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Observed and modeled effects of pH on bioconcentration of diphenhydramine, a weakly basic pharmaceutical, in fathead minnows

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Fathead minnows were exposed to diphenhydramine (DPH), a weakly basic pharmaceutical (pKa = 9.1), to examine pH effects on uptake and accumulation. Fish were exposed to 10 µg/L DPH in water for up to 96 h at three nominal pH levels: 6.7, 7.7, and 8.7. In each case, an apparent steady-state was reached by 24 h allowing for direct determination of the bioconcentration factor (BCF), blood/water partitioning value (total chemical basis; *P*BW,TOT), and apparent volume of distribution (*V*D; approximated from the whole-body/plasma concentration ratio). BCFs and measured *P*BW,TOT values increased in a non-linear manner with pH while *V*D the remained constant, averaging 3.0 ± 0.08 kg/L. The data were then simulated using an established model (Erickson et al., 2006, Environ. Toxicol. Chem. 25:1512) modified for fathead minnows, which accounts for acidification of the gill surface due to elimination of metabolically-derived acid. Good agreement between model simulations and measured data was obtained for all three tests by assuming that plasma binding of ionized DPH is about one-fifth that of the neutral form. This finding is consistent with measured binding of DPH in humans. A simpler model, which ignores elimination of metabolically-derived acid, performed much less well. These findings suggest that pH effects on accumulation of ionogenic compounds by fish are best described using a model that accounts for acidification of respired water. Moreover, measured plasma binding and *V*Ddata for humans, determined as part of the drug development process, may have considerable value for predicting the accumulation of pharmaceuticals in fish. The contents of this abstract do not necessarily constitute or reflect USEPA policy.

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