



# Pharmaceuticals in the Environment: *Ph*RMA Initiatives

Mary Buzby,  
Director, Environmental Technology  
Merck & Co., Inc.

Presented at:  
MASS-A&WMA Technical Conference  
April 6, 2006

# Issue

---

- Pharmaceutical products are being detected in the environment
- There is concern that human health and aquatic life impacts may result from environmental exposure to pharmaceutical compounds

***P/*PRMA**

# Industry Position

---

- PIE is a very important emerging issue
- We are working to understand PIE from many perspectives
  - Human health
  - Aquatic life impacts
  - Disposal of unused medicines
- The major source of PIE is patient use

**PhRMA**

# Science Based Approach is Needed

---

- PhRMA is committed to applying the same level of scientific rigor to PIE that we apply in other areas of our business
- We think a science based approach will:
  - provide confidence to the industry, communities and governments that safety of pharmaceuticals in the environment is well understood
  - provide data needed to prioritize issues requiring further investigation regarding existence and significance of potential impacts

The logo for PhRMA, featuring the letters 'PhRMA' in a stylized, serif font. The 'P' and 'h' are connected, and the 'R' is larger and more prominent than the other letters.

## Who Is *Ph*RMA

The Pharmaceutical Research and Manufacturers of America (*Ph*RMA) represents the country's leading pharmaceutical research and biotechnology companies, which are devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives. *Ph*RMA members invested an estimated \$38.8 billion in 2004 in discovering and developing new medicines.

The logo for the Pharmaceutical Research and Manufacturers of America (PhRMA). It features the word "PhRMA" in a bold, serif font. The "Ph" is written in a smaller, italicized font and is positioned to the left of the "RMA", which is in a larger, bold font.

# Characteristics of Pharmaceuticals

---

- Pharmaceuticals are often large, complex, ionic and hydrophilic compounds; these properties influence their environmental fate.
- These characteristics are not typical of most non-pharmaceutical chemicals evaluated for environmental fate and effects.
- Most pharmaceuticals enter the environment daily through patient use.
- Sources are geographically diffuse and may be influenced by regional use patterns.
- Pharmaceuticals in the environment may be parent, metabolites or conjugates.

**PhARMA**

# Characteristics of Pharmaceuticals

---

- Significance of ionic structure of some pharmaceuticals
  - Complex molecules, often with multiple ionic sites
  - Strongly influenced by pH
  - Tend to partition to aqueous phase
  - Susceptible to inherent biodegradation mechanisms
  - Models based on smaller, neutral models may not describe partitioning in the environment
  - Assumption that  $\text{Log } K_{ow} = \text{Log } P$  may over estimate sorption and bioaccumulation potential

**PhARMA**

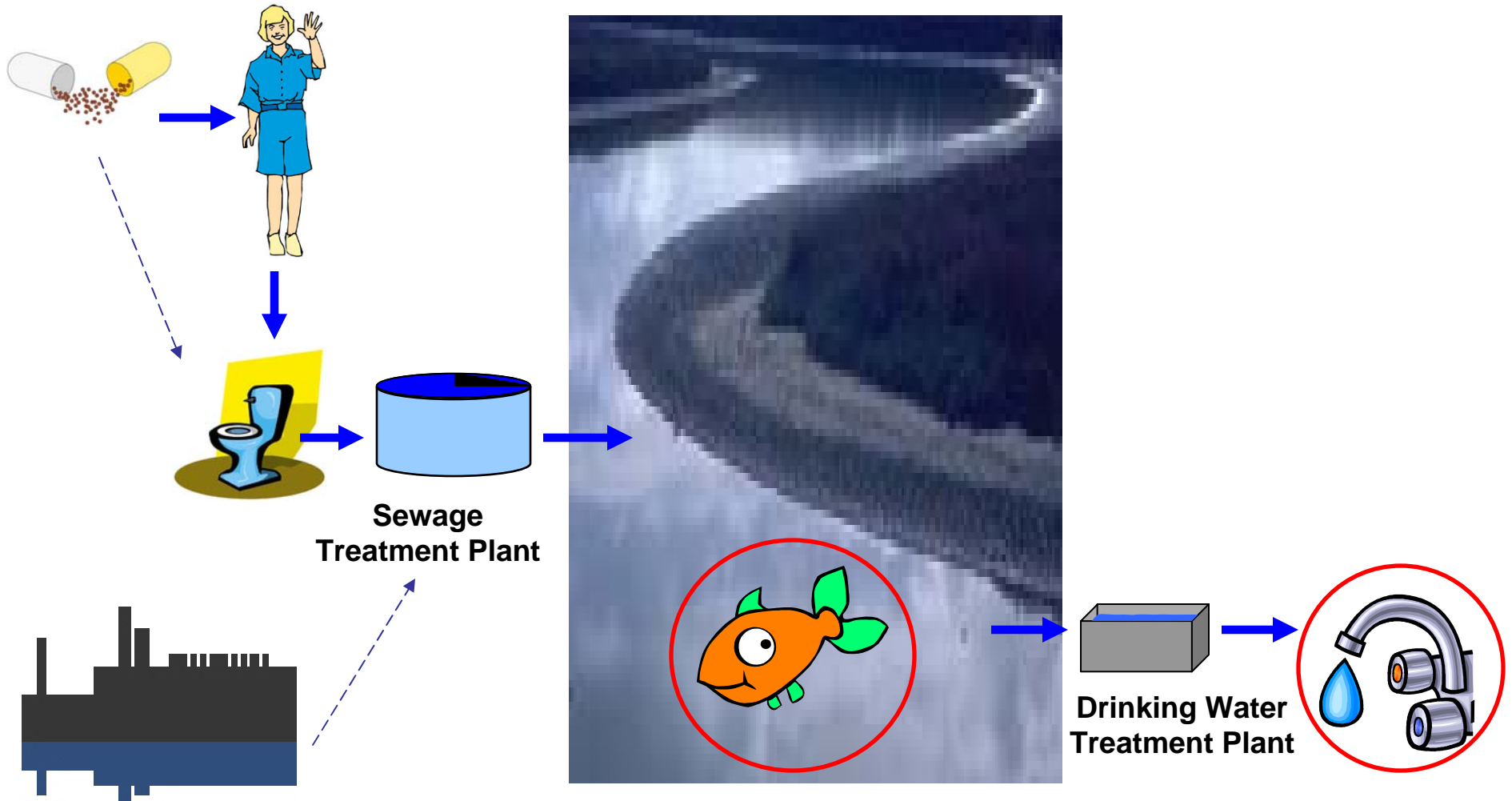
# Additional Considerations

---

- Pharmaceuticals are:
  - a group of diverse compounds
  - present in the environment at very low levels and as components of complex mixtures
  - designed to be biologically active
- Science challenges exist, e.g., testing methods, mixtures, chronic eco-toxicity endpoints, etc.
- Pharmaceuticals vary in their potency; in general, highly potent compounds will be used at lower volumes resulting in lower environmental concentrations. Some more potent compounds may be of environmental concern at lower concentrations.

**PhARMA**

# Pharmaceuticals in the Environment



Patient Use is the Primary Pathway by which Human Pharmaceutical Compounds Enter the Environment

# PhATE™ Model Development (2001)

---

## Needs:

- Evaluate potential distribution of pharmaceutical compounds in the environment
- Assess the significance of reported concentrations to humans and aquatic life

## Action:

- Develop tool to estimate concentrations of pharmaceutical compounds in the environment

**PhARMA**

# PhATE™ Model Development (2001)

---

- Watershed (drainage basin of receiving waterbody)
  - a geographic area in which water, sediments and dissolved materials drain to a common outlet
- Approach allows better understanding of the cumulative impact of human activities
- Many regions moving toward watershed based water quality management

**PhRMA**

# PhRMA – PhATE™ Model

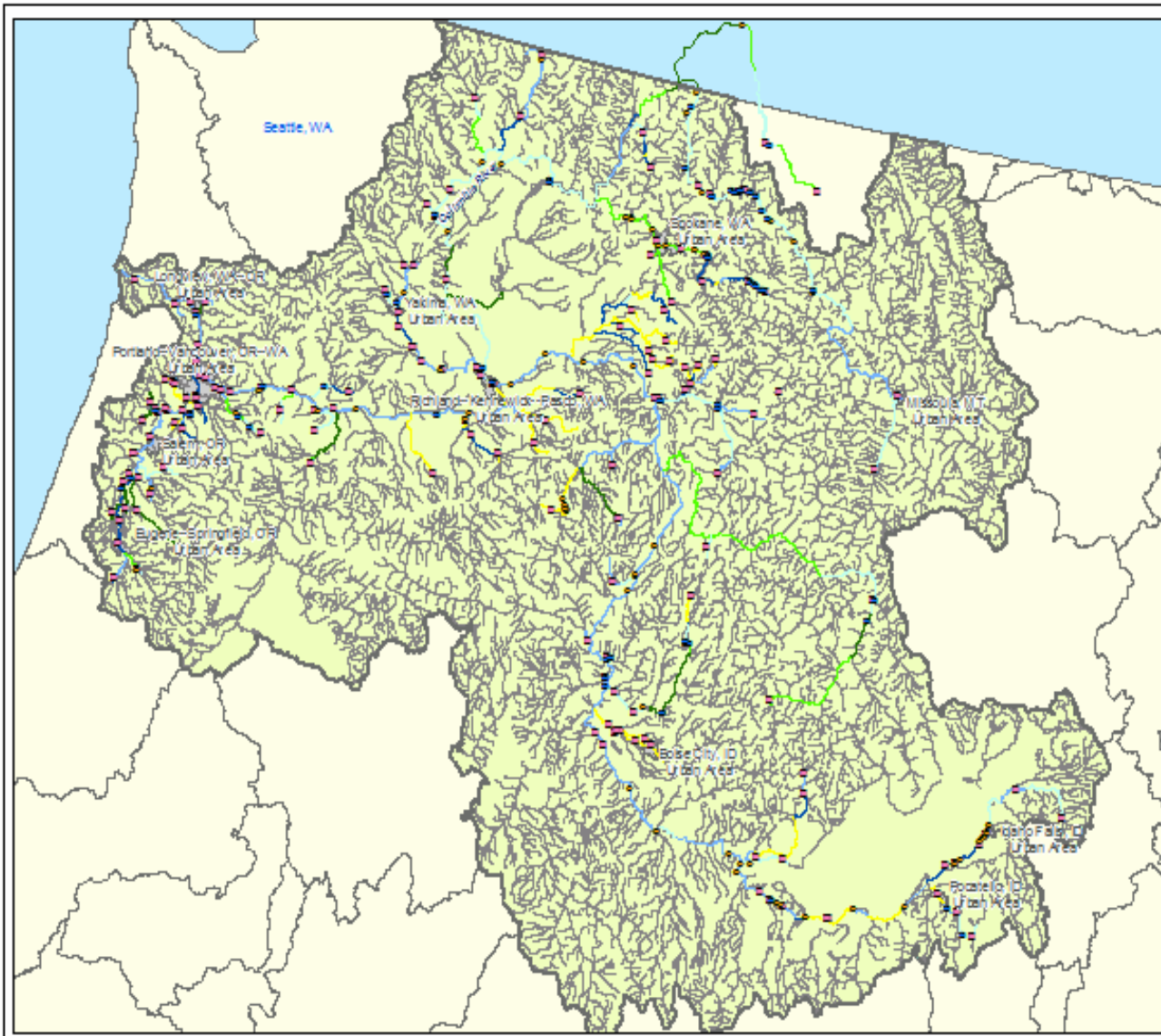
---

- Model predicts concentrations of pharmaceuticals in the environment due to patient use
- Model was developed by PhRMA PIE Task Force and AMEC Earth and Environmental
- Third party reviewers:
  - Dr. Josh Cohen, Harvard School of Public Health
  - Dr. Steve Chapra, Tufts University

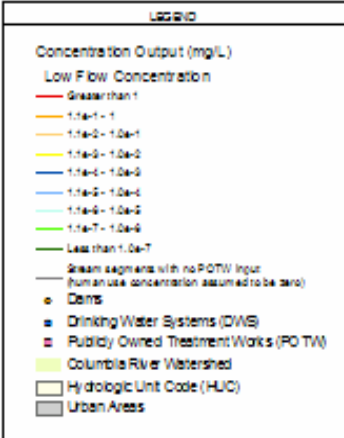
**PhRMA**

# Watershed Model Areas





### Columbia River Watershed



**NOTES & SOURCES**

Chemical output data generated with the PhATE model. Data used in the PhATE model include DWS, POTW, National Inventory of Dams (NID), and the map data. Data sources: U. S. EPA's EIS/IS (State/County-level) Estuaries Integrating Plan and Large Wetlands (S. C.); Stream map data source: USGS.

0 57 Miles

0 92 Kilometers

© 2010 PhATE Model, Inc.  
Portland, Oregon, USA

# Watershed Characteristics

Watershed	Total Population in the Watershed	POTW	DWS	Watershed Area [square miles]	Network Stream Length [miles]
Merrimack River	2,090,300	41	5	5,030	400
Miami River, Ohio	1,809,700	58	5	5,370	820
White River, Indiana	2,465,600	113	17	12,200	1,960
Mississippi Headwaters	5,291,500	363	5	67,465	7,355
Kansas River	1,333,700	99	12	60,100	3,760
Trinity River	5,104,300	114	26	17,970	2,030
Lower Colorado Basin	5,861,200	24	15	135,160	2,420
Sacramento River	2,589,100	19	15	27,900	720
Columbia River	6,306,400	162	57	220,130	5,870
Atlanta Headwaters	3,894,400	76	17	20,410	1,810
Schuykill River	1,950,400	43	11	1,930	310
<b>Total</b>	<b>38,696,600</b>	<b>1,112</b>	<b>185</b>	<b>573,665</b>	<b>27,455</b>

**Notes:**

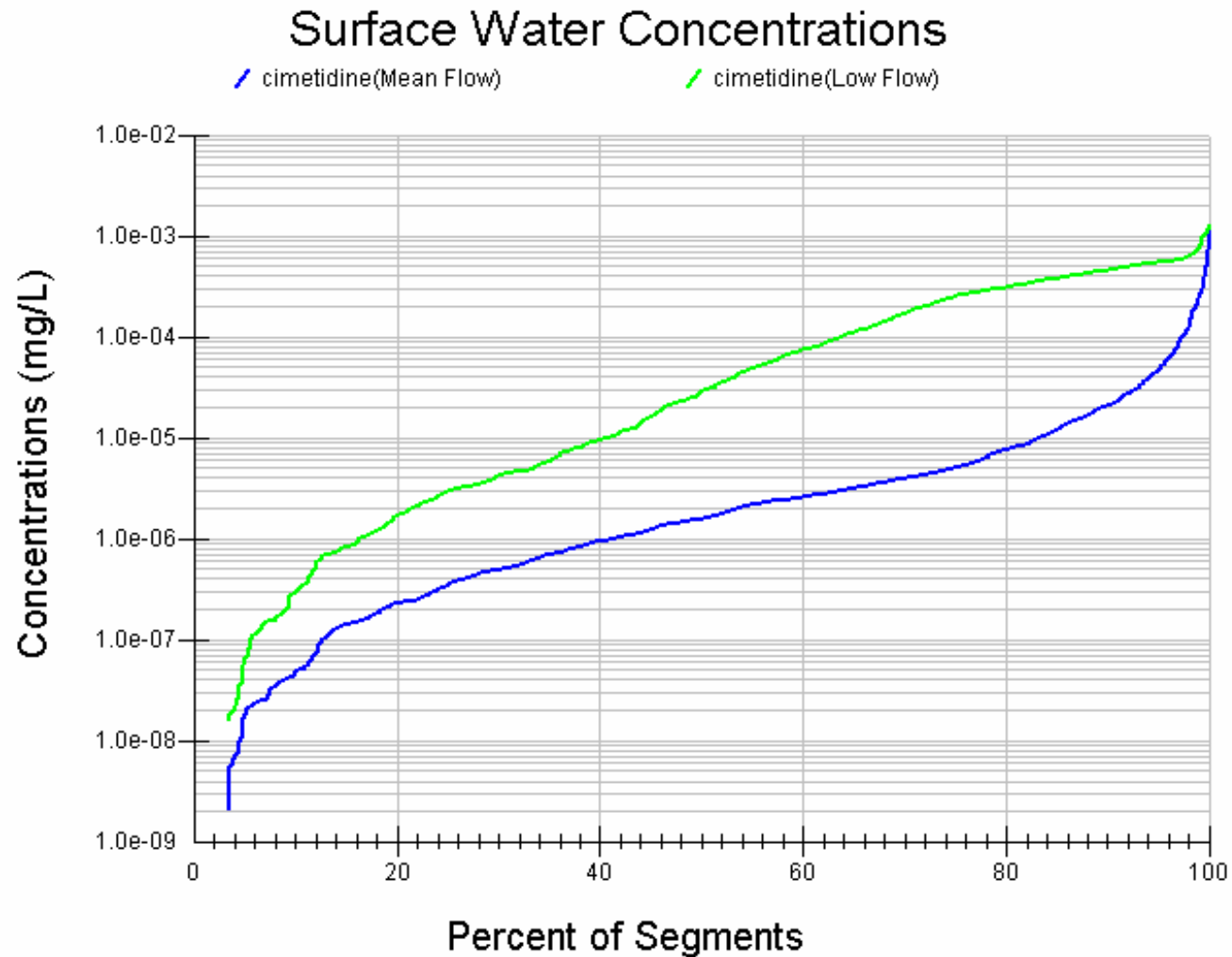
[1] Network Stream Length is the total stream length located downstream of at least one POTW, which is a subset of the total stream length within the watershed.

[2] Total may disagree with sum of watersheds due to round-off error.

# WWTP Removal Component

<b>"WW-TREAT" ACTIVATED SLUDGE MODEL</b>				
<b>Cowan <i>et al</i> ., Water Res, 1993, 27:561-573</b>				
	<b>compound =</b>	Cimetidine		
<b>PARAMETER</b>		<b>code</b>	<b>units</b>	<b>value</b>
influent fraction		Ci	N/A	1.00E+00
sludge/water partition coef.		Kp	N/A	871.0
fraction sludge removed in primary clarifier		Rp	N/A	0.6
TSS in influent		S	g/m3	220
gas flow rate		G	m3/hr	0.45
Henry's constant		H	m3*atm/mol	3.26E-09
hydraulic retention time		HRT	hr	6
biodeg rate of dissolved substance		K1	hr-1	0.03
biodeg rate of adsorbed substance		K2	hr-1	0.03
mixed liquor SS		MLSS	g/m3	2200
water flow rate		Q	m3/hr	18.75
gas constant		R	3*atm/mol*K	0.0821
fraction solids removed in reactor		Ra	N/A	0.99
sludge retention time		SRT	hr	96
temp		T	K	293
<b>PRIMARY TREATMENT MODULE</b>				
fraction on primary sludge		Cps	N/A	1.61E-01
fraction in effluent from primary settling		Ce1	N/A	9.04E-01
<b>FRACTION REMOVED IN PRIMARY</b>				<b>0.096</b>
<b>ACTIVATED SLUDGE MODULE</b>				
volatilization loss term		Kv	N/A	1.88E-09
biodeg loss term		Kb	N/A	1.95E+00
dissolved + sorbed cmpd fraction		Cr	N/A	3.06E-01
cmpd fraction sorbed to sludge		Cs	N/A	2.01E-01
final effluent fraction		Ce2	N/A	1.07E-01
removal via AS				0.797
<b>FRACTION REMOVED IN SECONDARY</b>				<b>0.893</b>
<b>FINAL DISTRIBUTION</b>				
<b>total removed</b>			N/A	<b>0.893</b>
<b>volatilization</b>			N/A	<b>0.000</b>
<b>biodegradation</b>			N/A	<b>0.692</b>
<b>adsorption</b>			N/A	<b>0.201</b>
<b>effluent</b>			N/A	<b>0.107</b>
		<b>sum</b>		<b>1.000</b>

# Example PhATE™ Output: cimetidine



# Publications

---

- USGS Paper:

Kolpin, et al., *Pharmaceuticals, Hormones, & Other Wastewater Contaminants in U.S. Streams, 1999-2000: A National Reconnaissance*, ES&T. 2002, 36, 1202-1211.

- PhATE™ Paper:

Anderson, et al., *Screening Analysis of Human Pharmaceutical Compounds in US Surface Waters*, ES&T. 2004, 38, 834-849.

**PhARMA**

# Summary of *Ph*A<sup>TM</sup> Manuscript Findings

---

- *Ph*A<sup>TM</sup> PECs generally had a good fit with USGS measured data.
- Comparing the PECs to the measured data identified some questionable analytical findings.
- *Ph*A<sup>TM</sup> PECs allow the evaluation of potential effects at concentrations below detection limits.
- Comparing PECs to measured data allows the evaluation of the adequacy of POTW and in-stream removal mechanism data.

***Ph*RMA**

# Publications

---

- USGS Paper:

Kolpin, et al., *Pharmaceuticals, Hormones, & Other Wastewater Contaminants in U.S. Streams, 1999-2000: A National Reconnaissance*, ES&T. 2002, 36, 1202-1211.

- PhATE™ Paper:

Anderson, et al., *Screening Analysis of Human Pharmaceutical Compounds in US Surface Waters*, ES&T. 2004, 38, 834-849.

**PhARMA**

# PhATE Model Enhancements

- Latest modifications (2005)
  - GIS module for enhanced presentation of PhATE results and geographic analysis tool
- Current modifications (2006)
  - Estimate partitioning and removal in POTWs
  - Estimate potential exposures to APIs in biosolids

**PhARMA**

# Human Health Screening Analysis

---

- Identified measured environmental concentrations for compounds reported in published articles (MEC)
- Used *PhATE*<sup>™</sup> in screening mode to predict concentrations in environment
- Developed predicted no effect concentrations (PNEC)
  - Considered drinking water and fish consumption exposure pathways
- Evaluated MEC/PNEC and PEC/PNEC ratios

*Ph*PRMA

# Human Health Screening Analysis

---

- Analysis included 26 USGS human health pharmaceuticals
  - Non-steroidal analgesics, non-steroidal anti-inflammatory
  - Opiate analgesic
  - Bronchodilator
  - H2 receptor antagonists
  - Antimicrobial, antibiotics, antibacterial
  - Calcium blocker, ACE inhibitor, anti-hypertensives
  - Serotonin uptake inhibitors, anti-depressive
  - Hypoglycemic
  - Anti-coagulant
  - Cardiac glycoside
  - Anti-hyperlipidemic
- Compounds studied excluded hormones which are being evaluated separately due to the complexity of that evaluation

**PRMA**

# Human Health Screening

---

- Results of human health assessment indicate that residues of these pharmaceuticals in water present no appreciable risk to human health.

***P*PRMA**

# Human Health Screening Analysis

---

*Human pharmaceuticals in US surface waters:  
A human health risk assessment, Schwab, et al.  
Regulatory Toxicology and Pharmacology, Volume  
42, Issue 3, Pages 296-312 (August, 2005)*

**PRMA**

# Other Human Health Publications

---

- Christensen, F.M. (1998) **Pharmaceuticals in the environment – A Human Risk?**, Reg. Toxicol. & Pharmacol., 28, 212-221.
- Schulman, et al., (2002) **A human health risk assessment of pharmaceuticals in the aquatic environment**, Human & Ecological Risk Assessment, 8 (4), pp. 657-680.
- Mons, M.N., (2003) **Pharmaceuticals and drinking water supply in the Netherlands**, Kiwa N.V. Water Research.
- Webb, et al., (2003) **Indirect human exposure to pharmaceuticals via drinking water**, Toxicology Letters, 142, 157-167.

All concluded that environmental exposure to human pharmaceuticals poses little human health risk.

**PhARMA**

# Development of Aquatic Life Data Base

- English language, peer-reviewed literature
  - chronic and acute effects to aquatic organisms
  - fate and transport and treatment removal
- Bibliographic information entered for 857 articles
- Progress to date
  - data from 290 articles have been evaluated and entered
  - data from 30-40 new articles evaluated and entered each quarter

***P/RMA***

# Current PhRMA PIE Publications

- Human Pharmaceuticals and Aquatic Life: Perspective on Environmental Effects.
  - Accepted for publication ES&T (A-Pages)
- Do pharmaceuticals in surface waters pose a risk to human health?
  - Submitted to Journal AWWA, Current Issues pages.
- Carbamazepine risk assessment.
  - Presentations at SETAC 2005 and 2006,
  - NGWA 2006, 2 posters at DIA Sweden 2006
  - Manuscript in preparation
- Analgesics case study.
  - SETAC poster 2005
  - Manuscript in preparation

The logo for PhRMA (Pharmaceutical Research and Manufacturers of America) is displayed in the bottom right corner. It features the word "PhRMA" in a bold, serif font. The letter "P" is significantly larger and more stylized than the other letters, with a vertical line through its center. The "R" and "M" are also large and bold, while the "A" is smaller and positioned to the right of the "M".

# Carbamazepine Risk Assessment

- Carbamazepine tends to be detected more frequently and at relatively higher concentrations than most other active pharmaceutical compounds (APIs).
- Studies of its fate in wastewater treatment systems and surface waters suggest that it may be more resistant to degradation than other APIs

***P/RMA***

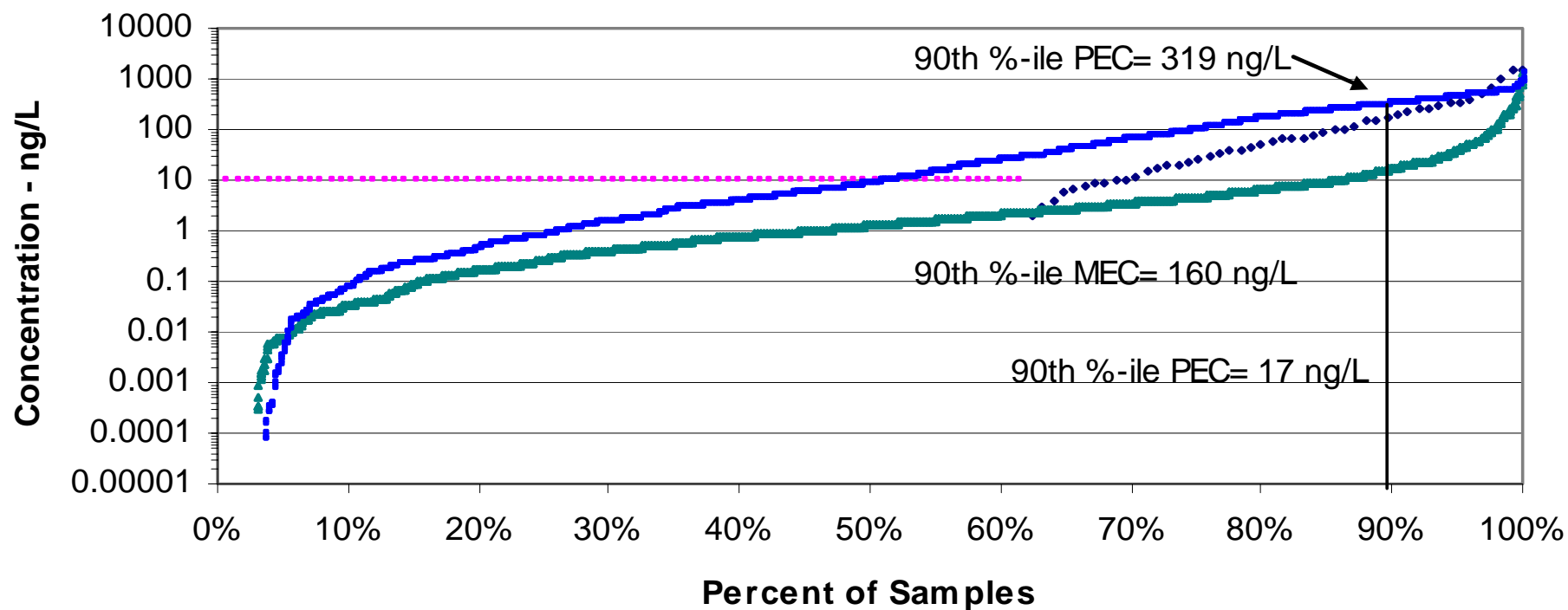
# Carbamazepine Risk Assessment

Objective:

- To present allowable surface water concentrations protective of human health and aquatic life, and compare those allowable concentrations to both measured and modeled concentrations in North America and Europe

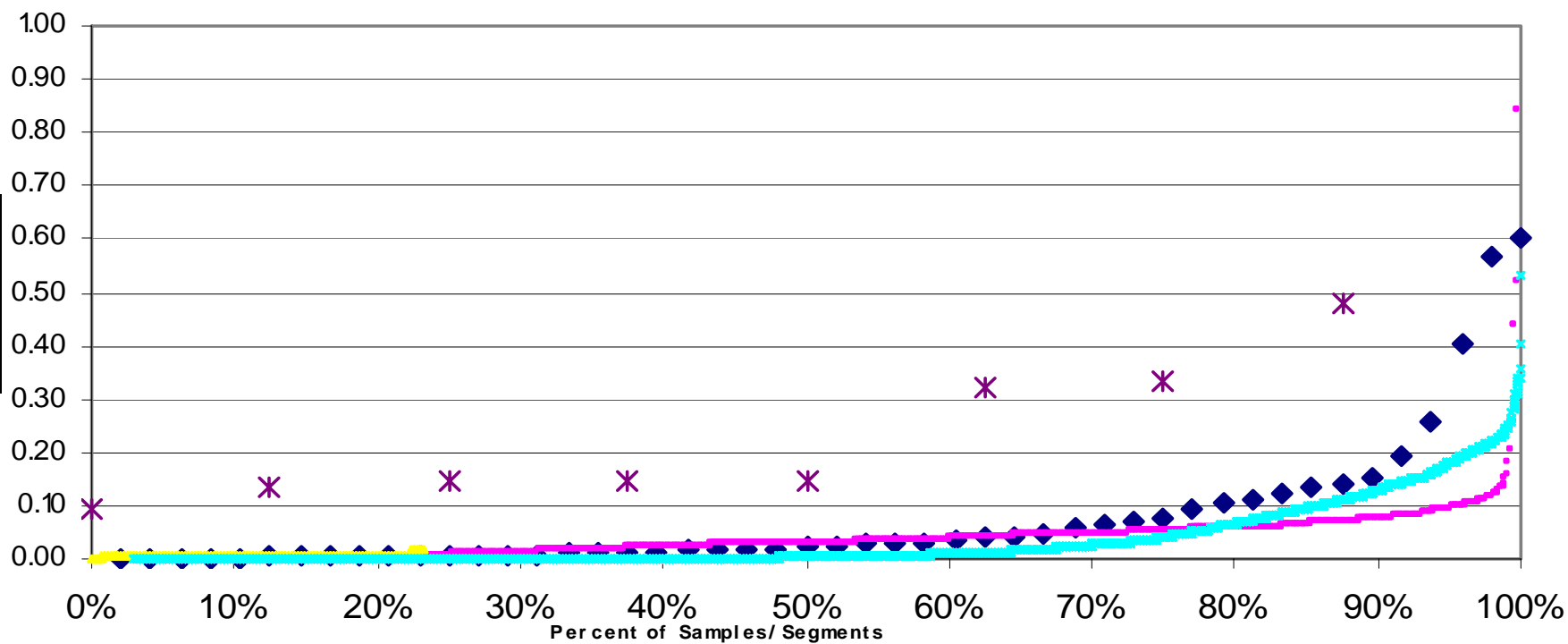
***P/RMA***

**Figure 1. Carbamazepine - Measured and Predicted Environmental Concentrations (MECs and PECs) in North America**



• MEC- Detected • MEC- Non-Detected ▲ Conc. Mean Flow - ng/L • Conc. Low Flow - ng/L

**Figure 3: Carbamazepine - MEC/PNEC and PEC/PNEC Ratios for North America and Europe**



◆ MEC/PNEC - NA    ● MEC/PNEC-EU    ▲ MEC LOD/PNEC - EU    × PEC/PNEC - NA    \* PEC/PNEC-EU

# Conclusions Concerning CBZ

- Carbamazepine has a human health risk ratio significantly less than one and therefore presents no appreciable risk to human health through environmental exposure.
- Carbamazepine has aquatic and sediment life risk ratios less than 1, and its major metabolites have aquatic life risk ratios less than 1.
- Carbamazepine and its major metabolites have a combined aquatic life risk ratio less than 1 (based on 90th percentile measured and predicted concentrations).
- These results indicate no need for further testing or for risk reduction measures beyond those already being applied. However, mitigation measures should be considered for especially vulnerable areas where local concentrations may result in occasional risk ratios greater than 1.

**PRMA**

# Summary

---

- The industry is committed to assessing the significance of pharmaceuticals in the environment using science- based approaches.
- The human health assessment indicates that pharmaceuticals in drinking water for the compounds investigated to date present no appreciable risk to human health.
- The industry is evaluating published data on aquatic life impacts and formulating an approach to assess the potential for impacts to ecosystems.
- The industry is seeking opportunities to collaborate with other stakeholders on PIE

**PhRMA**