Pharmaceuticals in the Environment PhRMA PIE Perspective

Pharmaceuticals and Personal Care Products in the Environment Symposium

California Department of Toxic Substances Control
May 22, 2007

Mary E. Buzby
Merck & Co., Inc.

PhRMA PIE Task Force

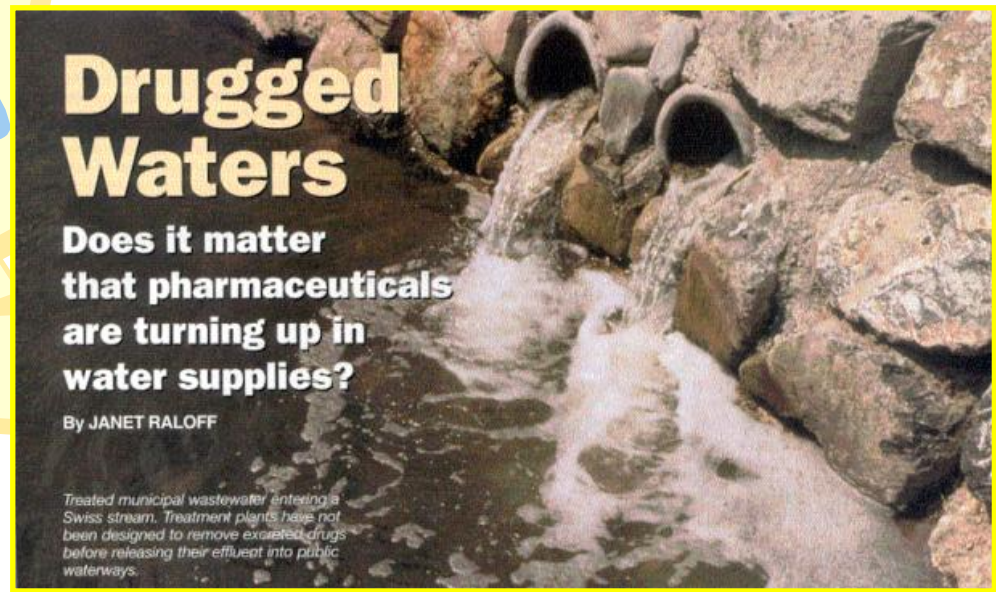
PhRMA

There is concern that human health and aquatic life impacts may result from environmental exposure to pharmaceutical compounds

Arizona Daily Star

Effluent alters sexuality of fish

By Tony Davis
12.11.2005



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Pharmaceuticals in the environment is of interest to a broad range of stakeholders

Health Canada Santé Canada

PhRMA

The research based pharmaceutical industry is working to understand PIE

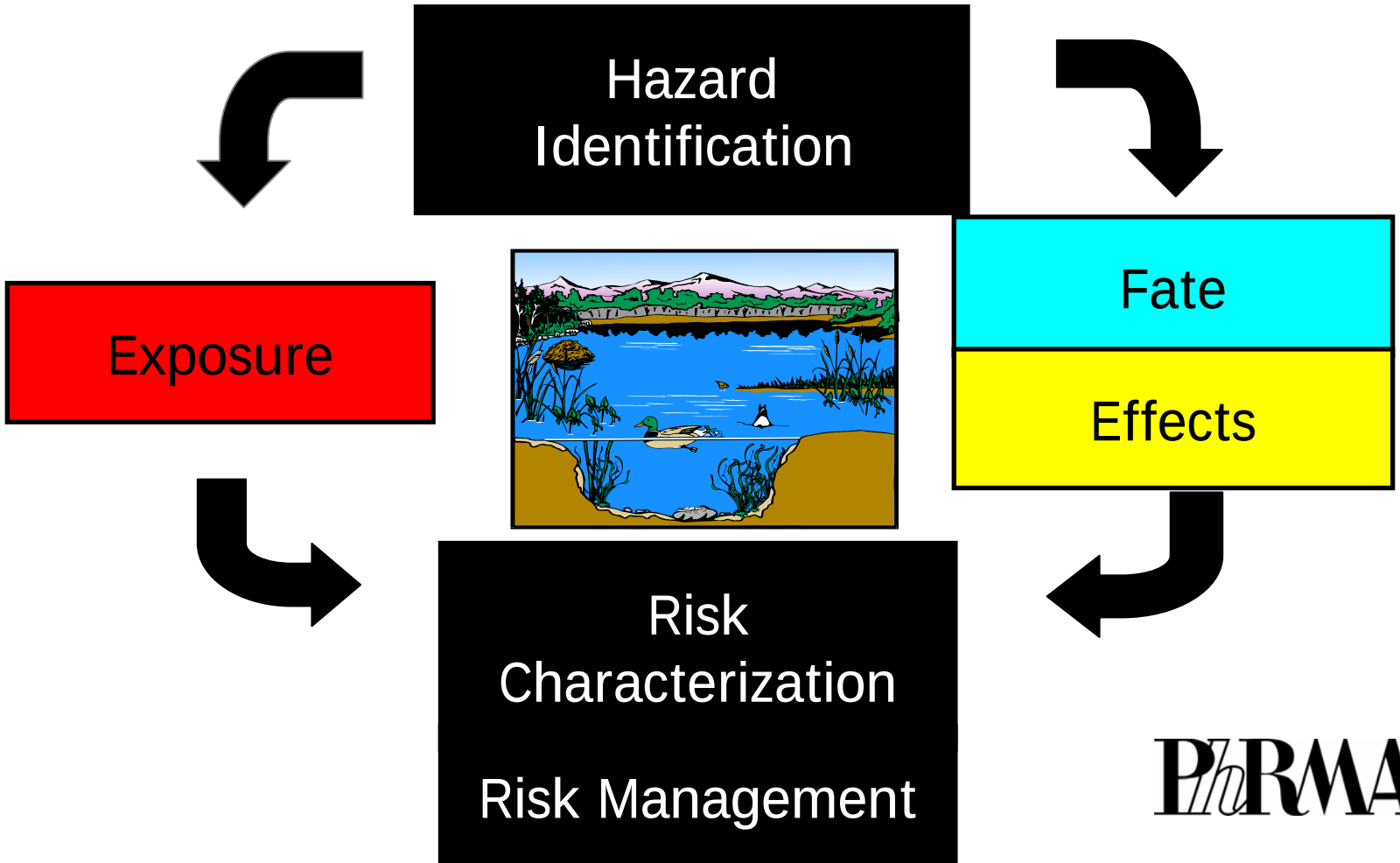
Human health

Aquatic life

Unused medicines disposal

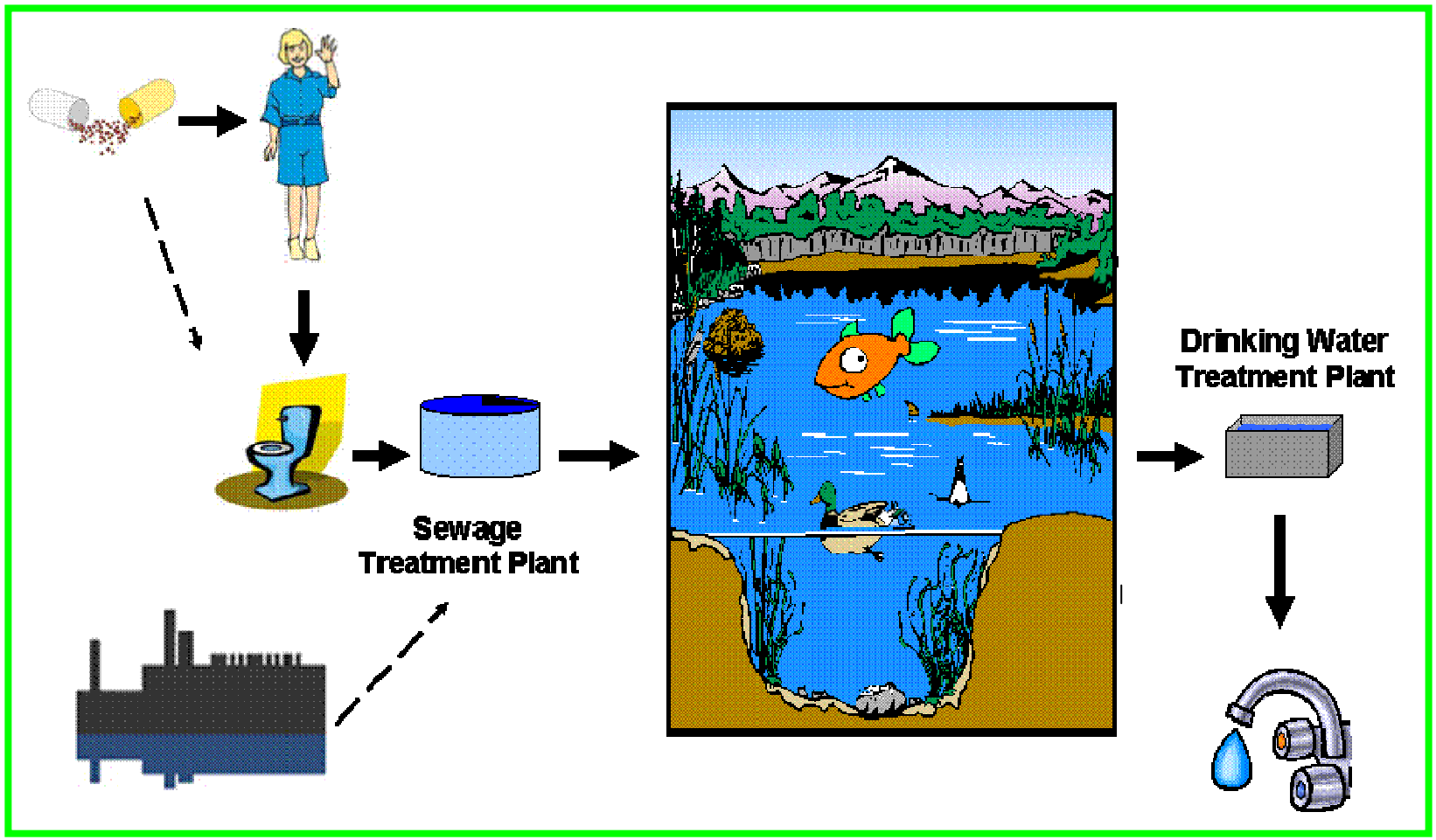
PhRMA

A science based approach is needed to evaluate the significance of pharmaceuticals detected in the environment.

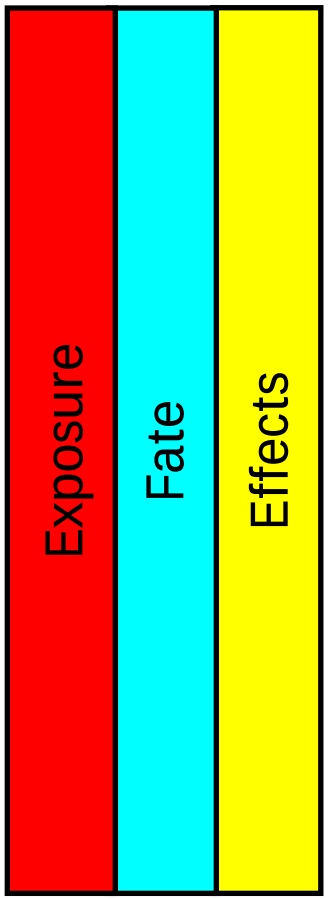


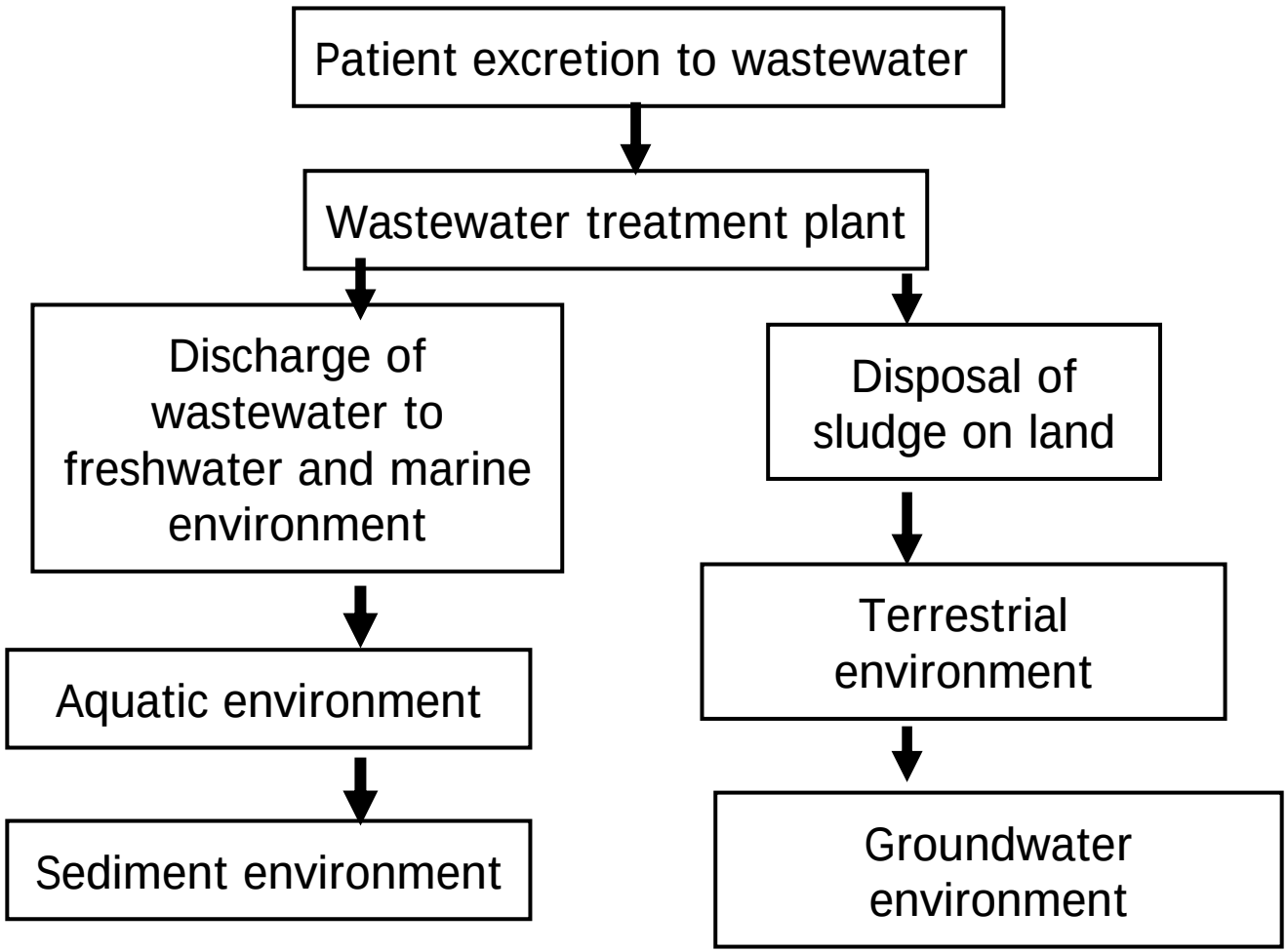
PhRMA

Pharmaceutical compounds primarily enter the environment through normal patient use

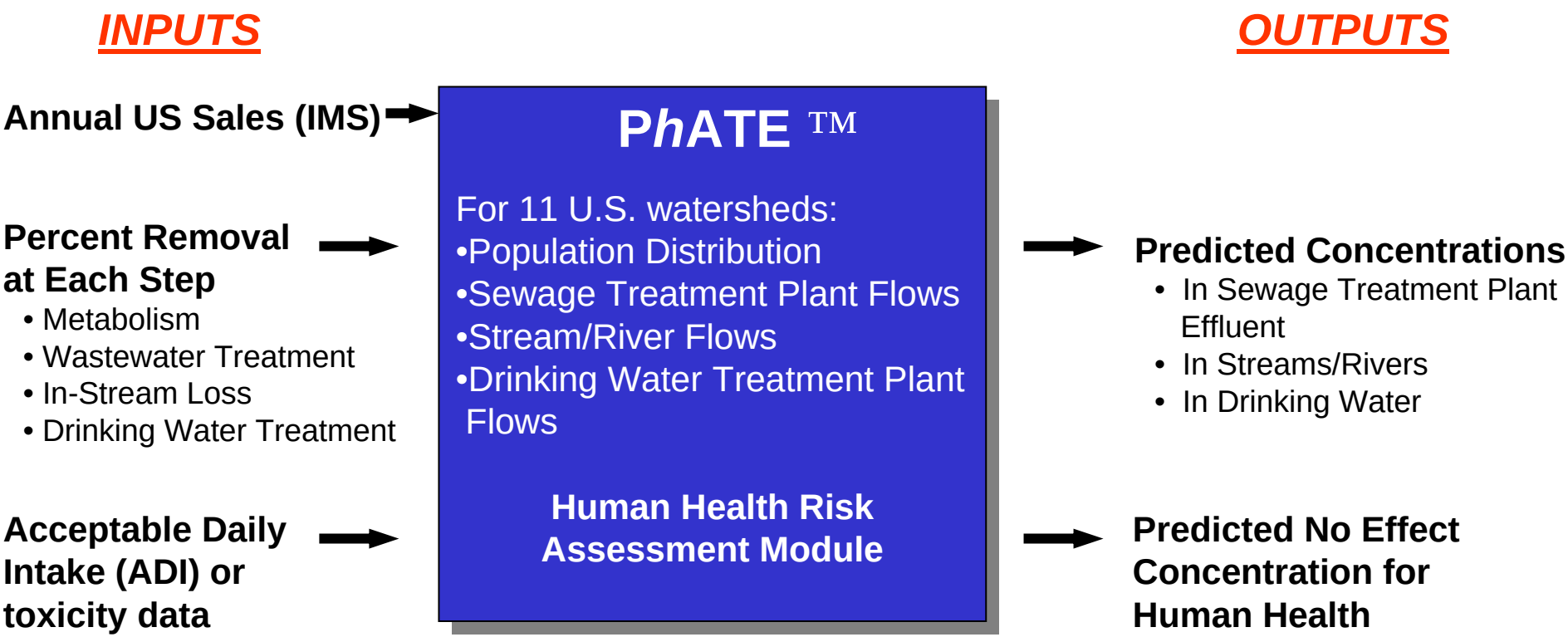


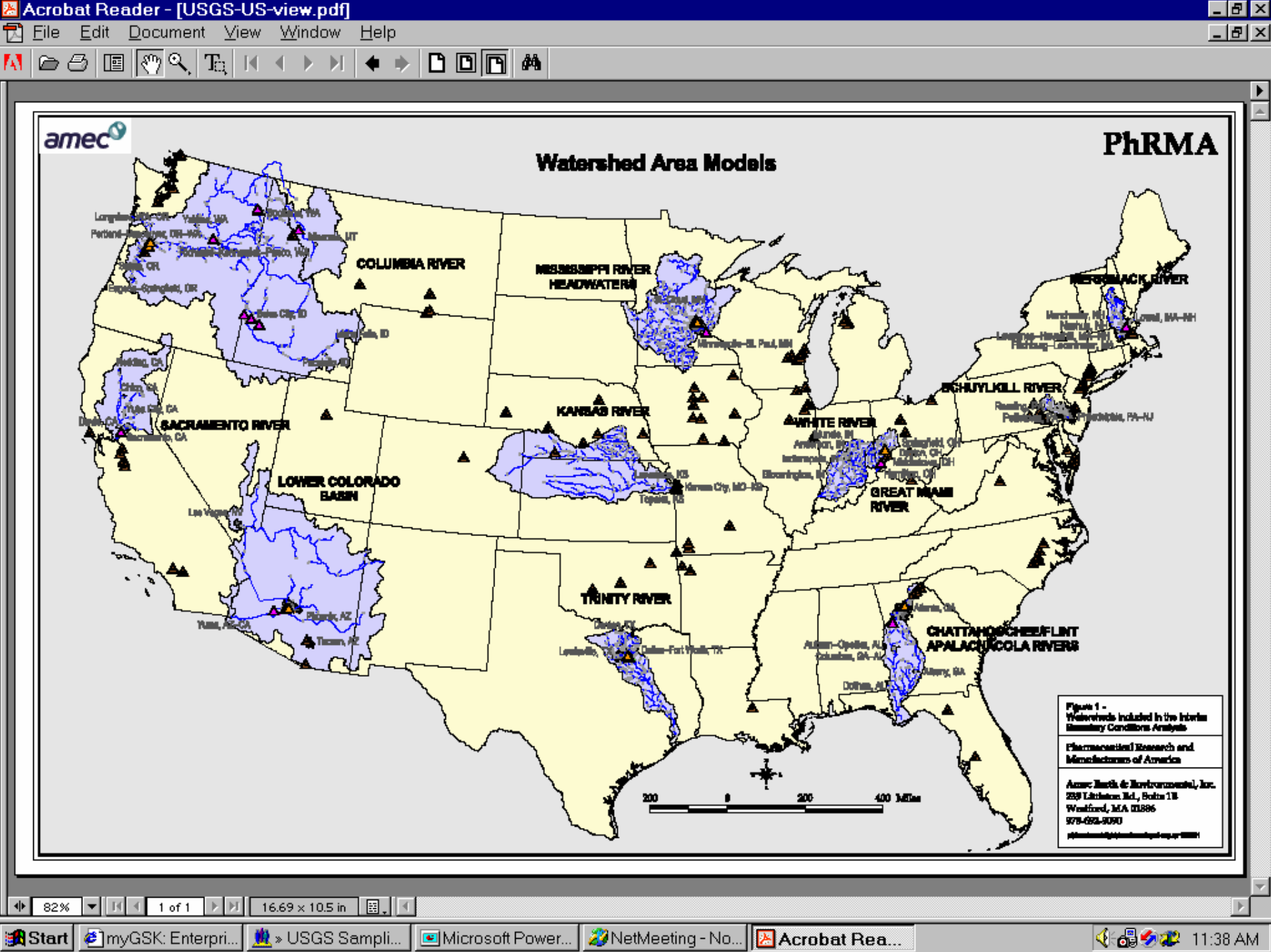
Knowledge about the concentrations of pharmaceuticals in the environment is needed to evaluate PIE





Modeling can be used to estimate concentrations of pharmaceuticals in the environment




Acrobat Reader - [USGS-US-view.pdf]
File Edit Document View Window Help
amec
PhRMA
Watershed Area Models
COLUMBIA RIVER
MISSISSIPPI RIVER HEADWATERS
MERRIMACK RIVER
SCHUYLKILL RIVER
KANSAS RIVER
WHITE RIVER
SACRAMENTO RIVER
LOWER COLORADO BASIN
GREAT MIAMI RIVER
TRINITY RIVER
CHATTAHOOCHEE/FLINT APALACHICOLA RIVERS
200 0 200 400 Miles
Figure 1 -
Pharmaceutical Research and Manufacturers of America
82%
1 of 1
16.69 x 10.5 in
Start
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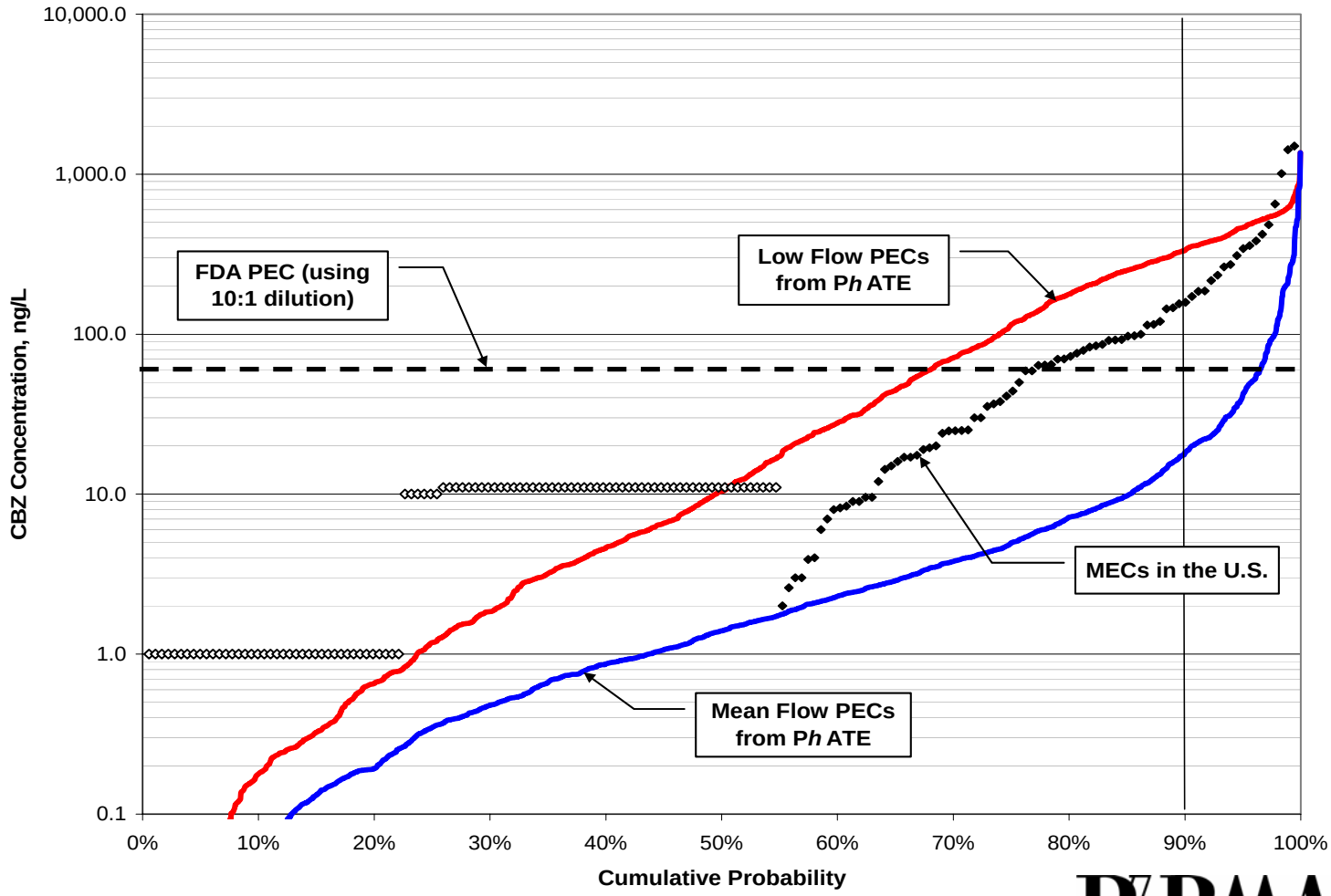
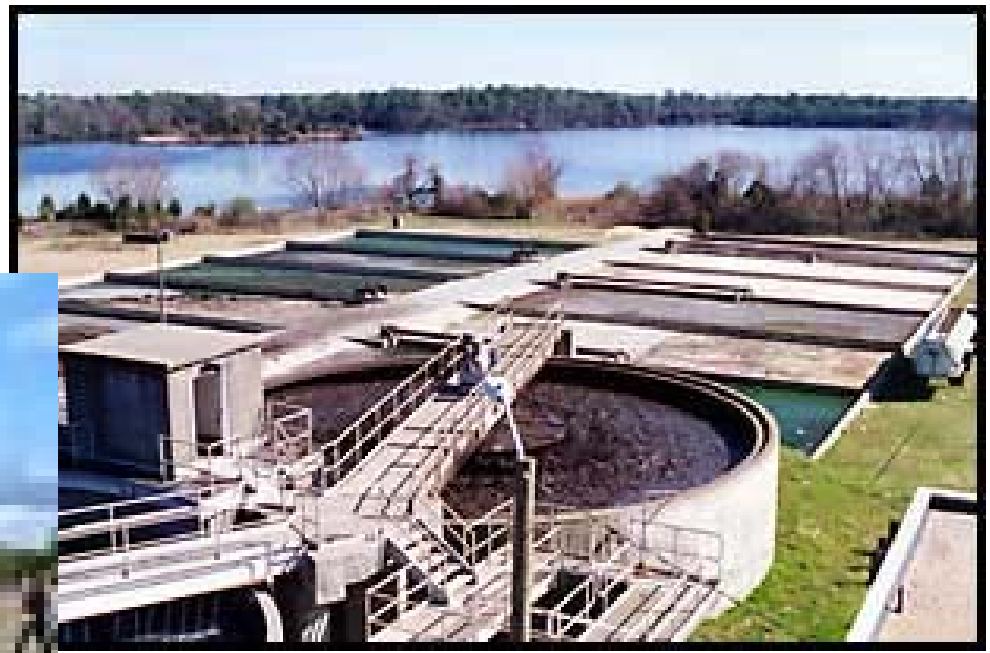
PhATE™ is an effective tool for estimating concentrations of pharmaceuticals in the environment



PhRMA

PhATE™ is being improved to include assessment of the partitioning and fate of pharmaceuticals in biosolids



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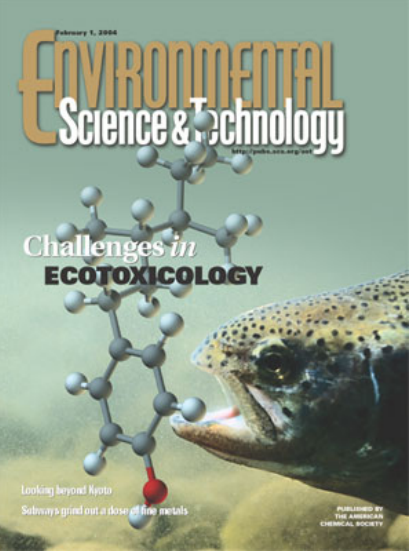

Screening Analysis of Human Pharmaceutical Compounds in U.S. Surface Waters

PAUL D. ANDERSON, VINCENT J. D'ACO, PETER SHANAHAN, STEVEN C. CHAPRA, MARY E. BUZBY, VIRGINIA L. CUNNINGHAM, BETH M. DUPLESSIE, EILEEN P. HAYES, FRANK J. MASTROCCO, NEIL J. PARKE, JOHN C. RADER, JOHN H. SAMUELIAN, AND BRADLEY W. SCHWAB

Pharmaceuticals for human use can enter the environment by excretion following therapeutic use, discharge of treated wastewater from manufacturing facilities, or disposal of unused medicines by the consumer. Flushing unused medicines down the toilet appears to be of minor importance, while patient excretion following therapy is widely considered to be the primary pathway to the environment. One of the main challenges in the development of pharmaceuticals is to identify molecules that are resistant to metabolic degradation processes and persist to exert the desired effect at the appropriate anatomical site. This persistence can potentially result in a fraction of an API being excreted unchanged, surviving wastewater treatment processes, and entering surface waters.

Environ. Sci. Technol. **38**, 838-849

P*h*ATE™ is available for use by collaborators

PhRMA

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Available online at www.sciencedirect.com

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Regulatory Toxicology and Pharmacology xxx (2005) xxx–xxx

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Regulatory Toxicology and Pharmacology

www.elsevier.com/locate/yrtph

Human pharmaceuticals in US surface waters: A human health risk assessment

Bradley W. Schwab [a], Eileen P. Hayes [b], Janice M. Fiori [c], Frank J. Mastrocco [d], Nicholas M. Roden [e], David Cragin [f], Roger D. Meyerhoff [c], Vincent J. D'Aco [g,*], Paul D. Anderson [a]

[a] *AMEC Earth and Environmental, 239 Littleton Road, Suite 1B, Westford, MA 01886, USA*
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[c] *Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA*
[d] *Pfizer, 235 East 42nd Street, New York, NY 10017, USA*
[e] *Schering-Plough, 1095 Morris Avenue, Union, NJ 07083, USA*
[f] *Merck and Co., Two Merck Drive, Whitehouse Station, NJ 08889, USA*
[g] *Quantum Management Group, 1187 Main Avenue, Clifton, NJ 07011, USA*

Received 24 December 2004

Regulatory Toxicology and Pharmacology, **42**, 296-312.

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

PhRMA

Other authors have concluded that environmental exposure to human pharmaceuticals poses little human health risk.

- *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)**
- 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.

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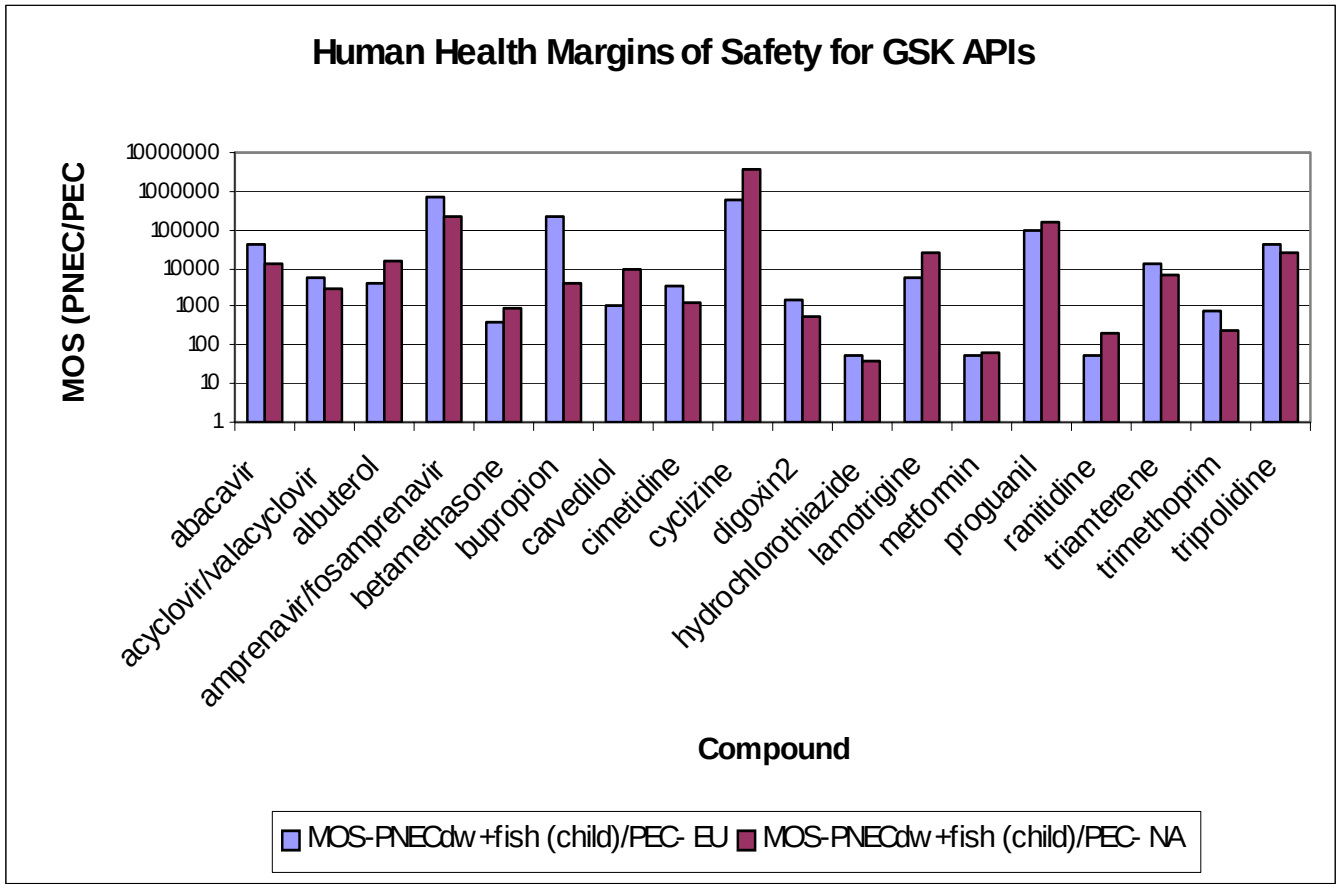
Manufacturers are investigating human health impacts of additional compounds

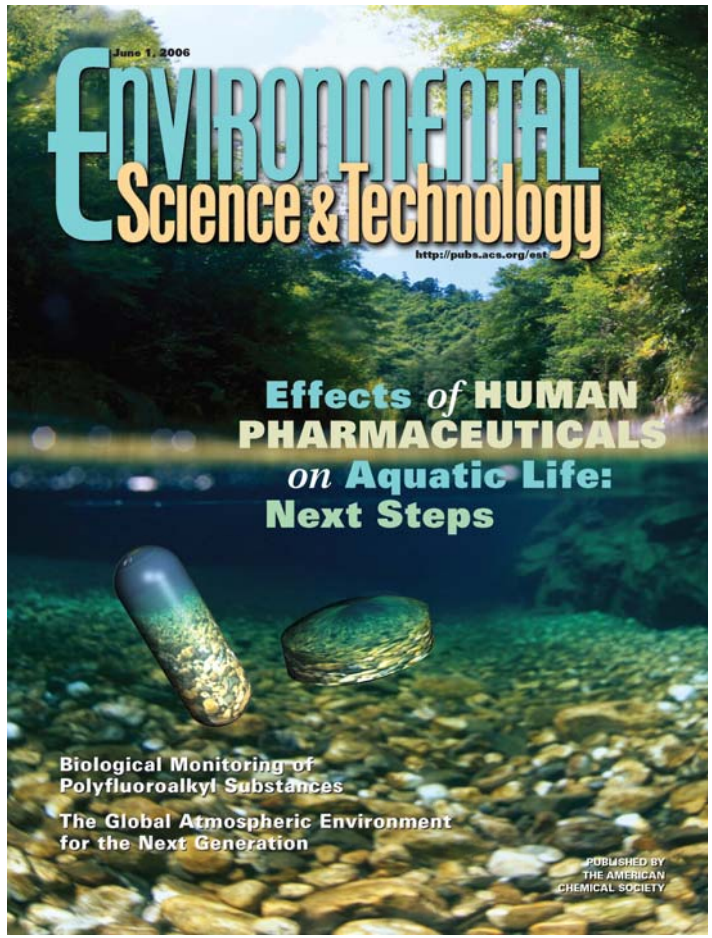


From: V.L Cunningham, S.P. Binks, R.E. Hannah and M.J.Olson, GlaxoSmithKline, Presented at SETAC North America 27th Annual Meeting, 5-9 November 2006

PhRMA

Human Pharmaceuticals: Next Steps towards Understanding Aquatic Life Effects

Virginia L. Cunningham, Mary Buzby, Thomas Hutchinson, Frank Mastrocco, Neil Parke, Nicholas Roden



How do human pharmaceuticals get into the environment and what effects can they have?

Human pharmaceuticals are designed to cure and treat disease and help people be healthy. However, the active pharmaceutical ingredients (APIs) in these medicines, either as the original drug API or as metabolites, can be released into the environment and be present in very low, but detectable concentrations. This is primarily from patient excretion.

Environmental Science and Technology, June 1, 2006

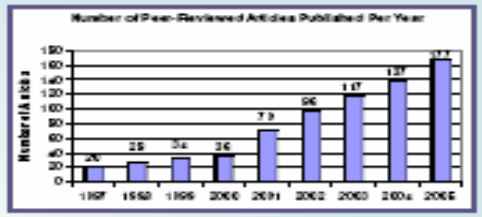
PhACT® (Pharmaceutical Assessment and Characterization Tool): Database to compile all of the peer-reviewed English language literature about aquatic effects, treatment, and environmental depletion of APIs.

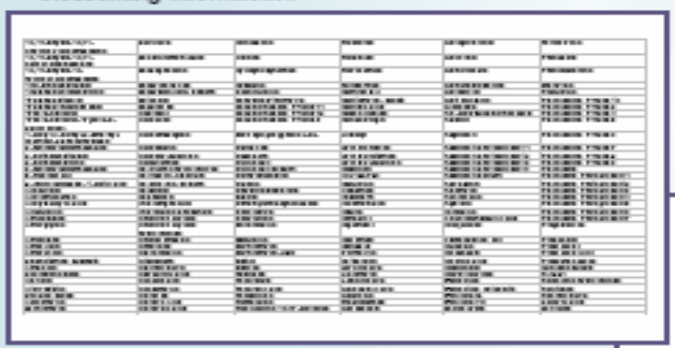
OVERVIEW OF PhACT DATABASE

- PhRMA has developed the PhACT (Pharmaceutical Assessment and Characterization Tool) database to compile all of the peer-reviewed literature about aquatic effects, treatment, and environmental depletion of APIs.
- This information will be used to understand the potential for effects of APIs on aquatic organisms.

WHY DO WE NEED PhACT?

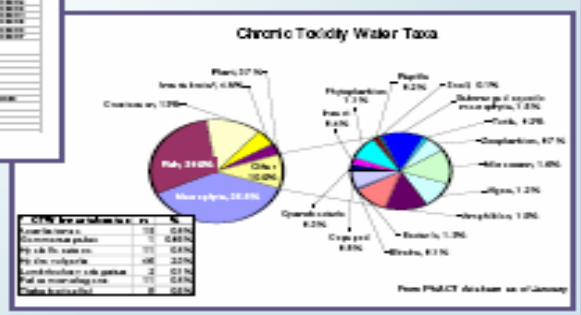
- Growing interest over the last 10 years in studying APIs in the environment.
- The figure to the right shows the exponential increase in the number of peer-reviewed articles about APIs in the environment that have been published between 1997 and 2005.
- PhRMA and its member companies need to stay on top of this blossoming information.





List of Compounds Currently Included in PhACT

- Over 230 compounds already included in PhACT.



Example of distribution of taxa in the chronic toxicity in water table

HOW HAS PhACT BEEN USED?

Although not even complete yet,

- Compile information on specific APIs (carbamazepine, ibuprofen, acetaminophen, aspirin, naproxen, estrone, 17 -estradiol, 17 -ethinylestradiol)
- Identify data gaps: evaluate representativeness of test species used by researchers to date

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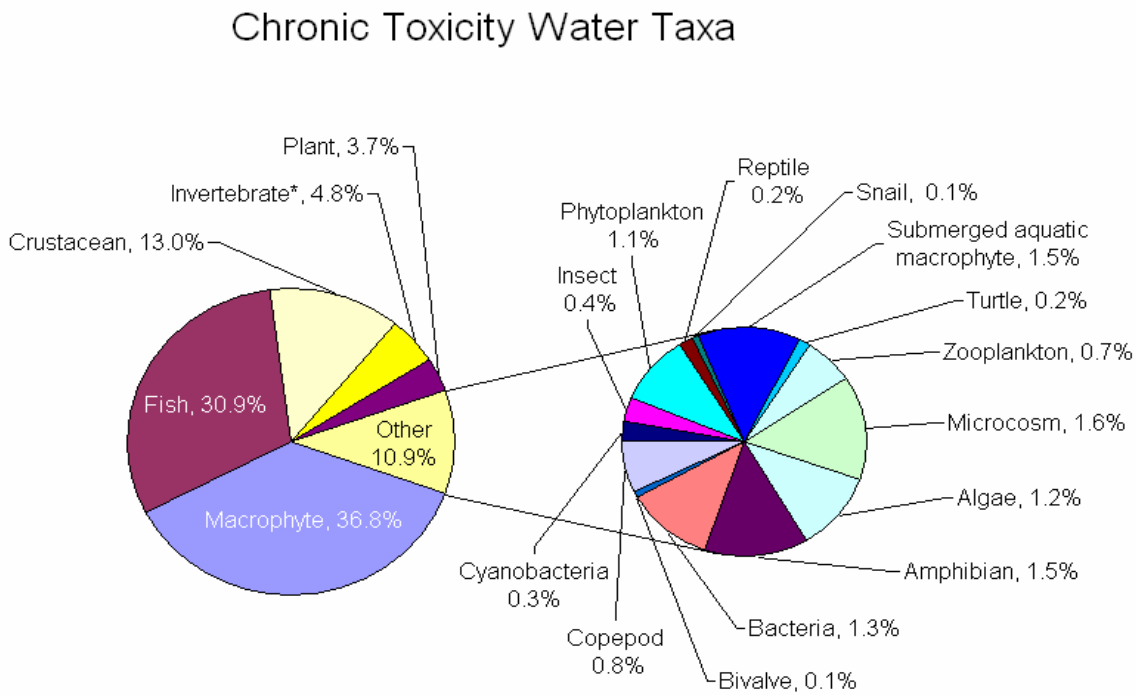
Numerous end-points are used to assess aquatic life impacts of pharmaceuticals



* CTW Invertebrates	n	%
Acartia tonsa	15	0.8%
Daphnia longispina	26	1.3%
Gammarus pulex	1	0.05%
Hyalella azteca	11	0.6%
Hydra vulgaris	46	2.3%
Lumbriculus variegatus	2	0.1%
Palaemon elegans	11	0.6%
Tisbe battagliai	9	0.5%

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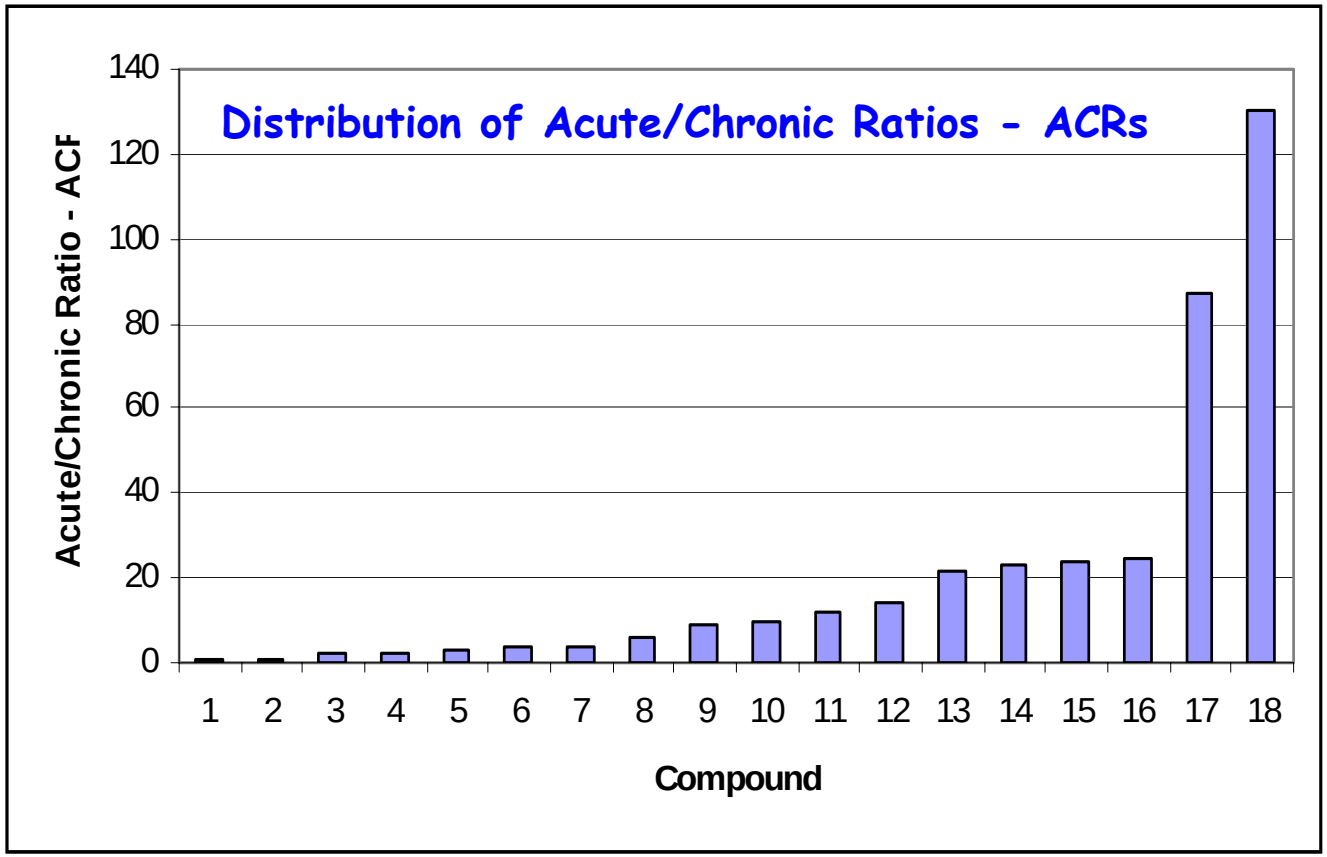
Traditionally, aquatic toxicity testing has focused on acute effects. More recently, testing for chronic endpoints is being performed



From: V.L Cunningham, S.P. Binks, R.E. Hannah and M.J.Olson, GlaxoSmithKline, Presented at SETAC North America 27th Annual Meeting, 5-9 November 2006

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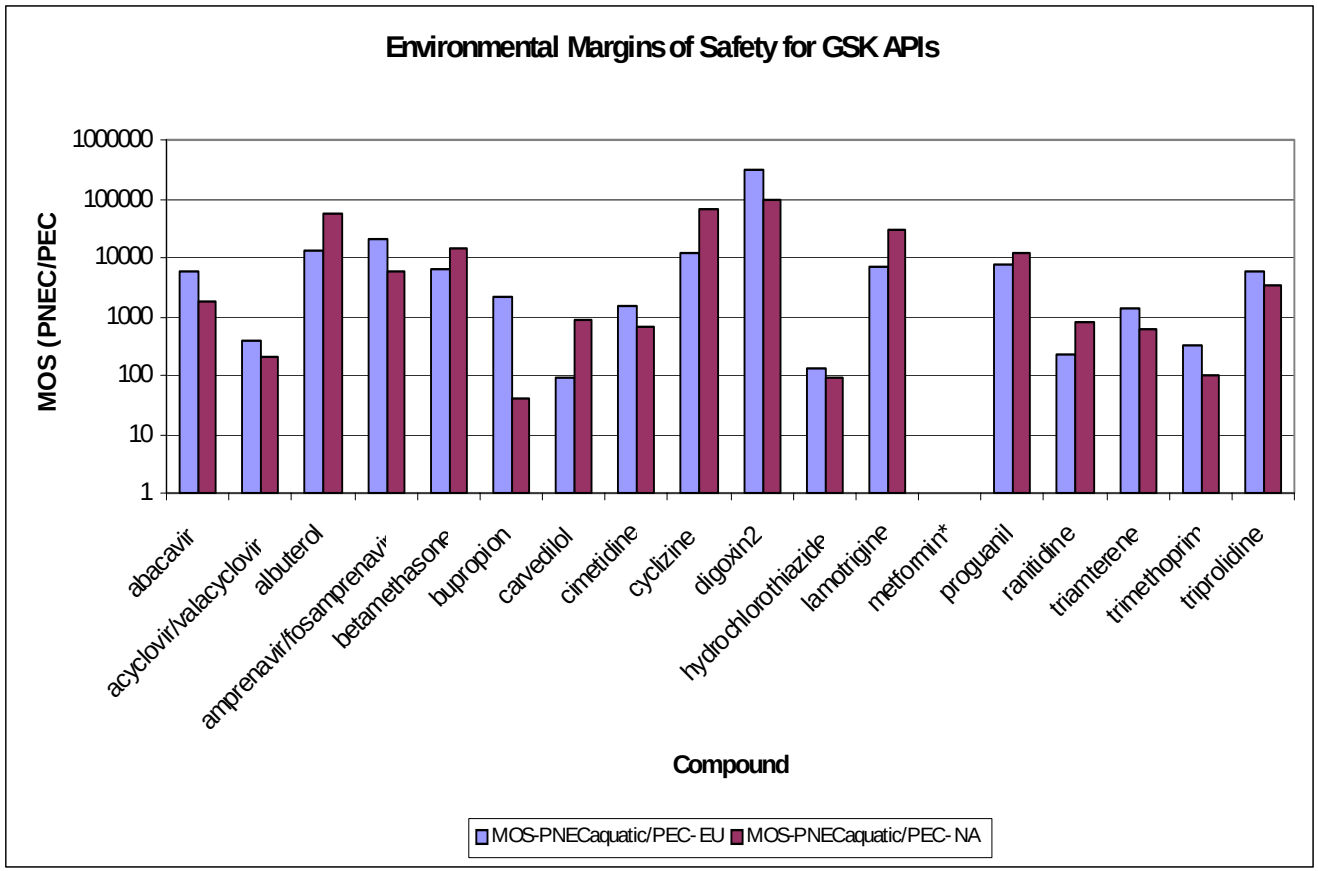
Manufacturers are also investigating environmental impacts of additional compounds



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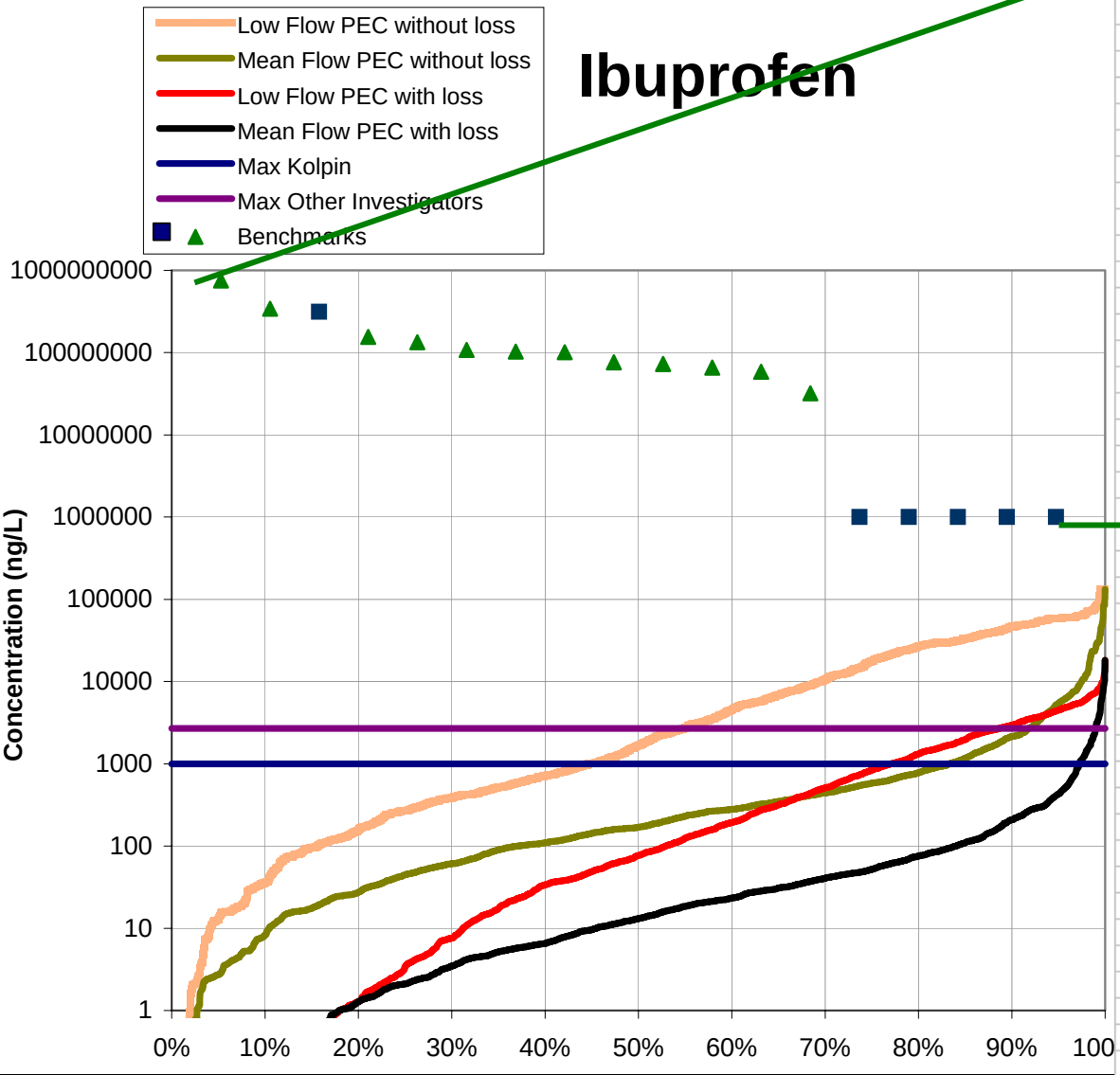
Ibuprofen



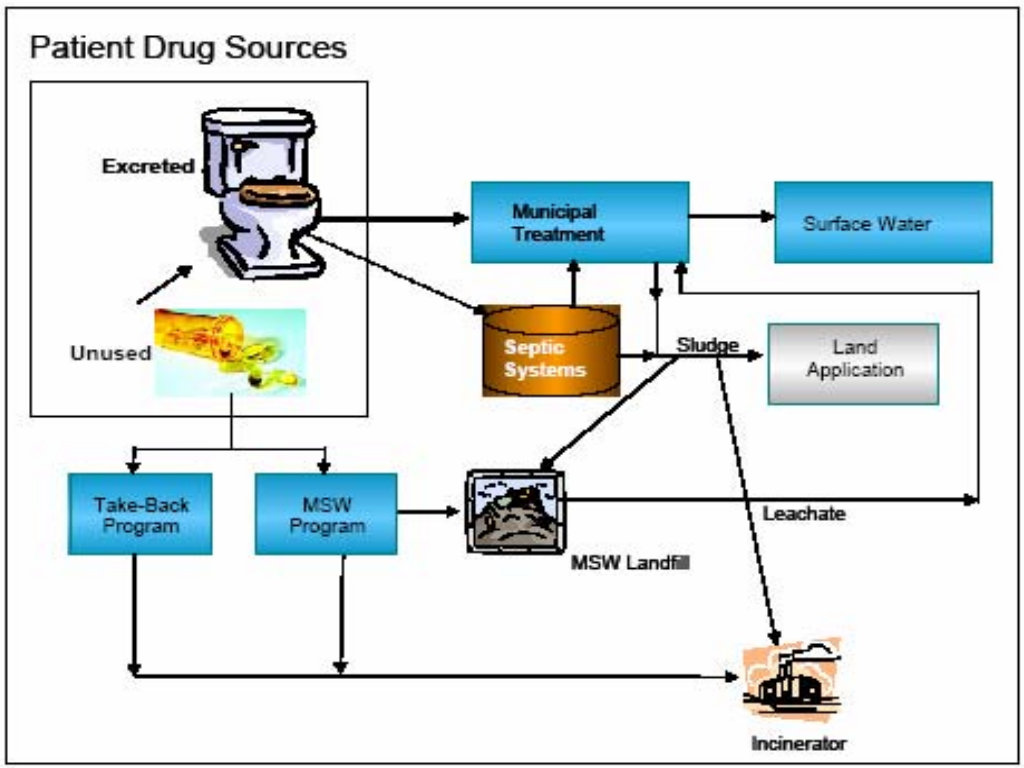
▲ Triangles represent acute benchmarks.

■ Squares represent chronic benchmarks.

NBR = Not biologically relevant

Value (ng/L)	Endpoint	Benchmark	Comment
753200000	Algae: Growth	EC80	
342200000	Algae: Growth	EC50	
315000000	Algae: Growth	EC50	
155500000	Algae: Growth	EC20	
134100000	Invertebrate: Immobilization	EC80	
108000000	Invertebrate: Immobilization	EC50	
102700000	Algae: Growth	EC10	
101200000	Invertebrate: Immobilization	EC50	
76400000	Invertebrate: Immobilization	EC20	
75000000	MIXTURE - Invertebrate: Immobilization	NOEC	Mixture
72900000	Algae: Growth	EC5	
66000000	Invertebrate: Immobilization	EC10	
58400000	Invertebrate: Immobilization	EC5	
32000000	MIXTURE - Invertebrate: Immobilization	NOEC	Mixture
22000000	Plant: Growth	EC50	
10000000	Invertebrate: Bud production	NOEC	NBR
4000000	Plant: Growth	EC50	
1000000	Plant: Wet Weight	NOEC	
1000000	Plant: Frond Number	NOEC	
1000000	Plant: Chlorophyll a	NOEC	
1000000	Plant: Chlorophyll b	NOEC	
1000000	Plant: Carotenoids	NOEC	
1000000	Plant: Wet Weight	EC10	Equal to NOEC
1000000	Plant: Frond Number	EC10	Equal to NOEC
1000000	Plant: Chlorophyll a	EC10	Equal to NOEC
1000000	Plant: Chlorophyll b	EC10	Equal to NOEC
1000000	Plant: Carotenoids	EC10	Equal to NOEC
1000000	Plant: Wet Weight	EC25	Equal to NOEC
1000000	Plant: Frond Number	EC25	Equal to NOEC
1000000	Plant: Chlorophyll a	EC25	Equal to NOEC
1000000	Plant: Chlorophyll b	EC25	Equal to NOEC
1000000	Plant: Carotenoids	EC25	Equal to NOEC
1000000	Plant: Wet Weight	EC50	Equal to NOEC
1000000	Plant: Frond Number	EC50	Equal to NOEC
1000000	Plant: Chlorophyll a	EC50	Equal to NOEC
1000000	Plant: Chlorophyll b	EC50	Equal to NOEC
1000000	Plant: Carotenoids	EC50	Equal to NOEC
600000	MIXTURE - Phytoplankton: Abundance	LC100	Mixture
600000	MIXTURE - Phytoplankton: Diversity	LOEC	Mixture
600000	MIXTURE - Zooplankton: Abundance	LOEC	Mixture
600000	MIXTURE - Plant: Growth	LOEC	Mixture
600000	MIXTURE - Zooplankton: Diversity	LOEC	Mixture
600000	MIXTURE - Fish: Mortality	LOEC	Mixture
60000	MIXTURE - Fish: Mortality	LOEC	Mixture
60000	MIXTURE - Plant: Growth	LOEC	Mixture
10000	Cyanobacteria: Growth	EC72	Stimulated growth
10000	Invertebrate: Polyp Structure	LOEC	NBR
10000	Invertebrate: Ingestion rate	LOEC	NBR
10000	Invertebrate: Polyp Regen.	NOEC	NBR
10000	Invertebrate: Polyp Regen.	NOEC	NBR
6000	MIXTURE - Fish: Mortality	NOEC	Mixture

Unused medicines can contribute to the amounts of medicines found in the environment



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The estimated quantity of unused medicines depends on the assumptions used.

Number of Prescriptions	Weight of (Non-Hospital and Clinic) Prescriptions
3.4 billion	Pills: 40.0 MM lbs. Pills & containers: 143.0 MM lbs.

% (Non-Hospital or Clinic) Prescriptions Unused			
20 %	10 %	5 %	Best Est. %
28.6 MM lbs	14.3 MM lbs	7.2 MM lbs	4.3 MM lbs

By weight of pills and containers

Based on blended individual and LTCF "wastage" rates

Unused medicines management practices vary depending on who generates the unused medicine

Pharmacies

- Most unused medicines returned for credit

Hospitals

- Use their pharmacies to return for credit
- Unreturnables:
  - Ordinary IV → drain
  - Chemo IV → HW
  - Pills → Medical Waste

Long Term Care Facilities

- Source of 34% (1.5 MM lbs) of unused
- 7% to 13% wastage
- Typical disposal practice is flushing down the drain

Individuals

- Source of 66% (2.8 MM lbs) of unused
- 2 to 3% wastage
- Typical disposal

	US	**UK & Canada w/ take back**
Trash	50%	50%
Drain	30%	10%
Pharmacy		20%

The majority of pharmaceuticals in the environment come from patient use.

PhRMA

Landfill disposal in the US accounts for less than 1% of the total surface water load due to patient dosing of selected pharmaceutical active ingredients

Compound	API Qt (kg/year)	5% API Disposed			10% API Disposed			15% API Disposed		
		API mass in POTW Effluent due to Patient Use (kg/yr)	API Mass in POTW Effluent from Unused Medicine in Landfills (kg/yr)	Percent of Total Load Resulting from Landfill Disposal	API mass in POTW Effluent due to Patient Use (kg/yr)	API Mass in POTW Effluent from Unused Medicine in Landfills (kg/yr)	Percent of Total Load Resulting from Landfill Disposal	API mass in POTW Effluent due to Patient Use (kg/yr)	API Mass in POTW Effluent from Unused Medicine in Landfills (kg/yr)	Percent of Total Load Resulting from Landfill Disposal
Acetaminophen	5691120	97318	0.060	0.0001	92196	0.120	0.0001	76830	0.180	0.0002
Albuterol Sulfate	3569	949	0.076	0.0080	899	0.152	0.0160	749	0.228	0.0240
Cimetidine	49980	6837	0.004	0.0001	6477	0.008	0.0001	5398	0.012	0.0002
Ciprofloxacin	85440	72239	1.835	0.0025	68437	3.670	0.0051	57031	5.505	0.0076
Codeine	15095	12906	0.167	0.0013	12227	0.333	0.0026	10189	0.500	0.0039
Digoxin	229	183	0.000	0.0001	173	0.000	0.0001	144	0.000	0.0002
Diltiazem	149295.76	1702	0.002	0.0001	1612	0.005	0.0003	1344	0.007	0.0004
Doxycycline	32784	31145	1.740	0.0056	29506	3.481	0.0112	24588	5.221	0.0168
Enalaprilat	772	462	0.271	0.0587	438	0.542	0.1173	365	0.814	0.1758
Erythromycin-H2O	64283	61069	0.002	0.0000	57855	0.004	0.0000	48212	0.005	0.0000
Fluoxetine	12434	177	0.000	0.0000	168	0.000	0.0001	140	0.000	0.0001
Gemfibrozil	231530	93612	2.192	0.0023	88685	4.385	0.0047	73904	6.577	0.0070
Ibuprofen	1035229	21636	2.027	0.0094	20498	4.055	0.0187	17081.3	6.082	0.0281
Lincomycin	328	312	0.000	0.0000	296	0.000	0.0000	246	0.000	0.0001
Metformin	1597887	1411733	2.835	0.0002	1337431	5.670	0.0004	1114526	8.505	0.0006
Norfloxacin	2700	2385	5.250	0.2196	2260	10.500	0.4382	1883	15.750	0.6559
Oxytetracycline	31	30	0.000	0.0005	28	0.000	0.0011	23	0.000	0.0016
Paroxetine metabolite	19474	2035	0.000	0.0000	1928	0.000	0.0000	1607	0.000	0.0000
Ranitidine	100417	62770	0.107	0.0002	59467	0.214	0.0003	49556	0.321	0.0005
Sulfamethoxazole	314389	35840	0.031	0.0001	33954	0.062	0.0002	28295	0.093	0.0003
Sulfathiazole	483	390	0.000	0.0001	369	0.001	0.0002	308	0.001	0.0002
Tetracycline	68569	65141	0.167	0.0003	61712	0.335	0.0005	51427	0.502	0.0008
Trimethoprim	64450	36951	0.000	0.0000	35006	0.000	0.0000	29172	0.000	0.0000
Warfarin	3999	304	0.000	0.0001	288	0.000	0.0001	240	0.001	0.0002
Aggregate		2018128	16.768	0.0008	1911911	33.536	0.0018	1593259	50.303	0.0032

PhRMA

Office of Drug Control Policy

Federal Guidelines for proper disposal of prescription drugs

February 20, 2007

Proper Disposal of Prescription Drugs

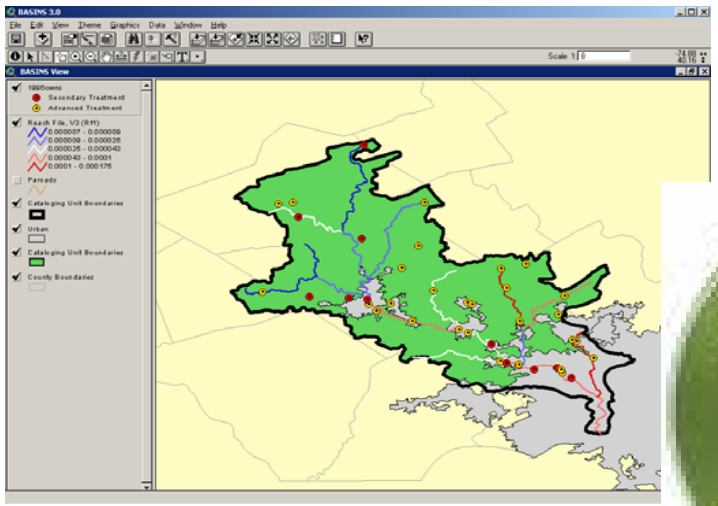
Office of National Drug Control Policy February 2007

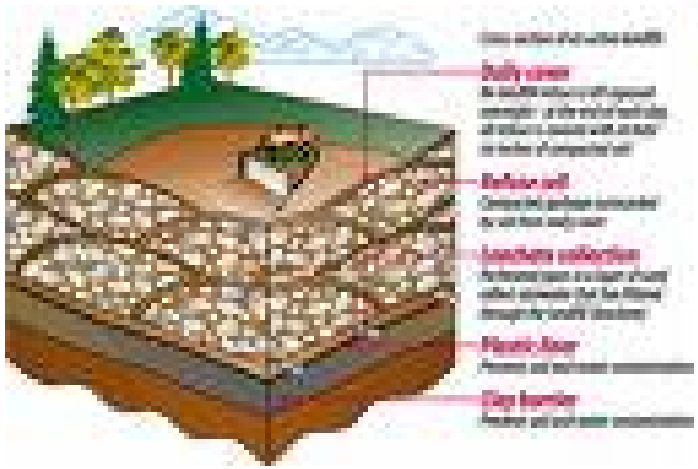
Federal Guidelines:

- Take unused, unneeded, or expired prescription drugs out of their original containers and throw them in the trash.
- Mixing prescription drugs with an undesirable substance, like used coffee grounds or kitty litter, and putting them in impermeable, non-descript containers, such as empty cans or sealable bags, will further ensure the drugs are not diverted.
- Flush prescription drugs down the toilet *only* if the label specifically instructs doing so.
- Take advantage of community pharmaceutical take-back programs that allow the public to bring unused drugs to a central location for proper disposal. Some communities have pharmaceutical take-back programs or community solid-waste programs that allow the public to bring unused drugs to a central location for proper disposal. Where these exist, they are a good way to dispose of unused pharmeceuticals.

Office of National Drug Control Policy
750 17th St. NW, Washington, D.C. 20503
p (202) 395-6618 f (202) 395-6730

Decisions on how to manage unused medicines need to consider all available information



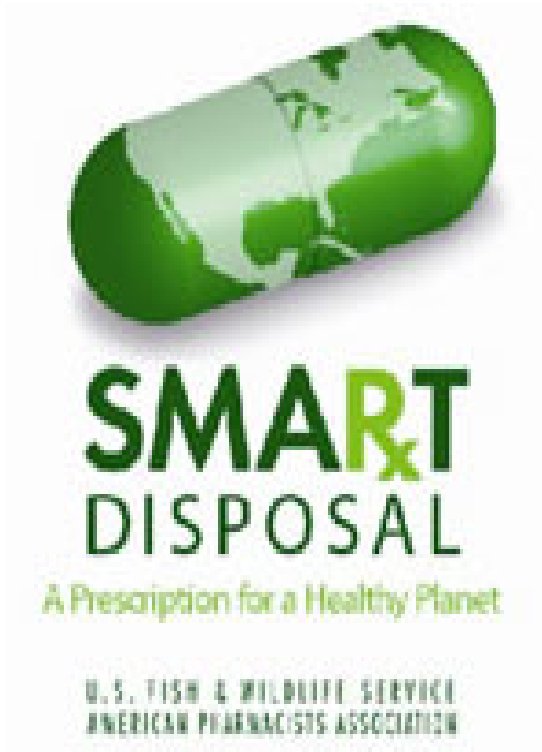


Certain elements of how to manage unused medicines disposal are clear

- Drain disposal should be avoided
- Dialogue among all interested stakeholders is needed
- Disposal alternatives should be evaluated based on assessments of all their potential environmental impacts
- Take-back pilot programs
  - Need to understand the types and amounts of medicines being collected, participation rates, management of regulatory compliance issues, program costs, funding sources, final disposal, obstacles and potential solutions

PhRMA

"The U.S. Fish and Wildlife Service and the American Pharmacists Association (APhA) have joined forces to help protect our nation's fish and aquatic resources from improper disposal of medication. As part of the effort - dubbed "SMARxT DISPOSAL" - the USFWS and the APhA will work to publicize the potential environmental and health impacts of unused medications when they are flushed into our nation's sewer systems."



In conclusion…

- 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 continuing to research sources of unused medicine, to identify options for their disposal and to participate in discussions with stakeholders on these issues.

PhRMA