# Characterization of Potential Risk for Several Active Pharmaceutical Ingredients: A Case Study of the Merrimack River

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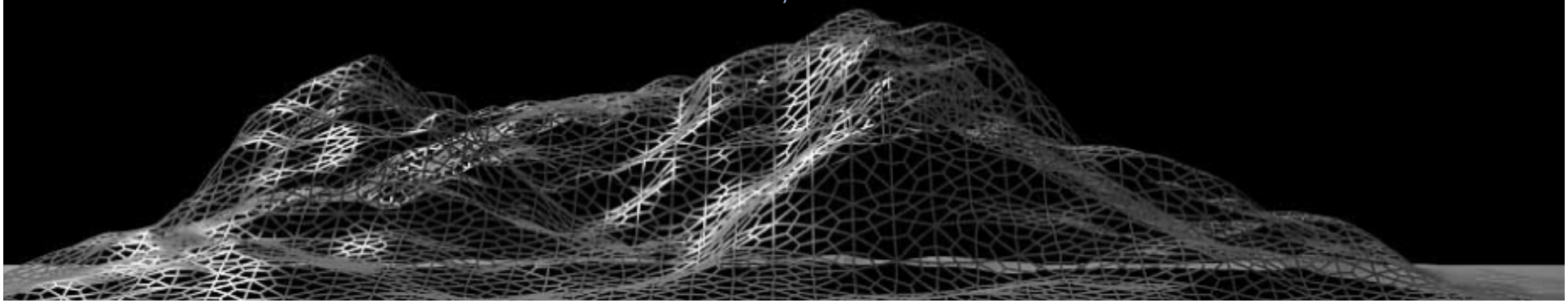


# Presentation Outline

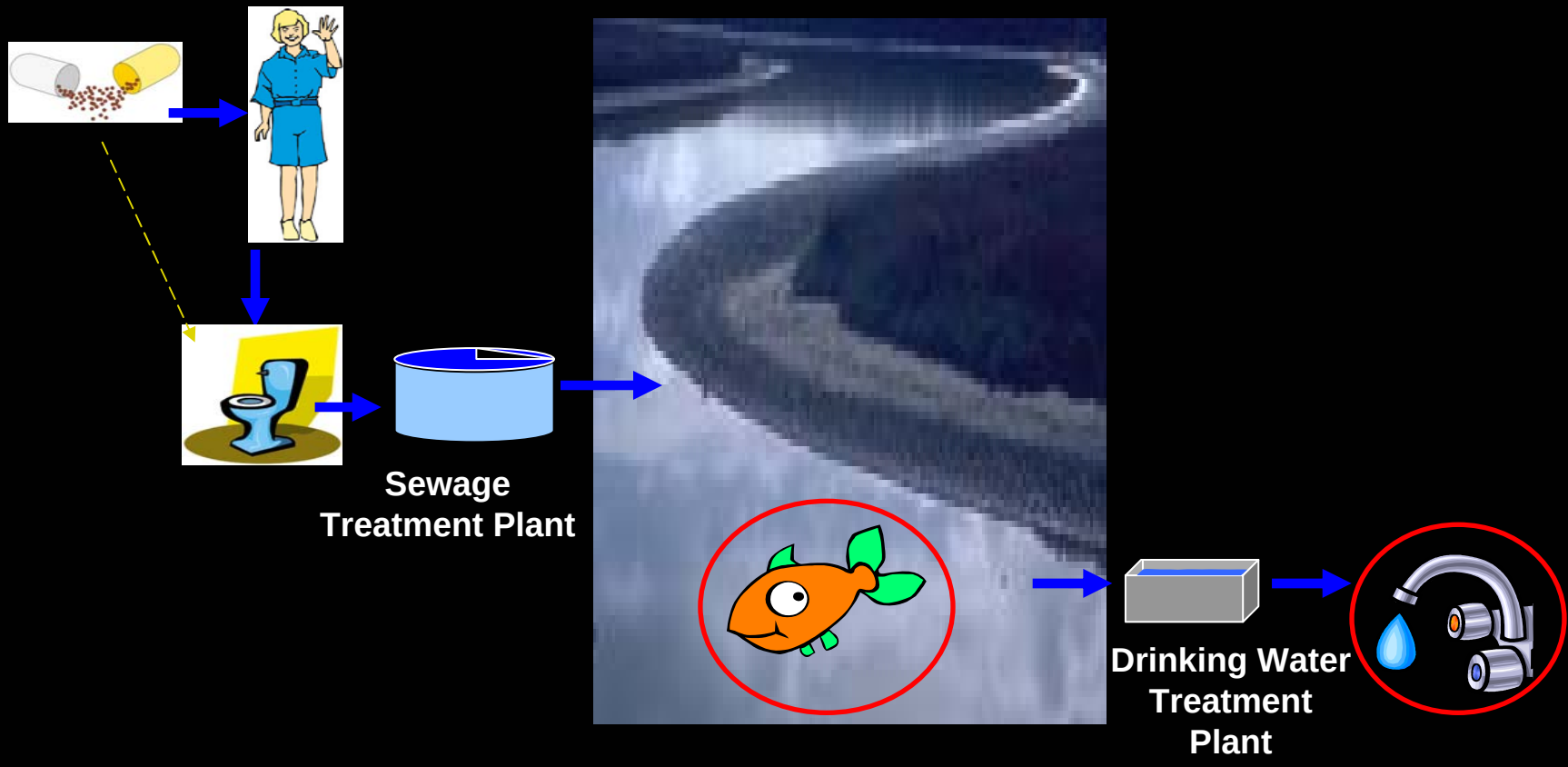
- Summarize model design and components
- Present results from assessment of 11 evaluated pharmaceuticals across 11 watersheds.
- Case study: Merrimack River

- Terminology:
  - API:  Active pharmaceutical ingredient
  - PEC:  Predicted Environmental Concentration
  - MEC:  Measured Environmental Concentration
  - PNEC:  Predicted No-Effect Concentration
  - STP: Sewage Treatment Plant

# P*h*ATE™ Model

- P*h*ATE™ Model: *Pharmaceutical Assessment and Transport Evaluation* model
  - Anderson et al. (2004). *Environmental Science and Technology*. 38(3): 838-849.
- Used to estimate environmental concentrations of active pharmaceutical ingredients (APIs) in U.S. surface waters that result from patient use (or consumption) of medicines.
- Screening mass-balance model.
- Uses EPA BASINS databases.
- Uses two flow conditions – mean flow and 7Q10 flow – and includes attenuation processes.

# PhATE™ Model Paradigm



# P*h*ATE™ Model Description

## *INPUTS*

**Annual US Sales (IMS)**

**Percent Removal at Each Step**
- Metabolism
- Wastewater Treatment
- In-Stream Loss
- Drinking Water Treatment

**Acceptable Daily Intake (ADI) or toxicity data**

***Fate and Transport Module***

*For 11 U.S. watersheds:*
- Population Distribution
- Sewage Treatment Plant Flows
- Stream/River Flows
- Drinking Water Treatment Plant Flows

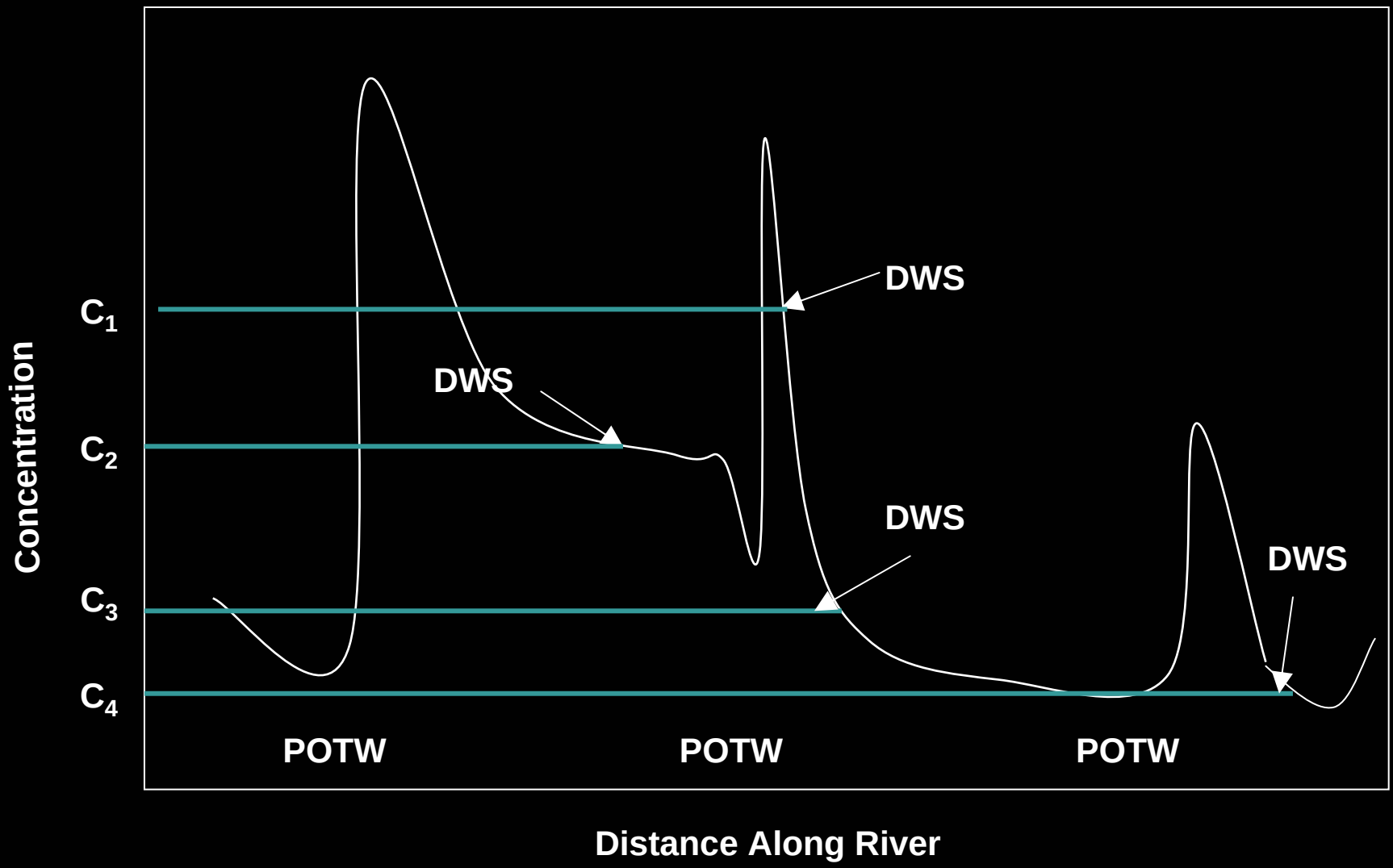
***Human Health Risk Assessment Module***
- Standard risk assessment equations

## *OUTPUTS*

**PECs**
- In STP Effluent
- In Streams/Rivers
- In Drinking Water
- (Biosolids)
- (Land applications)

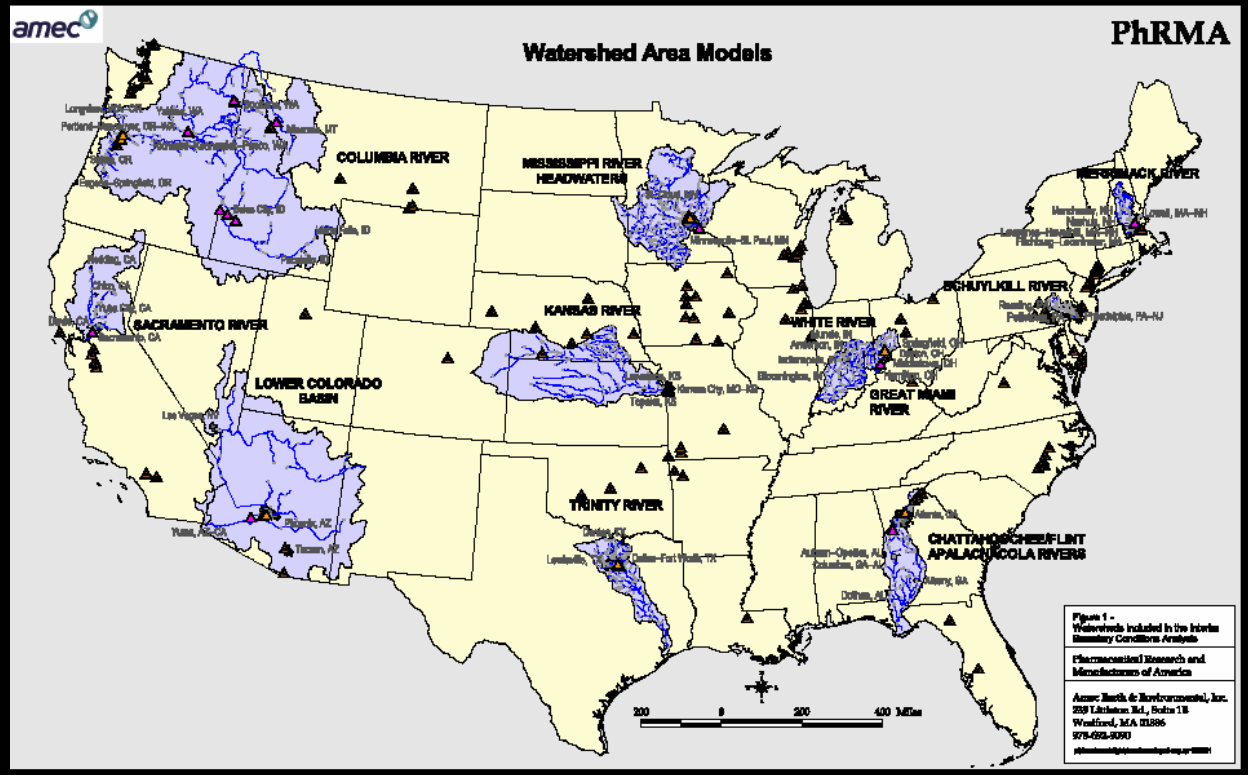
**PNECs**
- Human health
- (Ecological receptors)

# API Concentration Profiles



# P*h*ATE™ Evaluates 11 watersheds

- Selection process based on the following:
  - Presence of drinking water withdrawals on rivers that also have upstream STPs.
  - National coverage
  - Availability of key input data (from BASINS)



# P*h*ATE™ Initial Dataset: 11 APIs

| API | Drug Type | Chemical Functionality @ pH 7 | Annual Use (kg/year) | Human Loss (%) | POTW Removal (%) | | In-Stream Decay (per day) |
|---|---|---|---|---|---|---|---|
| | | | | | 1° | 1° and 2° | |
| Cimetidine | Ulcers | Base | 160,000 | 52 | 6 | 70 | 0 |
| Diltiazem | Blood pressure, angina | Base | 214,000 | 96 | 11 | 70 | 0.032 |
| Enalaprilat | ACE inhibitor | Zwitterion | 1,090 | 10 | 2 | 30 | 0 |
| Ethinyl estradiol (EE2) | Synth hormone | Neutral | 144 | 0 | 30 | 75 | 0 |
| Fluoxetine | Depression, OCD | Base | 22,700 | 90 | 10 | 85 | 0 |
| Gemfibrozil | Cholesterol, lipids | Single acid | 289,000 | 24 | 0.1 | 44 | 0 |
| Mestranol | Synth hormone | Neutral | 0.3 | 85 | 50 | 98 | 0 |
| Metformin | Diabetic | Base | 1,700,000 | 0 | 0.4 | 7 | 0 |
| 19-Norethisterone | Synth hormone | Neutral | 921 | 0 | 10 | 80 | 0.044 |
| Paroxetine metabolite | Antidepressant | Base | 21,400 | 0 | 10 | 89 | 0 |
| Ranitidine | Stomach acids | Zwitterion | 285,000 | 6 | 2 | 30 | 0 |

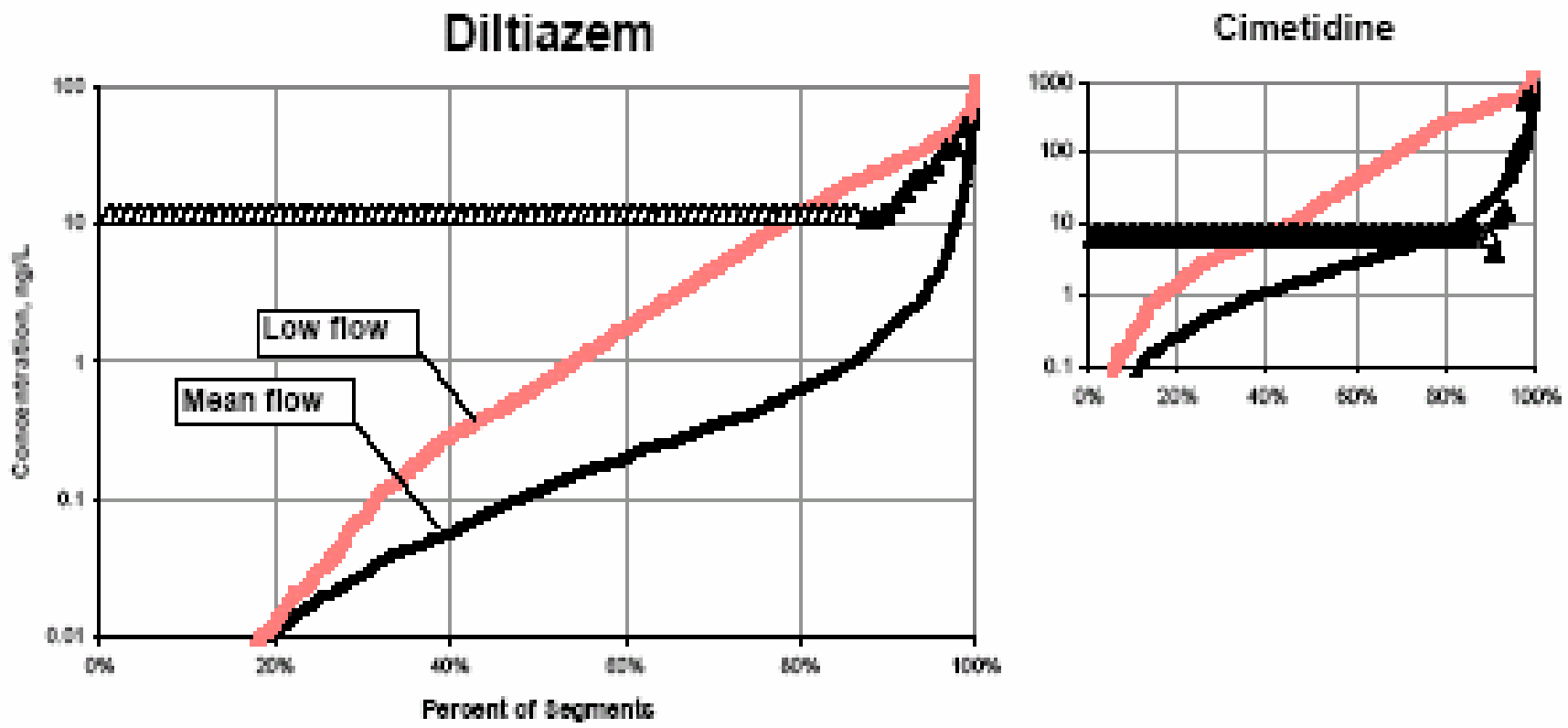
- Annual use based on IMS data from 2003.
- See ES&T article for data sources.

# Model Simulations

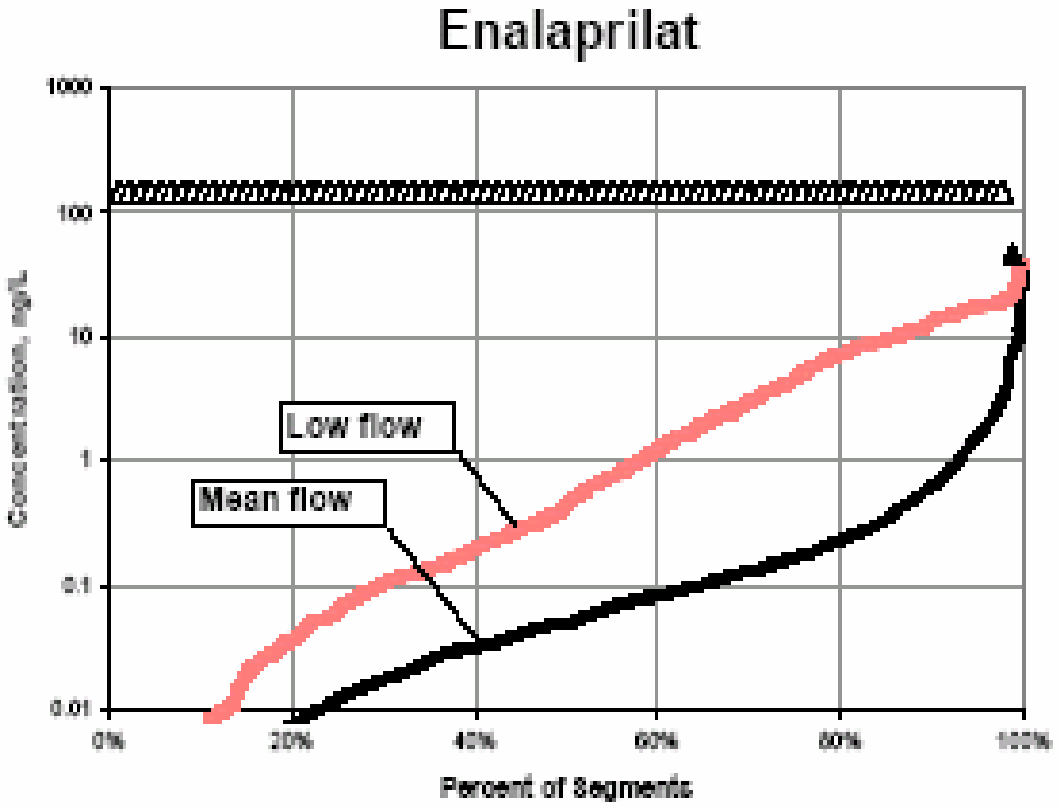
Compared model simulation results for 11 APIs against MEC data (e.g., USGS). This yielded four categories of results:

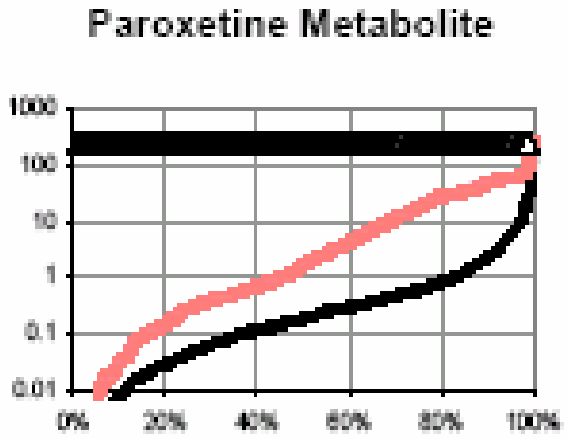
1. PECs fit measured data for two compounds.
2. PECs are below analytical method detection limits and thus are consistent with measured data for three compounds.
3. PECs are higher than (i.e., not consistent with) measured data for three compounds. However, this may be the consequence of as yet unidentified depletion mechanisms.
4. PECs are several orders of magnitude below some measured data but consistent with most measured data for three compounds.

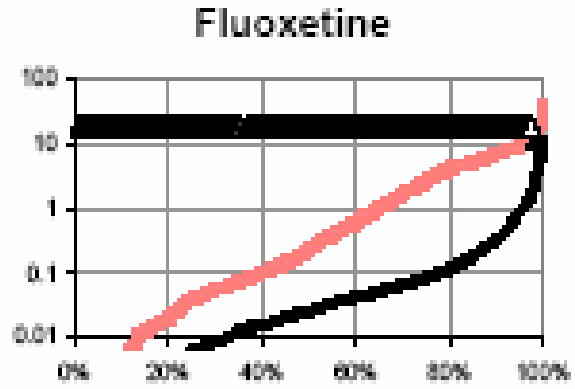
# PhATE™ PECs Consistent with Field Data



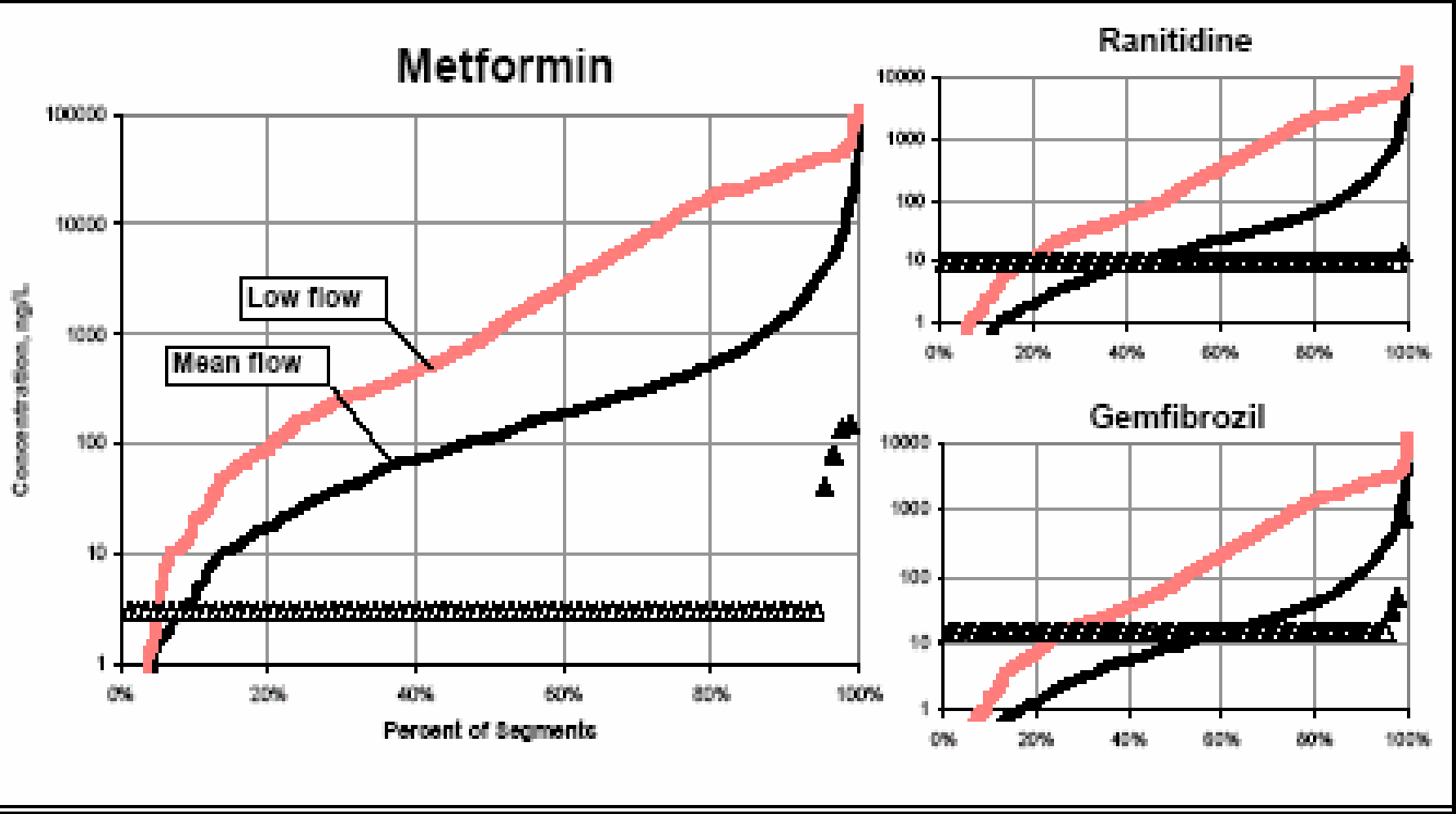
# P*h*ATE™ PECs Consistent with Non-Detect Field Data



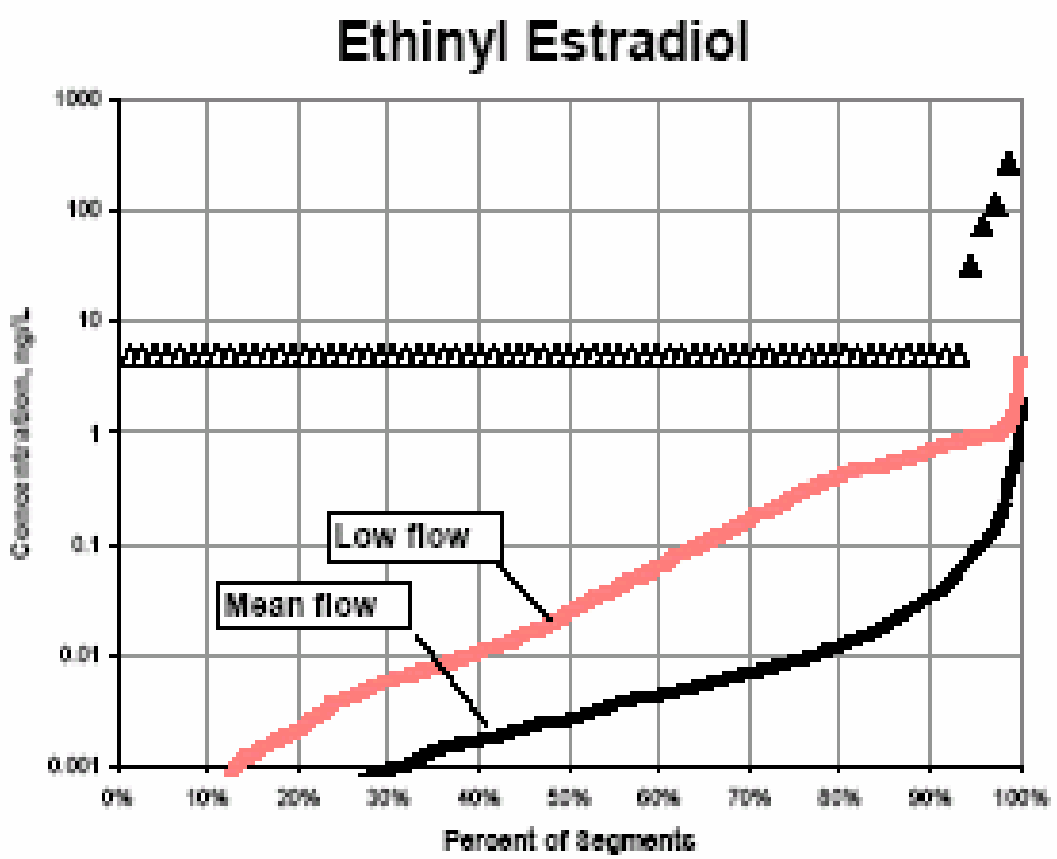



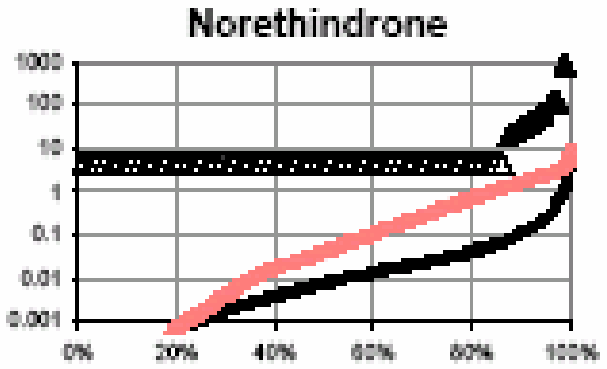



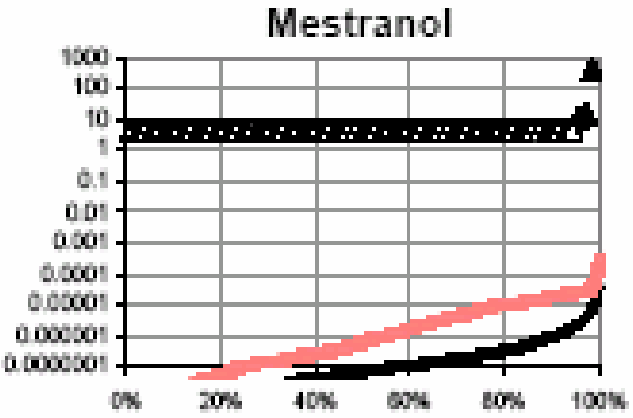
# P*h*ATE™ PECs Greater than Field Data



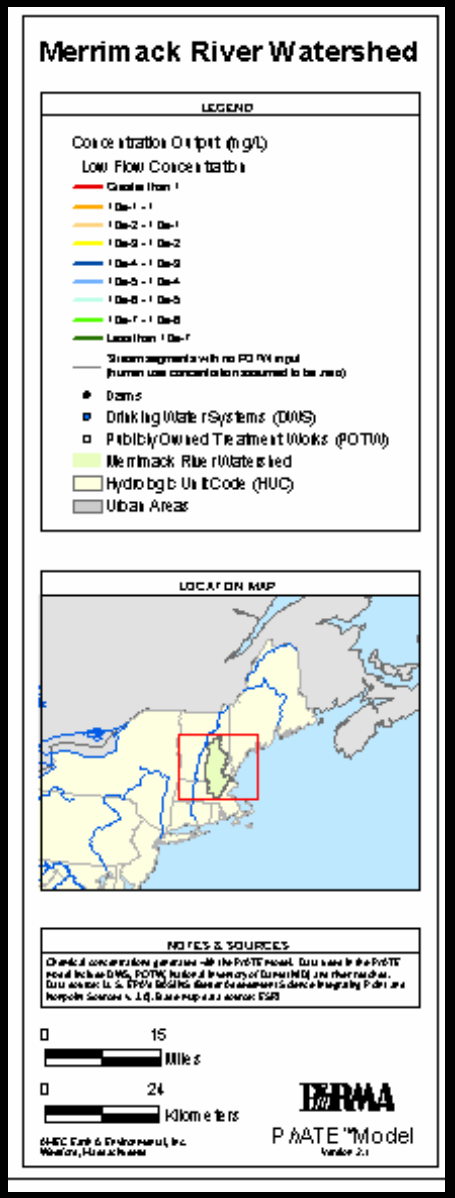
# P*h*ATE™ PECs Lower than Field Data



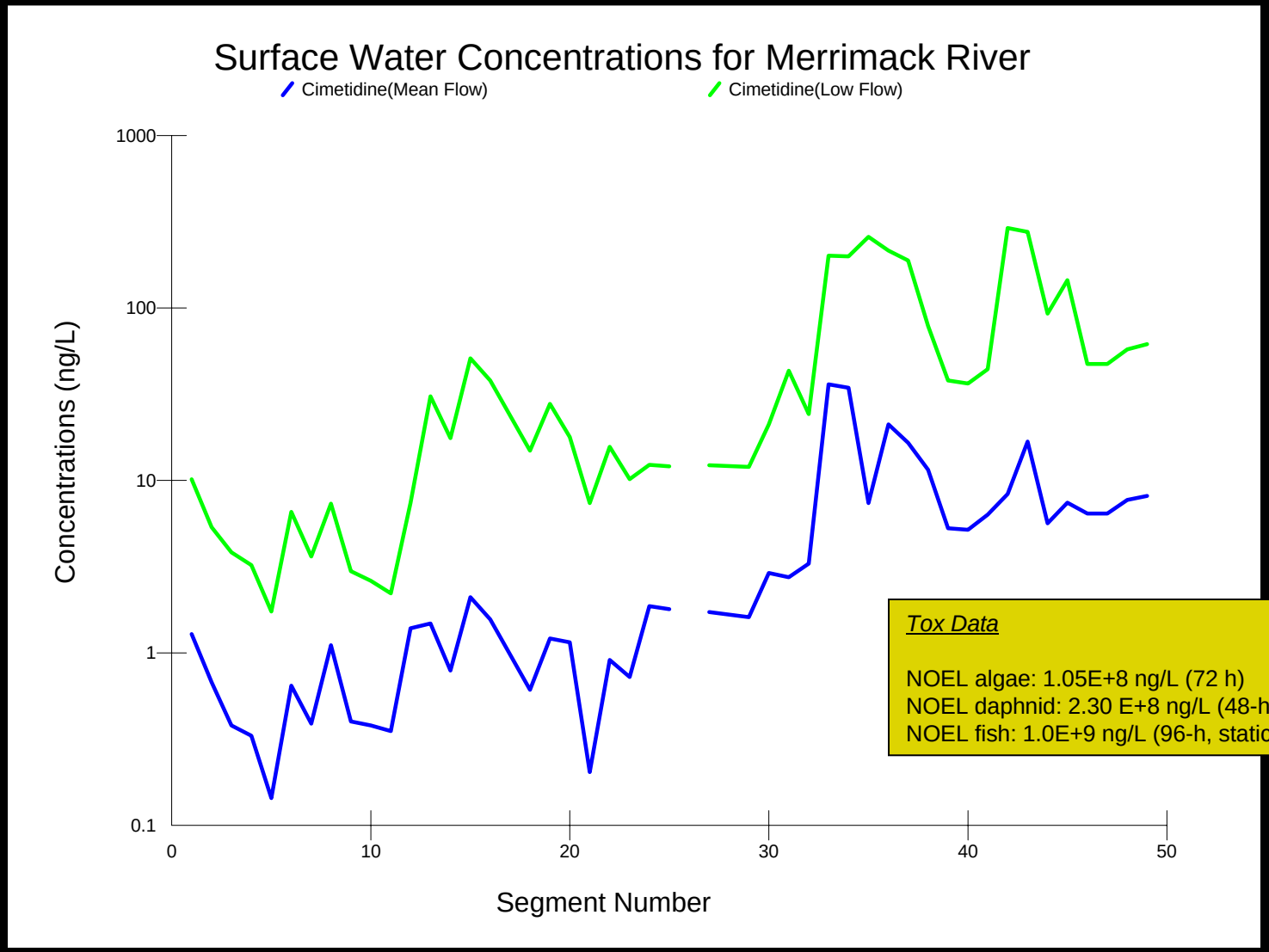
# Case Study: Merrimack River Watershed

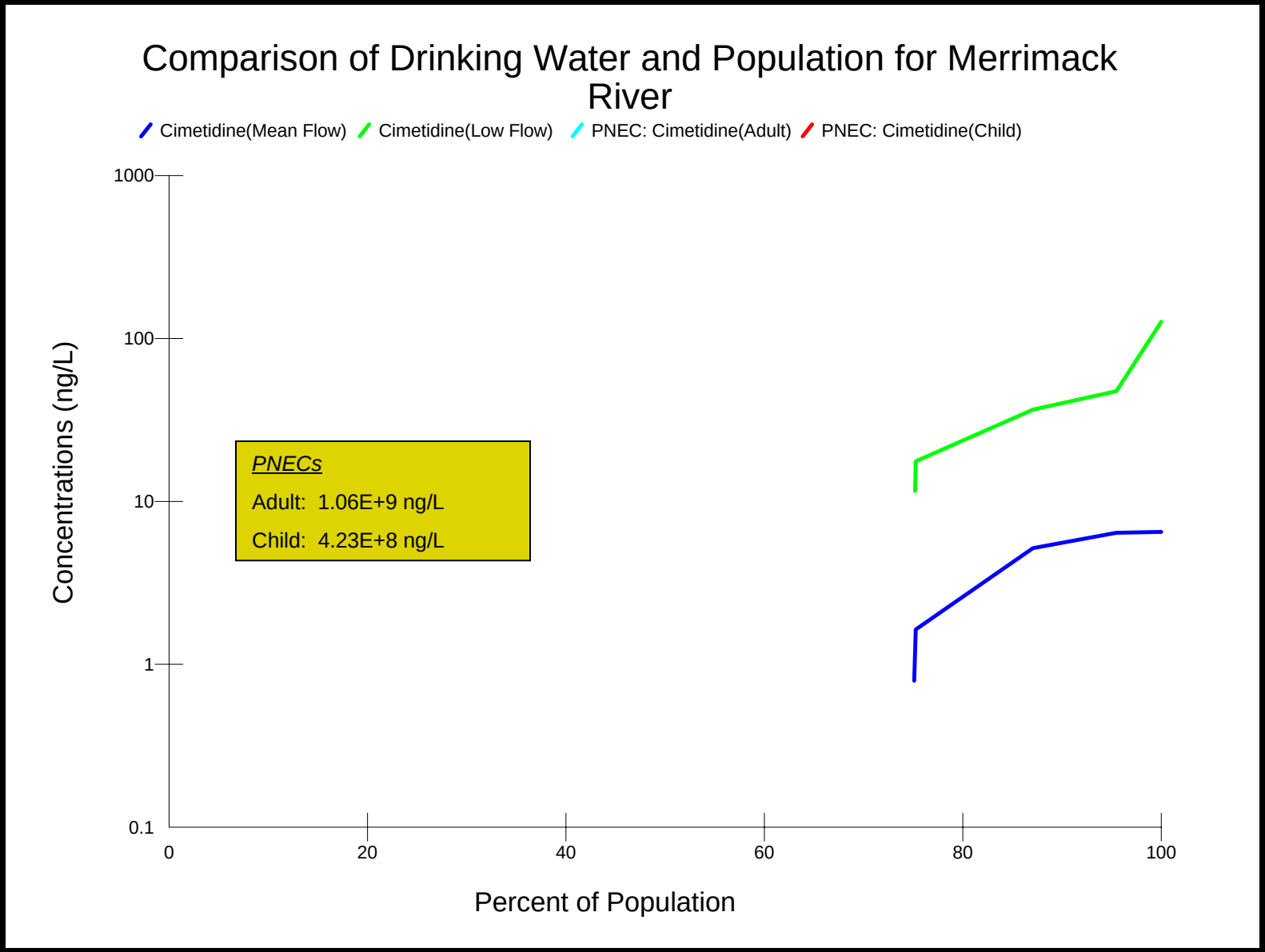
# Merrimack River Watershed Features

- Extends across two states – NH and MA
- Total Population in watershed: 2,090,300
  - Unexposed population: 597,243
- Number of POTWs: 41
- Number of DWS: 5
- Number of Dams: 32
- Watershed Area: 5,030 square miles
- Network Stream Length: 400 miles

# Cimetidine PECs in Merrimack River Surface Water



# Cimetidine PECs and PNECs in Merrimack River Drinking Water



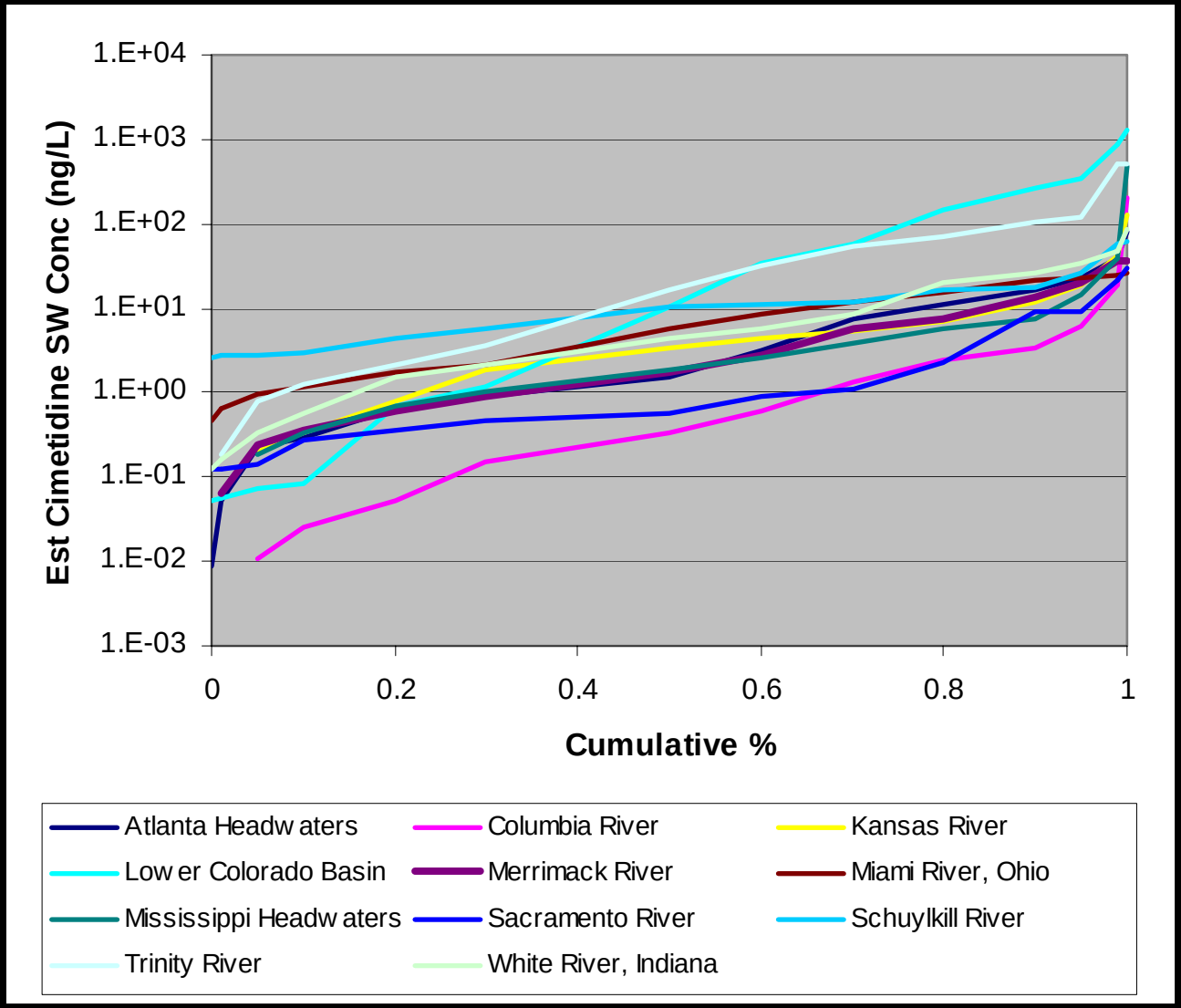
# Comparison of Cimetidine Surface Water PECs in Merrimack River to Other Watersheds

**Summary Statistics for Estimated Cimetidine Concentrations in Surface Water Across All Eleven Evaluated Watersheds**

| Watershed | 5th Perc | 25th Perc | 50th Perc (Median) | Mean | 75th Perc | 95th Perc |
|---|---|---|---|---|---|---|
| Atlanta Headwaters | 2.2E-01 | 8.6E-01 | 1.6E+00 | 6.2E+00 | 9.3E+00 | 2.3E+01 |
| Columbia River | 1.1E-02 | 9.8E-02 | 3.3E-01 | 1.9E+00 | 1.7E+00 | 6.1E+00 |
| Kansas River | 2.1E-01 | 1.0E+00 | 3.5E+00 | 5.8E+00 | 5.8E+00 | 1.9E+01 |
| Lower Colorado Basin | 7.6E-02 | 1.1E+00 | 1.0E+01 | 8.9E+01 | 6.7E+01 | 3.4E+02 |
| Merrimack River | 2.4E-01 | 7.0E-01 | 1.7E+00 | 5.2E+00 | 6.4E+00 | 2.0E+01 |
| Miami River, Ohio | 9.8E-01 | 1.9E+00 | 5.7E+00 | 8.6E+00 | 1.4E+01 | 2.3E+01 |
| Mississippi Headwaters | 1.8E-01 | 9.1E-01 | 1.9E+00 | 5.5E+00 | 4.4E+00 | 1.5E+01 |
| Sacramento River | 1.4E-01 | 3.8E-01 | 5.7E-01 | 2.4E+00 | 1.9E+00 | 9.4E+00 |
| Schuylkill River | 2.7E+00 | 4.7E+00 | 1.1E+01 | 1.3E+01 | 1.2E+01 | 2.7E+01 |
| Trinity River | 8.0E-01 | 3.0E+00 | 1.6E+01 | 4.4E+01 | 6.1E+01 | 1.2E+02 |
| White River, Indiana | 3.4E-01 | 1.8E+00 | 4.3E+00 | 9.7E+00 | 1.2E+01 | 3.5E+01 |

Note:
Units are ng/L

# Graphical Comparison of Cimetidine Surface Water PECs in Merrimack River to Other Watersheds



# P*h*ATE™ Model Modifications

- GIS-enabled system for presentation of key inputs and outputs.
- Recently added a module to estimate APIs in biosolids.
  - Based on the Part 503 regulations and supporting risk assessments
- Future module will estimate sediment concentrations in the 11 evaluated watersheds and related bioaccumulation/toxicity potential.
- Updating the hydrologic information for the latest version of BASINS.
  - Also considering adding other watersheds (e.g., Raritan)
- Integration of results from the development of the Aquatic Life toxicity database.

# Summary

- P*h*ATE™ model was developed as a screening tool to estimate environmental concentrations of PPCPs.
  - Developed for 11 watersheds across the US, but is flexible to add other watersheds.
  - Can also be extended to other countries (e.g., Japan)
- The human health assessment indicates that pharmaceuticals in drinking water for the compounds investigated to date present no appreciable risk to human health.
- Ecological risk potential under evaluation – PNEC development is key to this.
  - P*h*RMA compiling a database of aquatic toxicity values.
  - NOAA maintains useful database of some of this information [http://www.chbr.noaa.gov/peiar/default.aspx]

# P*h*ATE™ Model Development Team

- AMEC Earth & Environmental - Paul Anderson, Beth DuPlessie, Danielle Pfeiffer, John Samuelian
- Quantum Management Group - Vincent D'Aco
- HydroAnalysis, Inc. - Peter Shanahan
- Tufts University - Steven Chapra
- Pharmaceutical Research and Manufacturers of America (PhRMA)
  - Merck & Co., Inc. - Mary Buzby
  - GlaxoSmithKline - Virginia Cunningham
  - Bristol-Myers Squibb Company - Eileen P. Hayes
  - Pfizer Inc. - Frank Mastrocco
  - Eli Lilly and Company - Neil Parke
- *Acknowledgment*: The Pharmaceutical Research and Manufacturers of America (P*h*RMA) provided financial support for the development of the P*h*ATE™ model and related manuscripts and presentations.

# Any Questions?

From: "*Preserving Massachusetts' Water Resources: Merrimack Watershed*"
[http://www.mass.gov/envir/water/merrimack/merrimack.htm]