu[1], Andres Martinez[1], Dean Macken[2,] Kai Wang[3], Carolyn Persoon[1], Victoria Persky[4], Araceli Urquizo[4], and Craig Just[1].
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Polychlorinated biphenyls (PCBs) are semivolatile and are commonly measured in air throughout the globe. Unfortunately, atmospheric sources of PCBs are almost completely undefined. The extent of our understanding about atmospheric PCB sources is that they are larger in cities and they are dominated by volatilization sources. PCB concentrations are high in cities because they were used there. Cities in the North American Great Lakes basin have a long history of PCB use in many industries such as steel mills, aluminum processing, paper mills, electrical generation and distribution, packing plants, breweries, tanneries, machine shops, and foundries. PCBs are still easily measured in all environmental compartments and still ranked as one of the most important environmental problems by United Nations Environmental Programme, the International Joint Commission, the U.S. Environmental Protection Agency and the U.S. Agency for Toxic Substances and Disease Registry. Unfortunately, there is little information about the distribution of PCB sources within cities. The problem is that the nature of their emission mechanism – volatilization after historical contamination of surfaces- make makes it difficult to identify their location. We have begun a four year effort to measure airborne PCBs across the Chicago metropolitan area. The study uses a two-pronged approach for sampling. First, concentrations of airborne PCBs will be measured using mobile high volume air samples that are mounted on two asthma clinic vans. The vans are operated by Mobile CARE Foundation of Chicago and serve more than 40 schools in Chicago, with each school visited every three months. Second, concentrations of airborne PCBs will be measured using passive samplers (PAS-PUF design of Harner and coworkers) deployed at the same schools and also in East Chicago, Indiana – a heavily industrialized community on the south shore of Lake Michigan. The design and deployment of both sampler, as well as the congener-specific analysis by GC/MS/MS will be discussed and preliminary results presented.

Keywords:
Urban Air, PCB sources, mass spectrometry

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DO PCB CONGENER PROFILES DIFFER IN HUMANS DEPENDING ON THE ROUTE OF EXPOSURE? - A MODEL ASSESSMENT USING ACC-HUMAN

Karin Norström, Dept. of Applied Environmental Science (ITM), Stockholm University, Stockholm, Sweden, Gertje Czub and Michael S. McLachlan (Dept. of Applied Environmental Science (ITM), Stockholm University), Peter S. Thorne (Dept of Occupational and Environmental Health, University of Iowa), Keri C. Hornbuckle (department of Civil and Environmental Engineering, University of Iowa)

Diet is the major route of human background exposure to PCBs. The exposure is dominated by a selected number of persistent congeners, since many of the PCB congeners are metabolized in organisms in the human food web. However, in environments highly contaminated with PCBs, such as in the vicinity of contaminated sites or in buildings in which PCBs have been used, exposure via air may be comparable to or exceed the background exposure from food. This might be particularly true for congeners that are more volatile and those that are subject to considerable metabolism in the human food web. The objective of this study was to examine the hypothesis that inhalation exposure can increase the PCB concentrations and change the PCB congener pattern in human tissue.

For this study, the fugacity based non steady state bioaccumulation model ACC-HUMAN (1) was applied and parameterized to predict the body burden in a person living in the Midwest United States that eats a typical North American diet. Dietary exposure was estimated using measured data for 40 PCB congeners in different food groups (fish, meat, dairy products (2). Two scenarios for inhalation exposure were evaluated: one using ambient air concentrations measured in East Chicago, and a second using measurements in a rural area in Iowa. The metabolic rates and partitioning properties required for the model were taken from the literature (3-6). A time trend based on a global inventory of PCB emissions estimates from North America (7) and from PCB concentrations in herring gull eggs from the Great Lakes were used to generate historical exposure data for the food and air concentrations.
The model will be used within the Iowa superfund basic research program to evaluate the PCB profiles in the blood of mothers and children living in East Chicago and rural Iowa.

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Keywords:
PCB, exposure, air, model

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INVESTIGATING ATMOSPHERIC PCB SOURCE TYPES, LOCATIONS, AND MAGNITUDES IN URBAN AREAS OF NEW JERSEY

Lisa A. Rodenburg, Department of Environmental Sciences, Rutgers, the State University of New Jersey, New Brunswick, NJ, USA

New Jersey (NJ) is the most densely populated of the United States. Polychlorinated biphenyls (PCBs) are a significant concern in NJ due to their widespread use in urban areas in closed applications such as transformers and capacitors, as well as open applications such as paint and joint compounds. Two of the state's major waterways, the Delaware River and the New York/New Jersey Harbor, are on the 303(d) list for PCB contamination, resulting in fish consumption advisories. PCB concentrations in both systems exceed water quality standards by 2 to 4 orders of magnitude. In addition to the widespread use of Aroclors, inadvertent production of PCBs in current manufacturing processes has led to widespread contamination in both of these systems. This research has taken a holistic approach to investigating the location, type, and intensity of atmospheric PCB sources in the area by combining monitoring, mass balance approaches, source apportionment, statistical data analysis, trackdown studies, and examination of intermedia transfer, with focus on air/water and air/land interactions of PCBs. Atmospheric deposition of PCBs to these systems has been evaluated via the New Jersey Atmospheric Deposition Network (NJADN) which includes monitoring sites in urban, suburban, and rural areas. The NJADN data has been used to investigate atmospheric PCB source types and locations by the application of Positive Matrix Factorization (PMF) and the Potential Source Contribution Function (PSCF). Similarly, source types and locations have been investigated by passive air sampling throughout Philadelphia/Camden, and analysis of the results via PMF. Source intensities have been investigated using the Regional Atmospheric Model System (RAMS) combined with the Hybrid Particle And Concentration Transport (HYPACT) model. These investigations suggest that several types of PCB sources exist in urban areas, with different types of sources located in different areas. For example, industrial vs. population-driven sources have different source signatures and locations. The atmospheric modeling suggests that an urban area such as New York City emits at least 300 kg of PCBs to the regional atmosphere each year.

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A U.S. NATIONAL REFERENCE RANGE FOR PCB CONGENERS, TOTAL PCBS, AND TOTAL TEQ FROM THE NHANES 2003-2004 SURVEY

Donald G. Patterson Jr., Centers for Disease Control and Prevention, Atlanta, GA, USA, Lee-Yang Wong (CDC), Wayman E. Turner (CDC), Samuel Caudill (CDC), Larry L. Needham(CDC)

We have determined human serum reference ranges by age, sex, and race/ethnicity from a statistically representative sampling of the U.S. population during 2003 and 2004 for many chemicals that are part of the Stockholm Convention on Persistent Organic Pollutants and the Geneva Convention on Long-range Transboundary Air Pollution. The serum samples were collected as part of the National Health and Nutrition Examination Survey (NHANES) 2003/2004, which is administered by the CDC's National Center for Health Statistics. In this presentation, we will concentrate on three groups of these chemicals. The PCDDs and PCDFs are two groups of chemical compounds (75 and 135 different congeners respectively) that are produced as contaminants or by products in various chemical manufacturing or combustion processes. PCBs are chemicals (209 congeners) that were used as electrical insulating and heat-exchange fluids. Production of PCBs was banned in the U.S. in 1979. Together with the PCDDs and PCDFs, certain PCB congeners, the coplanar (cPCBs) and mono-ortho-substituted (mPCBs), are often referred to as "dioxin-like" because they act through a similar mechanism. To compare relative potency, each of the congeners in the four groups has been assigned a potency value relative to 2,3,7, 8-tetrachlorodibenzo-p-dioxin (toxic equivalency factor, TEF). The TEF values are multiplied by the respective congener concentration to give the congener WHO-toxic equivalency (TEQ) for each group and these are summed to give a total TEQ. Thus, the dioxin-like toxicity contribution of each chemical class can be compared. In this presentation, we will summarize the U.S. national reference ranges for the total TEQ by age, race/ethnicty, and sex. We will also present the U.S. national reference range results for the total PCBs and various PCB congeners by age, race/ethnicty, and sex. Where possible, we will present results using multiple regression models adjusted by age race/ethnicity, sex, and all possible two-way interactions to calculate the adjusted least square geometric mean concentrations. Various percentiles will be presented to provide additional information about the shape of the distributions. These reference ranges provide background exposure information that can be used to compare the levels in people thought to have an unusual exposure to these chemicals.

Keywords:
Human Biomonitoring, Reference Ranges, PCBs

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Monday, May 19th - CONTINUED

Session 2
Chiral aspects of PCBs transport, metabolism and distribution

Session Chairs Hans Lehmler (U Iowa) and Charles Wong (U Alberta)

14:00 – 14:30 **Heinrich Hühnerfuss** (University of Hamburg): Analysis of chiral PCBs and their metabolites

14:30 – 15:00 **Stuart Harrad** (University of Birmingham): Exploiting Chiral Signatures of PCBs for Atmospheric Source Apportionment

15:00 – 15:30 **Cindy Lee** (Clemson University): Biodegradation of chiral PCBs in soil and sediments

15:30 – 16:00 COFFEE BREAK & POSTER VIEWING

16:00 – 16:30 **Charles Wong** (University of Alberta): Chiral PCBs as a marker of biochemical weathering in aquatic food webs

16:30 – 17:00 **Izabela Kania-Korwel** (University of Iowa): PCB atropisomers in animal models – what we know about toxicity and disposition

17:00 – 17:30 **Hans-Joachim Lehmler** (University of Iowa): Enantiomeric fraction of chiral PCBs in humans – an overview

17:30 – 19:00 **POSTER SESSION** (Food and Libations will be provided)
(ODD NUMBERED POSTERS WILL BE ATTENDED)

ANALYSIS OF CHIRAL PCBS AND THEIR METABOLITES

Heinrich Hühnerfuss, Institute of Organic Chemistry, University of Hamburg, Hamburg, Germany, Åke Bergman, Dept. of Environmental Chemistry, Stockholm University, Stockholm, Sweden

Though PCBs are usually classified as “persistent environmental pollutants”, enzymatic transformation pathways may lead to stable products such as methylsulfonyl-PCBs or hydroxy-PCBs. In the present investigation, different transformation processes were studied using enantioselective HPLC/enantioselective GC. As a first step, chiral methylsulfonyl- and hydroxy-PCBs were separated into their enantiomers by enantioselective HPLC. Thereafter, their absolute structures were determined by vibrational circular dichroism and quantum chemical calculations. Thus, unequivocal assignments of the peaks, as obtained from extracts of environmental samples by means of enantioselective GC, to the respective enantiomers were accessible. On the basis of the above preparatory work, systematic studies about enzymatic transformation processes were carried out: the analyses of five human livers, stemming from an autopsy of two female and three male individuals, who had passed away due to heart failure or accidents, showed that in all liver samples highly enantioselective retentions of the second eluting *R*-enantiomers of $MeSO_2$-PCBs 3-149 and 3-132 were encountered. Furthermore, the presence of $MeSO_2$-PCB atropisomers was determined in liver, lung and adipose tissues of rats exposed to the technical PCB product Clophen A50. In all tissues analysed, especially lung, the *para*-$MeSO_2$-PCBs were more abundant than the *meta*-derivatives. Enantioselective analysis of the lung sample extracts showed an excess and dominance of the second eluting *R*-atropisomer of 3-$MeSO_2$-CB149. In both lung and adipose tissues, small amounts of the first eluting *S*-atropisomer of 3-$MeSO_2$-CB149 were present, but this atropisomer was not detected in the liver. No significant changes in the enantiomeric excess of 4-$MeSO_2$-CB91, 3-$MeSO_2$-CB132, 4-$MeSO_2$-CB132, 3-$MeSO_2$-CB149 and 4-$MeSO_2$-CB149 atropisomers were found in either lung, liver, or adipose tissues. The results suggest that enantioselective formations occur for both *meta*- and *para*- $MeSO_2$-PCBs. In order to answer the question as to whether the dramatic enantiomeric excess of the second eluting *R*-enantiomer found in rat liver extracts is caused by enantioselective transformation of the parent compound PCB 149 or, alternatively, by subsequent enantioselective transformation of the metabolite 3-149, incubation experiments with rat hepatocytes were carried out. It turned out that rat hepatocytes are able to transform the two PCB 149 enantiomers with comparable velocities thus giving rise to a nearly racemic metabolite 149, while the subsequent further transformation of the two 3-149 enantiomers by rat hepatocytes leads to a drastic transformation of the first eluting *S*-enantiomer. The second eluting *R*-enantiomer remains nearly unaffected, which is fully in line with the above enantiomeric excesses observed for rat liver extracts.

Keywords:
chiral PCBs, metabolites, enantioselective transformation processes, enantioselective HPLC, enantioselective GC

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EXPLOITING CHIRAL SIGNATURES OF PCBS FOR ATMOSPHERIC SOURCE APPORTIONMENT

Stuart Harrad, School of Geography, Earth, and Environmental Sciences, University of Birmingham, Birmingham, UK

Enantiomeric fractions (EFs) of the chiral PCB congeners 95 and 149 have been measured in samples of topsoil and outdoor air at numerous (predominantly urban) locations both in the UK and elsewhere. While EFs for each of the PCBs in air were essentially racemic, those for topsoil from most locations were usually non-racemic for PCBs 95 and 149. This suggests that a substantial proportion of atmospheric PCB in the contemporary atmosphere arises from racemic (*i.e.* primary) sources, rather than as a result of volatilisation from soil. Coupled with the fact that concentrations of PCBs in indoor air exceed substantially those in outdoor air, these results have important implications for public health and environmental protection, as they imply that destruction of PCB stocks remaining in use are likely to result in a significant reduction in atmospheric concentrations. As the atmosphere is the principal point of entry of PCBs into the food chain, and is also an important vector via which PCBs are transported from their source regions, such action is likely to reduce human exposure and limit the future spread of these compounds.

Keywords:
enantiomeric fractions, soil, air, source apportionment

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BIODEGRADATION OF CHIRAL PCBS IN SOILS AND SEDIMENTS

Cindy M. Lee, Environmental Engineering & Earth Sciences, Clemson University, Anderson, SC, USA

The microbial degradation of PCBs has been extensively studied since the emergence of PCBs as a contaminant class of concern in the 1970s. Over the years, laboratory and field studies discovered a complex microbial ecology that produce specific patterns of dechlorination that apparently depend on the specific conditions of the environment from which the enrichment cultures were developed and the chlorination of the congeners. The microbial ecology of dechlorinators had until recently defied isolation of a culture capable of growth on PCBs. Chiral analysis is a new addition to the tools that offer insight into the degradation pathways; as a result, a limited number of laboratory and field studies have been conducted. Our research group has studied microbial degradation of chiral PCBs in sediments, soils, and most recently, biofilms in streams. Studies conducted with anaerobic microcosms and sediment from Lake Hartwell, a PCB-contaminated reservoir on the South Carolina-Georgia border, as well as modeling results from field studies indicated that Processes M, LP, and Q are occurring in the sediments. In anaerobic microcosms spiked with chiral congeners 132 (234-236) and 149 (236-245), microbial removal of chlorine occurred in such a manner that both enantiomers of the starting congeners disappeared at the same rate and the enantiomer fraction (EF) remained racemic throughout the incubation. However, removal of chlorine from the first product resulting from the dechlorination favored one enantiomer over the other. Results from chiral analysis of cores collected in 1987, 1998, and 2004 provide evidence of more than one microbial consortium responsible for dechlorination in the reservoir sediment. Chiral analysis of semipermeable membrane devices deployed in Twelve Mile Creek, a tributary to Lake Hartwell, hint at microbial processes occurring in the sediment. Biofilm collected from rocky substrate in the same stream produce yet another picture of microbial degradation as elucidated by chiral analysis. Evidence is accumulating that more than one microbial community capable of PCB dechlorination can contribute to dechlorination in the same sediment. Soil microcosms from a composting treatment study that were maintained under anaerobic or aerobic conditions showed distinctively different behavior for some of the same chiral congeners that were in the sediment microcosms. Chiral analysis, especially in conjunction with molecular biology techniques, shows promise as a method to open new vistas on microbial degradation of PCBs.

Keywords:
enantioselective, reductive dechlorination, microbial ecology

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CHIRAL PCBS AS A MARKER OF BIOCHEMICAL WEATHERING IN AQUATIC FOOD WEBS

Charles S. Wong, Department of Chemistry, University of Alberta, Edmonton AB Canada

Chiral compounds, including atropisomeric PCBs, have properties that make them useful as tracers of biogeochemical activity in the environment. While physical and chemical processes are generally abiotic and affect both enantiomers of a chiral compound identically, biochemical processes can be enantioselective and can thus change enantiomer compositions of chiral compounds from the original value. These changes can be used to detect and gain insights into biological processes affecting chiral compounds that would otherwise be difficult if not impossible to measure. Pollutants such as PCBs are released into the environment as racemates, and nonracemic residues in environmental media are indicative of degradation processes, which enantioselective analysis has found to be important even in organisms thought not to degrade persistent organic pollutants to any significant event. Nonracemic PCBs were observed in aquatic invertebrates and fish, which was shown in the laboratory to be due to biotransformation. Mass balance calculations in food webs show that bioprocessing of PCBs in aquatic organisms is on the same scale as the organisms' lifetimes.

Keywords:
chiral PCBs, food webs, biotransformation

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PCB ATROPISOMERS IN ANIMAL MODEL- WHAT WE KNOW ABOUT TOXICITY AND DISPOSITION

Izabela Korwel, Department of Occupational and Environmental Health, University of Iowa, Iowa City, Iowa, USA

Although chiral polychlorinated biphenyls (PCBs) are important constituents of technical and environmental PCB mixtures, our understanding of their enantioselective toxicity and disposition is still limited. PCB atropisomers may elicit different biological responses. For example, (+)-PCB 139 induced cytochrome P450 (CYP) activities more potently than (-)-PCB 139 in rat hepatic microsomes. Furthermore, (-)-PCB 84 was slightly more potent than (+)-PCB 84 at altering PKC translocation in microsomes from adult rat cerebellum. The observation that pure PCB atropisomers can differ in their biological effects raises the question of the presence of enantiomer specific differences in the disposition of chiral PCBs. Indeed, several studies have shown an enrichment of (+)-PCB 136 in blood, tissues and feces from mice. In these studies the enantiomeric enrichment depended on the route of exposure, with more enrichment found in orally exposed than in intraperitoneally exposed mice. The extent of the enrichment of (+)-PCB 136 was independent of the gender and the dietary fat content, but decreased with decreasing dose. Although it is likely that cytochrome P450 enzymes play a role in the enantioselective enrichment of (+)-PCB 136, induction of CYP1A, 2B and 3A enzymes prior to PCB 136 administration increased the extent of the enantiomeric enrichment in liver to the same degree, independent of which P450 enzyme was induced. A more complex picture emerges when complex PCB mixtures were investigated. For example, only a limited enantiomeric enrichment of PCBs 95 and 149 was observed in Aroclor 1254 but not in Chlorofen-treated rats. Despite these recent advances in our understanding of the biological processes responsible for the enantiomeric enrichment of chiral PCBs in laboratory animals, further studies are needed to determine the role of cytochrome P450 enzymes and other biotransformation processes in their enantioselective disposition. [Supported by NIH grants ES05605, ES013661 and ES012475]

Keywords:
polychlorinated biphenyls, atropisomers, enenatiomeric fraction, disposition, orth-substituted PCBs, chiral PCBs

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ENANTIOMERIC FRACTION OF CHIRAL PCBS IN HUMANS – AN OVERVIEW

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Chiral polychlorinated biphenyls (PCBs) are important constituents of technical and environmental PCB mixtures. As a result, humans are exposed to chiral PCB congeners via the diet and, to a lesser extent, by inhalation. This raises the question if exposure to enantiomerically enriched PCBs via the diet and/or enantioselective (biotransformation) processes result in an enantiomeric enrichment of chiral PCBs in humans. The enantiomeric enrichment of PCBs has been investigated in human breast milk from Germany (Glausch et al., Chemosphere, 1995, 30, 2079; Blanch et al., Eur. Food Res. Technol., 1999, 209, 294), Spain (Bordajandi, Chemosphere, 2008, 70, 567) and Switzerland (Bucheli & Brändli, J. Chromatogr. A, 2006, 1110, 156). These studies consistently showed an enrichment of the second eluting atropisomer of PCB 132, whereas PCB 149 was racemic in all samples investigated. PCB 95 was racemic or displayed an enrichment of the second eluting atropisomers. Similarly, PCBs 135, 171, 176 and 183 displayed an enrichment of the second eluting atropisomer in breast milk from Spain, whereas no consistent trends were observed for PCBs 84 and 174. Similar to breast milk, the second eluting atropisomer of PCB 132 was enriched in several human liver samples from Belgium (Chu et al., Environ. Res., 2003, 93, 167). In the same study, the first eluting atropisomer of PCBs 95 and 149 was enriched in several liver samples. PCBs 95, 132 and 149 were racemic or near racemic in muscle, kidney and brain. Chiral signatures of PCB 95 in feces were mostly racemic, but showed an enrichment of the second eluting atropisomer in two samples (Harrad et al., Chemosphere, 2005, 63, 1368), which is opposite to the enrichment observed by Chu an co-workers in human liver. There is growing evidence that the enantiomeric enrichment observed in mammals and in humans is due to enantioselective biotransformation processes. However, further studies are needed to determine to which extent the enantiomeric enrichment observed in humans is a result of exposure to enantiomerically enriched PCBs or due to biotransformation processes. [Supported by NIH grants ES05605, ES013661 and ES012475]

Keywords:
PCB atropisomers, enantiomeric enrichment, PCB 95, PCB 132, PCB 149, breast milk, liver, feces

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Tuesday, May 20th

Session 3
New aspects of environmental metabolism of PCBs: From microbes to plants to animals

Session Chairs Mike Duffel (University Iowa), Jerry Schnoor (University Iowa)

08:30 – 09:00 **Paige Novak** (University Minnesota) Biostimulation of PCB Contaminated Sediment

09:00 – 9:30 **Mary Beth Leigh** (University Alaska) New insights into PCB degradation through stable isotope probing

9:30 – 10:00 **Benoit Van Aken** (West Virginia University) Biodegradation of Individual PCB Congeners by Rhizopshere Bacteria

10:00 – 10:30 COFFEE BREAK & POSTER VIEWING

10:30 – 11:00 **Jerry Schnoor** (University Iowa) Plant Degradation of Airborne PCB Congeners

11:00 – 11:30 **Margaret James** (University Florida) PCB Metabolism in Aquatic Animals

11:30 – 12:00 **Mike Duffel** (University Iowa) Interactions of Hydroxylated PCBs with Rat and Human Sulfotransferases

12:00 – 14:00 LUNCH & POSTER VIEWING

BIOSTIMULATION OF PCB CONTAMINATED SEDIMENT

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It is estimated that almost half a billion pounds of PCBs contaminate the environment; much of this contamination resides in lake, river, and marine sediments. The lipophilic nature and stable chemical properties of PCBs result in their bioaccumulation and biomagnification in the food chain. These compounds are also harmful to human and ecosystem health. In anaerobic sediments biological dechlorination is an important mechanism for PCB degradation. These compounds, however, biodegrade slowly and incompletely, making intrinsic bioremediation undesirable for the management of PCB-contaminated sites.

We have been working on understanding and identifying PCB degraders in a variety of sediments. In addition, we have been developing strategies to enhance the intrinsic bioremediation of PCBs in sediment. Dechlorination of PCB congeners was stimulated when sediment from Baltimore Harbor or Hudson River was incubated in the presence of low concentrations of H_2 or with fermentable organic acids. The addition of inorganic carbon also stimulated dechlorination if added in low concentrations. As dechlorination was stimulated, the growth of organisms phylogenetically similar to known dehalorespirers was observed in Baltimore Harbor, Hudson River, and Palos Verdes sediments, suggesting that although these organisms display different dechlorination patterns, they share a similar evolutionary history, and moreover, are similar to other known dechlorinating organisms (e.g. *Dehalococcoides ethenogenes*). Recent work has focused on understanding the evolutionary history of dehalorespirers more completely, providing additional options for stimulating these organisms through the use of abundant, non-toxic alternative electron acceptors.

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NEW INSIGHTS INTO PCB RHIZOREMEDIATION THROUGH STABLE ISOTOPE PROBING

Mary Beth Leigh, Institute of Arctic Biology, University of Alaska Fairbanks, Fairbanks, AK USA, Vivian H Pellizari (University of Sao Paulo, Sau Paulo, Brazil), Ondrej Uhlık (Academy of Sciences of the Czech Republic, Prague, Czech Republic), Robin Sutka (Michigan State University, East Lansing, MI), Jorge Rodrigues (Michigan State University, East Lansing, MI) Nathaniel E Ostrom (Michigan State University, East Lansing, MI), Jizhong Zhou (University of Oklahoma, Norman, OK) and James M Tiedje (Michigan State University, East Lansing, MI)

Understanding microbes involved in PCB biodegradation and the mechanisms for their rhizostimulation are important to the development of successful rhizoremediation technologies. In this study, we applied stable isotope probing and functional gene microarray techniques to identify active biphenyl-utilizing bacteria and their aromatic degradative genes in the root zone of Austrian pine (*Pinus nigra* L.) growing in a site contaminated with polychlorinated biphenyls (PCBs). Stable isotope probing (SIP) enables the direct identification of microorganisms that degrade pollutants within the complex soil community by tracing C from a ^{13}C-labeled compound into microbial DNA. SIP is advantageous over culture-based studies, which are limited by their ability to detect ≤ 1% of microorganisms in the environment and are unable to confirm which actively biodegrade pollutants in the community context. Culture-based studies at the site indicated that increased populations of PCB-degrading bacteria were associated with pine in comparison to other tree species. SIP revealed 75 different genera that derived carbon from ^{13}C-biphenyl, with *Pseudonocardia, Kribella, Nocardiodes* and *Sphingomonas* predominating carbon acquisition. *Rhodococcus* spp. were not detected with SIP, despite being the most abundant biphenyl-utilizers isolated from agar plates. The GeoChip, a functional gene microarray containing 6465 probes targeting microbial aromatic degradative genes, was used to explore the gene contents of the biphenyl utilizing population. The GeoChip detected several genes associated with catabolism of biphenyl, benzoate and various aromatic ring hydroxylating dioygenases (ARHD) subunits. Also detected were genes associated with the β-ketoadipate pathway, a conserved pathway for degradation of plant-derived aromatic compounds, lending support the hypothesis that plant aromatic compounds have the capacity to biostimulate PCB-degrading bacteria. SIP provided new insights into PCB degradation in soil and the rhizosphere and may benefit rhizoremediation research by facilitating the development of molecular tools to accurately detect, quantify and monitor important microbial populations.

Keywords:
polychlorinated biphenyls (PCBs), rhizosphere, stable isotope probing, rhizoremediation, aromatic dioxygenase, pine, bacteria, microbial ecology

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BIODEGRADATION OF INDIVIDUAL PCB CONGENERS BY RHIZOPSHERE BACTERIA

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Introduction: Polychlorinated biphenyls (PCBs) are persistent contaminants that threaten both the environment and human health. Phytoremediation, or the use of plants for the treatment of environmental pollution, is an alternative promising technology for the remediation of PCB-contaminated soils. One of the beneficial effect of plants is to enhance the microbial activity and biodegradation in the root zone, a process called *rhizosphere bioremediation*. Biological effects of PCB congeners are known to be dependent of the degree of chlorination and substitution pattern, which control the stereochemistry of the molecule. The hypothesis underlying this research is that different PCB congeners will affect differently the bacterial activity in soil, resulting in different biodegradation rates.

Objective: The objective of the described experiments is to investigate the effect of different PCB congeners on the soil microbial community structure, the expression of genes involved in PCB metabolism, and PCB degradation.

Methods: An enrichment experiment was conducted using aerobic agitated soil slurries prepared with poplar rhizosphere soil. Slurries were exposed individually to eight congeners with different degrees of chlorination: PCB 3, 12, 15, 28, 29, 52, and 77, and two commercial mixtures: Aroclor 1242 and 1254, at a final concentration of 60 μg mL^{-1}. After 6 weeks of incubation, microbial activity in soil was measured by cell counting and amplification of 16S rDNA. The microbial community structure was analyzed by real-time PCR using group-specific primers. Abundance and expression of biphenyl dioxygenase (BPH) genes were quantified by (reverse-transcriptase) real-time PCR using degenerate primers. (Primers were designed based on known sequences described in the literature.)

Results: Microbial numbers and activity in soil exposed to higher-chlorinated congeners and Aroclor mixtures showed a slight decrease as compared to non-exposed soil. On the other hand, the microbial community structure was significantly impacted by exposure to PCBs, showing a relative increase of Betaproteobacteria, Gammaproteobacteria, and Actinobacteria in soil exposed to higher-chlorinated PCBs and Aroclor. Similarly, expression of BPH was higher in soil contaminated with higher-chlorinated congeners and mixtures. These results show that different PCB congeners lead to different structures of microbial community and BPH expression patterns. Additional experiments are currently conducted using similar rhizosphere soil slurries exposed individually to different PCB congeners and mixtures. Besides microbial activity and BPH expression, PCB degradation is analyzed by accelerated solvent extraction and GC-MS. The structure of soil microbial community is further investigated using terminal restriction fragment analysis (TRF).

Keywords:
Polychlorinated biphenyls, biphenyl dioxygenase, phytoremediation, rhizosphere bioremediation

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PLANT DEGRADATION OF AIRBORNE PCB CONGENERS

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Phytoremediation is potentially a cost-effective method for scavenging airborne PCBs from the air and/or removing them from dredged material at confined disposal facilities (cdf) by microbial degradation in the rhizosphere (root zone). Plants may also play a role in the direct transformation and metabolism of PCBs at such locations, but little research has been reported on the uptake and transformation of PCB congeners in whole plants. In this paper, we examine the direct role of plants in the degradation of PCB congeners in hydroponic exposure systems. Hybrid poplars (*Populus deltoides x nigra*, DN34) were chosen as model plants for phytoremediation because of their rapid growth, high water utilization, clonal- propagation, and availability of genomic information. We exposed poplar plants to lesser-chlorinated PCB congeners known to be present in Chicago air and sediment samples (PCB 3, 15, 28, 52, and 77). PCB 14 was used as an internal standard.

Small poplar cuttings were vigorously grown in 300-mL Erlenmeyer flasks with silicon septa seals and sampling ports to extract hydroponic solution. The plants were exposed to relatively high concentrations of the PCB congeners in aqueous solution (on the order of half-solubility) with no evidence of toxicity. It was determined that a small portion of PCB 3 and 15 congeners were taken-up and translocated to the upper portions of shoots (stems) and leaves, but the more highly chlorinated congeners (PCB 28, 52, and 77) were not. The congeners accumulated most significantly in the bark of the stem, especially within the flask, where the bark was exposed to the semi-volatile PCBs in the head-space. The accumulation of PCB congeners on roots was strongly linearly correlated with the the octanol-water partition coefficient of the congeners (log Root Concentration Factor vs. log K_{ow}).

All five congeners were significantly lost from root tissues during the course of the 20-day experiment. Mass balances were closed to within $\pm$ 15% for all congeners except the volatile PCB 3. Identification of metabolites is still proceeding, and we have GC-MS confirmation of the hydroxylation of PCB 77 in whole plant tissues. We believe this is the first evidence of *in-vivo* PCB metabolism by whole plants.

Reverse transcriptase (quantitative) PCR (RT-qPCR) was used to measure the induction of candidate genes which may be responsible for the transformations observed. Two cytochrome monooxygenases (CYP 189 and CYP 567) were significantly induced in the presence of PCB congeners and not in controls. In addition, a glutathione-S-transferase (GST 173) was highly induced during the exposure experiment, consistent with the conjugation and compartmentation of some PCB metabolites in plant tissues.

Plants not only harbor bacteria in their rhizosphere but also may provide symbiotic environments for endophytic bacteria. We have evidence of a potentially novel bacteria living inside poplar (closely related to *Bacillus licheniformis*), and we will investigate this bacteria to determine if it could play a role in PCB transformations.

Keywords:
PCBs, phytoremediation, gene expression, plant uptake and metabolism
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PCB METABOLISM IN AQUATIC ANIMALS

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There is extensive evidence that aquatic animals, especially in cold-water regions, accumulate high concentrations of PCBs and related chemicals, and that people who eat fish and shellfish have higher body burdens of PCBs and PCB metabolites than those who do not. PCBs and their metabolites are potentially toxic, thus, it is important to human health to understand the uptake, biotransformation and elimination of PCBs in fish, since these processes contribute to their accumulation. The intestinal uptake of PCBs present in the diet of fish into fish tissues is a saturable process that can change with the lipid composition of the diet (Doi et al., Tox. Sci. 55: 85-96, 2000). Biotransformation of PCBs in fish, as in mammals, facilitates elimination. The first step in PCB biotransformation is cytochrome P450-dependent monooxygenation to PCB-epoxides and hydroxy-PCBs (OH-PCBs). In general, PCB congeners are biotransformed much more slowly in fish than in mammalian species. In the rat, induction by TCDD or Aroclor 1254 resulted in more rapid biotransformation of 3,3',4,4'-tetrachlorobiphenyl (PCB 77) (McKinley et al. Fund. Appl. Toxicol. 21: 425-432, 1993), while in the catfish neither β-naphthoflavone nor PCB 77 caused increased biotransformation of PCB 77 (Doi et al. Aq. Tox. 77: 33-42, 2006). In trout, pre-exposure to PCBs known to induce CYP1A did not increase the biotransformation of PCBs while exposure to PCBs that in rats induce CYP2Bs did increase PCB biotransformation (Buckman et al., Environ. Sci Technol. 41: 3856-3863, 2007). These results suggest the possibility that different cytochrome P450 isoforms are important in PCB metabolism in fish compared with rats. Another factor influencing PCB disposition in fish is water temperature. There is evidence that PCB biotransformation and elimination occur more slowly when the fish is held at low temperatures than at warmer temperatures (Buckman et al., 2007; Paterson et al., Environ. Sci Technol. 41: 824-829, 2007). Further biotransformation of OH-PCBs to glucuronides facilitates their elimination. There have been few studies of OH-PCB glucuronidation in fish. Catfish glucuronidated OH-PCBs more slowly than rats and there was evidence that in catfish, hepatic UDPGA concentrations were higher in November and December than in May (Sacco et al. Drug Metab. Disp. 36: 623-630, 2008), however it is not known if this results in more rapid glucuronidation in November or December than in May. In summary processes of uptake, biotransformation and elimination of PCBs are modulated by several factors in fish. Supported in part by P42 ES 07375

Keywords:
PCB metabolism, fish, cytochrome P450, glucuronidation, temperature effects

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INTERACTIONS OF HYDROXYLATED PCBS WITH RAT AND HUMAN SULFOTRANSFERASES

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Hydroxylated metabolites of polychlorinated biphenyls (OHPCBs) have been detected in blood and tissues of animals exposed to PCBs. One area of increasing interest in OHPCBs has been their ability to serve as potent inhibitors of phenol and estrogen sulfotransferases (e.g., family 1 sulfotransferases, or SULT1 isoforms), with potential consequences in disruption of endocrine hormone function. Such disruption would occur as a result of interference with the physiological inactivation of endocrine hormones by sulfation. We are currently investigating the extent to which OHPCBs interact with family 2 sulfotransferases (SULT2 isoforms; also known as either alcohol sulfotransferases or hydroxysteroid sulfotransferases) as substrates and inhibitors. Our studies utilize homogeneous recombinant enzymes that represent the major hepatic SULT2 isoforms in the rat and human (rSULT2A3 and hSULT2A1, respectively). We observe clear differences in the ability of OHPCBs to interact with the rat and human isoforms as substrates and inhibitors, with the human hSULT2A1 being much more sensitive to inhibition and capable of catalyzing sulfation of OHPCBs. Comparison of the major family 1 and 2 isoforms in the rat (i.e., rSULT1A1 and rSULT2A3) indicates very significant differences in their interaction with OHPCBs. Since there have been previous detailed mechanistic studies on the sensitivity of the rSULT1A1 to oxidation of key cysteine residues on the protein, we have examined the interaction of OHPCBs with the enzyme under oxidative conditions. We find significant differences in the specificity of rSULT1A1 for OHPCBs under fully reduced and partially oxidized conditions, with some OHPCBs that are inhibitors under reducing conditions becoming substrates for sulfation following pre-incubation of the rSULT1A1 with oxidized glutathione. Such changes in specificity for sulfation of OHPCBs may be important in conditions of oxidative stress. [Supported by NIH grant P42 ES013661]

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Tuesday, May 20th - CONTINUED
Session 4
Reproductive, developmental and cardiovascular effects of PCBs

Session Chairs: Surendra Sharma (Brown University) and Bernhard Hennig (University Kentucky)

14:00 – 14:30 **Surendra Sharma (**Brown University) Pregnancy and angiogenic disruption by PCBs

14:30 – 15:00 **Bernhard Hennig** (University of Kentucky) Nutritional modulation of PCB-mediated vascular endothelial dysfunction

15:00 – 15:30 **Lisa Cassis** (University of Kentucky) Obesity and PCBs

15:30 – 16:00 COFFEE BREAK & POSTER VIEWING

16:00 – 16:30 **Mary K. Walker** (University of New Mexico) Chronic activation of the aryl hydrocarbon receptor results in a predisposition to salt-sensitive hypertension

16:30 – 17:00 **Warren G. Foster** (McMaster University) Hormonal aspects of PCB congeners

17:00 – 19:00 **POSTER SESSION** (Food and Libations will be provided)
(EVEN NUMBERED POSTERS WILL BE ATTENDED)

PREGNANCY AND ANGIOGENIC DISRUPTION BY PCBS

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Polychlorinated biphenyls (PCBs) are ubiquitous environmental pollutants with estrogenic activity. Evidence from epidemiological and experimental observations strongly suggests their association with various human health conditions, including female reproductive health. The health consequences of environmental toxicants such as PCBs are likely top be most critical during the *in utero* fetal development. In this context, PCBs present a potential risk of disturbing the endocrine-immune-angiogenic axis, subsequently leading to adverse pregnancy outcomes. Gene-environment interactions also suggest that a genetic stress may predispose the individuals to reproductive health risks. Practical and ethical restraints make these studies in humans the greatest challenge. Therefore, a major goal of our studies has been directed toward gaining an understanding of the basic mechanisms by which PCBs affect the biological systems and the development and validation of experimental systems for evaluating gene-environment effects on female reproductive health. Here, we examined the effect of PCB exposure on pregnancy outcome in IL-$10^{-/-}$ and wild type mice. Pregnant IL-$10^{-/-}$ or congenic wild type mice were given i.p injections of Aroclor1254, a mixture of structurally different PCBs, at a dose of 500 ug/mouse from gestational day (gd) 4-12. Mice were euthanized on gd13, or allowed to deliver. Tissues and fluids were collected for further analysis. Aroclor1254 caused preterm birth in IL-$10^{-/-}$ mice along with increased amniotic-fluid, reduced placental and fetal weight, poor litter size, and neurocognitive anomalies as demonstrated by defective Righting Reflexes in newborns. Pregnancy outcome in wild type counterparts was normal. The results strongly suggest that Aroclor1254 induced reduction in the expression of water channel Aquaporin1 (AQP1) and VEGF R2 in utero-placental tissue. Further, our *in vitro* experiments showed that Aroclor1254 disrupted angiogenic interactions between endothelial cells and trophoblasts, a process dependent on AQP1 and VEGF R2. Taken together, our results suggest a role for IL-10 in protection against toxicant-induced pregnancy complications. AQP1 and angiogenesis are identified as novel targets of PCB action at the maternal-fetal interface. Supported by NIEHS SBRP award P42ES13660.

Keywords:
PCBs, intrauterine effects, pregnancy, angiogenesis, preterm birth, polyhydraminios

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NUTRITIONAL MODULATION OF PCB-MEDIATED VASCULAR ENDOTHELIAL DYSFUNCTION

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Nutrition and lifestyle are well-defined modulators of chronic diseases, and evidence is accumulating that dietary components can modulate toxic insults mediated by environmental pollutants. Results from epidemiological studies support the hypothesis that cardiovascular diseases such as atherosclerosis are linked to environmental pollution. There is also evidence linking the arylhydrocarbon receptor (AhR) with mechanisms associated with cardiovascular diseases and that AhR ligands such as coplanar PCBs may be atherogenic by disrupting the functions of endothelial cells in blood vessels. Because PCBs are in general very persistent and proinflammatory, life-long exposure to these pollutants may fuel vascular inflammation and the pathology of atherosclerosis. We are exploring the paradigm that nutrition can modulate environmental insults in the vasculature and thus modulate endothelial dysfunction induced by exposure to PCBs. Nutrition can dictate the lipid milieu, oxidative stress, and antioxidant status within cells. The modulation of these parameters through diets may influence the effects of environmental pollutants to cause disease such as vascular dysfunction. For example, certain dietary fats may increase the risk to environmental insults induced by PCBs, while fruits and vegetables, rich in antioxidant and anti-inflammatory nutrients or bioactive compounds, may provide protection. Our studies indicate that an increase in cellular oxidative stress and an imbalance in antioxidant status are critical events in PCB-mediated induction of inflammatory genes and endothelial cell dysfunction. We have demonstrated that diet-derived lipids and bioactive compounds can alter the cellular lipid milieu, oxidative stress and antioxidant status, and thus modulate mechanisms of cytotoxicity mediated by PCBs. We also have evidence that the plasma membrane microdomains called caveolae play an important role in endothelial activation and toxicity mediated by coplanar PCBs. Caveolae are particularly abundant in endothelial cells and play a major role in endothelial trafficking and the regulation of signaling pathways associated with the pathology of vascular diseases. There is a great need to further explore this nutritional paradigm in environmental toxicology and to improve our understanding of the relationship between nutrition and lifestyle, exposure to environmental toxicants and disease. (Supported by grants from NIEHS, NIH (P42ES07380) and the University of Kentucky AES).

Keywords:
PCB, nutrition, cardiovascular, endothelial cells

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OBESITY AND PCBS

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Background. Obesity, an inflammatory condition linked to cardiovascular disease, is associated with expansion of adipose tissue. Highly prevalent coplanar polychlorinated biphenyls (PCBs) such as PCB77 accumulate in adipose tissue due to their lipophilicity, and would increase with obesity. However, the effects of PCBs on adipocytes, obesity and obesity-associated cardiovascular disease are unknown.

Objectives. This study examined in vitro and in vivo effects of PCB77 on adipocyte differentiation, proinflammatory adipokines, adipocyte morphology, body weight, serum lipids and atherosclerosis.

Methods. PCB77 or PCB153 were incubated with 3T3-L1 adipocytes either during differentiation, or as mature adipocytes. Concentration-dependent effects of PCB77 were contrasted to those of TCDD. For in vivo studies, C57BL/6 wild type or arylhydrocarbon receptor (AhR) -/- mice were administered vehicle or PCB77 (49 mg/kg, i.p.) and body weight gain examined. In separate studies, apoE -/- mice were injected with vehicle or PCB77 over a 6 week period and body weight, adipocyte size, serum lipids and atherosclerosis were examined.

Results. Low concentrations of PCB77 or TCDD increased adipocyte differentiation, GPDH activity and expression of PPARγ, while higher concentrations inhibited adipocyte differentiation. Effects of PCB77 were abolished by the AhR antagonist, α-naphtoflavone (α-NF). PCB77 promoted the expression and release of various proinflammatory cytokines from 3T3-L1 adipocytes. Administration of PCB77 increased body weight gain in wild type, but not AhR-/- mice. ApoE-/- mice injected with PCB77 exhibited greater body weight, adipocyte hypertrophy, serum dyslipidemia and augmented atherosclerosis.

Conclusions. Our findings suggest that PCB77 may contribute to the development of obesity and obesity-associated atherosclerosis.

Keywords:
Adipose, obesity, PCB, atherosclerosis

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CHRONIC ACTIVATION OF THE ARYL HYDROCARBON RECEPTOR RESULTS IN A PREDISPOSITION TO SALT-SENSITIVE HYPERTENSION

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One gene-environment interaction that may increase the risk of human hypertension is the inappropriate activation of the aryl hydrocarbon receptor (AHR) by dietary and environmental xenobiotics. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is a ubiquitous environmental pollutant and the most potent exogenous AHR ligand. Epidemiology studies have shown that humans highly exposed to TCDD exhibit a significantly increased prevalence of hypertension many years after exposure. Our previous work has shown that continuous exposure of mice to TCDD induces hypertension and endothelial dysfunction. In this study, we tested the hypothesis that mice exposed to TCDD for a short duration would continue to exhibit alterations in blood pressure regulation months after the exposure. To test this, we exposed mice to 0, 15, or 150 ng TCDD/kg/d 5 d/wk by diet for 30 d, allowing the TCDD to accumulate to levels similar to those observed in modestly-to-highly exposed humans. After the 30 d exposure, the accumulated body burden of TCDD was allowed to depurate, returning to background levels after 30 d. Blood pressure was measured at the end of the exposure and 30 d after the exposure ended, using tail cuff. Then, 60 d after the exposure ended, mice were treated with 8% dietary NaCl and blood pressure was measured during and after treatment by radiotelemetry. We found that both TCDD doses increased blood pressure to similar levels after 30 d, compared to baseline (Low TCDD, baseline: 100.4 ± 3.0, d30: 111.9 ± 2.9 mm Hg, p=0.019); (High TCDD, baseline: 101.1 ± 2.5, d30: 110.7 ± 2.4 mm Hg, p=0.019), but that blood pressure remained significantly elevated even after the TCDD body burden had returned to background (control: 100.9 ± 4.8, low TCDD: 114.1 ± 3.3, high TCDD: 113.3 ± 2.0 mm Hg, p=0.033). In addition, TCDD-exposed mice exhibited salt-sensitive hypertension with MAP significantly increasing during the active hours at night (control high salt: 109.0 ± 5.0 mmHg; TCDD high salt: 120.4 ± 0.3 mmHg, p=0.012). Finally, blood pressure in TCDD-exposed mice was not different from controls after dietary salt was reduced to normal. These data suggest that a short duration exposure to modest levels of TCDD is sufficient to sensitize mice to salt-dependent hypertension months after exposure has ended.

Keywords:
Dioxin, hypertension, AHR

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HORMONE MIMICS AND HUMAN HEALTH

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Measurement of environmental contaminant residue levels in the serum and follicular fluid of women attending fertility programs coupled with reports of a global decline in semen quality have led to speculation that infertility rates are increasing and environmental toxicants are potentially important causal agents. Indeed, the circulating levels of the estrogenic environmental contaminant Bisphenol A have been linked with an increased risk for spontaneous abortion and have been demonstrated to be greater in women with PCOS compared to healthy controls. Further support for an environmental link between Bisphenol A exposure and infertility is derived from animal studies in which exposure to this contaminant has been associated with aneuploidy and infertility. In addition, we have demonstrated adverse effects of cigarette smoke and cigarette smoke constituents on folliculogenesis at concentrations representative of the levels measured in human ovarian follicular fluid. Our preliminary results reveal that cigarette smoke exposure in mice at levels equivalent to approximately 12 cigarettes/day results in a significant decrease in ovarian volume an effect that is consistent with observations in women who smoke. We and others have shown that cigarette smoke exposure or exposure to polyhalogentaed aromatic hydrocarbons (PHAH) such a benzo[a]pyrene (BaP) and benzanthracene results in a marked decrease in primordial follicles. In a subsequent study, we quantified the concentration of benzo[a]pyrene and several other PHAHs present in the reproductive fluids of women attending the Centre for Reproductive Care, Hamilton Health Sciences. Using an isolated follicle culture system we have shown that concentrations of benzo[a]pyrene representative of the levels measured in human follicular fluid attenuate follicle growth in a concentration dependent manner, an effect that is reversible by co-incubation with the aryl hydrocarbon receptor antagonist resveratrol. Furthermore, our preliminary results suggest that follicle loss is not mediated through an increase in apoptosis as previously thought but may result from changes in cycle length, an effect that is also consistent with the human literature. The mechanisms for these changes are uncertain; however toxicant induced changes in ovarian expression of cytokines such a growth differentiation factor-9 and bone morphogenic protein-15 are a focus of ongoing studies in my laboratory.

Keywords:
Environmental contaminants, toxicants, estrogenic, persistent organic pollutants, exposure, and reproductive toxicity

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Wednesday, May 21st
Session 5
Anniston: The most severe US PCB community exposure

Session Chairs Allen Silverstone (SUNY Upstate Medical University and University Rochester School of Medicine) and Marian Pavuk (ATSDR/CDC)

8:30 – 8:40 **Allen Silverstone** Opening Remarks: Anniston: One of the most impacted communities in the world.

8:40 – 9:10 **Shirley Baker** (Anniston Community Leader, Mothers and Daughters Protecting Children's Health) How the community discovered they were Exposed to PCBs and What they did about it

9:10 – 9:40 **Allen Silverstone** The Anniston-PCB Consortium Health Study: Origins and Objectives

9:40 – 10:10 **James Olson** (SUNY at Buffalo) Assessing Environmental Contamination and Human Exposure to PCBs in Anniston, AL

10:10 – 10:40 COFFEE BREAK & POSTER VIEWING

10:40 – 11:10 **Fred Biasini** (University of Alabama Birmingham) A Study of Neurocognitive and Neurobehavioral Function in Children in Anniston Following PCB Exposure

11:10 – 11:40 **Herman Russell Foushee** (University of Alabama at Birmingham) Community Health Survey: Self Reported Conditions and Perceptions of Exposure

11:40 – 12:10 **Allen Silverstone** PCBs, Diabetes and Cardiovascular Risk Factors in the Anniston Community Health Survey Population

12:10 – 12:20 **Marian Pavuk** Closing Remarks

12:20 – 14:00 LUNCH & POSTER VIEWING

HOW THE COMMUNITY DISCOVERED THEY WERE EXPOSED TO PCBS AND WHAT THEY DID ABOUT IT

Shirley Baker, Anniston Community Leader: Mothers and Daughters Protecting Children's Health, Anniston, Alabama

The Anniston Community has had a long post civil war history of industrial production. Once known as the "Pipe Capital" of the United States (which resulted in considerable lead pollution), it became the chief center for PCB production by Monsanto Corporation in 1929. Although the Community had protested pollution (including the Army chemical warfare incinerator) for a long time, high PCB levels were first officially found in fish, downstream from Anniston in 1994. In 1995 PCB's were found in 103 human blood samples collected by the ATSDR. EPA did environmental sampling shortly after that.

A number of law suits began in the mid 1990's to claim compensation for health consequences of PCB exposure. The two most recent involved 4800 individuals in a State case, and almost 15,000 in a federal case.

In 1993, before the lawsuits began, the group Community Against Pollution (CAP) was formed. Its first executive director was David Baker. CAP had a number of leaders and activists from its inception. Its most important activities were to educate and mobilize the community to get Monsanto to properly clean up its West Anniston pollution; to get government oversight of such clean-up; and, perhaps most important, to get Senator Richard Shelby and others to support a study of the health effects of PCBs on this community, one of the most highly exposed in the world.

I will present my personal story of this movement and its activities up to today.

Keywords:
PCBs, Community Action, Community Organizing

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THE ANNISTON/CALHOUN PCB CONSORTIUM HEALTH STUDY: ORIGINS AND OBJECTIVES

Allen E. Silverstone, (SUNY Upstate Medical University), Scott Bartell (University of California, Irvine), Marian Pavuk (ATSDR/CDC), and the Anniston Environmental Health Research Consortium

PCB's were produced in Anniston, AL from 1929 to the 1970's, by Monsanto Corporation. The production plant was built on a flood plain in West Anniston, surrounded by sharecroppers. Production waste was disposed of around the flood plain, resulting in a general contamination of the environment, the food chain, and individuals with very high levels of PCB's. Even though production stopped in the early 1970's, adult average levels still appear to be on average almost 4 fold higher than the US average. ATSDR and EPA began sampling and evaluating samples from air and soil and blood starting in 1995. In 2000, ATSDR wrote a report on these values, and in 2001 an Expert Panel convened by ATSDR recommended development of research activities to address PCB exposure and potential health effects.

In response to community concerns, Sen. Richard Shelby (R-AL) held hearings in 2003, and pushed for CDC/ATSDR funding of a health effects study. A RFP was issued, emphasizing a requirement of community participation and public university direction. Jacksonville State University received the grant and co-ordinated the establishment of a consortium of investigators from around the United States. The consortium involved representatives of community organizations from the beginning of the planning stages. Many studies were proposed, but after review by a top level Scientific Advisory Panel assembled by the consortium, the studies were limited (by available funding and resources) to

1- A characterization of environmental and individual PCB exposure levels and sites by geospatial analysis.
2- A randomized Community Health Survey, based on a questionnaire developed by consortium members, including life style and psychological issues as well as most major health concerns associated with PCB's.
3- Within the health survey a nested case control study on diabetes and some cardiovascular risk factors.
4- A Neurodevelopmental – PCB study on 321 children (ages 11-16) and 234 parents distinct from the health survey study.

Significant well controlled data has been acquired relating current PCB body burdens to neurocognitive and neurobehavioral function in children, diabetes, and cardiovascular risk factors. Additional data is being examined on autoimmunity, thyroid function, cancer, and reproductive outcomes. The body of data generated by this study will be one of the most detailed sources for examining the health consequences of PCB exposure. Some of the specific results will be presented in this panel, today. Funded by ATSDR grant. U50/ATU473215

Keywords:
PCBs, epidemiology, diabetes, cardiovascular disease, neurodevelopmental effects.

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ASSESSMENT OF HUMAN EXPOSURE TO PCBS AND DETERMINANTS OF EXPOSURE IN ANNISTON, AL

James R. Olson[1], Marian Pavuk[2] , Bryan Ha[1], Peter Rogerson[1], Ling Bian[1], and Matthew Bonner[1]

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PCBs were manufactured in only two facilities in the United States, one located in Anniston, AL and the other in Sauget, IL. During the 40 years PCBs were made in Anniston, PCB waste materials were buried on-site and PCBs were released into the environment. The University-Community Consortium for Anniston Environmental Health Research has recently completed community-based research on PCB exposures and health effects in Anniston. The goal for the exposure assessment study was to assess human exposure to PCBs in residents of Anniston AL and examine potential determinants of PCB exposure. The levels of 35 ortho-substituted PCBs were measured by the CDC in the serum of 765 residents participating in the Anniston Community Health Survey (ACHS) and in 321 children participating in the Neurocognitive Study. PCB levels in Anniston residents were compared with levels found in 2001 and 2002 in the general population of the U.S. (NHANES). PCB levels in children participating in the Anniston Neurocognitive Study (10 to 17 years of age) are similar to children throughout the United States. This suggests that current environmental and dietary exposures in Anniston do not appear to result in excess PCB levels in Anniston children. As expected, PCB levels in Anniston children were much lower than in adult residents. PCB levels of adults in the ACHS range from 0.05 to 170 ppb, wet wt and are about four times greater than in adults throughout the United States. As expected, PCB levels increase markedly with the age of participants (19 to 93 years). PCB levels in adult African American participants in the ACHS are on average about three times greater than the levels found in white participants across all age groups. The higher PCB levels in African American participants are at least in part due to the large number living in areas near the former PCB production facility with the greatest potential for environmental PCB exposure. GIS analysis of residential soil PCB levels found a significant relationship between ACHS serum PCB levels and geographically matched soil PCB levels. Other significant predictors of exposure include the consumption of local live stock and fish and the consumption of Anniston clay, all of which were reported more frequently in the African American participants. After controlling for age, race and what people ate, other variables such as gender, BMI, education, income, and potential past exposures to PCBs at work contributed little if at all to explaining differences in PCB levels. (Supported by ATSRD grant U50/ATU473215)

Keywords:
PCBs, human, serum, soil, GIS, fish, clay, live stock, Anniston, AL, NHANES

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A STUDY OF NEUROCOGNITIVE FUNCTION IN CHILDREN FOLLOWING PCB EXPOSURE

Fred Biasini, PhD[1] , Alan K. Percy, MD[2] , Jane B. Lane, RN, BSN[2] ,Jerry Childers[2] , Richard C. Rector, PhD[1]

University of Alabama at Birmingham - [1]Department of Psychology, [2]Civitan International Research Center

The impact of PCB exposure on general cognitive abilities of children has been an area of great concern. An early study (Jacobson, Fein, & Jacobson, 1985) suggested that infants exposed prenatally to PCBs performed more poorly on a test of visual recognition memory at 7 months. Differences in general cognitive, attention, and memory performance of exposed children have also been reported (Jacobson, Jacobson, Humphrey, 1990; Jacobson & Jacobson, 1996; Jacobson & Jacobson, 2003). Other studies have not substantiated these early findings. However, metacognitive or executive functioning abilities (decisions about what to remember and how to remember it) may be impacted adversely following PCB exposure and have seldom been assessed in older children. In Alabama, the Anniston community represented a unique opportunity to compare the effects of low versus high PCB exposure in children age 12 to 15, a key time for the development of executive function capabilities. It was hypothesized that children with high exposure to PCBs would perform more poorly on neurocognitve tests assessing executive function. The study included 321 6th through 8th grade students in the impacted communities of Calhoun County, Alabama. We also recruited one parent for each student participant, preferably the mother, to provide a possible surrogate for PCB exposure during gestation as well as postnatally. Cognitive tests were administered to 297 of the 321 children (93%) and 149 of 234 parents (64%). When the average IQ scores for the highest and lowest PCB levels (upper and lower 25%) were compared, a significant difference (p=0.02) was noted. However, when these groups were adjusted for Stanford Achievement Test scores for reading and language by school and ethnicity, parent education level, and the children's blood lead levels, this difference in IQ was no longer significant. In contrast, when the PCB blood levels of the parents for the highest and lowest quartiles of the children were used to group the children a highly significant IQ difference was noted (p=0.006). In terms of executive function testing, differences between the children's test scores in the highest and lowest quartiles were only noted for the Tower Test that does not have a verbal component (p=0.03). Finally, we examined the relation between the parents' PCB levels and their IQ scores. After controlling for education and ethnicity, a highly significant difference (12 IQ points) was noted between the parents with the highest and lowest blood PCB levels (Supported by ATSRD grant U50/ATU473215).

Keywords:
PCBs, IQ, neurocognitive development, executive functioning, Anniston, Alabama

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ANNISTON COMMUNITY HEALTH SURVEY: SELF REPORTED CONDITIONS AND PERCEPTIONS OF EXPOSURE

Herman R. Foushee Jr., Paul E. Wolf, Randolph Devereaux, University of Alabama at Birmingham

Anniston (population 24,276) lies in Eastern Alabama and was home to PCB manufacturing for over 40 years. Due to water runoff and soil backfilling high levels of PCBs have been found in much of the city. Subsequent litigation and remediation have heightened awareness of PCBs in the community which may have affected people's assessments of PCB exposure and its health effects. The Anniston Community Health Survey interviewed 1110 randomly selected adults in Anniston, AL on self-reported health conditions and perceptions of personal PCB exposure. The in-person, household-based survey was completed by a representative sample of residents 19 and older. Respondents were asked about their perceptions of environmental quality, PCB contamination in the community, personal PCB exposure and negative health effects, and health conditions associated with PCBs. Respondents were also asked a series of questions on being diagnosed with a variety of health conditions. The results showed overall ratings of poor soil, air, and water quality. Significant demographic differences were found where females, African Americans, and West Anniston resident rated environmental quality lower. The results further demonstrated that residents perceive the community as being highly contaminated with PCBs and they show a high level of concern about PCB contamination. Two-thirds of residents believe they have been personally exposed to PCBs and two-thirds of them believe they have suffered negative health effects as a result. The health effects attributed to PCBs include allergies, breathing problems, diabetes, cancer, and skin problems. Significant group differences included females more frequently saying they were exposed to PCBs and rated PCB health effects and amount of personal exposure more severely than males. African Americans more frequently said they were exposed to PCBs and rated PCB health effects and amount of personal exposure more severely than whites. West Anniston residents rated PCB health effects and amount of personal exposure more severely than East Anniston residents. In addition, results showed the most frequently reported health condition diagnoses were high blood pressure (42%), allergies (39%), and migraines (24%). Significant differences existed between the rates of reported health conditions by gender, race, residency, and PCB exposure perceptions. The implications of these findings on actions regarding PCBs in community are also discussed.

Keywords:
PCBs, community, health, survey

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PCB LEVELS, DIABETES AND CARDIOVASCULAR RISK IN THE ANNISTON COMMUNITY HEALTH SURVEY POPULATION

Allen E. Silverstone, Paula F. Rosenbaum, Ruth S. Weinstock (SUNY Upstate Medical University), Scott Bartell (University of California, Irvine), Rusty Foushee and Paul Wolff(University of Alabama, Birmingham), Christie Shelton (Jacksonville State University, AL), Marian Pavuk (ATSDR/CDC), and the Anniston Environmental Health Research Consortium

The Anniston Community Health Survey of 1110 adults, (ages 19-93), representing as many randomly selected households, recorded medical and family history (including history of diabetes, heart disease and stroke) and current medications. The percent of individuals with diabetes in all age groups was significantly higher than the US or Alabama prevalence in either the NHANES or BRFSS studies. 774 of those individuals came to the Anniston Environmental Health Consortium Office in a fasted state between 2005 and 2007 for measurements of height, weight, blood pressure, and waist circumference; a review of their medications; and laboratory blood work including fasting glucose and insulin levels, a lipid panel, PCBs (35 congeners), and diabetes-related autoantibodies. Of the 765 individuals with completed visits, 207 were found to have diabetes, including 29 newly discovered cases. 171 other individuals fulfilled the criteria for pre-diabetes. In these 765 individuals, PCB levels were found to correlate strongly with age and race and less so with BMI. Logistic regression analysis comparing those with diabetes to those without (excluding pre-diabetes), and controlling for known diabetes-related risk factors and confounders (age, BMI, race, gender, family history, lipid levels and lipid lowering drugs) found no statistically significant association between PCB levels and the prevalence of diabetes. Subgroup analyses of individuals ages 35-54, however, revealed a 2-4 fold increase in diabetes across PCB quartiles, comparing each to the lowest quartile (the US average), while statistically significant PCB effects for those 55 years and older were not observed. This suggests a significant association between PCB exposure and the development of diabetes in the younger age group. Similar associations between PCB levels and aggregate cardiovascular disease risk factors were also observed.
Funded by ATSDR grant. U50/ATU473215

Keywords:
PCBs, epidemiology, diabetes, cardiovascular disease, pre-diabetes.

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Wednesday, May 21st - CONTINUED
Session 6
TEFs: New and Novel approaches; Implications for Risk Assessment

Session Chairs Isaac Pessah (UC Davis) and Prasada Kodavanti (US EPA)

14:00 – 14:30 **Prasada Kodavanti** (US EPA) Introductory comments, what we know and what we need to know

14:30 – 15:00 **Pam Lein** (Oregon Health & Science U) How PCBs influence dendritic growth, complexity and neuronal plasticity - new concerns about PCB developmental neurotoxicity

15:00 – 15:30 **Rich Seegal** (U Albany) Effects of PCBs on dopaminergic systems, what we have learned from animal models and what we are learning from studies of capacitor worker

15:30 – 16:00 COFFEE BREAK & POSTER VIEWING

16:00 – 16:30 **Isaac Pessah** (UC Davis) Structure-activity relationship for non-coplanar persistent organic pollutants at Ca release channels- PCBs and beyond

16:30 – 17:00 **Ted Simon** Modes of action of polychlorinated biphenyls, brominated flame retardants and other chemicals: implications for environmental regulation

17:00 - 17:30 **Linda Birnbaum** (US EPA) summary and closing comments and general discussion.

19:00 - Evening - Banquet with local music

OVERVIEW OF CURRENT TEFS AS IT RELATES TO CURRENT PCB EXPOSURES: WHAT IS NEEDED?

Prasada Rao S. Kodavanti[1] and Linda S. Birnbaum[2]

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The toxic equivalency factor (TEF) approach is one of the ways to assess the risk associated with exposure to complex mixture of polychlorinated biphenyls (PCBs) and structurally related chemicals. This method is based on mode of action with the assumption that all chemicals in the mixture mediate the adverse effects through the Aryl hydrocarbon receptor (AhR). The toxic potential of each chemical in the mixture is compared against tetrachloro-dibenzo-dioxin (TCDD), which is the most potent ligand for AhR, resulting in a TEF value. The toxic equivalency (TEQ) value for the mixture is derived from the addition of all the concentration-weighted TEF values for chemicals in that mixture. This approach serves well if all chemicals in the mixture have TCDD like effects. However, there are many reports showing that all of the nervous system effects are not mediated through AhR. Environmental mixtures are composed of many chemicals and dioxin-like chemicals are often a very small part of these mixtures. Among PCBs, non-dioxin like PCBs are >99% total mass. Although there are reports indicating different PCB congeners interact in an additive manner, some studies showed nonadditivity, both antagonistic and synergistic. Recent reports indicate that the critical effect for PCBs and other related chemicals is on the developing nervous system, where neurite outgrowth was affected at picomolar concentrations. Structurally related chemicals such as polybrominated diphenyl ethers that coexist with non-dioxin like PCBs exert effects on the nervous system at similar concentrations both *in vitro* and *in vivo*. Based on the critical effect on the developing nervous system and greater amounts of non-dioxin like chemicals in the mixtures, TEFs based on AhR activity may not be sufficient to predict the risk associated with exposure to PCBs and structurally related chemicals. A new scheme for toxic equivalence based on neurotoxic endpoints has been developed recently, which may be considered in addition to current TEFs based on AhR for the human health risk assessment of halogenated chemical mixtures. *(This abstract does not necessarily reflex USEPA policy).*

Keywords:
polychlorinated biphenyls, neurotoxicity, TEFs, risk assessment, mixtures

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NON-COPLANAR POLYCHLORINATED BIPHENYLS (PCBS) MODULATE THE DEVELOPMENT OF NEURONAL CONNECTIVITY VIA EFFECTS ON THE RYANODINE RECEPTOR

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Perinatal exposure to PCBs is linked to behavioral deficits in humans and experimental animal models and it is generally agreed that these effects are mediated primarily by non-coplanar, as opposed to coplanar, congeners. Non-coplanar PCBs have been demonstrated to increase intracellular Ca^{2+} via several mechanisms including ryanodine receptor (RyR) activation, and to decrease serum thyroid hormones and deplete dopamine in the brain. However, the relevance of these effects to developmental neurotoxicity has been difficult to establish, in part because specific neurodevelopmental events targeted by PCBs have yet to be identified. Data will be presented to support the hypothesis that non-coplanar PCBs disrupt normal patterns of neuronal connectivity via effects on dendritic growth and plasticity. These data include *in vivo* studies demonstrating that developmental exposure to the commercial PCB mixture Aroclor 1254 impairs spatial learning and memory in weanling rats coincident with perturbations of basal and learning-induced changes in dendritic growth and RyR expression. Subsequent studies of dendritic growth in primary cultures of hippocampal neurons exposed to individual PCB congeners confirm that these neurodevelopmental endpoints are influenced by non-coplanar but not coplanar PCB congeners at concentrations as low as 2 pM and support a causal relationship between PCB effects on dendritic growth and RyR. These *in vitro* studies also identify a Ca^{2+}-dependent signaling pathway implicated in activity-dependent dendritic growth as a mediator of PCB effects on neuronal connectivity. In light of clinical and experiment evidence suggesting that altered dendritic growth and plasticity contributes to the clinical manifestations of a variety of environmentally induced neurodevelopmental disorders in humans, including autism spectrum disorders and ADHD as well as emerging data demonstrating that non-coplanar PCBs are particularly stable and predominate over their coplanar counterparts in environmental and human blood samples, our data suggest that AhR-independent endpoints warrant increased consideration in assessing the risks that PCBs pose to human health. This work supported by NIH.

Keywords:
non-coplanar PCBs, dendrite, neuronal connectivity, developmental neurotoxicity, ryanodine receptor, calcium signaling

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NON-COPLANAR POLYCHLORINATED BIPHENYLS ALTER DOPAMINE FUNCTION BOTH IN VITRO AND IN VIVO

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The earliest evidence that non-coplanar polychlorinated biphenyls (NCP-PCBs) are neurochemically active was elucidation of a structure-activity-relationship (SAR) demonstrating that NCP, but not co-planar PCBs, reduced dopamine (DA) content in cells in culture (Shain, Bush and Seegal, 1991). Subsequently, similar SARs for NCP-PCB effects on phorbol ester binding, inhibition of vesicular uptake of DA and activation of ryanodine receptors have been reported respectively, by Kodavanti *et al*., Mariussen *et al*. and Pessah *et al*. The most compelling evidence that NCP-PCBs are centrally active and alter DA function is based on studies we have conducted in both adult non-human primates. (NHPs) and individuals occupationally exposed to PCBs. Exposure of adult NHPs to either Aroclor 1016 or 1260, commercial mixtures devoid of coplanar PCBs, significantly reduced basal ganglia DA concentrations and the number of tyrosine hydroxylase positive neurons in the substantia nigra *pars compacta*. In additional experiments we demonstrated that basal ganglia DA concentrations did not return to pre-exposure levels even after removal from NCP-PCB exposure for forty-four weeks. Most recently we have shown that occupational exposure to NCP-PCBs resulted in a significant negative relationship between current serum PCB levels and reductions in basal ganglia beta-CIT binding (a measure of DA terminal densities) in women, but not in men. These latter findings not only demonstrate the ability of NCP-PCBs to alter central DA function in humans, but also illustrate the need to examine for gender differences following exposure to PCBs and related halogenated aromatic hydrocarbons. Potential mechanisms responsible for the strict SAR for changes in neuronal function following exposure to NCP-PCBs and the differential response of men and women to such exposures will be discussed. Supported in part by U.S. Army grant # DAMD17-02-1-0173 and NIH grant # R01 ES014675 to RFS.

Keywords:
polychlorinated biphenyls, dopamine, gender, structure activity relationship

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STRUCTURE-ACTIVITY OF NON-COPLANAR ENVIRONMENTAL CHEMICALS AT RYANODINE-SENSITIVE CALCIUM CHANNELS; BASIC AND CLINICAL IMPLICATIONS

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Ryanodine receptor (RyR) isoforms are expressed in both excitable and non-excitable tissues where they form highly regulated microsomal Ca2+ channels. RyR isoforms are broadly involved in shaping cellular signals by coupling the release of Ca2+ from ER/SR stores to voltage, ligand and store-operated Ca2+ channels of the plasma membrane. A detailed structure-activity relationship (SAR) for polychlorinated biphenyls (PCB) for enhancing RyR activity will be presented using [3H]ryanodine ([3H]Ry) binding, Ca2+ flux, and single channel gating analyses. The 2,3,6-Cl PCB configuration is most important for optimal activation of RyR, whereas para-substitutions sterically hinder or eliminate RyR activity. The molecular mechanism by which PCBs activate RyR is to stabilize the full conductance open state of the channel, prolonging mean open time >8-fold, and decreasing mean close time >2.5-fold. Separation of chiral PCB136 demonstrates stereospecificity toward RyR1 and RyR2 activity. Results from SAR studies with brominated diphenylethers indicate that BDE4 (2, 2'-diphenylether is a potent activator of RyR whereas para-substituted BDE15 and unsubstituted diphenylether are inactive. The widely used antibacterial triclosan possesses potent activity towards dysregulating basal and evoked Ca2+ signaling mediated by RyR activation in excitable cells. These results underscore the high degree of specificity of noncoplanar environmental chemicals toward RyR complexes. In light of the causative role of RyR isoforms in heritable human disorders, the basic and clinical implications of RyR-mediated mechanisms in PCB toxicity will be discussed. Supported by NIH and EPA.

Keywords:
PCB, new targets, calcium signaling

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MODES OF ACTION OF POLYCHLORINATED BIPHENYLS, BROMINATED FLAME RETARDANTS AND OTHER CHEMICALS: IMPLICATIONS FOR ENVIRONMENTAL REGULATION

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PCBs produce adverse effects in humans and animals by several modes of action – the best known mode is binding of dioxin-like PCBs to the aryl hydrocarbon receptor. But other PCB congeners, some brominated flame retardants, DDT, triclosan and possibly other chemicals have different modes of action. These chemicals act by at least two modes of action: 1) interference with intracellular signaling pathways dependent on Ca^{2+} homeostasis and 2) binding to thyroid hormone receptors and carrier proteins and subsequent disruption of thyroid hormone-related effects. So far, there exists a scheme of relative potency estimates (REP) for the non-dioxin-like PCB congeners based on disturbance of Ca^{2+} homeostasis known as the Neurotoxic Equivalence (NEQ) scheme. Here, the NEQ scheme is extended to include other PCB chemicals. In addition, REP estimates for thyroid hormone-related effects for both PCBs and other chemicals are developed. Although the dioxin-like toxicity of PCBs has received the majority of scientific attention, the endpoints related to Ca2+ homeostasis and thyroid hormone appear much more relevant for human health risk assessment. Consideration of these endpoints and the use of data-based uncertainty factors can enable the refinement of the reference doses for PCB mixtures on EPA's IRIS database. In addition, the use of toxic equivalence schemes based on multiple endpoints allows risk assessors to account for potential mixture effects among several classes of chemicals.

Keywords:
PCBs, BFRs, DDT, Triclosan, Modes of Action, Reference Dose

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POSTER LISTINGS

Presenters with posters designated with an (*) are the winners of the student/postdoctoral Travel Award

Poster 1

ATMOSPHERIC PCBs MEASURED IN CHICAGO USING VEHICLE MOUNTED HIGH-VOLUME AIR SAMPLERS

D Hu, K Hornbuckle

Poster 2

RECRUITMENT APPROACHES FOR THE AESOP STUDY OF PCB EXPOSURES

P Thorne, J DeWall, D Osterberg, V Persky, M Turyk

Poster 3

MEASURING OF PCB CONGENERS IN INDOOR AND OUTDOOR AIR OF EAST CHICAGO INDIANA AND IOWA CITY, IOWA

C.Persoon and K Hornbuckle

Poster 4

RESEARCH TRANSLATION, COMMUNITY OUTREACH AND EDUCATION AT THE UNIVERSITY OF IOWA SUPERFUND BASIC RESEARCH PROGRAM (ISBRP)

V Persky, P Thorne, D Osterberg, M Turyk, N Newkirk

Poster 5

IDENTIFICATION AND QUANTIFICATION OF HYDROXYLATED PCBs IN INDIANA HARBOR AND SHIP CANAL

R F Marek, A Martinez, A K Norstrom, C L Just

Poster 6

PREPARATION OF A PCB MIXTURE APPROXIMATING THE MEAN CHICAGO AIR SIGNAL FOR THE UNIVERSITY OF IOWA SUPERFUND BASIC RESEARCH PROGRAM

H Zhao, A Adamcakova-Dodd, C L Just, K Hornbuckle, D Hu, L W Robertson, P Thorne, H-J Lehmler

Poster 7

PCBs IN SURFICIAL SEDIMENTS IN EAST CHICAGO, INDIANA

A Martinez, K Norstrom, K Wang, K Hornbuckle

Poster 8

ENVIRONMENTAL FACTORS THAT PREDICT SERUM PCB CONCENTRATIONS IN MICHIGAN

D Garabrant, B Hong, Q Chen, C-W Chang, X Jiang, A Franzblau, J Lepkowski, P Adriaens, A Demond, E Hedgeman, K Knutson, T Towey, BW Gillespie

Poster 9

AIR-SOIL DISTRIBUTION OF PCB CONGENERS OVER THE VOJVODINA REGION

M Miloradov, M Sekulic, J Radonic (Presented by B Skrbic)

Poster 10
LONG TERM MONITORING FOR PCB IN AMBIENT AIR USING LOW VOLUME AIR SAMPLER
M Tsurukawa, C Matsumara, T Nakano

Poster 11
GENE EXPRESSION RELATIVE EFFECT POTENCIES (REPs) FOR 2,3,7,8-TETRACHLORODIBENZO-p-DIOXIN (TCDD)3,3,4,4,5-PENTACHLOROBIPHENYL (PCB126) & 2,3,7,8-TETRACHLORODIBENZOFURAN (TCDF) IN MOUSE LIVER
A Kopek, L Burgoon, A Lee, D Ibrahim-Aibo, J R Harkema, C Tashiro, B Chittm, T Zacharewski

Poster 12
COMPREHENSIVE TOXICOGENOMIC EVALUATION OF THE HEPATIC EFFECTS ELICITED BY 2,2',4,4',5,5'-HEXACHLOROBIPHENYL (PCB153) IN IMMATURE, OVARIECTOMIZED C57BL/6 MICE
A Kopek, L Burgoon, D Ibrahim-Aibo, J Harkema, C Tashiro, B Chittim, T Zacharewski

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#1

ATMOSPHERIC PCBS MEASURED IN CHICAGO USING VEHICLE-MOUNTED HIGH-VOLUME AIR SAMPLERS

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The magnitude, spatial extent and variation of PCBs in air were investigated in the urban/industrial complex of Chicago, Illinois using an innovative sampling strategy of mobile high-volume air samplers. Two high volume air samplers equipped with quartz fiber filters and XAD-2 resin cartridges were mounted on health clinic vans operated by Mobile C.A.R.E. Foundation of Chicago that served patients at 45 sites throughout Chicago. An air sample was collected when each van served one location, typically an elementary school, each school day. Here we describe results of sampling conducted November 2006 to March 2007. Concentrations of PCB congeners were determined using gas chromatography coupled to tandem mass spectrometry (GC-MS/MS). Gas phase ∑ PCB concentrations ranged from 20 to 1000 pg/m^3 with the average of 340 pg/m^3. The urban air contains more high chlorinated congeners than nonurban areas. Temporal and spatial variation of PCB concentrations was observed, but the influential factors have yet been fully determined.

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#2

RECRUITMENT APPROACHES FOR THE AESOP STUDY OF PCB EXPOSURES

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The AESOP Study (Airborne Exposures to Semi-volatile Organic Pollutants) is a component of the Iowa Superfund Basic Research Program and is an exposure assessment study for congener-specific PCBs primarily via the inhalation route. For this project we have recruited demographically-similar cohorts in two locations: East Chicago, Indiana and Columbus Junction, Iowa. East Chicago is at the southern end of Lake Michigan adjacent to Indiana Harbor and associated ship canals. A large navigational dredging project will begin here in 2009 that will place 4.5 million cubic yards of sediment contaminated with PCBs and other legacy pollutants into a confined disposal facility (CDF) located within 1 km of a middle and high school. Columbus Junction is a rural Iowa community with no known current or past industrial sources of PCBs. We are performing air monitoring at local schools and inside and outside homes of study subjects in both communities to characterize congener-specific PCB exposures. We are also collecting blood samples from adolescents and their mothers for analysis of lipid profiles and PCBs. It is hypothesized that subjects in East Chicago will have higher levels of household PCB exposures and higher blood levels of lower molecular weight (more volatile) PCB congeners than subjects in Columbus Junction, due to residing within the Chicago/Lake Michigan airshed. It is also hypothesized that the dredging and filling of Indiana Harbor and canals will increase airborne PCB exposures in East Chicago. In order to increase interest in the study and facilitate recruitment we have employed a three-tiered approach. 1) We have assembled community advisory panels in both communities that include local elected officials, civic leaders, and public health workers and provided information regarding environmental transport, exposure, and health effects of PCBs. 2) We have collaborated with the middle school science teachers to develop educational projects for their classes to teach basic principles of science needed to understand PCBs and environmental issues of legacy pollutants. 3) We have employed bilingual field staff from both communities to conduct enrollment, administer questionnaires and collect samples from study participants. All of these efforts have helped develop good will in the study communities and has resulted in successful recruitment among a challenging study population.
Support from NIH P42 ES013661

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#3

MEASURING OF PCB CONGENERS IN INDOOR AND OUTDOOR AIR OF EAST CHICAGO INDIANA AND IOWA CITY IOWA

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The use of passive samplers to measure semi-volatile organics is the atmosphere has become more common in recent years due to the ability of passive sampler to measure compounds over a large spatial region. However, the accuracy of quantifying concentrations of chemicals from the masses collected on the passive sampler media in both indoor and outdoor air is an area of major concern. We have evaluated different mathematical approaches to calculating a sampling rate (m^3/d) for the use of passive samplers measuring Polychlorinated Biphenyls (PCBs) in the air. We have compared the measurements of depuration compound loss rates (K_e) to that of native congener uptake rates (K_u). There is a difference between the mass transfer coefficients and sampling rates calculated from the two measurements. Here we recommend the application of these sampling rates for field samples collected in both indoor and outdoor environments of East Chicago Indiana and Iowa City, Iowa.

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#4

RESEARCH TRANSLATION, COMMUNITY OUTREACH AND EDUCATION AT THE IOWA SUPERFUND BASIC RESEARCH PROGRAM (ISBRP)

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One of the six projects of the Iowa Superfund Basic Research Program (isbrp) studies the area south of Lake Michigan in Indiana Harbor and its associated canals where a dredging project will begin in 2009. This effort will place 4.5 million cubic yards of PCB-contaminated sediment into a confined disposal facility (CDF) located within 1/2 km of a middle and high school in East Chicago, Indiana.

The Community Outreach Core of the isbrp has been working in the community of East Chicago, Indiana as well as an identified control community in Columbus Junction, Iowa. Outreach staff have taught classes in both school districts, presented to community forums and created Community Advisory Committees in both communities on the subject of PCBs and the goals of this project.

The Research Translation Core of the isbrp hosted a two-day workshop for state elected officials in the Midwest to explain the study and several other environmental health issues. Ten legislators and four legislative staff members from the states of Iowa, Minnesota, Nebraska, Illinois, Wisconsin and Missouri met with scientists from the isbrp and other researchers. Four staff members from the US EPA Regions 5 and 7, eleven members of the public, several students and three staff from state of Iowa environmental agencies also attended. State lawmakers learned about environmental health issues in the region and the isbrp work on PCBs in particular.

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#5

IDENTIFICATION AND QUANTIFICATION OF HYDROXYLATED PCBS IN INDIANA HARBOR AND SHIP CANAL

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Centered in heavily-industrialized East Chicago is the Indiana Harbor and Ship Canal. Branching off of the southwestern edge of Lake Michigan, the waterway is known to be contaminated with polychlorinated biphenyls (PCBs) and is designated as an Area of Concern by the International Joint Commission. PCBs can be metabolized to the hydroxylated form (OH-PCBs) by humans and other organisms, and it is possible that PCBs in the sediment are metabolized by microbial activity. This may be a removal mechanism for PCBs in sediment. Alternatively, OH-PCBs may come from exogenous sources. Yet OH-PCBs in sediment have not been reported. We hypothesize that OH-PCBs are present in the contaminated Canal and Harbor sediment. A method for the extraction and analysis of these OH-PCBs was developed. Herein we present preliminary results of OH-PCB congeners in surficial sediment of Indiana Harbor and Ship Canal.

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#6

PREPARATION OF A PCB MIXTURE APPROXIMATING THE MEAN CHICAGO AIR SIGNAL FOR THE UNIVERSITY OF IOWA SUPERFUND BASIC RESEARCH PROGRAM

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The Superfund basic research program at The University of Iowa (isbrp) is a collaborative endeavor investigating the consequences of exposure to atmospheric sources of semi-volatile polychlorinated biphenyls (PCBs). It deals with volatilization, transport and exposure of lower halogenated PCBs, especially those PCBs that are associated with contaminated waters, former industrial sites, and other atmospheric sources. One overarching aim of the isbrp is to study a PCB mixture representative of a mean air signal in the Chicago area. The target profile selected for this purpose is the average PCB profile recorded between 1996-2002 at the satellite station of the Integrated Atmospheric Deposition Network (IADN) located at the Illinois Institute of Technology (IIT) in Chicago, Illinois. Initial simulations using published PCB profiles suggested that a mixture 65% Aroclor 1242 and 35% of Aroclor 1254 represents a good approximation of the mean PCB signal in Chicago air. A mixture with this ratio of both Aroclors was prepared and continuously shaken to ensure complete mixing. Small aliquots were removed after 8, 14 and 30 days of shaking and the PCB profile was determined with GC/MS/MS. The PCB profile was comparable for all three time points, thus suggesting that the mixture was homogenous. Furthermore, the PCB profile of the mixture was comparable with the mean PCB signal in Chicago air, with a regression coefficient of 0.69, a similarity coefficient of 0.79, and an average relative percent deviation (RPD) of 95 for all congeners analyzed. This mixture is now available to study the biological effects of lower halogenated PCBs in the laboratory and to generate PCB atmospheres for inhalation toxicology studies. [Supported by NIH grant P42 ES013661]

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#7

PCBS IN SURFICIAL SEDIMENTS IN EAST CHICAGO, INDIANA

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East Chicago is a heavily industrialized urban community on the southern shore of Lake Michigan. Penetrating the city center is the Indiana Harbor and Ship Canal, an Area of Concern designated by the International Joint Commission due to contamination by many environmental pollutants including polychlorinated biphenyls (PCBs). PCBs are known to contaminate the harbor and canal, although there is little published data describing the spatial extent and concentration magnitude. Therefore, we have conducted a sampling expedition designed to allow a multimedia comparison of PCB concentrations and fluxes in the Harbor system. We collected surficial sediment, water, and air samples from the harbor and connected canal. The surficial sediment samples were extracted using accelerated solvent extraction. The extracts were analyzed for all 209 PCB congeners by tandem mass spectrometry. Preliminary results, which are presented in this poster, indicate an enrichment of PCBs in the canal in comparison to the harbor, as well as the open lake. Concentrations of total PCB in the samples range from 50 to 33,000 ng/g (dry weight). Average % recovery for surrogate standard – PCB 166 – was 86% and standard deviation of 16%, with a range from 58 to 114%.

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#8

ENVIRONMENTAL FACTORS THAT PREDICT SERUM PCB CONCENTRATIONS IN MICHIGAN

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We studied factors that predict serum concentrations of the polychlorinated biphenyls (PCBs) for which World Health Organization Toxic Equivalency Factors (TEFs) exist (PCB 77, PCB 81, PCB 126, PCB 169, PCB 105, PCB 114, PCB 118, PCB 123, PCB 156, PCB 157, PCB 167, and PCB 189), using data from 946 participants in the University of Michigan Dioxin Exposure Study (UMDES) in the general population in five Michigan counties. Participants were interviewed regarding potential exposure pathways (consumption of meat, fish, dairy, eggs, sport caught fish and game; activities in contaminated areas, occupations, residential locations), demographics, smoking, and breast feeding. Samples of blood, soil, and household dust were analyzed for PCBs using HRGC/HRMS. Important factors were identified using forward stepwise selection. Data were analyzed using linear regression for complex survey data, in which the $\log_{10}$(serum PCB) was a linear function of predictors.

Results: Serum PCB concentrations were detectable in at least 98% of subjects for all congeners except PCB 81 (53% above LOD). The most important congener was PCB 126 because it typically contributes about 10% to the TEQ (using 2005 WHO TEFs), whereas all the other PCBs combined contribute less than 10% to the TEQ. The regression model for PCB 126 explained 52 percent of the variation in the serum concentration (adjusted R^2). Most of the variation was explained by demographic factors (age, BMI, and sex), and smoking. Age was positively associated with serum levels, while smoking was inversely associated with serum levels. Neither living on contaminated soil nor contaminated household dust was associated with increased serum PCB 126 levels. Living on a farm in the 1940s-1950s and eating sport caught fish were positively associated with serum levels of PCB 126.

This study has strengths that make it valuable. Since it is a population-based study, the results apply to the general population. Few other studies have concurrent measurements of serum, soil, and household dust PCBs, as we have, nor do they include as many subjects. Our serum analyses were based on large samples (80 ml of blood), which allowed us to have measurable PCB levels for almost all subjects. Few other studies have achieved these levels and, as a result, have been limited by large numbers of non-detectable serum levels.

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#9
AIR-SOIL DISTRIBUTION OF PCB CONGENERS OVER THE VOJVODINA REGION

Mirjana Vojinovic Miloradov, Environmental Engineering, Faculty of Technical Sciences, University of Novi Sad, Novi Sad, Serbia, Maja Turk Sekulic, Jelena Radonic

Presented by Biljana Skrbik, Faculty of Technical Sciences, University of Novi Sad

Polychlorinated biphenyls are a well-known class of ubiquitous pollutants characterized by low hydrophilic and high lipophilic potential, extreme toxicity, and high resistance to chemical and biological degradation processes. PCBs were subsequently introduced into the environment and they are found in most animal and human adipose tissue, human milk, sediment, and numerous other environmental matrices. The number and location of the chlorines govern both the environmental fate and toxicity of each congener. Contaminated air reflects to all environmental media, biotic and abiotic. As the result of the air and soil sampling campaign conducted in 2006, the concentration levels of seven PCB congeners were measured in different air and soil samples to determine the spatial variation and air-soil partitioning over the Vojvodina, agriculture and industrial region. Atmospheric concentrations were determined using passive sampling method by samplers containing polyurethane foam filters. Samples were collected in five cycles of 28 days during the period of 5 continuously months simultaneously using two samplers at the two selected localities in Vojvodina. Gas chromatography coupled with mass spectrometry analysis was carried out in laboratories of Research Centre for Environmental Chemistry and Ecotoxicology (RECETOX), Masaryk University in Brno, Czech Republic. PCB congener pattern was used to illustrate the spatial differences and type of distribution for selected POPs after the bombing of the industrial and military targets accompanied by incomplete combustion during the NATO operation in Serbia (March-June 1999). Significant quantities of PCB congeners were released into the environment due to complete or incomplete destruction of the transformers containing pyralene oil. PCB concentrations in soil showed a large variation between sampling-areas with median concentrations ranging between 0.3 and 27.3 ng/g. The highest concentrations were found at two industrial sites, one with sandy soils, and other with extremely high organic carbon content. Concentration levels of PCB congeners in air ranged from 12.5 ng/filter to 60.5 ng/filter. Obtained results confirmed correlation between both types of data, compatibility of the concentration in the atmosphere and surface soil layers, as well as equivalent distribution of congeners in the air-soil. The relationship to different gas-solid parameters was studied and transfer of chemicals between the soil and air compartments was estimated. Residues of PCBs, HCH and DDT were also detected in human milk from healthy mothers.

Keywords:
PCBs, air, partitioning

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#10

LONG TERM MONITORING FOR PCB IN AMBIENT AIR USING LOW VOLUME AIR SAMPLER

Masahiro Tsurukawa, Chisato Matsumura, Takeshi Nakano

Presented by Takeshi Nakano

PCB concentration level in ambient air using a low volume air sampler was investigated.

Monitoring was carried out from 2000 to 2005 in Hyogo prefecture in Japan. Regarding the sampling location and period - sampling was carried out in urban, industrial and rural areas and collected continuously for about one month. PCB concentration declined year by year in industrial area, but other area remained at the same level (under 1ng/m3).

As for seasonal variations, the concentration is higher in summer than in winter because of volatility characteristics. With PCB isomer analysis, these phenomena are explained.

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#11

GENE EXPRESSION RELATIVE EFFECT POTENCIES (REPs) FOR 2,3,7,8-TETRACHLORODIBENZO-p-DIOXIN (TCDD), 3,3,4,4,5-PENTACHLOROBIPHENYL (PCB126) & 2,3,7,8-TETRACHLORODIBENZOFURAN (TCDF) IN MOUSE LIVER

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The toxic equivalency factor (TEF) approach was devised to estimate the risk associated with exposure to complex mixtures of dioxins, dibenzofurans and PCBs. A comprehensive toxicogenomic approach was used to provide hepatic gene expression relative effect potency (REP) data for 3,3',4,4',5-pentachlorobiphenyl (PCB126) and 2,3,7,8-tetrachlorodibenzofuran (TCDF) compared to the effects elicited by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD; TEF=1) in immature ovariectomized C57BL/6 mice. Mice were gavaged with 0.001, 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30, 100 or 300 µg/kg of TCDD or with 1, 3, 10, 30, 100, 300, 1000, 3000 µg/kg of PCB126 or TCDF or sesame oil vehicle for 24 hrs. Significant increases in relative liver weights were observed at 100 and 300 µg/kg TCDD, 1000, 3000 µg/kg TCDF and 300 µg/kg PCB126. Steatosis accompanied by inflammation and single-cell necrosis was present at the highest doses of all three compounds. Hepatic levels of the three dioxin-like compounds were also determined to associate changes in gene expression to tissue levels. Hepatic gene expression analysis by one-color Agilent microarrays, with confirmation of selected genes by quantitative real-time PCR, was used to determine the dose-response characteristics of differentially expressed genes. Overall, there were 325 TCDD (P1(t) > 0.99, |fold change| > 1.7, active in at least 3 doses), 278 TCDF (P1(t) > 0.95, |fold change| > 1.5, active in at least 2 doses), and 236 PCB126 (P1(t) > 0.95, |fold change| > 1.5, active in at least 3 doses) active genes. Of these, 165 overlapped between TCDD and TCDF, while 77 overlapped between TCDD and PCB126 using strict cut-off criteria. The top approximately 50 active genes (based on the stringent criteria of activity at 3 doses, |fold change| > 1.5, and P1(t) > 0.999 TCDD, and P1(t) > 0.99 TCDF and PCB126) from each congener were used for dose-response modeling and calculation of ED_{50} values. The ED_{50} values for Cyp1a1 (TCDD: 0.16µg/kg; TCDF: 1.22 µg/kg; PCB126: 8.60 µg/kg), Nqo1 (TCDD: 4.0 µg/kg; TCDF: 332.12; PCB126: 3.46 µg/kg), and Cyp1a2 (TCDD: 0.17 µg/kg; TCDF: 22.67 µg/kg; PCB126: not active) are given. REPs based on these ED_{50} values identified composite toxicogenomic REP averages of 0.025 and 0.09, respectively. If the REP for Nqo1 (an outlier in PCB126) is included, the composite REP average for PCB126 increased to 0.30. These gene expression REPs suggest the TEFs for TCDF and PCB126 may overestimate the relative toxicity of these congeners. This work was funded by Superfund P42ES04911.

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#12

COMPREHENSIVE TOXICOGENOMIC EVALUATION OF THE HEPATIC EFFECTS ELICITED BY 2,2',4,4',5,5'-HEXACHLOROBIPHENYL (PCB153) IN IMMATURE, OVARIECTOMIZED C57BL/6 MICE

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Polychlorinated biphenyls (PCBs) are ubiquitous contaminants found as complex mixtures of various dioxin and non-dioxin-like PCB congeners. 2,2',4,4',5,5'-hexachlorobiphenyl (PCB153) is a di-ortho-substituted, non-coplanar congener that exhibits the highest human body burdens of any PCB. However, it does not elicit dioxin-like effects, and therefore its toxicity cannot be equated to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). In this study, the dose-dependent hepatic effects elicited by PCB153 in the immature, ovariectomized C57BL/6 mice were examined. Animals (n = 5/ group) were orally gavaged with a single dose of 1, 3, 10, 30, 100, 300, 600 mg/kg of PCB153 or sesame oil vehicle and sacrificed 24 hrs following the treatment. Hepatic gene expression changes were measured using one-color Agilent microarrays and 249 differentially expressed genes (|fold change|≥1.5 and P1(t)≥0.99) were identified using an empirical Bayes method. All of the genes that met the filtering criteria were up-regulated, with ~40% of genes showing a dose-response profile. Functional annotation was performed using DAVID and Gene Ontology resources to associate differential gene expression with metabolism (cellular macromolecule, protein, coenzyme and RNA metabolism), alternative splicing, translation and protein synthesis, protein transport, cell division and apoptosis. The most significant changes included the induction of constitutive androstane receptor (CAR) activation biomarker Cyp2b10 (~16 fold increase) involved in xenobiotic metabolism. The study has also identified the induction of several PXR/CAR-regulated genes including Nr1i2, Nr1i3, Cyp3a11, Ugt1a1, Abcc2 and Abcc3. Complementary histopathology revealed minimal to slight vacuolization at 300 and 600 mg/kg PCB153, which correlated with the significant increases in relative liver weights at these doses. Preliminary comparative examination suggests that the PCB153 elicits a unique gene expression profile when compared to TCDD that may be mediated by PXR/CAR. This work was funded by Superfund P42ES04911.

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TRAVEL AWARD

#13

PCB INDUCED CONGENER SPECIFIC OXIDATIVE STRESS RESPONSE BY MICROARRAY ANALYSIS USING HUMAN LIVER CELL LINE

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Polychlorinated biphenyls (PCBs) are ubiquitous and persistent pollutants whose role in toxicity in public health is of great concern. The toxic effects of different PCB congeners are structure-dependent and may produce different transcriptional activation and functional effects *in vitro*. In this study, we have examined the effect of induction of different congeners of PCBs and their role in oxidative stress response that may ultimately lead to apoptotic cell death. A metabolically competent human liver cell line (HepG2) was exposed with two prototype congeners of PCBs: PCB-77 and PCB-153. After the predetermined time of exposure (0-24 hours), the HepG2 cells showed significant apoptotic changes by fluorescent microscopy and DNA fragmentation assays beyond 12 hours of exposure. Unsupervised cluster analysis using hierarchical clustering of the data sets obtained from the Affymetrix HG-U133-Plus-2 microarrays showed that length of exposure to PCBs was the dominant variable. Gene set enrichment analysis (GSEA) identified oxidative stress as the predominant enrichment. Further, Paraquat assays showed that PCB congeners lead to oxidative stress to different extents, PCB-77 being more toxic. This study, with emphasis on all recommended quality control steps, showed that apoptosis was the most significant cellular process as a result of oxidative stress. Each of these congeners has an unique gene expression signature, which was further validated by Taqman real time PCR and immunoblotting. *In-sillico* analysis showed that PCB-153 probably acted through the TNF receptor, leading to oxidative stress through the involvement of metallothionein gene families and causing apoptosis mainly by the Fas receptor signalling pathway. In contrast, PCB-77 acted through the aryl hydrocarbon receptor. It induces oxidative stress through the involvement of cytochrome P450 (CYP1A1) leading to apoptosis through AHR/ARNT pathway. Interestingly, in contrast to co-planner PCB-77, non-coplanner PCB-153 could involve mitochondrial genes leading to accelerated apoptotic cell death.

Keywords: PCBs, HepG2, Mitochondria, Toxicity, Microarray, Differential gene expression

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TRAVEL AWARD

#14

THE END DRAWS NEAR: TELOMERE SHORTENING INDUCED BY A QUINONE METABOLITE OF PCB3

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Recent studies have reported surprisingly high levels of predominantly mono and di- chlorinated biphenyls in several indoor and outdoor samples. One of these semivolatile PCB congeners is 4-chlorobiphenyl (PCB3), a major component of one commercial PCB Aroclor mixture and indoor air samples. PCB3 is more easily converted to mono- and dihydroxy-metabolites than higher chlorinated congeners, which makes metabolites of PCB3 particularly interesting for toxicological research. Previous studies have shown that PCB3 induces point mutations and its metabolites increase oxidative stress and form covalent adducts with DNA. Telomeres, which protect the ends of the chromosomes from damage, play an important role in carcinogenesis and senescence. They are damaged by oxidative stress. Our working hypothesis is that PCB3-quinone metabolites are carcinogenic by producing oxidative stress-related damage to the telomeres. Human keratinocytes (HaCaT cells) and primary human fibroblasts were treated continuously for 12 weeks with **2-(4'-chlorophenyl)-1,4-benzoquinone** (PCB3pQ). Telomere length was determined using a quantitative polymerase chain reaction (qPCR) method. Telomeric DNA levels decreased approximately 40% in HaCaT cells treated with PCB3pQ at 5 µM compared to solvent control-treated cells. The telomere signal of primary fibroblasts also shows a decreasing trend with PCB3pQ treatment, but this effect was not statistically significant and confounded by differences in cell doublings during the 12 week period. These preliminary results urge further mechanistic studies concerning the effects of PCB congeners and metabolites on telomeres. (Supported by an Iowa CHEEC Seed Grant and NIEHS P42 ES013661.)

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#15

TIME-DEPENDENT CHANGES OF PCB AND MESO2-PCB LEVELS IN C57BL/6 MICE AFTER ORAL ADMINISTRAION OF A PCB MIXTURE

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Polychlorinated biphenyls (PCBs) remain an important class of environmental contaminants, with dietary exposure still being a concern for humans. Multiple-ortho substituted PCBs have been implicated in many adverse health effects, including neurotoxicity. Most PCB congeners are metabolized to hydroxy and methylsulfonyl PCBs ($MeSO_2$-PCB) *in vivo*; however, time-dependent changed of PCB metabolite levels are only poorly investigated. This study was designed to investigate changes of PCB and $MeSO_2$-PCB levels over time. Female C57Bl/6 mice (7 weeks old) received a single oral dose (50 mg/kg body weight) of a PCB mixture containing multiple-ortho substituted PCBs in corn oil. The mixture consisted of selected PCB congeners (PCBs 91, 95, 132, 136, 149, 174, 176 and 183) in the ratios detected in PCB-contaminated fish from the Fox River. Control animals received vehicle alone (10 ml/kg body weight). The mice were sacrificed 1, 3, 6, 9, 12, 24, 72, 144, 192, 240, 312 and 384h after PCB administration. Whole blood was collected by cardiac puncture and the liver was excised en bloc. PCBs and $MeSO_2$-PCBs were extracted from blood and liver, and analyzed by GC-ECD. The ΣPCB levels in blood and liver peaked at 3h. PCBs 95 and 149, the main congeners in the mixture, had the highest PCB levels 12h after PCB administration, whereas levels of PCBs 136 and 176 dropped quickly below the limit of detection. The Σ$MeSO_2$-PCBs in liver had the highest level after 24h (330 ng/g wet weight), declined to 200 ng/g after 72h and stayed at this level until the end of the experiment (384h). The main methylsulfonyl metabolites observed were 4-$MeSO_2$-CB 91, 3- $MeSO_2$-CB132, 4-$MeSO_2$-CB132 and 4-$MeSO_2$-CB 149. These findings suggest that $MeSO_2$-PCBs have longer half-lives and, thus, may be suitable markers for past PCB exposures.

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#16

3,3',4,4',5-PENTACHLOROBIPHENYL - INDUCED ALTERATIONS IN SELENIUM AND COPPER HOMEOSTASIS IN RAT LIVER: DETERMINATION OF METAL CONCENTRATIONS WITH INDUCTIVELY COUPLED PLASMA – MASS SPECTROMETRY

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As part of an interdisciplinary study to explore selenium's role in the liver's response to PCB exposure, metal concentrations were determined in rat tissues using Inductively Coupled Plasma - Mass Spectrometry (ICP-MS). Rats were fed three refined diets containing different selenium concentrations, and after three weeks of acclimatization, one of three dosages of PCB126 (3,3',4,4',5-pentachlorobiphenyl), was injected into each dietary group. The rats were sacrificed after two weeks and liver, lungs, kidneys, testis and whole blood were harvested for ICP-MS measurements, together with other measurements. For organs other than blood, about 0.5 ~ 1.0 g of tissue was digested in closed-vessel microwave digestion system with nitric acid and the resulting solution was further diluted prior to the measurement. Blood samples were directly diluted 1:50 into a basic solution containing tetramethylammonium hydroxide, ammonium pyrrolidine dithiocarbamate, isopropanol, Triton X-100. Total metal concentrations of manganese, iron, copper, zinc and selenium were then measured using ICP-MS. Among the results of metal concentrations in different rat tissues, dietary selenium levels are mirrored in selenium concentrations with nearly all organs showing three levels of selenium concentrations. The PCB injections have the most significant effects on hepatic metals with decreasing selenium concentrations and increasing copper concentrations with increasing PCB 126 dosage, among other observations. Integrated with other findings from this study (please see the neighboring poster), the metal measurements reveal some new insights into metals homeostasis following exposure to a toxic PCB. (Supported in part by P42 ES 013661.)

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#17

SUPPLY AND DEMAND: WILL SELENIUM SUPPLEMENTATION BE ABLE MEET THE DEMANDS CAUSE BY THE EFFECTS OF 3,3',4,4',5-PENTACHLOROBIPHENYL EXPOSURE?

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Selenium (Se) is a critical trace element in the antioxidant defense system, and is incorporated amino acids and antioxidant enzymes. Previous studies have shown that homeostasis of selenium and the selenium-dependent glutathione peroxidase (SeGPx) can be disrupted by exposure to an aryl hydrocarbon receptor (AhR) agonist, 3,3',4,4',5-pentachlorobiphenyl (PCB126), is able to mimic dioxin and exert its toxicity by increasing oxidative stress and diminishing antioxidant levels in the liver. Here we examined the ability of supplemental selenium to mitigate the potent effects elicited by PCB126. Male Sprague-Dawley rats were fed an AIN-93M diet with deficient, adequate, and supplemental selenium levels (0.02, 0.2, 2ppm, respectively). Following three weeks of acclimatization, rats from each dietary group were given a single ip injection of corn oil (control), 0.2, 1, or 5 mmol/kg body weight PCB126. Two weeks later rats were euthanized. We observed dose-dependent increases in liver wet weights (20-80%), accompanied by decreases in whole body weight gains (5-100%) caused PCB exposure. Hepatic CYP1A1 was significantly induced (20-fold) even at the lowest dose of PCB126, while total SOD levels remained unaffected despite MnSOD being dose-dependently diminished (15-60%), potentially increasing the risk of elevation in steady-state levels of reactive oxygen species. Consistent with other findings in this study (please see the neighboring poster), SeGPx activity was diminished (20-45%) in a dose-dependent manner by PCB exposure, but these effects were partially mitigated (30-50%) by selenium supplementation. (Supported by NIEHS P42 ES013661)

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#18
GENETIC SUSCEPTIBILITY TO PCB-INDUCED DEVELOPMENTAL TOXICITY

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Polychlorinated biphenyls (PCBs) include both coplanar congeners that bind and activate the aryl hydrocarbon receptor (AHR) and noncoplanar congeners that are unable to bind the AHR. It is well known that hepatic CYP1A2 – a member of the [*Ahr*] battery – can sequester coplanar PCBs. Humans vary ~10-12 fold in AHR inducibility and ~60-fold in basal hepatic CYP1A2 levels. Previous studies have demonstrated that Ahr^b mice with a high-affinity AHR and *Cyp1a2(-/-)* mice show greater developmental toxicity when exposed to planar AHR ligands such as PCBs and dioxin. We have extended the previous work by exploring the gene-gene interactions and the relative importance of each gene in developmental toxicity. Mice varying at the *Ahr* and *Cyp1a2* loci were exposed to an environmentally relevant mixture of PCB congeners (coplanar PCB 77, 126, and 169 and noncoplanar PCB 105, 118, 138, 153, and 180). Four genotypes were tested: $Ahr^bCyp1a2(+/+)$, $Ahr^dCyp1a2(+/+)$, $Ahr^bCyp1a2(-/-)$, and $Ahr^bCyp1a2(-/-)$. Pregnant dams were dosed by gavage once at gestational day 10 (GD 10) and again at postnatal day 5 (PND 5) to assure AHR activation in the high-affinity mice from late gestation until weaning. Control animals were treated with the corn oil vehicle. Litter size was not significantly different, and there was no difference in several developmental landmarks recorded. These included dates of pinna detachment, development of skin pigmentation, appearance of fur and eye opening. Rates of dystocia (21-26%) and abnormal gestation length (21-22%) were highest in the two PCB-treated Cyp1a2(-/-) lines. Birth weights were significantly lower for both PCB-treated *Cyp1a2(-/-)* lines, and growth rates were significantly reduced for PCB-treated $Ahr^bCyp1a2(-/-)$ pups from P0 through weaning at PND 28. Plasma thyroxine (T4) levels were significantly reduced (80% lower) at PND 6 for PCB-treated $Ahr^bCyp1a2(-/-)$ pups. At PND 28, T4 levels were significantly reduced in both PCB-treated $Ahr^bCyp1a2(-/-)$ and $Ahr^dCyp1a2(+/+)$ pups. Tissues were collected from treated and control pups at PND 6, 13, and 28. Consistent with previous reports, mice with a high-affinity AHR showed the greatest decreases in thymus and spleen wet weights. All PCB-treated mice showed increased liver wet weight at PND6; however, the effect was only persistent in PCB-treated $Ahr^bCyp1a2(-/-)$ pups. Interestingly, a histological examination showed the greatest liver damage in PCB-treated $Ahr^dCyp1a2(-/-)$ mice. We conclude that $Ahr^bCyp1a2(-/-)$ are most susceptible to developmental exposure to environmentally relevant PCB mixtures while *Cyp1a2(-/-)* dams are most affected by gestational PCB exposure, regardless of *Ahr* genotype.

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TRAVEL AWARD

#19

POLYBROMINATED DIPHENYL ETHER (PBDEs) GENERATES FREE RADICALS DURING PHOTODEGRADATION

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Among the polybrominated diphenyl ethers (PBDEs), deca-bromodiphenyl ether (deca-BDE) is the most commonly used brominated flame retardant. Levels of PBDEs in the environment and in humans have recently increased. Photodegradation of deca-BDE with UV light results in PBDEs with fewer bromines. We hypothesize that photodegradation will result in free radical formation. Electron paramagnetic resonance (EPR) was used to detect free radical formation using 5,5-dimethyl-1-pyrroline N-oxide (DMPO) and 2-methyl-2-nitrosopropane (MNP) as spin traps. A commercial deca-BDE (DE-83R) and octa-BDE mixtures (DE-79), deca-bromobiphenyl (PBB 209), deca-chlorinated biphenyl (PCB 209) and phenyl ether (PE) were dissolved in tetrahydrofuran (THF), dimethylformamide (DMF), or toluene. Samples were irradiated with a xenon lamp with a 309 nm or 280 nm cut-off filters. Irradiation of deca-BDE resulted in EPR spectra that were distinctly different in each solvent; spin adduct concentrations increased with the deca-BDE concentration (THF and DMF) and irradiation time (THF, DMF and toluene). GC-MS data indicate that deca-bromodiphenyl ether (deca-BDE) in toluene is sequentially degraded to nona- and octa-BDEs with increasing irradiation time. Radical formation with structurally similar compounds was much weaker, i.e. deca-BDE > octa-BDE (DE-79) > deca-bromobiphenyl (PBB 209) > deca-chlorinated biphenyl (PCB 209) >> diphenyl ether (DE), indicating that bromine and an ether bond enhance radical formation. With deca-BDE in THF, an MNP adduct of hydrogen atom was detected. In deuterated THF, a different set of EPR spectra was observed. These results suggest that the radical formation of deca-BDE is related to hydrogen abstraction from THF. The hyperfine splittings of the spin adducts suggest radical formation is initiated, or enhanced, in organic solvents with deca-BDE and light via debromination and hydrogen abstraction from the solvents. Our findings that UV irradiation of deca-BDE in organic solvents produces oxidizing free radical indicates that synergism in toxicity between PBDEs and UV light should be examined. (Supported by NIEHS P42ES013661, DOD DAMD17-02-1-0241, EPA R-82902102-0 and CHEEC)

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#20

SEMIQUINONE RADICALS FROM PCB QUINONE/HYDROQUINONE METABOLITES: ELECTRON PARAMAGNETIC RESONANCE STUDIES

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Polychlorinated biphenyls (PCBs) can be oxygenated to form very reactive hydroquinone and quinone products. A guiding hypothesis in the PCB research community is that some of the detrimental health effects of some PCBs are a consequence of these oxygenated forms undergoing one-electron oxidation or reduction, generating semiquinone radicals ($SQ^{\cdot-}$). Using EPR to detect $SQ^{\cdot-}$ formation, we observed that: (a) xanthine oxidase can reduce quinone PCBs to the corresponding $SQ^{\cdot-}$; (b) the heme-containing peroxidases (horseradish and lactoperoxidase) can oxidize hydroquinone PCBs to the corresponding $SQ^{\cdot-}$; (c) mixtures of PCB quinone and hydroquinone form $SQ^{\cdot-}$ *via* a comproportionation reaction; (d) tyrosinase acting on PCB *ortho*-hydroquinones leads to formation of $SQ^{\cdot-}$; (e) $SQ^{\cdot-}$ are formed when hydroquinone-PCBs undergo autoxidation in high pH buffer (»>pH 8); and surprisingly, (f) quinone-PCBs in high pH buffer can also form $SQ^{\cdot-}$; (g) these observations along with EPR suggest that hydroxide anion can add to quinone ring; and (h) H_2O_2 in basic solution reacts rapidly with PCB-quinones; (i) SOD can catalyze the oxidization of PCB-hydroquinone to quinone, yielding H_2O_2. However, using 5,5-dimethylpyrroline-1-oxide (DMPO) as a spin trapping agent, we did not trap superoxide, indicating that generation of superoxide from $SQ^{\cdot-}$ is not kinetically favorable. These observations demonstrate multiple routes for the formation of $SQ^{\cdot-}$ from PCB-quinones and hydroquinones. Our data also point to futile redox cycling as being one mechanism by which oxygenated PCBs can lead to the formation of reactive oxygen species, but this is most efficient in the presence of SOD.

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SYNTHESIS AND EPR PROPERTIES OF PCB QUINONE AND HYDROQUINONE METABOLITES WITH DIFFERENT DEGREES OF CHLORINATION ON THE OXYGENATED PHENYL RING SYSTEM

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Polychlorinated biphenyls (PCBs) comprise a group of persistent organic pollutants that differ significantly in their physicochemical properties, their persistence and their biological activities. They can be metabolized via hydroxylated and dihydroxylated metabolites to PCB quinone intermediates. We have recently demonstrated that both dihydroxy PCBs and PCB quinones can form semiquinone radicals *in vitro*. These semiquinone radicals are reactive intermediates that have been implicated in the toxicity of lower chlorinated PCB congeners. Here we describe the synthesis of a series of PCB metabolites with different degrees of chlorination in the oxygenated phenyl ring. First, several chlorinated 1,4-dimethoxybenzenes were synthesized using several different strategies. 1-Bromo-4-chloro-2,5-dimethoxybenzene was synthesized by chlorination of 1-bromo-2,5-dimethoxybenzene with H_2O_2/HCl. 1-Bromo-3,6-dichloro-2,5-dimethoxybenzene was prepared via 2-bromo-3,6-dichloro-4-methoxy-phenol as an intermediate by bromination of 1,4-dichloro-2,5-dimethoxybenzene with Br_2/Fe, followed by methylation with dimethyl sulfate. Subsequently, a series of dimethoxy PCB derivatives (e.g., 4,4'-dichloro-2,5-methoxyl-biphenyl, 3,4',6-trichloro-2,5-methoxyl-biphenyl and 3,4,4',6-chloro-2,5-methoxyl-biphenyl) were synthesized by coupling the chlorinated dimethoxybenzenes with 4-chlorobenzene boronic acid in the presence of $Pd(PPh_3)_4$ as catalyst. Finally, the dimethoxy PCBs were converted into the corresponding dihydroxy PCB derivative by demethylation with boron tribromide or the PCB quinone by oxidation with cerium ammonium nitrate. The chemistry of the semiquinone radicals formed by these compounds is currently under investigation. Different degrees of chlorine substituted quinone/hydroquinones give us different EPR pattern signal and the quinone/hydroquinone with higher degree of chlorine give the more stable signal.

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#22

SYNTHESIS OF ORTHO SUBSTITUTED PCBS AND THEIR METABOLITES USING MODIFIED SUZUKI AND ULLMANN COUPLING REACTIONS

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Polychlorinated biphenyls (PCBs) are an important group of environmental contaminants. The synthesis of PCB derivatives for biological studies is challenging because of the large number of possible PCB congeners and PCB metabolites. Especially the synthesis of PCB derivatives with multiple ortho substituents poses a synthetic challenge. Here we describe improved approaches, such as modified Suzuki and Ullmann coupling reactions, for the synthesis of this group of PCB derivatives. Conducting the Suzuki coupling reaction of iodo/bromobenzenes with chlorinated boronic acids at 110 °C (instead of 80 °C) gave PCB congeners with the desired 2,2′-dichloro substitution pattern in good to excellent yields. However, PCB congeners with three or four ortho chlorine substituents could not be obtained using these modified reaction conditions. Performing the Ullmann coupling reaction in solution gave symmetrical PCB congeners and unsymmetrical nitro PCB derivatives in moderate to good yields. These coupling reactions could be performed at 110°C (copper-bronze, 20% CuCl and NMP as solvent) or 150°C (copper-bronze, NMP as solvent), which is lower compared to classical Ullmann coupling conditions. PCB congeners synthesized using the Ullmann coupling reactions were also used as intermediates for the synthesis of several PCB derivatives. The respective PCB congener was nitrated, reduced to the respective amino PCB, and the desired functional group (-Cl or -SMe) was introduce using a Sandmeyer-type reaction. Methyl sulfonyl PCBs were subsequently obtained by oxidation with hydrogen peroxide. Overall, the modified synthetic approaches can be used for the synthesis of a large number of PCB derivatives for toxicological studies.

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#23

THE MULTI-FACETED CHEMISTRY OF PCB-QUINONES AND HYDROQUINONES IN CELL CULTURE MEDIA

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Thorough chemical as well metabolic studies are needed to better understand the impact of PCB contamination on human and environmental health. It is through these basic studies that new principles and ideas will come that can be used in hazard assessments. Here we investigate the auto-oxidation of PCB quinones and hydroquinones. We found that the PCB 4-chloro-2,5 hydroquinone auto-oxidizes very slowly in neutral, metal-free phosphate buffer. The rate of auto-oxidation increases upon the addition of superoxide dismutase yielding hydrogen peroxide. However, when placed in mammalian cell culture media (MEM media with 10% FBS) the rate of autoxidation is rapid, without added SOD; oxygen is reduced to hydrogen peroxide. Using EPR, the expected semiquinone radical was initially observed, but over time, this radical disappeared with concomitant formation of persistent secondary radicals. These results suggest an entirely new view on the potential chemical reactions of quinones and hydroquinones in vivo. The actual toxicological chemistry of these compounds in vivo appears to be quite different than that the original quinone/hydroquinone.

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#24
SYNTHESIS OF MONOSULFATE METABOLITES OF PCBS

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Sulfation of xenobiotics and endogenous compounds is an important reaction in intermediary metabolism contributing to the generation of bioactive metabolites and to their excretion. Organic molecules possessing sulfate moieties are widespread in biological systems and play an important role as modulators of physiological and pathological function. Polychlorinated biphenyls (PCBs), a major class of persistent organic pollutants, are metabolized to hydroxylated PCBs (HO-PCBs). Several HO-PCBs are substrates of sulfotransferases. In order to investigate the potential role of PCB sulfates in PCB toxicity, we have synthesized a series of ten HO-PCB sulfates. In the initial step of the synthesis, the respective methoxy PCBs were synthesized by the Suzuki coupling of different chlorinated benzeneboronic acids with appropriate brominated (chloro)benzene. The respective methoxy PCBs were demethylated with boron tribromide, followed by sulfation with 2,2,2-trichloroethyl chlorosulfate using DMAP as base. Finally, the 2,2,2-trichloroethyl protection group was removed by reduction with zinc powder at the presence of ammonium formate. The structure of the PCB sulfates was confirmed by NMR spectroscopy and mass spectrometry. The structures of several 2,2,2-trichloroethyl protected PCBs sulfate also verified by x-ray diffraction. These compounds are now available to investigate the metabolism of (OH-)PCBs in this pathway and the possible implications of PCB sulfates in the adverse health effects of PCBs. [Supported by NIH grants ES05605, ES013661 and ES012475]

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PCB INDUCED DOWN-REGULATION OF MNSOD EXPRESSION DELAYS QUIESCENT CELLS' ENTRY INTO THE PROLIFERATIVE CYCLE

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Polychlorinated biphenyls (PCBs) and their metabolites are environmental chemical contaminants which can produce reactive oxygen species (ROS) by autoxidation of dihydroxy PCBs or by reduction of quinones and redox-cycling. We investigate the hypothesis that PCB induced ROS-signaling regulates quiescent cells' (<5%S-phase) entry into S-phase. Monolayer cultures of quiescent human non-malignant breast epithelial cells (MCF10A) were incubated with 0-3 micromolar of PCBs for 4d, and re-plated at a lower cell density. Cells were harvested at the time of re-plating and various times thereafter for flow- cytometry assays of cell cycle phase distributions, ROS levels, and antioxidant enzyme activities. PCB (4-chloro-1, 4-benzoquinone (4-Cl-BQ), 2, 2', 4, 4', 5, 5'-hexachlorobiphenyl (PCB153), and aroclor 1254) treated quiescent cells exhibited a dose-dependent delay entering S-phase following re-plating, with maximal delay in 3 micromolar 4-Cl-BQ-treated cells. 4-Cl-BQ treated quiescent cells showed 2-fold decrease in Manganese superoxide dismutase (MnSOD) and Catalase activities, which correlated with increase ROS levels as seen by DHE and DCFH fluorescence compared to non-treated cells. The decrease in MnSOD activity was associated with decrease in MnSOD protein and mRNA levels. Interestingly, quiescent cells treated simultaneously with 4-Cl-BQ and PEG-catalase did not perturb entry into S-phase following re-plating. Overall, our results suggest that the down regulation of antioxidant enzymes, particularly MnSOD increased cellular redox environment towards a more oxidizing state, which delays quiescent cells' entry into the proliferative cycle. An additional significance of our study is the use of quiescent cell culture, which mimics more closely with *in vivo* cellular growth states. (NIEHSP42ES013661)

Keywords:
MnSOD, ROS, Quiescence, Cell proliferation, PCB

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CAVEOLIN-1 MEDIATES UP-REGULATION OF PRO-INFLAMMATORY CYTOKINES BY 3, 4,3',4'-TERTRACHLOROBIPHENYL (PCB77)

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Polychlorinated biphenyls (PCBs) are persistent organic pollutants that are ubiquitous in the environment. They can contribute to the development of atherosclerosis by endothelial activation, a critical first step in the development of the atherosclerotic plaque. PCBs in plasma are carried mainly by albumin and lipoprotein particles that interact with endothelial cells through their receptors in caveolae. Our recent data suggest that caveolae, membrane microdomains that regulate multiple signaling pathways in particular in endothelial cells, play a role in coplanar PCB77 toxicity. Endothelium-derived monocyte chemoattractant protein-1 (MCP-1) is a key activator of monocyte adhesion to activated endothelium, whereas interleukin-6 (IL-6) is an inflammatory mediator associated with increased risk of cardiovascular disease. The hypothesis that lack of caveolin-1, the major structural protein of caveolae can prevent up-regulation of these cytokines in endothelial cells was tested. PCB77 up-regulated both MCP-1 and IL-6 expression in primary porcine endothelial cells, with MCP-1 up-regulation being more pronounced. Subsequently, treatment with PCB77 induced gene expression of MCP-1 in primary mouse aortic endothelial cells and this was prevented in cells isolated from caveolin-1-deficient mice. The hypothesis that caveolae are mediators of PCB77-induced cardiovascular toxicity was also tested *in vivo*. PCB77 induced gene expression of inflammatory MCP-1 and IL-6 in the aortic tissue of control, but not in caveolin-1 -/- mice. As a result of this up-regulation, plasma levels of both MCP-1 and IL-6 were up-regulated by PCB77 in control, but not caveolin-1 -/- mice. In conclusion, these data show that induction of pro-inflammatory parameters, such as IL-6 and MCP-1, by coplanar PCBs in the vasculature is regulated through caveolae and can be prevented in the absence of caveolin-1. This suggests that caveolin-1 might be an important target for preventing PCB toxicity in exposed human populations. (Supported by grants from NIEHS, NIH (P42ES07380) and the University of Kentucky AES).

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CHARACTERIZATION OF GENE EXPRESSION RESPONSES ELICITED BY TOXIC AND NON-TOXIC AhR LIGANDS IN MURINE HEPA1C1C7 CELLS

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In order to characterize and distinguish the responses between toxic and non-toxic aryl hydrocarbon receptor (AhR)-mediated ligands, gene expression effects elicited by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and 3,3',4,4',5-pentachlorobiphenyl (PCB126) were compared to indolo[3,2-b]carbazole (ICZ) and β-naphthoflavone (βNF) in murine Hepa1c1c7 hepatoma cells. Dose-response studies at 12 hrs confirmed lower EC_{50} gene expression values for TCDD and PCB126 when compared to ICZ and βNF. For example, Cyp1a1 EC_{50} values were 21 pM, 231 pM, 27.1 nM and 1.2 μM for TCDD, PCB126, ICZ and βNF respectively. Temporal gene expression profiling using cDNA microarrays was also performed with 10 nM TCDD, 1 μM ICZ, 10 μM βNF or vehicle (DMSO) for 1, 2, 4, 8, 12, 24 or 48 hrs. Empirical Bayes analysis of the microarray data identified 459 and 221 gene responses elicited by toxic and non-toxic AhR ligands respectively, and in total, 524 gene responses were elicited by at least one AhR ligand. Comparison of the responses identified many toxic and non-toxic specific gene responses, however, hierarchical clustering results of 524 genes revealed that PCB126, βNF and ICZ possessed temporal gene expression signatures similar to TCDD. The difference in the signatures with respect to those elicited by TCDD is an overall reduction in the magnitude of the responses. Given the diverse structural nature of these toxic and non-toxic AhR ligands, the results suggest that the differences in the associated toxicity/non-toxicity are a reflection of differences in the relative potency of elicited gene responses. Supported by NIH T32 ES07255.

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SPECIFICITY OF HUMAN HYDROXYSTEROID SULFOTRANSFERASE HSULT2A1 FOR HYDROXYLATED POLYCHLORINATED BIPHENYLS

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Sulfotransferases (SULTs) catalyze the transfer of a sulfuryl group from the physiological donor 3'-phosphoadenosine-5'-phosphosulfate (PAPS) to endogenous molecules (e.g., steroids, catecholamines, bile acids, and others) and exogenous compounds such as drugs, carcinogens and other xenobiotics. Previous work has suggested that the hydroxylated metabolites of polychlorinated biphenyls (OHPCBs) interact primarily with phenol sulfotransferases (family 1 SULTs). We have recently shown that these compounds also interact with hydroxysteroid (alcohol) sulfotransferases (family 2 SULTs). We hypothesized that OHPCBs affect the activity of hSULT2A1 by serving as inhibitors and/or substrates for the enzyme. Thirteen congeners of OHPCBs were examined as substrates and inhibitors of recombinant hSULT2A1 that had been purified to homogeneity by anion exchange and hydroxyapatite chromatography. Of the congeners tested, six were inhibitors of the hSULT2A1-catalyzed sulfation of dehydroepiandrosterone, with IC_{50} values ranging from 4 microM to 120 microM. *para*-Hydroxybiphenyls with an unsubstituted phenolic ring, and most with a single chlorine or hydroxyl substituent ortho to the phenolic hydroxyl, were inhibitors of hSULT2A1. The most potent inhibitor was 4'-OH PCB 9. Seven of the OHPCBs examined were substrates for hSULT2A1, indicating sulfation as a potential metabolic reaction for these compounds. Those OHPCBs with a 3,5-dichloro-4-hydroxy substitution were the most effective substrates for hSULT2A1. Future studies will yield additional information on the potential for OHPCB-mediated interference with physiological sulfation reactions catalyzed by hSULT2A1 as well as the potential role for this enzyme in the metabolism of hydroxylated PCB metabolites in humans. [Supported by NIH grant P42 ES013661]

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#29

GENOTOXICITY OF PCB3 METABOLITES IN VITRO - WHICH ONE IS THE BAD GUY?

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A hot summer day in Chicago or in a classroom building built in the 70s- both are scenarios for the possibility of exposure to elevated levels of lower chlorinated PCBs. PCB3 (4-monochlorobiphenyl), a member of this group of semivolatile PCB congeners, is readily metabolized to monohydroxy- and dihydroxy-biphenyls (2,5-hydroquinone, 3,4-catechol), and further to quinones (PCB3-2,5-pQ and PCB3-3,4-oQ). We demonstrated that PCB3 has an initiating potential in rat livers and the quinoid metabolites induce gene mutations in cultured Chinese hamster V79 cells. Our question was what type of genotoxic damage and which metabolite(s) is/are responsible for this effect. Here we measured the effects of PCB3 and its dihydroxy- and quinone metabolites on sister chromatid exchange frequency and cell cycle progression. SCE are coordinated reciprocal single strand break-and-rejoining events during the S-phase. Only the PCB3-3,4-HQ significantly increased SCE levels, but on the other hand PCB3-2,5-HQ doubled the chromosome number (4n) in >90% of all metaphases after exposure for 2 cell cycles. A delay in the cell cycle progression and later reduction chromosome number was observed. Since nearly all cancer cells are hyperdiploid, polyploidization and uneven chromosome loss is hypothesized as one possible mechanism of carcinogenesis. Also, the ability to induce SCE and cell transformation in vitro correlates surprisingly well. Thus different PCB3 metabolites may be involved in cancer initiation by different mechanisms, i.e. gene mutation (quinones), SCE (3,4-catechol) or polyploidization (2,5-hydroquinone). More studies are needed to understand the importance of each mechanism for PCB3's potential as carcinogen in vivo.

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CELL GROWTH PHASE SPECIFIC PCB-INDUCED ALTERNATIONS IN THE SUPEROXIDE LEVELS IN HUMAN PROSTATE EPITHELIAL CELLS

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PCBs are a general class of compounds that bio-accumulate in the environment as mixtures comprising several individual PCB congeners, each of which has different biological effects. PCBs were used in transformers, capacitors, and other electrical equipment and represent contaminants found in air, water, and soil during their manufacture, use, and disposal. PCBs have shown to cause adverse health effects possibly thought to be mediated *via* altering cellular reactive oxygen species. Some selected PCBs are shown to increase the cellular reactive oxygen species and specifically superoxide levels. We know that the effect of any drug exposure on cells depends on the various phases of the cell cycle. Therefore we hypothesize that the induction of superoxide levels could differ when the cells are treated with PCBs in early exponential and late exponential phase. We have used PCB 3, PCB 77, PCB 153, 4-BQ and Aroclor 1254 to study the levels of superoxide in human non- malignant prostate epithelial cells. By DHE fluorescence assay, we observed Aroclor 1254 and 4-BQ increased superoxide levels significantly in early exponential cells whereas no significant increase was seen in late exponential cells. Similarly, using the mitosox fluorescence assay, PCB 153, Aroclor 1254 and 4-BQ showed significant increase in superoxide levels in early exponential cells whereas only 4-BQ showed significant increase in late exponential cells. Our results reveal that induction of ROS in cells by PCBs is a function of cell growth phase (Supported by NIEHS P42 ES013661).

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INTERACTIONS OF HYDROXYLATED POLYCHLORINATED BIPHENYLS WITH RAT SULFOTRANSFERASES AND THEIR MODIFICATION BY OXIDIZED GLUTATHIONE

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Potential metabolic differences between rats and humans can be a significant challenge in the extrapolation of studies between these species. Recent reports have indicated that hydroxylated PCBs (OHPCBs) can serve as inhibitors and substrates for human sulfotransferase 1A1 (hSULT1A1) and hSULT2A1. We hypothesized that OHPCBs also interact with the homologous hepatic enzymes in the rat, i.e., rSULT1A1 and rSULT2A3. Among 15 OHPCBs investigated, 4-OH PCB 8, 4'-OH PCB 3, 9, 12, and 35, and 6'-OH PCB 35 were substrates for rSULT1A1, while the others were inhibitors. Those OHPCBs with a 3,5-dichloro-4-hydroxy substitution displayed the lowest IC_{50} values (0.3 - 4.4 microM) with rSULT1A1. Differences in chlorine atom substitutions between the 2 and 3 positions, or 2' and 3' positions, of *para*-hydroxybiphenyls create large alterations in interactions observed with rSULT1A1. None of the OHPCBs examined were substrates for rSULT2A3, and 11 were weak inhibitors. Thus, the major family 2 SULT in rat liver is much less sensitive to interactions with these OHPCBs than the major SULT2 isoform in human liver. Our second hypothesis was that regulation of rSULT1A1 by oxidation of cysteines in the protein would alter its specificity for OHPCBs. After treatment of rSULT1A1 with 1mM GSSG, four of the OHPCBs that were not substrates under reducing conditions became substrates for the enzyme, and two of these four were sulfated in reactions catalyzed by rSULT1A1 that had been pretreated with 0.85 mM GSH: 0.15 mM GSSG. The reversibility of this effect was examined with 4'-OH PCB 6. The shift in specificity for OHPCBs upon oxidation of rSULT1A1 was found to be reversible upon reduction of the oxidized enzyme by subsequent incubation with dithiothreitol (5 mM), wherein no sulfation of 4'-OH PCB 6 was observed with the resultant re-reduced enzyme. Such modification of the specificity of rSULT1A1 for OHPCBs by its oxidative environment may have relevance to sulfation of these PCB metabolites under conditions of cellular oxidative stress. [Supported by NIH grant P42 ES013661]

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XENOBIOTIC GEOMETRY AND MEDIA PH DETERMINE CYTOTOXICITY THROUGH SOLUBILITY

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Biological activity is dependent upon the solubility of the xenobiotic, but very little is known about the factors that influence solubility in cell culture. In the present study we used a series of monofluorinated analogues (F-PCBs 3) of 4-chlorobiphenyl (PCB 3) as model compounds to investigated the effects of the dihydral angle, modeled with semiempirical and *ab initio* molecular orbital methods, and the dipole moment, calculated in vacuum and in water, on solubility, measured by diffraction spectroscopy. As biological endpoint we determined cytotoxicity in human liver (HepG2), colon (CaCo2) and skin keratinocyte (HaCaT) cell lines. We found a strong positive correlation between the dihedral angle, the cavitation energy, the solubility, and the cytotoxicity in those three human cell lines. The dipole moment was of minor influence. We also analyzed the influence of pH changes in cell culture medium containing 10% fetal bovine serum (FBS), changes that may occur in many cell culture media by temporary exposure to non-CO_2-buffered air. We observed that the solubility was strongly affected by the pH and that this effect was not reversed by subsequent pH re-adjustment to neutral levels. In addition, the cytotoxicity study showed that both, the actual pH and the pH history of a medium containing FBS, had a strong influence on toxicity. We hypothesize that pH-driven changes in the tertiary and quaternary structure of albumin are responsible. These observations have implications for studies of the biological activity of semi-soluble compounds, like PCBs and related compounds. (Supported by P42ES013661 from NIEHS, Alexander von Humboldt Foundation, Germany, and DAMD 17-02-1-0241 from DOD).

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OPTIMIZATION OF THE GAS CHROMATOGRAPHY PARAMETERS FOR IMPROVING THE SEPARATION OF PCB CONGENERS IN AROCLOR MIXTURES

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Polychlorinated biphenyls (PCBs) are widespread environmental pollutants and have been determined in most environmental laboratories for many years. The need to identify the individual PCB congeners in environmental and biological matrices results from the fact that they are characterized by very differential levels of toxicity. The capillary gas chromatography (CGC) admittedly introduced the possibility of congener-specific analysis, nevertheless the results of interlaboratory studies show that identification and quantification of individual PCB congeners are still a problem. The aim of this study was to identify individual PCB congeners in technical Aroclors 1242:1254:1260 (1:1:1) as well as to optimize the gas chromatography parameters of the separation. In the first step of this experiment the sequence of PCBs separation was evaluated on two capillary columns (Rtx-XLB and ZB-5). Identification of PCB congeners was made by using: the results of GC-MS analysis of standard mixture PCB_{17MS}, the retention times from Rogers database and the comparison of the % share of individual congeners in Aroclors mixture according to Frame database. Finally 105 of the individual PCB congeners in Aroclors mixture were identified using the results from two GC columns. The next stage of this study was the optimization of the gas chromatographic separation and detection of selected PCBs. An L_{27} Tagouchi orthogonal array method was employed. The system of tabulated designs (arrays) and enabled estimation of the maximum number experimental variables in an unbiased (orthogonal) manner with a minimum number of experiments were used. In twenty seven experiments total of six factors in three levels each were accommodated. The influence of the column phase, temperature program, the carrier gas pressure program, the injector temperature program and the make-up gas flow in detector has been studied. The effects, individual or synergistic, of all factors on the performance of the GC system were elucidated using the statistical method of analysis of variance (ANOVA). ANOVA results show that first oven temperature increase following by type of the column and the make-up gas flow in the ECD detector influenced the PCB separation to the largest extent. The effect of first carrier gas pressure increase was noticed but it was not statistically significant. Statistical analysis allowed finding the optimum conditions for the two columns. The optimum parameters are: the first oven temperature increase 1°C/min, the first carrier gas pressure increase 0.3 psi/min and the make-up gas flow in ECD detector 30 ml/min.

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INVESTIGATION OF 4-CHLOROBIPHENYL (4-CB) AND ITS PHASE I METABOLITES AS SUBSTRATES OF HUMAN RECOMBINANT PROSTAGLANDIN H SYNTHASE-2

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Polychlorinated biphenyls (PCBs) are environmental pollutants primarily metabolized by hepatic cytochrome P-450 (CYPs) to phenols, catechols and hydroquinones which can undergo redox interconversion to quinones. These quinones are electrophilic and are highly reactive to nucleophiles, such as proteins and DNA. Recent studies have shown that electron rich xenobiotics, such as phenolic compounds, can serve as reducing cosubstrates during the peroxidase reaction of prostaglandin H synthase (PGHS). Therefore, we hypothesize that PGHS oxidizes the dihydroxy metabolites of PCBs to the corresponding quinones. 4-Chlorobiphenyl (4-CB) and its analogues, 4'-hydroxy-4-chlorobiphenyl (4-CB-4'-OH), 2',3'-dihydroxy-4-chlorobiphenyl (4-CB-2',3'-OH), 3',4'-dihydroxy-4-chlorobiphenyl (4-CB-3',4'-OH), and 2',5'-dihydroxy-4-chlorobiphenyl (4-CB-2',5'-OH) were selected as the model compounds to test the hypothesis. The model compounds were initially tested for their ability to inhibit PGHS-2 activity. Instead of inhibition, the dihydroxy-4-CBs increased the formation of prostaglandin F2a. Based on these findings, further investigation using incubation methods of the 4-CB-2',3'-, 3',4'-, 2',5'-OH with human recombinant PGHS-2 (hPGHS-2) were conducted using N-acetyl cysteine (NAC) as a trapping agent for the corresponding electrophilic quinones. We found that hPGHS-2 catalyzed oxidation of 4-CB-2',5'-, 2',3'-, and 3',4'-OH to the corresponding quinones which rapidly reacted with NAC to form mono-, and di-NAC adducts in vitro. These adducts were identified and quantified by LC-MS and 1H-NMR. The addition of NAC to quinones occurred via a nucleophilic addition at the beta-position of 4-CB benzoquinones. PGHS-2 may, therefore, contribute to the activation of PCBs and metabolites, especially in non-hepatic tissues. (Supported by P42 ES 013661)

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INVESTIGATION OF MECHANISM(S) OF DNA DAMAGE INDUCED BY 4-MONOCHLORO-BIPHENYL (PCB3) METABOLITES

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4-Monochlorobiphenyl (PCB3) is readily converted by xenobiotic-metabolizing enzymes to dihydroxy-metabolites and quinones. Our analysis of their-genotoxic activity in V79 cells indicates so far that chromosome loss is the most sensitive (2.5 μM) endpoint for the hydroquinone [2-(4'-chlorophenyl)-1,4-hydroquinone; 4ClPh-HQ], whereas *para*-quinone [2-(4'-chlorophenyl)-1,4-benzoquinone; 4ClPh-pQ], it's oxidized form, induces point mutations at concentrations of 0.5 μM. We hypothesized that these two interrelated metabolites induce genotoxicity by different mechanisms, possibly redox cycling with ROS generation or binding to nucleophilic sites in DNA and/or proteins. For further elucidation we employed two cell lines with different myeloperoxidase activities, HL-60 and Jurkat, and measured cytotoxicity, DNA damage (COMET assay) and intracellular levels of reactive oxygen species (ROS) at 37 °C and enzyme inhibiting 6 °C. 4ClPh-pQ induced DNA damage in HL-60 cells and increased intracellular ROS levels in HL-60 and Jurkat cells at both 37 and 6 °C. 4ClPh-HQ induced DNA damage and ROS production only at 37 °C in HL-60 cells; no significant DNA damage and ROS production were observed at 6 °C. These studies reveal that ROS production and DNA damage by 4ClPh-HQ is temperature and enzyme dependent, whereas this is not the case with the 4ClPh-pQ, indicating that 4ClPh-pQ may be active by non-enzymatic mechanisms (binding to GSH and/or other nucleophiles (DNA?)), whereas 4ClPh-HQ may be oxidized by myeloperoxidase (MPO) in HL-60 cells with the generation of ROS. Further experiments with GSH-depleted/supplemented cells and MPO-inhibition will clarify the role of these mechanisms in PCB3 genotoxicity. (Supported by NIEHS P42ES013661, DOD DAMD17-02-1-0241, EPA R-82902102-0 and CHEEC)

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#36
GAS CHROMATOGRAPHIC SEPARATION OF METHOXYLATED PCB ATROPISOMERS

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Polychlorinated biphenyls (PCBs) and their metabolites may exist as stable rotational isomers (or atropisomers) that form non-superimposable mirror images. Changes in the enantiomeric enrichment have been used to study the disposition of PCBs and their methylsulfonated metabolites in laboratory animals. However, little is know about the enantiomeric enrichment of hydroxylated PCBs (OH-PCB) in biological samples. The aim of this study was to separate several chiral methoxylated PCB derivatives (MeO-PCB) by chiral gas chromatography using the Chirasil-Dex column (25 m x 0.25 mm id x 0.25 m, Varian, Palo Alto, CA). MeO-PCBs were chosen because OH-PCB metabolites are typically derivatized with diazomethane and analyzed as the corresponding MeO-PCBs. Towards this goal, several chiral MeO-PCBs with a 3-methoxy-2,4,6-trichlorophenyl moiety (i.e., 3-MeO-CB 98, 3-MeO-CB 100, 3'-MeO-CB 140 and 3-MeO-CB 154) were synthesized using the Cadogan coupling reaction. In addition, 3-MeO-CB150 and 4-MeO-CB 136 were included in this study because the corresponding OH-PCBs are metabolites of PCB 136. Under isothermal conditions, the atropisomers of several MeO-PCBs could be separated using the Chirasil-Dex column, with resolutions of 0.80 for 3-MeO-CB 98 (140°C), 0.42 for 3'-MeO-CB (140°C), 0.87 for 3'-MeO-CB 154 (150°C), 0.57 for 3-MeO-CB 150 (160°C) and 0.79 for 4-MeO-CB 136 (140°C). No chiral separation was observed for 3-MeO-CB 50 and 3-MeO-CB 100. To shorten the analysis time, the effect of the several gas chromatographic parameters (initial temperature, temperature increment and carrier gas flow) on the resolution of the MeO-PCBs was investigated. Under optimized conditions, it is possible to obtain resolutions >0.7 for the above mentioned MeO-PCBs with a 5 hours temperature program. The only exceptions are 3'-MeO-CB 140 (resolution of 0.45), 3-MeO-CB 50 (no resolution) and 3-MeO-CB 100 (no resolution). These resolutions are sufficient to allow preliminary investigations of the enantiomeric enrichment of OH-PCB in vitro and in vivo. [Supported by NIH grants ES05605, ES013661 and ES012475]

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(+)-PCB 136 BINDS MORE EFFICIENTLY TO MOUSE HEPATIC MICROSOMES THAN (-)-PCB 136

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PCB 136 is a neurotoxic PCB congener that displays axial chirality. (+)-PCB 136 has been shown to be enriched in tissues from mice treated with racemic PCB 136. Spectral interactions of PCB 136 atropisomers with hepatic microsomal cytochrome P450 (CYP) enzymes were investigated to test the hypothesis that enantioselective binding to CYP enzymes causes the enrichment of (+)-PCB 136 in vivo. Female C57Bl/6 mice were treated by intraperitoneal injection with phenobarbital (PB, 400 μmol/kg body wt), dexamethasone (Dex, 123 μmol/kg body wt), β-naphthoflavone (NF, 100 μmol/kg body wt) or corn oil (CO) (10 ml/kg body wt) for three consecutive days. Hepatic microsomes were prepared and binding of PCB 136 atropisomers to microsomal CYP enzymes was assessed by difference spectroscopy using a dual wavelength/split beam spectrometer. Sample and reference microcuvettes both contained microsomes diluted to 4 nmol CYP/ml in 0.1 M K_3PO_4 buffer (pH 7.5). The maximal absorbance change (ΔA_{max}) values, a measure of PCB binding to CYP enzymes, were derived by nonlinear regression analysis from the absorbance change versus PCB concentration curves. Binding of racemic PCB 136 was greatest with microsomes from PB- (ΔA_{max}=0.027) followed by Dex- (ΔA_{max}=0.020), CO- (ΔA_{max}=0.012), and NF- (ΔA_{max}=0.008)-treated mice. (+)-PCB 136 bound significantly better to microsomes from PB-treated mice than did (−)-PCB 136 (ΔA_{max}=0.028 and 0.020, respectively). In addition, (+)-PCB 136 bound most effectively, followed by (±)-PCB 136 and (−)-PCB 136, to the other microsomal preparations. The results suggest that (+)-PCB 136 binds more efficiently than (−)-PCB 136 to different hepatic microsomal CYP enzymes, an observation that may explain the enantioselective enrichment of (+)-PCB 136 in mice. [Supported by NIH grants ES05605, ES013661 and ES012475]

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UPTAKE OF POLYCHLORINATED BIPHENYLS IN SOIL USING MEDICAGO SATIVA

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Potential of phytoremediation for polychlorinated biphenyls (PCBs) was investigated by using alfalfa, *Medicago sativa*. Soil was prepared by spiking Aroclor 1254 at 1 mg/kg-dry weight. Alfalfa was grown in the contaminated soil for 5-week. Upon harvest, aerial tissues of the plants from each assay were combined, freeze-dried and analyzed for PCBs. Soil analysis was performed for pre-growth and post-harvest soil. The major 17 PCB congeners in Aroclor 1254 were identified and grouped into tetra-, penta- and hexachloriated biphenyls. A significant decrease of total PCBs by 90% was observed in the control soil after the growth period mainly due to the decrease of penta- and hexachlorianted biphenyls. The decreases for penta- and hexachlorinated biphenyls were 82 and 100%, respectively. For tetrachrorinated biphenyls, the decrease was 6 % in control soil, whereas a 57% of decrease was observed in the soil planted with alfalfa. No evident uptake of PCBs by alfalfa was observed in this study. However, possible biotransformation of PCB by alfalfa might have occurred.

Chemical analysis of PCBs in plant and soil were conducted using stir bar sorptive extraction (SBSE) coupled with thermal desorption followed by gas chromatography-mass spectrometry (GC-MS). SBSE condition was optimized to extract Aroclor 1254.

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TRAVEL AWARD

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PCB MONITORING WITH BIVALVES AS A BIOINDICATOR IN WESTERN JAPAN

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In recent years, influence of POPs on humans and the ecosystem has been concerned and international monitoring and control has been more required than ever. Because POPs concentration is commonly very low in the environment, it is difficult to measure the concentration directly. In contrast, biomonitoring is efficient because the concentration can be increased due to bioaccumulation.

In this study, distribution of PCBs concentration was monitored with bivalves as a bioindicator in water area of western Japan. Accumulation characteristics of PCBs and the availability for the PCBs monitoring were discussed. Field surveys were conducted, and bivalves (mussels in seawater area and corbiculas in freshwater area) and water samples were collected from 13 points in the Seto Inland Sea in 2004 and 8 points in lakes and rivers in western Japan in 2005. All isomers of PCBs were targeted and their concentrations in the bivalves and water samples were determined using high-resolution GC-MS. As a result, range of PCBs concentration in bivalves was 0.78~46 (ng/g-wet) and that in water was 0.74~53 (ng/L). Concerning homologue of PCBs, total ratio of total homologue amount from M1CB to T4CB to total PCBs was 70% in water, however, that of PCBs from P5CB to D10CB was 60% in bivalves. Therefore it was found that high chlorinated PCBs can be more accumulated than low chlorinated PCBs from water to bivalves. Based on the principal component analysis which was applied to PCB homologue, the sampling points could be classified and sources of PCB pollution could be predicted. In respect to accumulation characteristic of PCBs, it was found that as PCBs was highly chlorinated, bioaccumulation factor could be increasing from 10^2 to 10^4. But bioaccumulation factor of PCBs after H7CB (logKow$\leqq$6.8) could be decreasing from 10^4 to 10^2. And also the 2,4,5-substituted isomers of the PCBs were easily to be accumulated, whereas 2,3,4,5-substituted isomers were difficult to be accumulated. Moreover, it was suggested that there is a same tendency between the accumulation characteristic from seawater to mussels and that from freshwater to bivalves. Based on the results, it was verified that PCB monitoring method with bivalves as a bioindicator in water area is efficient.

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#40

ARE ORTHO-SUBSTITUTED PCBs SUBSTRATES FOR THE MULTIDRUG RESISTANCE TRANSPORTER MDR1A/1B IN MICE?

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It is believed that the absorption of polychlorinated biphenyls (PCBs) and their transport to target sites is governed by passive diffusion. If this hypothesis is correct, there should be no selective processes for the absorption, distribution and excretion of individual PCB congeners and their metabolites. However, there are several studies showing selective enrichment of PCB congeners in certain tissues in wildlife, laboratory animals and humans. These studies suggest that some PCB congeners may be subject to active transport processes *in vivo*. Based on established structure-activity relationships we hypothesize that the multidrug resistance (MDR) transporter is responsible for the tissue-selective enrichment of PCB congeners. To test this hypothesis we investigated if the MDR transporter influences the absorption and disposition of PCBs using the mdr1a/1b knockout mouse model. An environmentally relevant mixture containing PCBs 91, 95, 132, 136, 149, 174, 176 and 183 was administered as a single oral dose (5mg/kg body weight) to female FVB or mdr1a/1b knockout mice. Mice were sacrificed after 24h, and brains were collected for PCB analysis. The tissue samples were homogenized and extracted first with 2-propanol-DEE (5:2, v/v) and then with hexane-DEE (9:1, v/v). The solvent was evaporated and the extractable lipid content was determined gravimetrically. The extracts were redissolved in hexane and derivatized with diazomethane. The PCB, OH-PCB and $MeSO_2$-PCB fractions were separated by liquid-liquid partitioning, purified by column chromatography and analyzed by gas chromatography with an electron capture detector. The analysis method was linear over a concentration range from 9.86 to 514,00 ng/g of wet tissue weight. Recovery rates were 108 ± 9%, 95 ± 15% and 50 ± 20% for PCBs, OH-PCBs and $MeSO_2$-PCBs, respectively (n = 20). No significant differences in the extractable lipid content (8.50 ± 0.36% and 8.37 ± 0.41% for FVB and mdr1a/1b knockout mice, respectively; n= 9) and tissue levels of PCBs, OH-PCBs and $MeSO_2$-PCBs were observed between wild-type and mdr1a knockout mice. These studies suggest that MDR does not influence the levels of PCBs *in vivo*; however, further studies are currently underway to investigate if MDR alters the enantioselective disposition of PCBs in different tissues. [Supported by NIH grants ES05605, ES013661 and ES012475]

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#41

MICROBIAL DEGRADATION OF PCBS IN SEDIMENT AMENDED WITH ACTIVATED CARBON.

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A novel in-situ strategy for remediation of polychlorinated biphenyl (PCB) contaminated sediment involves addition of activated carbon as a sorbent to sequester PCBs and consequently reduce environmental exposure and risk to human health. Although PCBs are extremely persistent in the environment, microbial transformation has been shown to occur. Understanding these microbial processes is critical for making decisions concerning remediation and risk assessment of PCB impacted sediments. The objective of this research is to understand how addition of strong sorbents like activated carbon alters the availability of PCBs to microorganisms that degrade PCBs aerobically.

Grasse River sediment was chosen for this study because nearly 50% of the total PCBs in the sediments are di-and tri-chlorobiphenyls which are amenable to aerobic microbial degradation. Aerobic slurry of the sediment showed a significant decrease in the mass of di, tri, and tetrachlorobiphenyls as compared to an abiotic control after 60 days of incubation. Activated carbon amended sediment showed slower biodegradation and also a decrease in the volatilization of PCBs. Ongoing laboratory work is assessing the microbiology of the sediment to identify the microbial population that is involved in the degradation of PCBs in Grasse River sediment.

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MANIPULATION OF SOIL/SEDIMENT GEOCHEMISTRY TO CONTROL PCB TRANSPORT AND BIOACCUMULATION

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Bioavailability of PCBs in sediments depends on site-specific sediment geochemistry and association of PCBs with weak or strong geosorbents. Recent findings demonstrate that contaminant bioavailability and transport pathways in impacted sediments can be interrupted by modifying and enhancing the binding capacity of natural sediments. This presentation will provide an overview of the technology development process starting from the laboratory-scale findings of fundamental revelations of contaminant sorption in sediments at the microscale to PCB bioaccumulation reduction with carbon amendment in laboratory studies and engineering methods used in pilot technology demonstrations at the field scale.

The effect of activated carbon amendment in four freshwater sediments from the Great Lakes Areas of Concern sites was assessed through the measurements of PCB desorption rates, PCB equilibrium partitioning into the aqueous phase, and PCB uptake in the oligochaete *Lumbriculus variegatus*. PCB biouptake reduction of up to 95% was observed with two minutes of mixing of activated carbon into sediment [1, 2]. Addition and mixing of activated carbon in soil showed similar reductions in PCB biouptake in the earthworm *E. fetida*. We demonstrate through these studies that PCB bioavailability reductions may be achieved in both saturated sediments and unsaturated soil environments through the amendment and short-term mixing of activated carbon. Results from the present bioaccumulation studies indicate that application of activated carbon to PCB-contaminated sediment or soil can be an effective in-situ stabilization method to reduce contaminant availability to aquatic and terrestrial food chains.

In support of this technology development, three pilot-scale technology demonstrations are ongoing: 1) in a tidal mudflat in San Francisco Bay, 2) in river sediments in Grasse River, NY, and 3) in marine sediments in Trondheim Harbor, Norway. The pilot-scale demonstrations are evaluating different engineering methods of application of activated carbon to PCB-impacted sediments to alter sediment geochemistry and thereby the bioavailability of PCBs to benthic organisms. The three sites pose a wide range of engineering challenges in the application of carbon and monitoring of the effectiveness of the remediation process.

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Keywords:
PCB bioavailability, geochemistry, remediation, activated carbon
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#43
BIOTRANSFORMATION OF PCB 77 BY POPLAR TREES

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Polychlorinated biphenyls (PCBs) are very stable chemically, but biodegradation of some congeners has been reported. Bacteria can degrade PCBs by anaerobic dechlorination and aerobic degradation. Animals can metabolize PCBs to form hydroxyl and methylsulfonyl metabolites. The metabolism in animal livers is first by the introduction of oxygen via cytochrome P-450 monooxygenases, then by conjugation with glutathione S-transferases leading to methylsulfone metabolites. According to the *Green Liver* model, the biotransformation of xenobiotics via plants is similar to that in animal livers. Plant cell cultures have been reported to transform less-chlorinated PCBs to hydroxylated PCBs. This is the first report to study the *in vivo* transformation of PCBs by intact whole plants. Poplar plants (*Populus deltoides ´ nigra*, DN34) were hydroponically exposed to PCB 77 (IUPAC No.), 3,3',4,4'-tetrachlorobiphenyl, for 5 days. The root tissue and hydroponic solution were sampled and analyzed. Dechlorination of PCB 77 to PCB 3 was determined by GC-MS/MS. One hydroxylated product of PCB 77 (6OH-PCB 77) was analyzed qualitatively by GC-MS in both root tissue and hydroponic solution. In conclusion, the co-planar PCB 77 can be taken up and biotransformed by whole poplar roots. Persistence and toxicity of the metabolites is under further investigation.

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DIABETES AND EXPOSURE TO PCBs, DDE, PBDEs IN FREQUENT AND INFREQUENT GREAT LAKES SPORT FISH CONSUMERS

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The relationship of dioxin exposure with diabetes has been investigated in a number of cohorts, many with high occupational exposures, with mixed findings. More recently, polychlorinated biphenyls (PCBs) and p,p´-diphenyldichloroethene (DDE) have been investigated as potential etiological factors for diabetes, predominantly in cross sectional studies.

This study included both cross sectional and prospective data from a cohort of adults from the Great Lakes basin. The cohort, which was established in 1992, is composed of Great Lakes Charter boat captains and their spouses, Wisconsin anglers, and referents from the same geographic areas that have low sport fish consumption. Participants have been followed periodically for health parameters and fish consumption habits. PCBs, DDE, and polybrominated diphenyl ethers (PBDEs) were measured in a subgroup of participants in 1994-5 and 2004-5.

Serum PCB and DDE levels decreased during the study period in both anglers and referents, while PBDEs increased. In 2004-5, median DDE and PBDEs were similar and PCBs were slightly higher than levels measured in 2001-4 in a random sample representative of the US population (National Health and Nutrition Examination Survey, NHANES). Analysis of the 2004-5 cross sectional data from 498 participants revealed associations of serum DDE and dioxin-like PCBs with diabetes. PBDEs and non-dioxin like PCBs were not associated with diabetes.

An important limitation of the cross sectional analysis is the lack of knowledge of the temporality of exposure and disease, with the possibility that associations could be related to alterations in contaminant metabolism by diabetes. Prospective studies with insufficient elapsed time between exposure assessment and disease incidence could also be subject to this limitation. Prospective analyses in the cohort were consistent with cross sectional results and showed that incident diabetes was associated with serum DDE levels, but not with PCBs, in 471 participants followed for an average of 8 years. The association of DDE with diabetes remained when cases occurring during the first 6 years of follow up were excluded, reducing the possibility that reverse causality was responsible for the relationship. Furthermore, no evidence was found to support decreased metabolic rates of DDE or PCBs in relation to diabetes in 293 participants who had repeat measurements of serum PCBs and DDE.

This study is one of the first prospective studies showing an association of DDE with development of diabetes. Further studies will follow up the cohort to identify additional incident diabetes cases and explore biological mechanisms.

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PCBs, THYROID DISRUPTION AND BRAIN DEVELOPMENT: WHAT IS IT THAT WE DON'T KNOW?

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Thyroid hormone (TH) is essential for normal brain development and there is significant evidence that polychlorinated biphenyls can produce neurotoxic effects in part by disrupting TH signaling in the developing brain. The idealized model of the thyroid axis is that TSH is regulated by TH negative feedback, protecting the individual from small (or even moderate) changes in serum TH. From this view, if TSH levels do not rise, observed decreases in serum TH are not physiologically relevant. In contrast, PCBs can reduce serum T4 without increasing TSH. One possibility is that PCBs can also act as TH receptor (TR) agonists. To study this, we compared the effects of PCB exposure with that of exposure to propylthiouracil (PTU, blocks thyroperoxidase) on TH levels and on measures of TH signaling in various brain regions and in various tissues. We find that endpoints of TH signaling in different tissues are differentially sensitive to TH reduction caused by PTU. This also applies to different brain regions. Likewise, endpoints of TH signaling in different tissues respond differently to PCB exposure – both from each other and from the effects of PTU. We find that specific individual non coplanar PCBs can be metabolized by CYP1A1 to form TR agonists in vitro. In addition, tissues that respond to PCB exposure the least also have the smallest CYP response to PCB exposure. Although provocative, TH transport and metabolism are clear points of regulation of TH action, and toxicant effects on these processes may clarify current paradoxes. These effects may account for some of the effects of PCB exposure on brain development.

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CATALASE AMELIORATES POLYCHLORINATED BIPHENYL-INDUCED CYTOTOXICITY IN NON-MALIGNANT HUMAN BREAST EPITHELIAL CELLS

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Polychlorinated biphenyls (PCBs) are environmental chemical contaminants believed to adversely affect cellular processes. We investigated the hypothesis that PCB-induced changes in the levels of cellular reactive oxygen species (ROS) induce DNA damage resulting in cytotoxicity. Exponentially growing cultures of human non-malignant breast epithelial cells (MCF10A) were incubated with PCBs for 3 days and assayed for cell number, ROS levels, DNA damage, and cytotoxicity. Exposure to **2-(4-chlorophenyl) benzo-1,4-quinone** (4-Cl-BQ) or 2, 2,2',4,4',5,5'-hexachlorobiphenyl (PCB153) significantly decreased cell number, MTS reduction, and increased the percentage of cells with sub G_1 DNA content. Results from electron paramagnetic resonance (EPR) spectroscopy showed a 4-fold increase in the steady-state levels of ROS, which was suppressed in cells pre-treated with catalase. EPR measurements in cells treated with 4-Cl-BQ detected the presence of a semiquinone radical, suggesting that the increased levels of ROS could be due to the redox-cycling of 4-Cl-BQ within cells. A dose-dependent increase in micronuclei frequency was observed in PCB-treated cells, consistent with an increase in histone 2AX-phosphorylation. Treatment of cells with catalase blunted the PCB-induced increase in micronuclei frequency and H2AX phosphorylation that was consistent with an increase in cell survival. Our results demonstrate a PCB-induced increase in cellular levels of ROS causing DNA damage, resulting in cell killing.

Keywords:
polychlorinated biphenyls, oxidative stress, DNA damage, MCF10A, antioxidants, catalase, free radical

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PRE- AND POSTNATAL PCB CONCENTRATIONS AND CHILD IQ AT 45 MONTHS OF AGE

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Objective: To examine the association between pre- and postnatal PCB exposures and children's IQ at 45-months of age.

Methods: Data for the current study were collected as part of a longitudinal study of PCB exposures and child development in eastern Slovakia. Mothers were initially recruited at their child's birth, and PCB concentrations (for 17 congeners) have been measured in maternal and cord serum, and in the child's serum at 6- and 16-months of age using high-resolution gas chromatography with electron capture detection. At the time of enrollment, we excluded: 1) mothers with more than 4 previous births, 2) mothers less than 18 years old, 3) mothers who had resided in the district for fewer than five years, 4) mothers who had a major illness during pregnancy, and 5) infants born with severe birth defects. To date, 274 children have been examined with the Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III) out of approximately 550 children participating in the 45-month follow-up. To estimate and test the association between pre- and postnatal PCB concentrations and IQ at 45-months of age, we used general linear models, adjusted for maternal Raven's Progressive Matrices test score, HOME score, and ethnicity (Romani vs. non-Romani).

Results: Forty-five-month IQ scores showed good convergent validity with Bayley mental (MDI) and psychomotor (PDI) development index scores determined at age 16 months ($r=0.58$ and 0.49, respectively; $p<0.0001$) and with maternal scores on Raven's Progressive Matrices ($p=0.70$; $p<0.0001$). IQ scores ranged from 42 to 149, and averaged 105 (median 107, standard deviation, 18). Median total maternal PCB concentration (sum of IUPAC congeners 118, 138, 153, 156/171, 170, 180) was 5.82 ng/mL (wet-weight). Median total cord PCB concentration was 1.31 ng/mL; total PCB concentration increased to 3.69 ng/mL at 6-months of age, and then declined to 2.53 ng/mL at age 16-months. Of the 274 children with a valid IQ test at 45-months, 255, 175, 86, and 182 maternal, cord, 6-month, and 16-month PCB concentrations were determined, respectively. Multivariate models with adjustment for maternal Raven's score, HOME score, and ethnicity showed little relation between any of the time points and IQ at 45-months. The only noteworthy association was with cord blood: Each 10 ng/mL increase in total cord PCB concentrations was associated with a 1.1 point decline in IQ at 45-months ($p=0.84$).

Conclusions: Further analyses with a larger dataset are needed before strong conclusions can be made regarding the potential effect of PCBs on cognitive development in this cohort.

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PRINCIPAL COMPONENT ANALYSIS OF INDICATOR PCB PROFILES IN BREAST MILK IN POLAND

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Human milk, with a relatively high fat content, is perceived as a suitable matrix for studies of a long-term exposure to PCBs. Many factors influence the PCB levels and patterns in breast milk such as the molecular structure of PCBs and their characteristics governing the bioaccumulation in body fat, (re)mobilisation to human milk, time of lactation, mothers' dietary habits, occupational exposure, etc. Thus, the application of multivariate statistical approaches such as principal component analysis (PCA) seems to be a very useful task for the interpretation of such large sets of data.

The objective of this study was to apply PCA in order to search the influence of specific variables such as mother age, body mass index (BMI), duration of residence in the locality, smoking status, dietary habits such as frequency of fish, beef and milk consumption, newborn's gender, weight at birth, as well as their weight and age at time of sampling on the PCB-burdens and profiles in human milk samples. The concentrations of seven PCBs in the extracts of breast milk samples obtained from 50 mothers living in Poland were determined by gas chromatography and electron capture detection. The sampling and individual interviews of donors were organized according to the WHO protocol. Various combination of the GC results and measured variables of mothers and newborns were subjected to PCA in order to achieve a more meaningful and interpretable overview of the data, including the correlation patterns and latent factors responsible for the sample classification.

The most variances of the data could be explained by the first principal component (PC1) significantly associated with persistent congeners 118, 138, 153, and 180, while non-persistent ones (28, 52, 101) accounting for less variance of the data. The component scores showed relatively low levels of PCBs in most of the samples, which could be related to the agricultural characteristics and the limited industrial activities in the sampling region, subjected to a long-range atmospheric transport of PCBs rather than short-range transport from local sources. According to a WHO questionnaire fulfilled in by donors, we could not determine whether few outliers emerged on the plot had been accidentally exposed to PCBs, implying that the questionnaire should be designed in a way to assess other exposure roots (e.g. indoor) besides the nutritional and occupational one, more details about the previous breast-feeding episode and current weight trend (gaining/losing/stable), season of sampling, etc.

Keywords:
indicator PCB, human milk, WHO questionnaire, principal component analysis

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POLYCHLORINATED BIPHENYL (PCB) EXPOSURE IN GENETICALLY STRESSED MICE LEADS TO PREGNANCY ANOMALIES MEDIATED THROUGH MODULATION OF AQUAPORIN1 WATER CHANNEL AND VEGF R2.

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Polychlorinated biphenyls (PCBs) belong to a large group of halogenated aromatic hydrocarbons. Although their toxicity for biological systems was recognized in 1960's and their production ended in the late 1970's, vast amount of PCBs is still present in different matrices of environment. Indeed, this group represents the most widely distributed and persistent environmental pollutants. Their lipophilic character and non-biodegradability lead to bioaccumulation in the food chain. Numerous epidemiologic and laboratory observations suggest their association with endocrine, reproductive and neurological effects in wild life, laboratory animals and humans. PCBs possess weak estrogenic activity and are thought to be potential risk factors for perinatal development and neonatal neurocognitive health. It is possible that genetic stress predispose individuals to pregnancy disruption effects of toxicants like PCBs. We hypothesize that environmental stress induced by sub-toxic doses of PCBs combined with genetic disruptions in pregnancy compatible loci (IL-10 deficiency) predisposes individuals to adverse pregnancy outcomes. To test our hypothesis, pregnant C57/BL6 IL-$10^{-/-}$ or congenic wild type mice of 6-8 weeks age were given i.p injections of Aroclor 1254 (PCB mixture of structurally different congeners) at a dose of 500 ug/mouse in 100 ul corn oil (vehicle) or 100 ul of corn oil from gestational day (gd) 4 to gd12. Mice were euthanized on gd 13, or allowed to deliver. Pregnancy outcome was recorded. Aroclor 1254 did not affect the pregnancy outcome in wild type mice. However, IL-$10^{-/-}$ mice experienced several complications, including preterm birth on gd 17.5, two fold increased amniotic fluid, decreased placental and fetal weight, decrease in litter size with low birth weight. Our data on molecular mechanisms strongly suggest that in vivo exposure to Aroclor 1254 induced reduction in expression of water channel Aquaporin 1 (AQP1) in placental tissue of IL-$10^{-/-}$ mice. From our in vitro studies it was observed that Aroclor 1254 treatment also inhibited VEGF-mediated signaling as demonstrated by reduced VEGF R2 expression and its phosphorylation as well as by disruption of capillary tube formation in a three dimensional culture system on metrigel. Thus modulation of Aquaporins and VEGF functions at the maternal-fetal interface is being considered as a potential pathway for altered amniotic fluid volume in IL-$10^{-/-}$ mice. Our results strongly suggest that PCB-mediated toxicity and IL-10 deficiency lead to pre-term birth probably mediated through modulation of Aquaporin water channels and pro-angiogenic VEGF signals at maternal-fetal interface.
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TRAVEL AWARD

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PARAOXONASE (PON1) ACTIVITY IN RATS AFTER EXPOSURE TO POLYCHLORINATED BIPHENYLS (PCBs)

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Paraoxonase (PON1, EC 3.1.8.1), an antioxidant due to its peroxidase activity, is synthesized in the liver and secreted into the blood where it is associated with HDL and protects LDL against lipid peroxidation, a major risk factor in atherosclerosis, cardiovascular and neurodegradative disease, and cancer. The objective of this study was to determine if PCBs influence PON1 activity in blood and liver. Rats were injected intraperitoneally with PCB3, 4-OH-PCB3, PCB47, PCB136 (2x100 µmol/kg, day 1 & 4, euthanized on day 8), or PCB 126 (1 injection of 0.2, 1 or 5 µmol/kg, euthanized day 15, males only, different Se-diets,), corn oil (negative control), or a classical cytochrome P450 inducer (β-NF, 3-MC, Phenobarbital and Dexamethasone, 3 or 4 times within 7 days). The serum or plasma and liver microsomal PON1 activities were measured spectrophotometrically using two substrates, paraoxon and phenylacetate. In male rats plasma PON1 activities were significantly reduced, up to 54%, by 4-OH-PCB3, PCB47 and PCB136 compared to the control measured with either substrate. Female control rats had a 15 or 34 % (phenylacetate and paraoxonase, respectively) higher PON1 activity compared to males and the plasma PON1 activity was only reduced significantly (49-53%) by PCB136 (phenylacetate) and PCB3 (both substrates). PCB126 significantly increased both, serum and liver microsomal PON1 activities (both substrates) in a dose dependent way. Selenium levels in the diet were of minor influence. Intrinsic differences in activity of this congener and/or the differences in exposure schedule, dose, and tissue (serum and liver vs plasma) may be the cause for the opposite effects. Both CYP1A inducers (β-NF and 3-MC) reduced plasma PON1 activity in male rats, but only 3-MC in female rats. Phenobarbitol (CYP2B inducer) and Dexamethasone (CYP3A inducer) had no significant effect on PON1 activity in either gender. Our findings indicate that PCBs can influence the PON1 activity in the blood and liver and may thereby contribute to the risk of cardiovascular and other diseases. (Supported by NIEHS P42ES013661 and DOD DAMD17-02-1-0241).

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UPREGULATION OF P-GLYCOPROTEIN EXPRESSION IN BRAIN MICROVASCULAR ENDOTHELIAL CELLS BY POLYCHLORINATED BIPHENYLS

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Blood-brain barrier (BBB) is composed of capillary endothelium expressing low paracellular permeability and potent, multispecific drug-efflux pumps, such as P-glycoprotein (P-gp). As a primary gatekeeper of the BBB, P-gp acts as a major impediment to central nervous system (CNS) pharmacotherapy. Physiological regulation of this xenobiotic transporter is affected by a variety of environmental stimuli. Polychlorinated biphenyls (PCBs) are an example of such environmental toxicants, known to induce neurotoxicity and a range of other harmful health effects. Here we investigate the effects of specific PCB congeners on expression and activity of P-gp. Treatment of human brain endothelial cells (HBMEC) with PCB 126 and 153 dose-dependently increased P-gp protein levels, but did not significantly alter mRNA expression, suggesting changes at the translational or posttranslational level.
PCB-mediated changes in P-gp expression correlated with increased rhodamine 123 efflux, indicating the up-regulation of transporter functions of P-gp. Rhodamine 123 accumulation was modulated by a variety of P-gp inhibitors, which exhibited different rates of effectiveness. These results suggest that PCB-induced overexpression of P-gp in brain microvessels may reduce the efficacy of pharmacological treatments of the CNS disorders in PCB-exposed population.
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PCB153 INDUCES UPREGULATION OF ICAM-1 THROUGH CHOLESTEROL-DEPENDENT SRC KINASE/AKT SIGNALING IN HUMAN BRAIN ENDOTHELIAL CELLS

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During formation of blood-borne metastasis, vascular endothelial cells function as a selective barrier to the passage of cancer cells from blood stream to the underlying tissues. Endothelial dysfunction has a significant influence on the fate of circulating cancer cells in the blood vessel. Specifically, direct adhesive interaction between tumor and endothelial cells is the critical step in the formation of blood-borne metastasis. It requires the binding of tumor cells to specific adhesion molecules on the surface of endothelial cells. Upregulation of endothelial cell adhesion molecules can accelerate metastatic process through increased adhesion of tumor cells to the endothelium and facilitated transmigration of cancer cells across the microvascular endothelial monolayer. Chronic exposure to PCBs produces a variety of effects including neurotoxicity, pro-inflammatory effects, carcinogenesis as well as tumor-promoting effects. We previously reported that exposure to selected highly *ortho*-substituted non-coplanar PCBs, including PCB 104 and PCB153, can accelerate transendothelial migration of breast cancer cells through the disruption of endothelial integrity. However, the mechanisms by which PCBs alter adhesion of tumor cells to the endothelium are not completely understood. Because the cerebrovascular endothelium can play a regulatory role in tumor metastatic process in the brain, we have explored whether PCB 153 upregulates adhesion of breast cancer cells, MDA-MB-231, and monocytic lymphoma cells, U937, to the brain endothelium. Exposure to PCB 153 increased expression of ICAM-1 and VCAM-1, and increased adhesion of MDA-MB-231 and U937 cells to endothelial cells. PCB 153-induced ICAM-1 expression was blocked by pretreatment of membrane cholesterol-depleting agent, methyl-beta-cyclodextrin (MbCD) or chemical inhibitors against Src family kinases or phosphatidylinositol 3-kinase (PI3K)/Akt. MbCD also inhibited PCB 153-induced phosphorylation of Src kinase and Akt. Because cholesterol is a main component of caveolae, we also accessed the role of these lipid domains in PCB 153-induced adhesion molecules expression. Knockdown of caveolin-1 using siRNA interference did not affect PCB153-mediated upregulation of ICAM-1 and VCAM-1. Results of the present study indicate that PCB 153 can increase adhesion of tumor cells to brain microvascular endothelial cells and transendothelial migration of tumor cells through increased expression of ICAM-1 and VCAM-1 via cholesterol-dependent activation of Src family kinases and/or PI3K/Akt signaling pathways. Supported in part by P42 ES 07380, MH63022, MH072567, and NS39254.

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THE EFFECT OF OLESTRA ON THE ABSORPTION, EXCRETION AND STORAGE OF 2,2',5,5' TETRACHLOROBIPHENYL, 3,3',4,4' TETRACHLOROBIPHENYL, AND PERFLUOROOCTANOIC ACID.

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The non-absorbable dietary liopid, olestra, has been shown to decrease the absorption of organochlorine compounds. We have extended these observations to the measurement of the effect of olestra on two PCB congeners, and on perfluorooctanoic acid in mice. Mice were gavaged with either [^{14}C]-labeled 2,2'5,5' tetrachlorobiphenyl; 3,3',4,4' tetrachlorobiphenyl; or perfluorooctanoic acid. Absorption of these compounds was determined by assay of feces collected for 48 hours after the gavage. Dietary olestra was included in test diets during this 48-hour period to determine its effect on absorption of the compounds. Mice that received the diet without olestra during this 48-hour period were divided into groups that either continued the diet without olestra or changed to a diet containing olestra. These diets were continued for 7 days, and a second 48-hour fecal collection was made to measure the effect of olestra on enterohepatic circulation of the compounds and their metabolites. The animals were sacrificed, and blood, fat, and liver concentrations of ^{14}C were made. Olestra decreased the absorption of 2,2',5,5' tetrachlorobiphenyl. It also reduced tissue and blood concentrations of this compound. Olestra also decreased the absorption of 3,3',4,4' tetrachlorobiphenyl, but it did not alter enterohepatic circulation or tissue concentrations. Olestra significantly increased the excretion of perfluorooctanoic acid in the second 48-hour collection, suggesting an effect on enterohepatic circulation. It did not, however, alter tissue conentrations of perfluorooctanoic acid. These data are consistent with previously observed effects of olestra on the absorption and storage of lipophilic compounds.

This work was carried out as part of the Breast Cancer and the Environment Research Centers with funding from NIEHS and NCI (U01 ES/CA 012770); additional funding was provided by the UC Cancer Programs/Barrett Center's 2004 Breast Cancer Luncheon.

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COGNITIVE AND AUDITORY DEFICITS ASSOCIATED WITH PERINATAL PCB EXPOSURE CAN BE ATTENUATED WITH CO-EXPOSURE TO MEHG

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Polychlorinated biphenyls (PCBs) and methylmercury (MeHg) are two well known neurotoxicants that are both found in fish. We hypothesized that co-exposure to these contaminants would produce additive or synergistic deficits on cognitive and auditory function because the two contaminants produce similar effects on these measures when given alone. In addition, a previous study in our lab found motor function to be more impaired following co-exposure to PCBs and MeHg than following exposure to either contaminant alone. Female Long-Evans rat dams were orally exposed to corn oil vehicle (control), PCBs alone (3 or 6 mg/kg), MeHg alone (0.5 or 4.5 ppm), the low combination (3 mg/kg PCBs + 0.5 ppm MeHg), or the high combination (6 mg/kg PCBs + 4.5 ppm MeHg) throughout gestation and lactation. One male and one female offspring per litter were trained to asymptotic performance on a differential reinforcement of low rates (DRL) operant task as adults, while a second male and female littermate were tested for distortion product otoacoustic emissions (DPOAEs) as an assessment of cochlear function and auditory brainstem responses (ABRs) to determine effects on central auditory pathways. On the DRL task, males (but not females) exposed to either dose of PCBs alone did not perform as well as controls. DPOAE amplitudes were decreased, and DPOAE and ABR thresholds were elevated across a range of frequencies in PCB-exposed rats. Surprisingly, no MeHg-associated deficits were observed on the DRL task and the deficits found in the PCB-exposed males were not seen when PCBs were administered with MeHg. Likewise, no MeHg auditory deficits were observed and the decrease in DPOAE amplitude and increased DPOAE and ABR thresholds seen with PCB exposure alone were absent (DPOAE amplitude) or less pronounced (thresholds) with co-exposure. Overall these results indicate PCBs and MeHg may interact in complex ways to produce functional changes. Together with our previous results, the findings suggest that the type of interaction observed may be highly dependent on both the doses and duration of exposure and the type of endpoint that is assessed. Supported by PO1 ES11263 and T32 ES07326 (Eubig) from NIEHS and R82939001 from USEPA.

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TRICLOSAN IS A POTENT INHIBITOR OF ESTRADIOL AND ESTRONE SULFONATION IN THE SHEEP PLACENTA.

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The personal care product Triclosan, 5-chloro-2(2,4-dichlorophenoxy)phenol, is widely used in consumer products as an antibacterial agent and is increasingly found in the environment as a contaminant of sewage sludge and wastewater. This compound has been identified in plasma and urine of people in the United States, Sweden and Australia (Calafat, A.M. et al. Environ. Health Persp. 116:303,2008; Allmyr, M. et al. Sci Total Environ.372: 87, 2006; Allmyr, M. et al. ibid 393:162, 2008). Triclosan was previously shown to inhibit sulfonation of xenobiotic phenols (Wang L.Q. et al Drug Metab. Disp 32: 1162, 2004) and is structurally related to known inhibitors of estrogen sulfotransferase, such as polychlorobiphenylols. Previous work demonstrated that sheep placenta expresses estrogen sulfotransferase, and that the sulfate conjugates of estradiol and estrone formed in the sheep placenta are transferred to the fetus, where they are hydrolyzed, and are important sources of estrogen for normal fetal development (Wood, C.E. J. Soc. Gynecol. Invest. 12:67, 2005). In this study, we examined the effect of triclosan on sheep placental cytosolic estrogen sulfotransferase activity with 17-beta-estradiol (E2) and estrone (E1) as substrates. The apparent K_m for placental cytosolic sulfotransferase activity with E2 as substrate was 0.26 ± 0.08 nM (mean ± S.D., n=3) and with E1 as substrate was 1.86 ± 0.22 nM. Partial substrate inhibition was observed with both substrates at concentrations higher than 10-20 nM, as is typical of other estrogen sulfotransferases. Studies of the effect of triclosan on estrogen sulfotransferase activity were conducted with several concentrations (0.25-5 nM) of E2 and with 2 nM E1. Triclosan was a very potent inhibitor of both E2 and E1 sulfonation. For E2 the inhibition was shown to be competitive, with Ki of 0.09 ± 0.01 nM. The IC_{50} for inhibition of E1 sulfonation was 0.06 ± 0.05 nM. Triclosan was not a substrate for glucuronidation in sheep placental microsomes, and was a very poor substrate for sulfonation, with no detectable sulfation at 1 nM triclosan. The high potency of triclosan as an inhibitor of estrogen sulfotransferase activity raises concern about its possible effects on fetal growth and development.

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A HOLISTIC APPROACH TO EFFECTIVE NUTRITION PROGRAMS FOR AFFECTED SUPERFUND COMMUNITIES

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Since 2000, the University of Kentucky's (UK's) Superfund Basic Research Program (SBRP) Community Outreach Core has provided direct support and guidance through Superfund Community Action through Nutrition (SCAN) nutrition education programs. SCAN personnel begin by identifying, recruiting, and listening to community members affected by the specific Superfund site. A holistic approach is used to define significant community characteristics in order to (1) engender trust with affected community members, and (2) develop programs that effectively meet the nutrition and health needs of the diverse communities affected by Superfund contaminants. The holistic approach evaluates demographic, social, cultural, perceptual, ecological, economic, health, and legal/political characteristics of the affected Superfund community. A series of fourteen SCAN programs presented to affected community members near Dayhoit, Harlan County, Kentucky provided direct interaction to better understand the community's specific characteristics. Quantitative and qualitative outcome measures used with SCAN programs provided responses relating to traditional foodways, family health and social customs, cancer and chronic disease incidence within families, perceptual barriers intrinsic to outsiders, limited incomes, loyalty to Superfund employers, and legal issues. Community members demonstrated increased trust and knowledge, as well as improved attitudes about both SCAN personnel and the nutrition message. SCAN personnel are Registered Dietitians and are trained in the science of nutrition and its role in both prevention of and therapy for chronic diseases. SCAN, in full partnership with affected communities, further defined its role in translating safe, effective nutrition information to reduce health risks that may be associated with exposure to Superfund pollutants.

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INDUCTION OF CYTOCHROME P450 1A1 AND 1B1 IN MCF-7 HUMAN BREAST CANCER CELLS BY 4-BIPHENYL. COMPARISON WITH ACTION OF 17²-ESTRADIOL.

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Introduction: Estradiol (E2) is an essential hormone that controls the normal physiology of the mammary gland and breast cancer development. The cytochrome P450 monooxygenases (CYP) are involved in the metabolism of E2 to catechol estrogens in extra- hepatic tissues such as breast. CYP 1A1 is primarily an 2OH-E2 whereas CYP 1B1 is primarily an 4OH-E2. 2OH-E2 and 4OH-E2 can be oxidized to quinines, which are putative tumor initiators, but 4-hydroxylated form of E2 appears to be one of the most genotoxic metabolites of E2. Thus, the 2OH-E2/4OH-E2 ratio could be a critical parameter of the carcinogenicity of E2. Polychlorinated biphenyls (PCB) belonging to a large group of persistent environmental contaminants which are capable of mimicking some of the biological activities of estrogens including induction of estrogen -responsive enzyme activities.

Aim We have hypothesized that PCB might activate CYP 1A1 and CYP1B1 and cause E2 to be primarily metabolized by CYP 1B1, inducing more tumorigenic E2 4-hydroxylation pathways.
Material and Methods: MCF-7 human breast cancer cells were treated with different doses E2 (0,1; 1.0 or 10 nM) or PCB 3 (0,6; 6.0 or 60 ng/ml). To evaluate the influence of E2 and PCB 3 on the activity of CYP 1A1, we used the EROD assay. Western Blot analysis was performed for CYP1A1 and CYP1B1 protein expression.

Results: Basal CYP1A1 measured by EROD decreased from 78.8 ±8.3 pmol/100 µg protein/min in 6 hrs to 9.74 ±1.3 pmol/100 µg protein/min in 48 hrs of culture. Activation of EROD in cells exposed on the PCB3 was noted till the 48hrs of culture, while E2 increased EROD activity only in 6hrs of culture. Both E2 and PCB3 increased CYP1A1 protein expression in 6 hrs of culture. Activation of CYP1B1 protein expression was noted in 48hrs of culture under the influence of E2. PCB3 did not stimulate CYP1B1 protein expression.

In conclusion, we suggested that: 1) PCB 3 seem to be not only the inducer of CYP1A1 expression but also substrates for this enzymes, 2) E2 by activation of CYP1B1 shifts the metabolism of estradiol into 4OH-E2, which has strong mutagenic activity.

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TRAVEL AWARD

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POLYCHLORINATED BIPHENYLS (PCB-153) AND (PCB-77) ABSORPTIONS IN HUMAN LIVER (HEPG2) AND KIDNEY (HK2) CELLS IN VITRO: PCB LEVELS AND CELL DEATH

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We have demonstrated earlier that congener specific Polychlorinated biphenyls (PCBs) induce cytotoxicity, as evidenced by decreased cellular viability and accelerated apoptotic death. The exposure of PCBs in human cell line *in vitro* have also shown that chronic exposure to PCB-153 can induce cell survival by altering several apoptotic and tumor suppressor proteins. We have also demonstrated that CYP1A1 and MT1K are Congener Specific Biomarker Genes for Liver Diseases Induced by PCBs.There is very little, if any, information available on the differences in toxicity due to the nature of absorption of PCB-153 (hexachlorobiphenyl) and PCB-77 (tetrachlorobiphenyl) in human liver (HepG2) and kidney (HK2) cells. We exposed HepG2 cells to 70μM of both PCB-153 and PCB-77. The HK2 Cells were exposed to 80 and 40 μM of PCB - 153 and PCB-77 respectively, based on their LC_{50} values. The medium and cells were collected separately at each time interval from 30 minutes to 48 hours, and PCB concentrations were analyzed by GC-MS using biphenyl as an internal standard following hexane: acetone (50:50) extraction. We also performed trypan blue exclusion, DNA fragmentation and fluorescence microscopic studies in assessing cell viability and apoptotic cell death. About 40% of PCB-153 (35 μM out of 70 μM initial media concentration) was detected in HepG2 cells within 30-90 minutes, and it reached its highest concentration at 24 hours (60 μM), corroborated with the PCB depletion in the medium (5μM). For PCB-77, the highest concentrations within the cells were reached between 2-3 hours. However, the absorption levels of PCB-77 and PCB-153 over HK2 cells reached their peaks at 6 and 12 hours respectively. Exposure of human liver and kidney cells to PCB-153 and PCB-77 caused accelerated apoptotic cell death in a time-dependent manner. The studies demonstrated that (1) liver cells initiate the absorption of PCBs much faster than kidney cells; however, the concentration reaches its maximum level much earlier in kidney cells , indicating initial faster metabolism of PCBs in liver cells; (2) both PCB-153 and PCB-77 induced enhanced apoptotic death in liver and kidney cells; (3) kidney cells were more prone to be toxicated by PCBs (measured by apoptotic death) due to a rapid tissue burden of PCBs; and (4) PCB toxicity is predominantly tissue-specific in liver and kidney cells; however, no such correlation was found with the cellular absorption rate.

Keywords: PCBs, HepG2 Cells, HK2 Cells, Cellular absorption, GC-MS, DNA Fragmentation

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PCB-EXPOSED HUMAN POPULATION: SEARCH FOR POTENTIAL GENOMIC BIOMARKERS

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This study is a collaborative effort under NIH Genes, Environment and Health Initiative to improve our ability to study the process of developmental toxicities in the early stage before the clinical sign arises. We have selected an unique study population consisting of mother-child pairs (cohort design) from two districts of Slovakia: **Michalovce** (with 'highest' PCB contamination), and **Svidnik**, (with 'background' levels of PCBs) during the years 2002-2005 to achieve early disease biomarkers for PCB-exposed human population.

The Slovakian children's data from birth through 16 months of age have shown that mothers of newborns, aged 18-42 years have PCB exposure with a median value of 430 ng/g serum lipids (mean 620 ng/g serum lipids). As expected, the PCB concentrations in serum in our subjects showed skewed distribution toward the higher values. The maternal PCB contents demonstrate that PCB congeners 153, 138, 170 and 180 are the most predominant congeners. This same pattern of 153, 138, 170 and 180 being the most abundant can be seen in the cord PCBs also. The 6 month and 16 month PCBs continue the trend seen in the maternal and cord PCBs. OH-PCB 187 congener is the most abundant. It also showed that prenatal PCB exposures were not associated with a global reduction in birth weight in the Slovak newborns, but did appear to induce deficits in intrauterine growth for Romani boys. This finding mirrors several studies that showed male neonates to be at higher risk for PCB-induced intrauterine growth restriction.

In preliminary studies, we have also shown that in an in vitro studies with human liver cell line, the over expression of MT1K (Metallothionein) and CYP1A1 P450 (Cytochrome P450) can be associated with PCB toxicity. We have identified two most potentially significant biomarker genes, CYP1A1 (69.81 up-regulation) and MT1K (14.66 up-regulation), showing highest over-expression at p-value <0.005. We are continuing gene-expression profiling studies on PCB exposure using human PBMC cell from healthy blood donors. The isolated PBMC cells were exposed to median level of prevalent PCB 153 and PCB 138 in the blood samples of our selected cohort from Michalovce (1.381 ng/ml of serum for PCB 153 and 0.877ng/ml of serum for PCB-138) for 0, 8, 24, and 48 hrs with a control of same exposure time, where no PCBs were added. The microarrays were done comparing the two groups to see the global gene expression.

Key Words: PCB, Human exposure, PBMC, Microarray, Global Gene-expression, Biomarkers.

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DIETARY FLAVONOIDS BLOCK PCB-INDUCED PROINFLAMMATORY RESPONSES IN VASCULAR ENDOTHELIAL CELLS

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PCBs are widespread environmental contaminants that can cause a wide variety of toxic effects in exposed organisms. Co-planar PCBs can induce oxidative stress and activation of pro-inflammatory signaling cascades which are associated with atherosclerosis. The majority of the toxicological effects elicited by co-planar PCB exposure are associated to activation of the aryl hydrocarbon receptor (AHR) and subsequent induction of responsive genes. Recent studies from our laboratory demonstrated the important role of lipid rafts, or caveolae, in PCB toxicity as well as in activation of AHR. Caveolae are particularly abundant in endothelial cells, and there is evidence that the lack of the caveolin-1 gene, a structural component of caveolae, may provide protection against the development of atherosclerosis. Quercetin, a dietary flavonoid, has been demonstrated to possess antioxidant and anti-inflammatory properties in various in vivo and in vitro models. Previous studies from our group have shown that flavonoids can significantly reduce PCB77 induction of oxidative stress and expression of the AHR responsive gene cytochrome P450 1A1 (CYP1A1). To determine if quercetin can block PCB77 induced expression of pro-inflammatory genes associated with atherosclerosis, porcine endothelial cells were exposed to PCB77 in combination with quercetin, and expression of pro-inflammatory proteins was analyzed by western blot. Upon confluence, cells were serum deprived for 8 h, then treated with PCB77, quercetin, or PCB77 plus quercetin for a period of 16 h. Quercetin co-treatment significantly blocked PCB77 induction of the pro-oxidative and inflammatory proteins: CYP1A1 and vascular cell adhesion molecule 1 (VCAM1). Quercetin treatment was also able to decrease the basal levels of caveolin-1, possibly providing a means of protection against PCB77 induced insult. These results suggest that quercetin intervention can block co-planar PCB activation of the AHR pathway and induction of responsive pro-inflammatory genes (Supported by grants from NIEHS, NIH (P42ES07380), the University of Kentucky AES and KRF-2007-357-F00045).

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PPAR-ALPHA EXPRESSION AND FUNCTION IS ALTERED BY EXPOSURE TO 3,3,4,4-TETRACHLOROBIPHENYL (PCB77)

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Exposure to persistent organic pollutants, such as PCBs and dioxins, has been shown to induce a wide variety of toxic effects, including induction of xenobiotic metabolizing enzymes, inflammation and cardiovascular diseases. Epidemiological studies have shown positive correlations between exposure to persistent organic pollutants and increased serum levels of hepatic enzymes. In human populations, prolonged intake of diets high in fat/calories can promote inflammatory diseases, including obesity, and fatty liver diseases (including steatosis and cirrhosis). The hepatic responses to dietary fatty acid exposure are orchestrated, in part, by the Peroxisome Proliferator Activated Receptor-alpha (PPAR-alpha) pathway. In vascular endothelial cells exposure to PCB77 significantly reduced basal mRNA expression of PPAR-alpha and the PPAR responsive gene CYP4A1 as well as PPAR-alpha protein expression. We tested the hypothesis that PCB toxicity and altered lipid metabolism is associated with dysfunctional PPAR signaling. To determine how high fat diets can affect PCB-induced pathological liver responses, male mice (C57BL/6) were exposed to diets enriched with safflower oil (20 or 40% fat calories) for a total of four months. During the last two months of the study, mice were administered every other week with PCB77 (170 micro-mol/kg) or vehicle (safflower oil). Liver tissues were sampled, and ribonucleic acids (RNA) were extracted to measure mRNA abundance through expression microarray. The gene expression patterns demonstrate that the high fat diet (40%) induced expression of genes that play a critical role in fatty acid metabolism and are regulated by PPAR-alpha. Treatment with PCB77 blocked induction of these genes and reduced expression of PPAR-alpha. These results suggest that by inhibiting PPAR-alpha expression and function, PCB77 exposure can accelerate the detrimental effects of a high fat diet associated with inflammatory diseases. Current experiments are aimed at validating the microarray data through real time-PCR. (Supported by grants from NIEHS, NIH (P42ES07380) and the University of Kentucky AES).

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DIFFERENTIAL GENE EXPRESSION PROFILING OF KIDNEY (HK-2 CELL) INDUCED BY PCBS

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Human genome-wide (mRNA) expression profiling has been helpful to develop biomarkers for early disease diagnosis. Polychlorinated Biphenyls (PCB) have been demonstrated to cause a variety of multiple diseases and renal injuries, which in turn had potential carcinogenic effects. However, there have been no systematic research reports about toxic effects on human renal proximal tubular cells. In this study, we have used Affymetrix human genome expression arrays to systematically examine the gene expression profiles of human kidney derived HK-2 cells induced by two congeners of PCBs. This study explores the potential for predictive biomarkers. We have evaluated the differential effects of both of non-coplanar PCB-153 and coplanar PCB-77 by time-dependent microarray experiments. Time point effects that have been examined include 0, 0.5, 6, and 24 hours. The results show that a total of 2257 and 2543 differentially expressed genes were identified in PCB-153 treated HK-2 cells and PCB-77 treated HK-2 cells respectively, among them 399 are common to both congeners. Several genes related to renal cancer were expressed when treated with PCB -153 or PCB-77. Our findings show that a few specific genes out of several expressed genes, such as Annexin A4 (AIV) and human lysyl oxidase (LOX) can be used as the potential diagnostic biomarkers for PCB induced renal diseases.

Key words: PCBs, HK-2 Cells, Gene expression, Renal disease.

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POLYCHLORINATED BIPHENYL (PCB)-INDUCED OXIDATIVE STRESS MEDIATES CYTOTOXICITY IN HUMAN BREAST EPITHELIAL CELLS

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Recent data suggested that PCBs and PCB metabolites may induce oxidative stress and cytotoxicity. To study the role of oxidative stress in PCB-induced toxicity, growth curves and clonogenic cell killing of MCF-10A human nonmalignant breast epithelial cells were measured following 5 consecutive days of media changes using serum free MEGM media with or without 3 μM PCBs in 0.1% DMSO. The results showed that Aroclor 1254, PCB153, and the 2-(4-chlorophenyl)-1,2-benzoquinone metabolite of PCB3 (4ClBQ) were cytotoxic and growth inhibitory to MCF-10A cells, with the 4ClBQ having the most pronounced effects. Using fluorescence labeling with dihydroethidine (DHE), and Mitosox, the same PCBs that were found to be cytotoxic were also found to increase steady-state levels $O_2^{\cdot-}$. Moreover, toxic PCBs and their metabolites were also shown to induce 40-50% depletion of glutathione and 3-5 fold increases in manganese superoxide dismutase (MnSOD) activity. Finally, treatment with the combination of polyethylene glycol conjugated catalase (50 U/mL PEG-CAT) and superoxide dismutase (50 U/mL PEG-SOD) or the non-specific thiol antioxidant N-acetyl-cysteine (5 mM, NAC) added 1 hour after PCB exposure significantly protected the MCF-10A cells from the toxicity caused by PCBs and their metabolites. These results demonstrate that exposure to PCBs and their metabolites can induce oxidative stress and cytotoxicity in human breast epithelial cells as well as suggesting that clinically relevant thiol antioxidants such as NAC can be used to protect mammalian cells from PCB-induced cytotoxicity following exposure. (supported by NIEHS P42 ES013661)

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BENCHMARK DOSE CALCULATION FROM HUMAN HEALTH OUTCOMES AFTER LONG-TERM AND LOW-DOSE ENVIRONMENTAL EXPOSURE TO PCBS

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Until now, most risk assessments performed for environmental regulations were based on a NOAEL or LOAEL approach. As a recent alternative, benchmark dose (BMD) calculations have been applied. The BMD is defined as the dose that corresponds to a specific change in an adverse response compared to the response in unexposed subjects, and the lower 95% confidence limit is termed the benchmark dose level (BMDL). In calculation of BMD the following parameters can be manipulated: P_0, the risk of an abnormal response in unexposed subjects; and Benchmark response (BMR), the increase of the risk of performance below the designated cutoff score by a prespecified amount at the BMD. Most studies utilizing the BMD approach substitute either 0.05 or 0.1 as the value for P_0, and 0.05 for BMR. The benefit of BMD analysis is that it avoids the identification of specific threshold values, and uses statistical and policy criteria to establish cutoffs for risk assessment. We found BMD analysis particularly well suited for risk assessment based on continuous health outcome data from our human PCB exposure studies. Endpoints from three cohorts were used: The 2047 adults and 434 8-9-year old children from the EU 5thFP PCBRISK project and the 575 12-year old children from a recent follow-up study. BMDs for PCB exposures were calculated for free thyroxine (FT4) and thyroid volume in adults, and in children: 1) pure tone audiometry at frequencies of 125, 250 and 500 Hz; 2) transient evoked otoacoustic emissions (TEOAE) responses for 1000 and 1500 Hz grouped into half octave bands; 3) amplitudes of distortion product otoacoustic emissions (DPOAE) for 1000 and 2000 Hz; 4) simple reaction time; 5) tapping test; and 6) Vienna discrimination test. Our results show that for FT4 and thyroid volume (P_0=0.05 and BMR=0.05) BMD and BMDL was around 14000 and 10000 ng PCB/g serum lipids, respectively. The cutoff value for serum FT4 was around 21 pmol/L and for thyroid volume 16 ml. For all endpoints studied in children for both P_0=0.05 and P_0=0.1 and BMR=0.05 the BMDs and BMDLs were in the interval 1013-2420 and 673-1375 ng PCB/g serum lipids, respectively. The proportion of the sample considered at risk (concentration>BMDL) ranged from 2.1% for the least protective criteria, to 23.7% for the most protective. Our BMD data calculated from neurobehavioral parameters are in agreement with those published by Jacobson and colleagues (EHP 2002; 110:393-8).

Keywords:
PCBs, health effects, benchmark dose, environmental exposure

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OPENREP: A COMMUNITY-BASED DELIBERATION PLATFORM FOR DEBATING DIOXIN AND DIOXIN-LIKE CHEMICAL TOXIC EQUIVALENCY DATA AND ASSIGNED FACTORS

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Toxic equivalency factors (TEFs) are used to assess the relative risk of mixtures of toxic polychlorinated dibenzo-p-dioxins, dibenzofurans and biphenyls relative to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). The World Health Organization's International Programme on Chemical Safety (IPCS) has selectively used relative effect potency (REP) data reported in the literature to establish TEFs with limited input from affected stakeholders, advocacy groups and data providers. OpenREP was created to facilitate open and public deliberation, in order to capture commuity input using a wiki framework to support REP and TEF data presentation, stakeholder comments and facilitate the debate regarding the weighting of REP values, as well as the (re)assessment of current TEF values. In OpenREP each toxic congener has a Risk Assessment Dossier consisting of general chemical information, the current WHO TEFs, stakeholder-based recalculated TEFs, stakeholder discussion forums, and the *in vivo* and *in vitro* study summaries used to estblish the current TEF values. General chemical information includes the chemical name, Entrez PubChem link, the IUPAC name, and structure information (canonical SMILES, and InChI structure codes). The *in vivo* and *in vitro* study summaries include REP values, assay system, route of administration, study quality weighting, and quality weighting justification sections. Links to the PubMed record for each citation are also listed. Stakeholders may also submit new literature for consideration. Curators will monitor the dossiers and discussion sections to ensure that posted data accurately reflect current stakeholder discussions regarding REP calculations and study weights. All stakeholders will be able to participate in the deliberation process, and the contents and deliberation materials will be freely available to government regulators and members of the WHO TEF committee. The underlying literature database will also be freely available to the scientific community.

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#66
TOOL BOX FOR RISK ASSESSMENT OF HUMAN EXPOSURE TO NDL-PCB

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Of the estimated 116 721 t of Pyralenes produced by Prodelec / Rhone Poulenc in France since 1954, about 30 000 t remains as stockpiles, and a significant part of environmental load was associated with soils, and sediments, especially in vicinity of former producers, industrial areas, industrial harbours. Most trend data indicate concentrations are declining while the remaining background level may concern for possible health effects.

Risk evaluation was first based on commercial mixtures toxicity. In 1991 TDI were proposed by several National agencies based on liver toxicity and were ranged from 1 µg/kg/g (Canada) to 5 µg/kg/d (France and Japan). Maximum Limits of PCB mixtures were proposed for different foods at national levels, especially in fish (2 ppm ww in France). International harmonization appeared when WHO proposed to apply in TEQ approach to DL-PCBs. Thus Dioxin TDI was applied to DL compounds in 1998. New ML in food were established at EU level and applied in 2006. However DL-PCBs are only 10% of total PCBs but contribute to 50% to the total TEQ, reaching 75% in fish. On the other hand, toxic mechanisms were quite different between DL and NDL-PCBs.

Revision of Risk assessment related to PCB exposure in France was undertaken in 2002 based on NDL-PCBs by the AFSSA. A TDI for NDL-PCB of 10 ng/kg bw/d was adopted in 2003, based on developmental toxicity induced by prenatal exposure to reconstituted PCB mixtures. Average dietary exposure to 6 NDL-PCBs was estimated to 7.7 and 12.9 ng/kg bw/d in adults and children respectively, increasing to 57 ng/kg bw/d for high consumers of fishery products (Calypso Study). Exposure to NDL PCBs exceeds the TDI for 58.4% of children and 20% of and adults. Fish consumption contributes to about 50% of the food exposure. Thus more than 60% of adult high fish consumers exceeded the TDI. The first evaluation of the human blood contamination in France (1030 adults) was presented in November 2006 by the InVS and AFSSA. The sum of four PCBi (CB 118, 138, 153 and 180) were ranged from 8 to 2400 ng/g blood lipid and mean values were from 300 to 600 ng/g blood lipid related to age and sex categories. About 20% of the general population appeared to exceed the Benchmark Body Burden estimated for Humans, based on newborn behavioural assessments.

Keywords:
NDL-PCB, risk assessment, food exposure, Blood levels

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#67

PCBs IN FRENCH RHONE RIVER : RISK ASSESSMENT BY AFSSA

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PCBs are chemically stable, slowly biodegradable and lipophilic substances which are to be regarded as persistent organic pollutants (POPs). PCBs actually concentrate throughout the food chain and are ultimately found predominantly in animal fat. In France, production and uses of PCB were restricted during the 1970s to closed systems such as electric transformers and capacitors and were definitely banned in 1987. In 2006, Maximum levels (MLs) for the sum of dioxins and DL-PCBs were fixed in U.E., particularly for fishes (8pg TEQ/g w/w) except eels for which a specific ML of 12 pg TEQ/g w/w was determined. European ML proposals are based on the ALARA ("as low as reasonably achievable") approach derived from contamination data collected by the Member States in order to discard highly contaminated products from the market. Although overall results indicate that dioxins concentrations are declining, reduction of PCBs contamination cannot be readily achieved, since it results predominantly from environmental pollution associated with past uses.

Since 2005, some elevated levels of polychlorinated dibenzo-p-dioxins (PCDD), polychlorinated dibenzofurans (PCDF) and polychlorinated biphenyls (PCB) were detected among 386 fish samples of the Rhone River. Data on PCDD/F and PCB contamination were collected in various freshwater species for assessing contamination variability according to size, locations, trophic level and ecological exigencies. Results showed that current ML was exceeded, due to contamination of fish species especially by DL-PCBs (and NDL-PCBs), but not by dioxins. The mean concentration of dioxins and DL-PCBs in fish samples were found to exceed the ML by 50% of benthic fish and 16% of the pelagic fish. An overall pattern of contamination decline from the upstream towards downstream areas was observed. Concentrations of PCBs were found to be highly variable according to size, locations and trophic level ; nevertheless, a strong correlation between sum of dioxins and DL-PCBs levels and NDL-PCBs concentrations was observed but no significant statistical correlation between sediment and fish contaminations was evidenced.

On the basis of a food risk assessment related to PCB exposure undertaken for the French population which showed that exposure to 6 NDL-PCBs exceeds the TDI (of 10 ng/kg b.w./d adopted by Afssa) for 58.4% of children and 20% of women of childbearing age and adults, several recommendations had been proposed by Afssa for managing the risk related to fish contamination. A national survey of occurrence of PCBs (DL- and NDL-PCBs) in blood of high consumers of freshwater fishes including women of childbearing age is planned for 2008 and results will be available in spring 2011.

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#68

REMOVAL OF CHLORINATED AROMATIC COMPOUNDS FROM INSULATING OILS BY CHANNEL-TYPE CYCLODEXTRIN ASSEMBLY

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We report here the removal of chlorinated aromatic compounds from insulating oil by a channel-type g-cyclodextrin (g-CD) assembly, in which g-CD molecules are stacked in a head-to-head or head-to-tail orientation to form a column in the crystal, as a new adsorbent. Using this type of adsorbent (50-60 wt% of oil), 1,2,4- and 1,3,5-trichlorobenzenes (1,2,4- and 1,3,5-TrCBzs), 2- and 4-chlorobiphenyls (2- and 4-MCBs), 4,4'-dichlorobiphenyl (4,4'-DiCB), and 3,4,4'-trichlorobiphenyl (3,4,4'-TrCB), whose initial concentrations were 100 ppm, were completely removed from the insulating oil. Competitive adsorption experiments using a mixture of 2-MCB and 4-MCB or a mixture of 4-MCB, 4,4'-DiCB, and 3,4,4'-TrCB revealed that selective adsorption based on the shape and size of the chlorinated aromatics was achieved by the channel-type g-CD assembly, implying that inclusion into the cavity of the channel-type g-CD was responsible for the removal of chlorinated aromatics from insulating oil. It was also found that the adsorbed chlorinated aromatics was easily recovered from the channel-type g-CD by simply washing with *n*-hexane, and chlorinated aromatics were completely removed from the insulating oil even by the regenerated adsorbent, indicating that the g-CD assembly can be easily regenerated and recycled.

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#69

DETECTION OF Co-PCB IN THE $FeCl_3$ MANUFACTURING PROCESS

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Co-PCB and Co-PXB (Polyhalogenated Biphenyls) have been detected as contaminants in the production of $FeCl_3$. Relative PCB concentrations were #126 > #169 > #189. Monobromo congeners of Co-PCB #126, #169 and #189 were also detected. The concentration order of Monobromo biphenyl that replaced Cl with Br of Co-PCB was #126 R #169 > #189. The concentration order was #126 (pentachloro biphenyl) > #126 (Monobromo-Tetrachloro Biphenyl) > #126 (DibromoTrichloro Biphenyl). Tribromo substituted Biphenyls were not detected. PBrDPE in the printed circuit board might be decomposed to polybromophenol and polybromobenzene radical in strongly acidic solution in the presence of HCl, $FeCl_2$ and $CuCl_2$. Dimerization of polybromobenzene radical forms Co-PXB with selective debromination and Br-Cl substitution.

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