PCBs and Cytosolic Phenol and Steroid Sulfotransferases

Polychlorinated biphenyls (PCBs) continue to persist in our environment and are linked to multiple threats to human health. Of most recent concern is the ongoing contamination by PCBs in older buildings (e.g., public school buildings) and in the air of these and other indoor and outdoor environments.

Those PCBs with lower numbers of chlorine atoms (i.e., semi-volatile PCBs in air) are metabolized in humans and other mammals to hydroxylated derivatives (OH-PCBs), and these metabolites are important in their toxicities. OH-PCB-mediated inhibition of mammalian cytosolic sulfotransferases (SULTs) that are important in endocrine hormone function has been the subject of increasing attention, however, relatively little is known about the formation, disposition, and biological activities of the sulfated metabolites of OH-PCBs (i.e., PCB sulfates).

Project 3 has made substantial progress in studies on the potential for hydroxylated and sulfated metabolites of PCBs to have biological effects that result in human toxic responses such as altered thyroid hormone status and changes in localized steroid hormone concentrations. The long-term goal of Project 3 is to understand the relationships between human SULTs and toxic responses to the lower chlorinated PCBs present in air.

Aim 1: Identify the specificities of key enzymes catalyzing the sulfation of physiological steroids with respect to their interactions with OH-PCB and PCB sulfate metabolites of the most frequently detected PCBs in air samples. Researchers have published results on the inhibition of purified human SULT1E1 and SULT2A1 by OH-PCBs and PCB sulfates (Parker). They have continued their focus on the possible role that OH-PCB-mediated inhibition of estrogen sulfotransferase SULT1E1 might play in the differentiation of adipocytes. These studies were carried out in collaboration with Professor Aloysius Klingelhutz and utilized an innovative cell culture model of human adipogenesis.

Aim 2: Determine the binding affinities of PCB sulfates with serum thyroid hormone transport proteins, evaluate the potential for alteration of thyroid hormone concentrations, and determine the distribution of PCB sulfates to relevant tissues. Researchers have incorporated collaborative efforts with Projects 1 and 7 and the Synthesis and Analytical Cores to study exposure of rats to a mixture of PCBs that serves as a model for indoor air samples from public schools in the AESOP study (Projects 4 and 6). In this study, female Sprague-Dawley rats were exposed by nose-only inhalation for 4 hours/day, 6 days per week over a period of 90 days. Data analysis of changes in gene expression relevant to adipogenesis and SULT1E1 is ongoing.

Aim 3: Evaluate the enzymatic potential for metabolic generation of PCB sulfates in humans and relate this to concentrations of sulfated PCB metabolites in human serum.
Research has centered on development of new methodology for determination of PCB sulfates in serum and urine and on understanding the role that hydrolysis of PCB sulfates catalyzed by intracellular human sulfatases may play in determining the concentrations of circulating PCB sulfates. Researchers have now published studies on a human hepatocyte cell line that indicate that there is uptake and congener-specific hydrolysis of PCB sulfates in these cells (Rodriguez). In following up on these studies, they have now examined 13 PCB sulfates as substrates for the steroid sulfatase present in a mixed gender pool of human hepatic microsomes.

Recent Publications:


Project Leader: Michael W. Duffel, PhD

Dr. Duffel is responsible for overall direction of the project, including the planning and design of all experiments, data collection, analysis and interpretation of results, preparation of manuscripts, and progress reports. In addition to experimental design of all phases of Project 3, he will coordinate joint studies with Project 1 [5] of the ISRP, and interact directly with both the Synthesis Core [6] and the Analytical Core [7] for preparation of OHPCBs and the analysis of peptide disulfides, respectively.

Larry W. Robertson, PhD, MPH

Dr. Robertson will be directly involved in the design and interpretation of the results of all in vivo studies on the effects of PCBs and OHPCBs in rats. Dr. Robertson and Dr. Duffel will coordinate all aspects of the treatment and acquisition of tissues from rats treated with these agents.

Hans J. Lehmler, PhD

Dr. Lehmler will provide expertise in those portions of the studies that relate to crystal structure- and computationally-based analysis of torsion angles in PCBs and OHPCBs. The Synthesis Core [6], directed by Dr. Lehmler, will provide synthesis of PCBs and OHPCBs to Project 3. He will also guide conformational analyses of torsion angles compounds for Project 3.