

Species-Specific Differences in Dioxin Toxicity: Differences in Gene Regulation?

James S. Smith Jr., Ph.D., OAK CREEK, Inc., 60 Oak Creek, Buxton, ME 04093

Dioxin down regulation of the rat phosphoenolpyruvate carboxykinase (PEPCK) gene is the putative mechanism by which dioxin causes body weight loss, wasting, and death in rats. A search of the DNA sequence coding for the PEPCK gene, including significant non-coding flanking sequences, identified significant homology with the 10 base pair (bp) functional consensus sequence for the dioxin response element (DRE). Ten putative DREs with exact homology to the 5-bp core binding sequence (5'-GCGTG-3') and more than 70% homology to the functional consensus sequence (5'-T/GNGCGTGA/CG/C-3') occur in close proximity to the PEPCK gene and within a region previously suggested to be of significance in this genes regulation. Eight of these DREs contain specific nucleotide substitutions known to abolish DRE functionality and are therefore not functional as enhancers of gene transcription. The remaining two putative DREs are potentially functional transcriptional enhancers. Two potentially functional DREs and four non-functional DREs are located in a unique overlapping arrangement within a 102-bp region downstream of the PEPCK gene in a manner that suggests coordinate regulation of the gene by the aryl hydrocarbon receptor (AhR). The location, binding affinity, and potential functionality of these putative DREs suggest a novel mechanism by which dioxin may regulate this genes transcription. In contrast, the available sequence of the human PEPCK gene does not contain similarly arraigned DREs, an observation which may explain the apparent lack of dioxin-mediated acute body weight loss, wasting, and death in humans.