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Toxicogenomics

Subchronic Exposure to TCDD, PeCDF, PCB126, and PCB153: Effect on Hepatic Gene Expression

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Running Title
Gene Expression Analysis of Dioxin and Related Compounds.

Key Words
TCDD, Liver, microarray, PCB, *AhR*, HAH

Abbreviations
AhR: aryl hydrocarbon receptor, *ARNT*: *AhR* nuclear transporter, *CAP2*: adenylate cyclase-associated protein 2, *C-CAM4*: carcinoembryonic-cell adhesion molecule 4, *CYP*: cytochrome P450, DRE: dioxin response element, HAH: Halogenated aromatic hydrocarbon, NTP: National Toxicology Program, PCA: Principal Components Analysis, PCB: polychlorinated biphenyl, PCB126: 3,3',4,4',5-pentachlorobiphenyl, PCB153: 2,2',4,4',5,5'-hexachlorobiphenyl, PCDD: polychlorinated dibenzo-*p*-dioxin, PCDF: polychlorinated dibenzofuran, PeCDF: 2,3,4,7,8-pentachlorodibenzofuran, PTM: Pavlidis Template Matching, SD: Sprague Dawley, TCDD: 2,3,7,8 tetrachlorodibenzo-*p*-dioxin, TEF: Toxic Equivalency Factor.

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IV. Results
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ABSTRACT

We have employed DNA microarray to identify unique hepatic gene expression patterns associated with subchronic exposure to TCDD and other halogenated aromatic hydrocarbons (HAHs). Female Harlan Sprague-Dawley rats were exposed for 13 weeks to toxicologically equivalent doses of four different HAHs based on the toxic equivalency factor of each chemical: 2,3,7,8 tetrachlorodibenzo-*p*-dioxin (TCDD; 100 ng/kg/day), 2,3,4,7,8-pentachlorodibenzofuran (PeCDF; 200 ng/kg/day), 3,3',4,4',5-pentachlorobiphenyl (PCB126; 1000 ng/kg/day), or 2,2',4,4',5,5'-hexachlorobiphenyl (PCB153; 1000 μg/kg/day). Global gene expression profiles for each exposure, which account for 8,799 gene probe sets contained on Affymetrix RGU34A GeneChips, were compared by principal components analysis (PCA). The aryl hydrocarbon receptor (*AhR*) ligands TCDD, PeCDF, and PCB126 produced very similar global gene expression profiles that were unique from the non-*AhR* ligand, PCB153, underscoring the extensive impact of *AhR* activation and/or the resulting hepatic injury on global gene expression in female rat liver. Many genes were co-expressed during the 13 wk TCDD, PeCDF, or PCB126 exposures, including classical *AhR* regulated genes and some genes not previously characterized as being *AhR* regulated, such as carcinoembryonic-cell adhesion molecule 4 (*C-CAM 4*) and adenylate cyclase-associated protein 2 (*CAP2*). Real time RT-PCR confirmed the increased expression of these genes in TCDD, PeCDF, and PCB126 exposed rats as well as the up- or downregulation of several other novel dioxin-responsive genes. In summary, DNA microarray successfully identified dioxin responsive genes expressed following exposure to *AhR* ligands (TCDD, PeCDF, PCB126), but not following exposure to the non-*AhR* ligand, PCB153. Together, these findings may help to elucidate some of the fundamental features of dioxin toxicity and may further clarify the biological role of the *AhR* signaling pathway.