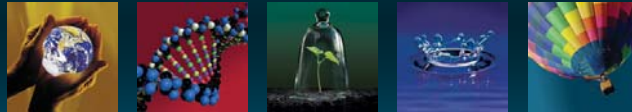


*Environmental Risk Assessment for  
Pharmaceuticals:*

*Establishing a Methodology to Evaluate  
Population-Derived Pollutants*



Robert P. DeMott, Ph.D., DABT

rdemott@environcorp.com

**2007 NE Water Science Forum – Portland, ME**

August 2007

**ENVIRON**



## Outline

- Introduction/Rationale
- Optimizing Risk Assessment Steps
  - Bioassessment, Bioassay, Biomonitoring
  - Deriving toxicity-based criteria
  - Risk mapping – spatial and seasonal perspectives
- Pilot Testing FDA-Based Test Information

**ENVIRON**



## Abstract

Surveys of surface water systems have now made it clear that pharmaceutical compounds and hormones derived from human populations routinely pass through treatment plants and enter waterbodies receiving treated wastewater. While merely detecting such compounds is not sufficient information to characterize environmental and human exposure risks, the recognition that specific human contributions to wastewater do, in fact, make it through treatment plants to surface water yields negative reactions from many in the public. Because of such adverse associations with exposure to constituents from wastewater, pressures to manage and regulate these environmental releases will result in demands by decision-makers for assessment methods and tools specifically effective for characterizing potential risks and prioritizing the various pharmaceutical and hormone-related constituents detected. While EPA, FDA and various state agencies have established risk assessment methodologies, several factors relating to the chemistry, potency and nature of testing done on pharmaceutical compounds necessitate specialized and updated risk assessment methods for considering surface water exposures to these compounds. We have developed approaches for optimizing pharmaceutical/recalcitrant compound evaluations that incorporate field assessments of the ecological communities around points of discharge, seasonal/temporal variability related to both stream flow and compound loading, and derivation of toxicity-related benchmark values from pharmaceutical testing designed for other endpoints. This presentation will proceed step by step through implementation of such approaches in a hypothetical test case to illustrate how actual priorities can be drawn from lists of compounds that were simply detected.

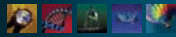
ENVIRON



## What the Abstract Says

- Detection  Risk
- Prevalence & Perception Require Action
- State-of-the-Science Risk Assessment must address:
  - Critical receptors, exposure pathways
  - Complex metabolites and surrogate issues
  - Spatial and seasonal dynamics

ENVIRON



## Population Pollutants



- Focus on wastewater treatment discharges
- Emerging recognition as pathway for releases
- UK - late '90s
- Watershed moment in U.S. – USGS survey (Kolpin et al. 2002, *Environ Sci Technol* 36:1202)

ENVIRON

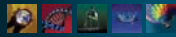


## Key Compound Types

- Endocrine active
  - Endogenous
  - Pharma (birth control, HRT)
- Other pharma.
  - NSAIDs (ibuprofen, indomethacin)
  - Antibiotics (erythromycin, sulfa's)
  - Receptor-related (fluoxetine, diltiazem)



ENVIRON



## Emerging Science / Emerging Pressures

- **Good news:** science driving interest, need for evaluation
- **Bad news:** pressures for regulation build faster than research
- Perceived regulatory gap is a motivator



ENVIRON



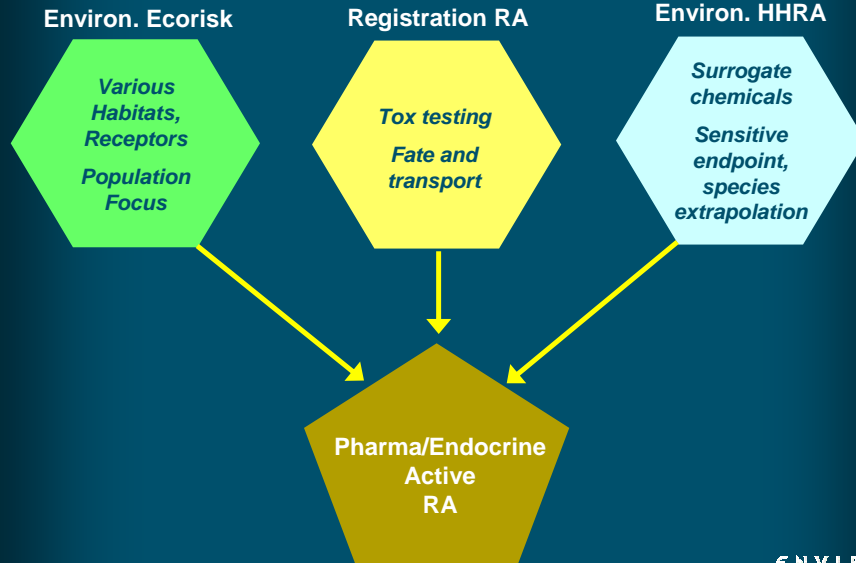
## Lost in the Alphabet Soup

- Pharmaceuticals and Consumer Products as new horizons --  
    “**Products**” are not  
    “**environmental contaminants**”
- Who’s Method / Approach
  - FDA, CPSC (product labeling, registration)
  - EPA (environmental risk assessment)
  - CWA – NPDES permitting

ENVIRON



## Need for New Framework



## Critical Receptors / Pathways

- Perceived human (**NOT aquatic**) risks will drive regulatory pressure
- BUT, aquatic systems most relevant receptors / pathways



ENVIRON



## Habitat/Receptor Characterization First

- **Typical EPA ecoRA process:**
  - **Screen first**
  - **Habitat/ecosystem considerations later**
- **Pharma/Endocrine Active RA should incorporate habitat/bioassessment early**
  - **Distinct point of discharge to characterize**
  - **Limited toxicity data makes evaluation / extrapolations time consuming, uncertain**

ENVIRON



## Field-Based Approaches

- **Bioassessment –**
  - **In-the-field habitat/organism descriptions**
  - **Expected sensitive receptor (e.g., sediment invert. vs. fish vs. upper trophic level)**
- **Bioassay / Biomonitoring**
  - **WET-type approach**
  - **Look for markers, indicators of effects**

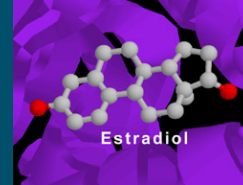


ENVIRON



## Complex Metabolite / Surrogate Issues

- Many pharma compounds / hormones
  - active and inactive forms / metabolites
  - environmental reactivation occurs
- Limited testing information
  - Parent compounds vs. isomers/metabolites
  - Limited/absent aquatic species testing



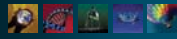
ENVIRON



## Equivalency Factors

- Well-established approach
  - Estrogens, PCBs, dioxins, PAHs
- Establish for
  - Androgens
  - Antibiotics (e.g., tetracycline family)
  - Enzyme/receptor interacting compounds
- Can be based on receptor activity vs. tox.

ENVIRON



## Spatial & Seasonal Dynamics

- Human activities, demographics vary
  - cold/flu season – more antibiotics
  - increased median age – more HRT, cardiac meds.
- Treatment plant technologies vary
  - Controls nature and activity of effluent
- Receiving water body
  - Seasonal changes in flow – dilution
  - Seasonal changes in receptors and life stages

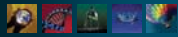
ENVIRON



## “Snapshot” vs. “Video”

- Typical risk assessment rely on one-time or latest round of sampling – specifically aim to be worst-case snapshot
  - Risk characterization – table of HQs (static)
- Pharma/Endocrine Active RA
  - incorporate multiple rounds of data (seasonal)
  - account for receptor/lifestage sensitivity changes

ENVIRON



## Risk Characterization Representation

- Map risk levels to capture spatial dynamics
- Create multiple “frames” to show changes across time/season



ENVIRON



## Pilot Testing Equivalence Factor Development

- Toxicity vs. Efficacy Testing
  - Limited aquatic toxicity data
  - Limited analysis for sensitive endpoints
- Data available in testing, FDA submission packages
  - Receptor or enzyme-binding
  - Metabolism/breakdown information available
- Can extrapolations fill the tox data gap?

ENVIRON



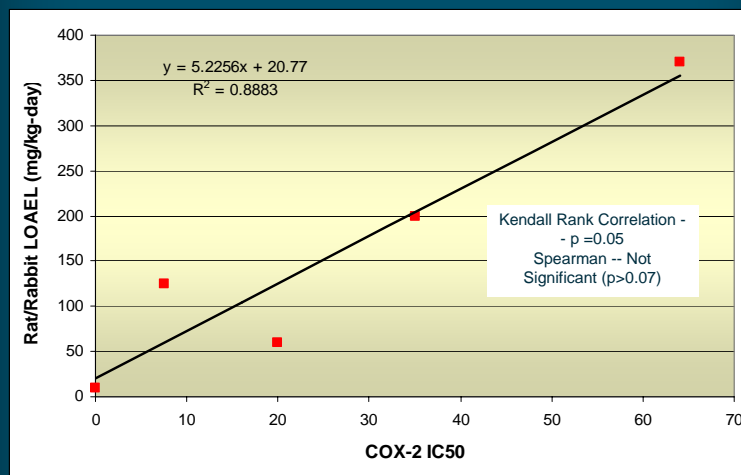
## NSAID Enzyme/Toxicity Values

Compound	Mammal LOAEL (mg/kg-day)		Notes:
	COX-1 IC50 ( $\mu$ M)	COX-2 IC50 ( $\mu$ M)	
diclofenac	0.075	0.02	10 maternal & fetal toxicity, rat & rabbit - Boehringer Ingelheim, 2006
aspirin	1.7	7.5	125 decr. fetal length & wt., rat - Lubawy and Garrett, 1977
ibuprofen	7.6	20	60 decr. implantations, live fetuses, rabbit - Adams et al. 1969
naproxen	9.3	35	200 fertility or fetal effects, rat & rabbit - Roche Inc., 2004 <sup>1</sup>
acetaminophen	100	64	370 decr. pup growth - Lamb et al., 1997

ENVIRON



## COX-2 Inhibition Reasonably Predictive of Toxicity



ENVIRON



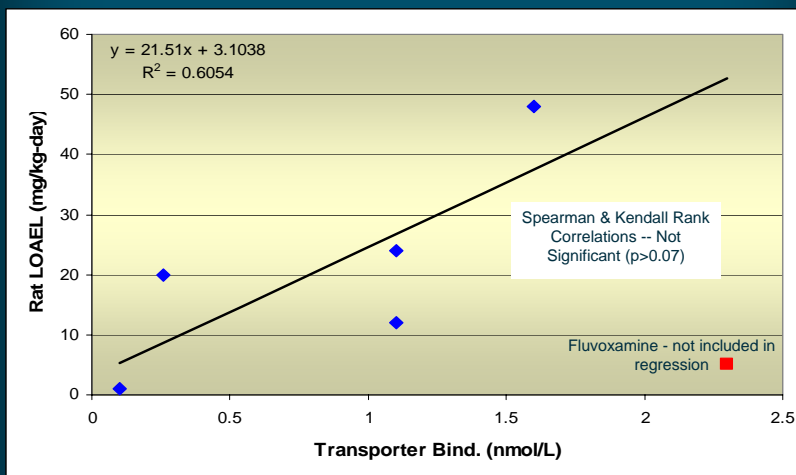
## SSRI Receptor/Toxicity Values

Compound	5-HT		Mammal LOAEL (mg/kg day)	Notes:
	Transporter Binding ( <i>K<sub>i</sub></i> - nmol/L)	5-HT Uptake Inhibition ( <i>K<sub>i</sub></i> - nmol/L)		
fluoxetine	1.1	5.7	12	incr. post-natal mortality, decr. birth wt., rats - Vorhees et al., 1994
sertraline	0.26	2.8	10	decr. birth wt, rats - Davies and Kluwe, 1998
paroxetine	0.1	0.34	1	decr. neonatal survival, rats - GlaxoSmithKline 2005
citalopram	1.6	9.6	48	incr. stillborn pups, decr. viability index, rats - CDER, 2001
escitalopram	1.1	2.5	24	decr. viability index, rats - CDER, 2001
fluvoxamine	2.3	11	5	incr. post-natal mortality, rats- Apotex, 2001

ENVIRON



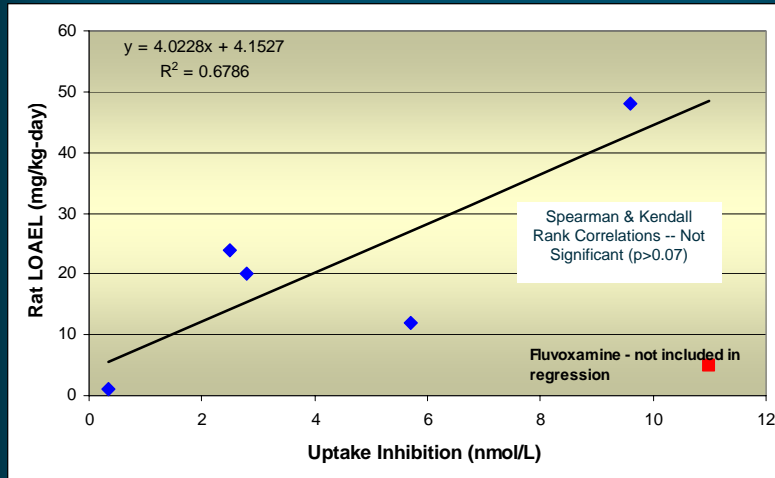
## Serotonin Transporter Binding Partially Predictive of Toxicity



ENVIRON



## Serotonin Uptake Inhibition Partially Predictive of Toxicity



ENVIRON



## Potential for Pharma Testing – Based Equivalence Factors

- Enzyme inhibition of certain NSAIDS correlates with mammalian reproductive/ developmental toxicity
  - *in vitro* testing for other compounds or metabolites may be useful for risk assessment purposes
- Endocrine-activity of SSRIs made them a good candidate for developing a predictive relationship
  - Predictive factors more complex than evaluated so far
- Test cases show potential for extrapolating from pharmaceutical testing and registration information to develop equivalence factors

ENVIRON

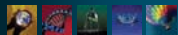


## Summary

- Regulation, thus prioritization -- a foregone conclusion
- Specialized risk assessment paradigm needed
- Elements from NPDES programs, product registration programs can be incorporated



ENVIRON



## Acknowledgements

- H. I. Williams
- P. Begemann
- A. B. Santamaria
- M. Vulli, NEIWPCC

ENVIRON