The PhATE™ Model: Estimating the Distribution of Pharmaceuticals in the Environment

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Recent advances in instrumental analytical detection capabilities, such as gas chromatography and liquid chromatography coupled with mass spectrometry have led to the detection of human active pharmaceutical ingredients at very low concentrations in the aquatic environment. These findings are of course not surprising; pharmaceutical compounds, like many of the chemicals regularly consumed by people as food, medicines, or nutritional supplements, are not always completely metabolized and some portion may pass unchanged through people and into the environment. This has been recognized by the U.S. Food and Drug Administration (FDA) for many years. As early as 1977, the National Environmental Policy Act required federal agencies to take environmental risk assessment into account in their decision-making, and the FDA inserted these requirements into regulations for approving new drugs. New drug applications were required to include an environmental assessment that provided data and information evaluating the new drug's potential risk to the environment.

In 1995, following several years of data evaluation, the FDA revised its regulations to reduce data requirements for low-volume active pharmaceutical ingredients. After this rule change, only compounds that could be expected to be present in the environment at a concentration greater than 1 microgram per liter (1 part per billion [ppb]) were required to have an environmental assessment. This decision was based on a review of ecotoxicity data that indicated most human pharmaceutical compounds had their lowest acute ecotoxic effect at concentrations greater than 1 milligram per liter (1 part per million). Using standard risk assessment methods, a safety factor of 1,000 is applied to the lowest acute ecotoxicity value to approximate a "predicted no-effect level."

Thus, for most compounds, a 1 ppb concentration in the environment was assumed to have no adverse effect on any organism. Scientific research continues, but since the methodology is based on acute toxicity, it may not take into account chronic effects or potential synergistic or additive toxicity associated with mixtures of chemicals.

Estimates Yield National Average

Using FDA guidance, calculation of the predicted environmental concentration (PEC) became very straightforward. Maximum sales volumes (in kilograms) are estimated, based usually on fifth year sales projections, and this amount of drug substance is assumed to be uniformly distributed throughout the United States. Dividing this amount of material by the total U.S. sewer flow results in a PEC for the drug substance in U.S. waters. Usually the first calculation assumes no dilution in the environment and no depletion of the drug substance through human metabolism, in wastewater treatment plants, or in the environment. If the result of this calculation is less than 1 ppb, no further work is required and a categorical exclusion may be applied in lieu of an environmental assessment.

PhATE™: Watershed-Based Estimates

The FDA approach, while useful from a regulatory perspective, may result in an overly simplistic assessment of potential environmental exposure. In response to this concern, the research-based pharmaceutical industry, through its trade association P*h*RMA (Pharmaceutical Research and Manufacturers of America), developed a state-of-the-art spatially explicit model to facilitate a deeper understanding of potential environmental distribution of pharmaceuticals at a local or regional level. The P*h*ATE™ (Pharmaceutical Assessment and Transport Evaluation) model is a watershed-based approach that was developed as a tool to more realistically estimate concentrations of active pharmaceutical ingredients (APIs) discharged to U.S. surface waters through consumption of medicines.

P*h*ATE uses a mass balance approach to model PECs in eleven watersheds that are felt to be representative of most hydrologic regions of the United States. Upon dividing the associated rivers into discrete segments, the model estimates the mass of API that enters a segment from upstream or from publicly owned treatment works (POTWs) and the mass that is subsequently lost from the segment via instream loss mechanisms or flow diversions (manmade withdrawals). POTW discharge loads are estimated based on the population served, API use per capita, and the mass of the API removed in the POTW.

Environmental concentration data reported by the U.S. Geological Survey (USGS) provided the means by which the model could be corroborated (Kolpin et al., 2002; Tabor and Barber, 1993). Details of the model development will be reported shortly (Anderson et al., in review).

More Data Desired for the Southwest

Although the P*h*ATE model is still under active development, it currently allows potential concentration profiles to be evaluated across diverse geographic localities. As might be expected in arid regions of the Southwest characterized by a significant percentage of surface water flow composed of POTW effluents and minimal dilution, residual concentrations of pharmaceuticals and other compounds may be higher. In these cases, additional data on POTW removal efficiencies, in-stream depletion, and data on other potential depletion mechanisms would be helpful in refining the model predictions. However, it should be noted that for most pharmaceutical compounds, measured concentrations are generally low (nanograms per liter to micrograms per liter range), and the potential for adverse acute environmental impacts is anticipated to be low as well. Work continues within and among the pharmaceutical industry, academia, government labs and other scientific institutions, to further our understanding of these issues.

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References

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