Abstract

Perfluoroalkyl acids (PFAAs) are found globally in the environment, detected in humans and wildlife, and are typically present as mixtures of PFAA congeners. Mechanistic studies have found that responses to PFAAs are mediated in part by PPARα. Our previous studies showed that individual PFAAs activate PPARα transfected into COS-1 cells. The goal of the current study was to determine if binary combinations of perfluorooctanoic acid (PFOA) and another PFAA act in an additive fashion to activate PPARα in the mouse one-hybrid in vitro model. COS-1 cells were transiently transfected with mouse PPARα luciferase reporter construct and exposed to either vehicle control (0.1% DMSO or water), PPARα agonist (WY14643, 10 μM), PFOA at 1-128μM, perfluorononanoic acid (PFNA) at 1-128 μM, perfluorohexanoic acid (PFHxA) at 8-1024 μM, perfluorooctane sulfonate (PFOS) at 4-384 μM or perfluorohexane sulfonate (PFHxS) at 8-2048 μM to generate sigmoidal concentration-response curves. In addition, cells were exposed to binary combinations of PFOA+either PFNA, PFHxA, PFOS or PFHxS in an 8×8 factorial design. The concentration-response data for individual chemicals were fit to sigmoidal curves and analyzed with nonlinear regression to generate EC_{50}s and Hillslopes, which were used in response-addition and concentration-addition models to calculate predicted responses for mixtures in the same plate. All PFOA+PFAA combinations produced concentration-response curves that were closely aligned with the predicted curves for both response addition and concentration addition at low concentrations. However, at higher concentrations of all chemicals, the observed response curves deviated from the predicted models of **additivity**. We conclude that binary combinations of PFAAs behave additively at the lower concentration ranges in activating PPARα in this in vitro system.