The ISRP Synthesis Core is responsible for providing researchers with authenticated test compounds and analytical standards, such as PCB sulfates and other PCB metabolites, which are not available from commercial sources and need to be custom synthesized.

These compounds enable ISRP researchers to address questions relevant to environmental public health and the mission of the Superfund Research Program that can only be studied with access to these compounds. In addition to providing these compounds to individual research projects and the Analytical Core, the Synthesis Core also makes them available to other researchers, especially researchers from other Superfund Research Programs. The Synthesis Core has four aims:

Aim 1: Maintain and prepare PCB mixtures and pure PCB congeners.
Aim 2: Prepare hydroxylated PCB derivatives.
Aim 3: Synthesize PCB sulfate metabolites.
Aim 4: Prepare miscellaneous compounds, including diazomethane.

Despite the limitations to normal laboratory operations due to the COVID-19 pandemic in 2020, the Synthesis Core synthesized, purified, and authenticated PCB congeners and metabolites. These compounds—some in large quantities—were provided in the current funding cycle to Research Projects #1 and #2 of the ISRP, as well as the Analytical Core, for in vitro and in vivo studies and as analytical standards. Also, several PCBs and PCB metabolites were provided to researchers elsewhere. The Synthesis Core finalized the synthesis and authentication of a series of PCB11 PCB28 metabolites as test compounds and analytical standards. The Synthesis Core supplied the following individual PCB congeners, hydroxylated PCB metabolites (OH-PCBs), PCB sulfates, and diazomethane.

Project #1: Thirteen PCB congeners (i.e., PCB30, PCB28, PCB52, PCB84, PCB95, PCB101, PCB118, PCB135, PCB138, PCB149, PCB153, PCB180 and PCB204); four hydroxylated PCBs (i.e., 4'-OH PCB52, 5'-4-OH-PCB26, 5-F-4-OH-PCB11, 4-OH-PCB95); and four PCB sulfates (i.e., 4'-OH PCB3 sulfate, 4'-OH-PCB25 sulfate, 4-OH-PCB52 sulfate, 4-OH-PCB11 sulfate) were provided to Project #1. These compounds were used as analytical standards for PCB metabolism studies in mice and neurotoxicity studies in cells in culture. Gram quantities of PCB52 were provided in preparation for an acute inhalation study supporting Projects #1 and #2. Biphenyl-4-ol was provided to develop polymeric implants for the sustained subcutaneous delivery of human-relevant OH-PCB in adolescent rats.

Project #2: Four PCBs, (i.e., PCB28, PCB52, PCB126) and one hydroxylated PCB (i.e., 4-OH-PCB52 were provided to Project #2. These compounds were used to study the roles of PCBs in adipogenesis, adipose functions, and metabolic syndrome.

Analytical Core: The Synthesis Core continues the routine synthesis of diazomethane for the Analytical Core. A solution of diazomethane in diethyl ether is used to derivatize hydroxylated PCB metabolites for gas chromatographic analysis. A total of 277 samples were derivatized with diazomethane to quantify OH-PCBs in human tissue and serum samples and sediment cores. Diazomethane was also provided to develop a method for the targeted analysis of PCB sulfates as OH-PCBs after deconjugation with purified sulfatase.

Recent Publications:
Dhakal R, Li X, Parkin SR, Lehmler HJ, Synthesis of mono- and dimethoxylated polychlorinated biphenyl derivatives

Fabian A. Grimm, William D. Klaren, Xueshu Li, Hans-Joachim Lehmler, Moumita Karmaka, Larry W. Robertson, Weihsueh A. Chiu, Ivan Rusyn, >Cardiovascular effects of polychlorinated biphenyls and their major metabolites, (link is external) [3] Environmental Health Perspectives (EHP), PMC777239. [Synthesis Core, Previous Cycle Project 1, Texas A & M SRP]

Riann Jenay Egusquiza, Maria Elena Ambrosio, Shuyi Gin Wang, Kaelen Marie Kay, Chunyun Zhang, Hans-Joachim Lehmler, and Bruce Blumberg, >Evaluating the Role of the Steroid and Xenobiotic Receptor (SXR/PXR) in PCB-153 Metabolism and Protection against Associated Adverse Effects during Perinatal and Chronic Exposure in Mice(link is external) [4], Environmental Health Perspectives, Vol 128 (4), April 2020, 047011-1 to 047011-16, PMC7228131 [Synthesis Core, Analytical Core]

Xueshu Li, Yanna Liub, Jonathan W. Martin, Julia Yue Cui, Hans-Joachim Lehmler, Nontarget

Analysis Reveals Gut Microbiome-dependent Differences in the Fecal PCB Metabolite Profiles of Germ-Free and Conventional Mice.(link is external) [5] Environmental Pollution, 2020 Sep

25;268(Pt A):115726, PMC7746632 [Synthesis Core, University of Washington SRP]

X. Li, C. Zhang, K. Wang, H.-J. Lehmler, Fatty liver and impaired hepatic metabolism alter the congener-specific distribution of polychlorinated biphenyls (PCBs) in mice with a liver-specific deletion of cytochrome P450 reductase. (link is external) [6] Environ. Poll. 2020: 266,

115233. PMCID: PMC7492420 [Synthesis Core]

Joe Jongpyo Lim, Xueshu Li, Hans-Joachim Lehmler, Dongfang Wang, Haiwei Gu, Julia Yue Cui;

Gut Microbiome Critically Impacts PCB-induced Changes in Metabolic Fingerprints and the Hepatic
Transcriptome in Mice [link is external] [7], Toxicological Sciences, 2020 Sep

1;177(1):168-187, PMC7553702 [Synthesis Core, University of Washington SRP]


c. Zhang, S. Flor, G. Ludewig, H.-J. Lehmler, >Atropselective partitioning of polychlorinated biphenyls in a HepG2 cell culture system: experimental and modeling results. (link is external)


Lehmler, 3,3'-Dichlorobiphenyl is metabolized to a complex mixture of oxidative metabolites, including novel methoxylated metabolites, by HepG2 cells. (link is external) [10] Environ. Sci. Technol. 2020: 54, 12345-12357. PMC7544623 [Synthesis Core in collaboration with ASTDR]

Datasets:

Core Leader: Hans-Joachim Lehmler, PhD

Dr. Lehmler is an experienced synthetic organic chemist with over twelve years of experience in the synthesis of polychlorinated biphenyls and their metabolites. He is currently a Professor in the University of Iowa Department of Occupational and Environmental Health. He has been involved in the NIEHS Superfund Program since 1998-first at the University of Kentucky and since 2003 at the University of Iowa. As Core Leader he will oversee and coordinate the chemical synthesis and the chemical characterization of synthetic compounds.

Co-Investigator: Xueshi Li, PhD

Dr. Li is currently an Assistant Research Scientist in the Department of Occupational and Environmental Health. Xueshi has extensive experience with the synthesis of a broad range of PCB derivatives and carbohydrate surfactants. He developed the synthetic strategies that are current used by the Synthesis Core staff for the synthesis and authentication of a range of PCB derivatives. As Co-Investigator, he will work with Lehmler to ensure the timely synthesis of all test compounds requested by individual research projects and the Analytical Core.

Contact

Please e-mail any inquiries relating to the Synthesis Core to Hans-Joachim Lehmler at hans-joachim-lehmler@uiowa.edu [12].

Attach files: Standard Operating Procedure for the synthesis and handling of diazomethane [13]

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