

AH receptor agonist activity in human blood measured with a cell-based bioassay: Evidence for naturally occurring AH receptor ligands in vivo

Connor, K.T., M.A Harris, M.R. Edwards, R.A. Budinsky, G.C. Clark, A.C. Chiu, **B.L. Finley**, and J.C. Rowlands

In the present study, an aryl hydrocarbon receptor (AHR)-driven reporter gene bioassay was used to measure the activity, measured as an induction equivalent (IEQ) as compared to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), or IEQ concentration in human blood samples from 10 volunteers under different dietary regimens. Blood concentrations of polychlorinated dibenzo-*p*-dioxins/furans (PCDD/Fs) and polychlorinated biphenyls (PCBs), as determined by analytical chemistry (HR-GC/MS), and expressed as toxic equivalents (TEQs) with the use of TCDD equivalency factors (TEFs), were within a range that has been reported in the general US population, ranging from 0.022 to 0.119 ppt (whole blood basis). However, the human blood IEQ measured directly via bioassay ranged from 13.4 to 218 ppt (whole blood basis). These order of magnitude greater IEQs compared to the TEQs for dioxins, furans, and certain PCBs suggests that human blood contains a relatively high level of AHR agonists able to activate the CYP1A1 dioxin response element (DRE)-linked reporter gene bioassay and that this AHR activity is not accounted for by PCDDs/Fs and dioxin-like PCBs based on standard HR-GC/MS and TEF analysis. When study participants switched from a "baseline" to a high-vegetable diet, increases in bioassay IEQ were observed that were statistically significant ($P < 0.05$). In addition, IEQ activity was elevated above levels observed following dietary intervention in two subjects given indole-3-carbinol (I3C) supplements. We conclude that a substantial portion of the IEQ activity occurred as a result of the increased intake of natural AHR agonists (NAHRAs) present in many fruits, vegetables, and herbs. Our findings also suggest that dietary NAHRAs constitute a substantial daily dietary intake of AHR-active compounds, and these NAHRAs could influence AHR status in humans and play a role in a basal level of AHR activation.

Keywords: 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), aryl hydrocarbon receptor (AHR), reporter gene bioassays, human blood, dietary intervention, toxicity equivalency (TEQ)