PCBs: Metabolism, Genotoxicity and Gene Expression in Vivo

The goal of Project 1 is the identification of targets and mechanisms of toxicity that will form a basis for our understanding of PCBs risks to human health and their amelioration. Special emphasis is given to school air PCBs.

The broad differences in the physical structures of PCBs and their metabolites presents a plethora of possible mechanisms of toxicity, including metabolically driven and receptor-driven targets and toxicities. Therefore, Project 1 studies include investigations of the redox environment, of receptor driven effects in organs, of gene expression and macromolecular changes, and finally exploration of the changes in humans exposed to PCBs.

Aim 1: Examine the disruption of the redox environment, redox networks, and basic energy metabolism-respiration of cells and tissues upon exposure to PCBs and their metabolites. Preliminary findings suggest that addition of 100 nM Se as selenomethionine maximizes both GPx1 and GPx4 activities in MIA PaCa-2 cells. Researchers are extending this to other cell lines. In another example, supplementation of U937 cells with 0.05 mM vitamin C as ascorbate 2-phosphate leads to an intracellular concentration of 4 mM; increasing the supplementation to 1.0 mM leads to 7 mM intracellular ascorbate. These levels are achieved after about 24 hours.

Aim 2: Identify genotoxic PCB congeners and metabolites, their mechanisms, rank them in importance to human health, and examine additive/synergistic/protective interactions and molecules. In collaboration with Project 7, they are examining the toxicity and changes in the redox networks of liver and lung tissue upon chronic inhalation of an airborne PCB mixture in an animal model. In a 28 day study of female Sprague Dawley rats that were exposed for 4 h/day, by nose-only inhalation to a PCB vapor that closely resembled a school air mixture (SAM) from a Chicago school, there was significantly decreased telomerase activity and TERT expression in bone marrow cells and an increase in bone marrow hematopoietic stem cell (HSC) differentiation into the granulocytic and macrophage, as indicated by changes in the colony forming units (CFU), in the PCB exposure group.

Aim 3 (in vivo): Analyze organ specificity and mechanisms of effects of airborne PCBs, establish LOAELs/NOAELs to assist in the calculation of reference values, and explore mechanisms to protect against PCB toxicity. In cooperation with researchers from Kansas University Medical Center, Iowa State University, Louisiana State University, and the University of Louisville, Project 1 studied the effect of PCB 126 on energy homeostasis. The expression of genes encoding enzymes related to gluconeogenesis, glycogenolysis, and fatty acid oxidation was unaffected in the knock out rats following PCB exposure as opposed to wild type rats, where
expression of these genes was significantly down regulated. This shows that glucose homeostasis is severely altered by PCB 126 and this is mediated through the AhR. Project 1 is also analyzing results from their studies on reproductive toxicity of PCBs.

**Aim 4:** Examine human mother & child samples with known PCB/OH-PCB body burden and PCB sources to identify biomarkers of exposure and effect and susceptible populations. Researchers are just beginning to analyze blood and urine from Project 6 participants in East Chicago and Columbus Junction for indications of oxidative stress, metabolic disturbance, and DNA damage and correlate their findings with exposures and PCB body burden.

The ultimate goal of Project 1 is to identify protection methods for exposed populations.

**Recent Publications:**


**Project Leader: Larry Robertson, PhD, MPH**

Dr. Robertson oversees and coordinates the entire project and designs, plans and supervises the proposed experiments listed. He will be responsible for analyzing and publishing the results of the proposed experiments. Dr. Robertson was the Director of the Iowa Superfund Research Program (ISRP) for 12 years. He has been doing PCB research for the ISRP since 2006. Prior to that he was the Program Director of the University of Kentucky Superfund Research Program.

**Co-Project Leader: Gabriele Ludewig, PhD**

Dr. Ludewig is trained as a toxicologist. She has led an effort to study the metabolites of airborne PCBs and to identify their individual geno-toxicities. Her systematic research employing in vitro and in vivo methods has led to the identification of mutations, sister chromatid exchanges, micronuclei, shortened telomeres, reduced telomerase activity, polyploidy induction, DNA stand breaks and others, depending on the metabolite. Her research was key in the IARC re-evaluation of cancer risk relating to PCB exposures. She has been Director of the ISRP Training Core since 2006.
she was the co-PI of the University of Kentucky Superfund Research Program Training Core.

**Co-Project Leader: Garry Buettner, PhD**

Dr. Buettner is Professor of Radiation Oncology/Free Radical and Radiation Biology and Director of the ESR Facility [9] at the University of Iowa College of Medicine. He has over twenty years of research experience in free radical biology.

**Kai Wang, PhD**

Dr. Wang is a Professor of Biostatistics in the University of Iowa College of Public Health. Dr. Wang has served as Biostatistician for the ISRP since its inception in 2006, and has extensive experience in analyzing data arising from ISRP projects.

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