PhD Dissertation Final Oral Defense

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Effects of Inter-Strain Differences in the Metabolism of Trichloroethylene on Liver and Kidney Toxicity

Tuesday, June 17 2014 | MHRC 2005 | 1:00pm

Trichloroethylene (TCE) is an environmental and occupational health hazard which is characterized as 'carcinogenic to humans' by the IARC and U.S. EPA. However, several issues critical for assessing human health risks from TCE remain unresolved, such as (1) the amount of metabolites formed in various tissues, and possible inter-individual differences; and (2) the mode of action involved in toxicity in organs of concern. In this study, we tested a hypothesis that amounts of metabolites of TCE in mouse liver and kidney are associated with tissue-specific toxicity by evaluating the quantitative relationship between strain-, dose-, and time-dependent levels of trichloroacetic acid (TCA), dichloroacetic acid (DCA), trichloroethanol (TCOH), *S*-(1,2-dichlorovinyl)glutathione (DCVG), and *S*-(1,2-dichlorovinyl)-L-cysteine (DCVC) in serum, liver, and kidney and various toxicity phenotypes in tissues using a panel of inbred mouse strains. Sub-acute (600 mg/kg/d of TCE for 5 days) and sub-chronic (100 or 400 mg/kg/d of TCE for 1, 2, or 4 weeks) designs were used. In addition, this study investigated relationship between oxidative TCE metabolism and tissue-specific toxicity in the context of PPARα status (wild-type, *Ppara*-null, and humanized *Ppara*). In specific aim 1, we demonstrated the inter-strain differences and the decreasing trend of metabolism over time in TCE metabolism in liver. Across varying genetic background, levels of TCA and DCA in liver were correlated with PPARα activation but not with hepatocellular proliferation. In specific aim 2, we found a significant correlation between renal levels of TCA and kidney injury molecule-1 expression, both of which decreased over time. However, the significant increase in cellular proliferation in proximal tubular epithelium was evident only in NZW/LacJ strain treated for 4 weeks, which may characterize the sub-chronic toxicity in kidney as cytotoxicity followed by compensatory proliferation. In specific aim 3, it was shown that TCA may be associated with oxidative stress and liver enlargement through PPARα-independent pathway. Overall, this body of work makes a novel and significant contribution to the field of environmental health science, providing the quantitative data on time-, tissue-, and strain-dependent variations in TCE metabolism and the experimental evidence regarding relationship between metabolism and toxicity.

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