Pharmaceuticals in the Environment – Exposure, Effects, and Risks to Humans and Ecosystems: What We Think We Know, and What We Need to Know "

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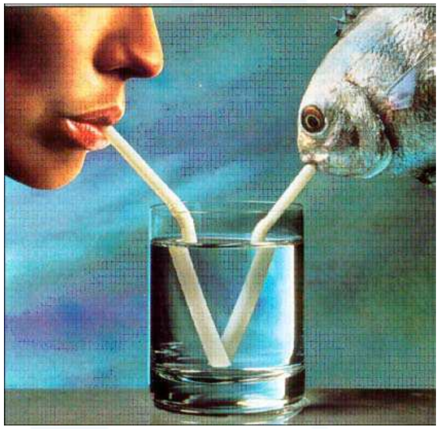
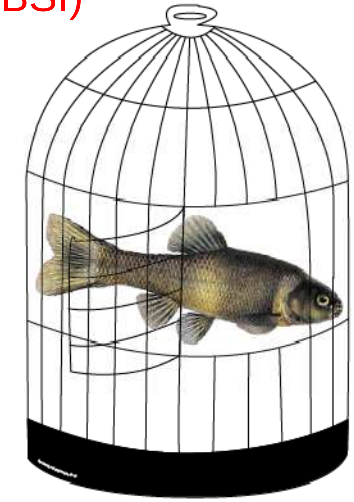
Environmental Health Summit – November 10-11, 2008

Not EPA Policy – Jim, Mitch and Susan's Best Scientific Interpretation (BSI)





Definition of a Pharmaceutical

For the purposes of this presentation, pharmaceuticals are defined as: **Active pharmaceutical ingredients** in FDA-approved products for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, or intended to affect the structure or any function of the body of humans or animals. This definition **excludes ingredients that do not provide pharmacological activity, such as excipients and additives**. This definition is also consistent with the FDA definition of **active pharmaceutical ingredient (API).**

What We Think We Know

Sources:

Wastewater treatment plant (WWTP) effluents

Onsite septic Systems and Direct discharges

Runoff from application of Biosolids and Manure (Soil rehabilitation - Fires)

Animal Feedlot Operations (AFOs) or Concentrated Animal Feedlot Operations (CAFOs).

Aqua Culture Facilities (Freshwater and Marine)

Companion Animals (Pets)

Landfill Leachates – 20% to the environment

What We Think We Know

Occurrence, Transport, and Fate in the Environment.

U.S., European, and Korean Environmental monitoring and research programs have confirmed the occurrence of low levels of pharmaceuticals in stream waters, in soils and streambed sediments, in ground water, in estuaries, and in drinking water.

Pharmaceutical compounds **can be transformed to other compounds**, or

Completely mineralized to their constituent parts during metabolism by organisms, within waste treatment processes, while in the environment, or during drinking water treatment.

Also, during transport, there is the potential that a pharmaceutical may partition from one media to another (e.g. from water to sediment).

What We Think We Know

Ecological Exposure and Exposure Pathways:

- Most exposure is expected to occur via surface or groundwater, but exposure through sediment, biota and/or soil has also been demonstrated. Studies have measured pharmaceuticals in fish tissue, earthworms present in soils amended with biosolids or manure, and plants *.*
- Exposure through inhalation of pharmaceuticals that may be volatile or adsorbed to dust particles is considered a minor route in the natural environment.
- Actual environmental exposures of organisms to some pharmaceuticals are expected to occur at concentrations of parts per trillion, possibly for prolonged periods of time in streams and rivers receiving wastewater discharges.
- Intermittent pulses of pharmaceuticals at higher concentrations might occur in streams and rivers receiving waste from septic and livestock waste or combined sewer overflows.

What We Think We Know

Ecological Effects

Several studies have shown indirect evidence of effects on fish populations (e.g., histological changes in gonads) exposed to effluents that contain chemicals.

Acute Wildlife Effects

- Vulture populations in India and Pakistan decreased by 95 % in three years. Most died of renal failure.
- Coincided with use of diclofenac in cattle.
- Vultures ate carcasses of recently dosed cattle.
- Unable to excrete diclofenac (Oaks et al., Nature 2004).

From: www.birdlife.org

EPA United States Environmental Protection Agency

What We Think We Know

Ecological Exposure Research Division

Ecological Effects

Collapse of a Fish Population Following Exposure to a Synthetic Estrogen, Karen Kidd et. al. **PNAS May 22, 2007, 104,21 8897–8901**

51. Wastewater Decimates Minnows

Discover Magazine's Top 100 Science Stories of 2007 Published online January 9, 2008

Environment / Pollution by Megan Mansell Williams.

Synthetic Hormones released in Waters could lead to Fish extinctions

EPA United States Environmental Protection Agency

What We Think We Know

Ecological Exposure Research Division

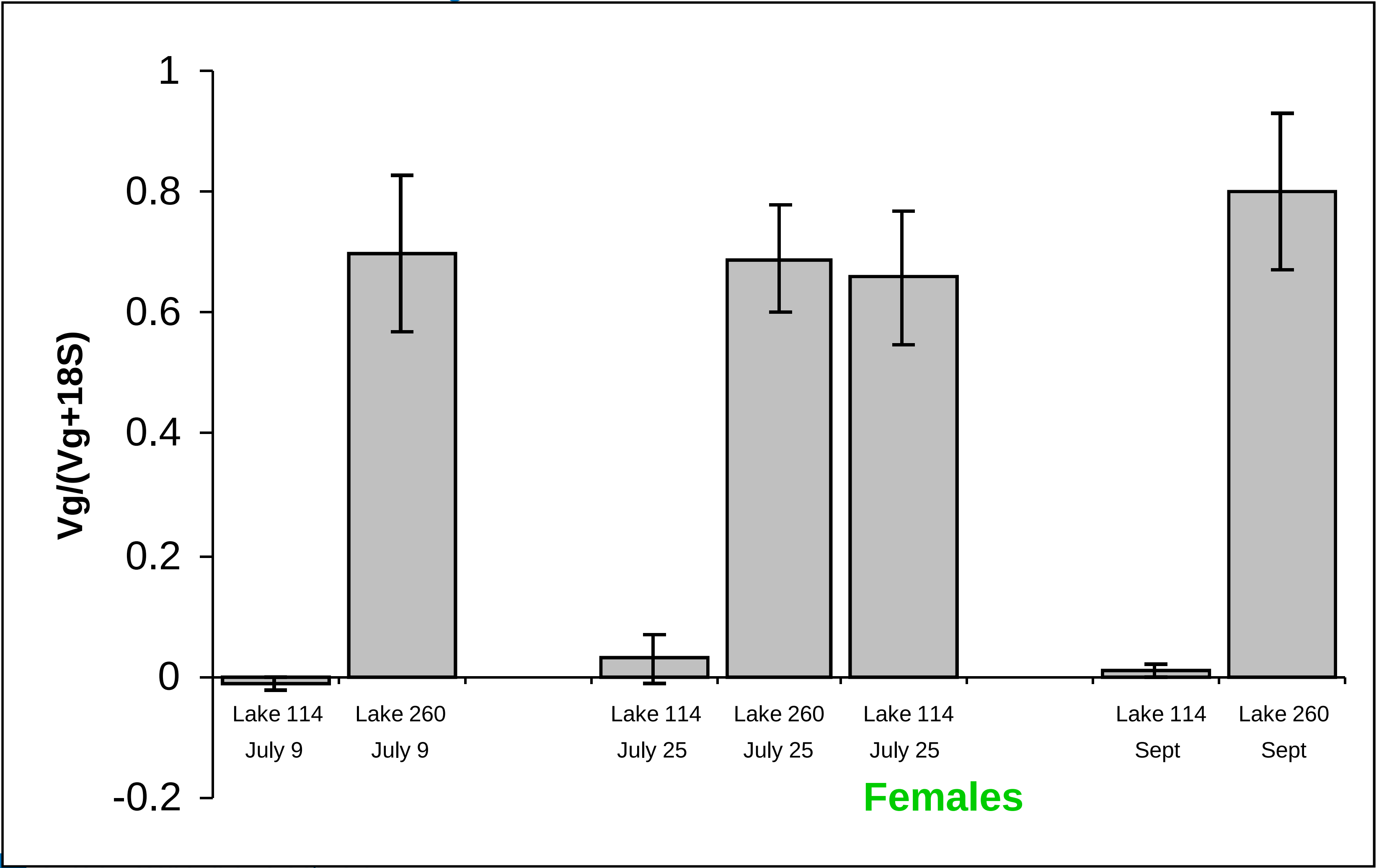
Ecological Effects – Molecular to population level

- Vitellogenin gene expression (spring, mid-Summer, fall), R. Flick, J. Lazorchak,B. Wiechman,
- Vitellogenin (spring, mid-summer, fall) V. Palace
- Liver, kidney and gonad histopathology (spring & fall) B. Evans
- Male reproductive behavior (mid-summer) P. Blanchfield
- Population size structure, growth, abundance (spring and fall) K. Mills

What We Think We Know

Ecological Effects – Molecular Level

2001 Summer & Fall Results of Indigenous Male & Female Fathead Minnows Collected from Lakes 260 & 114



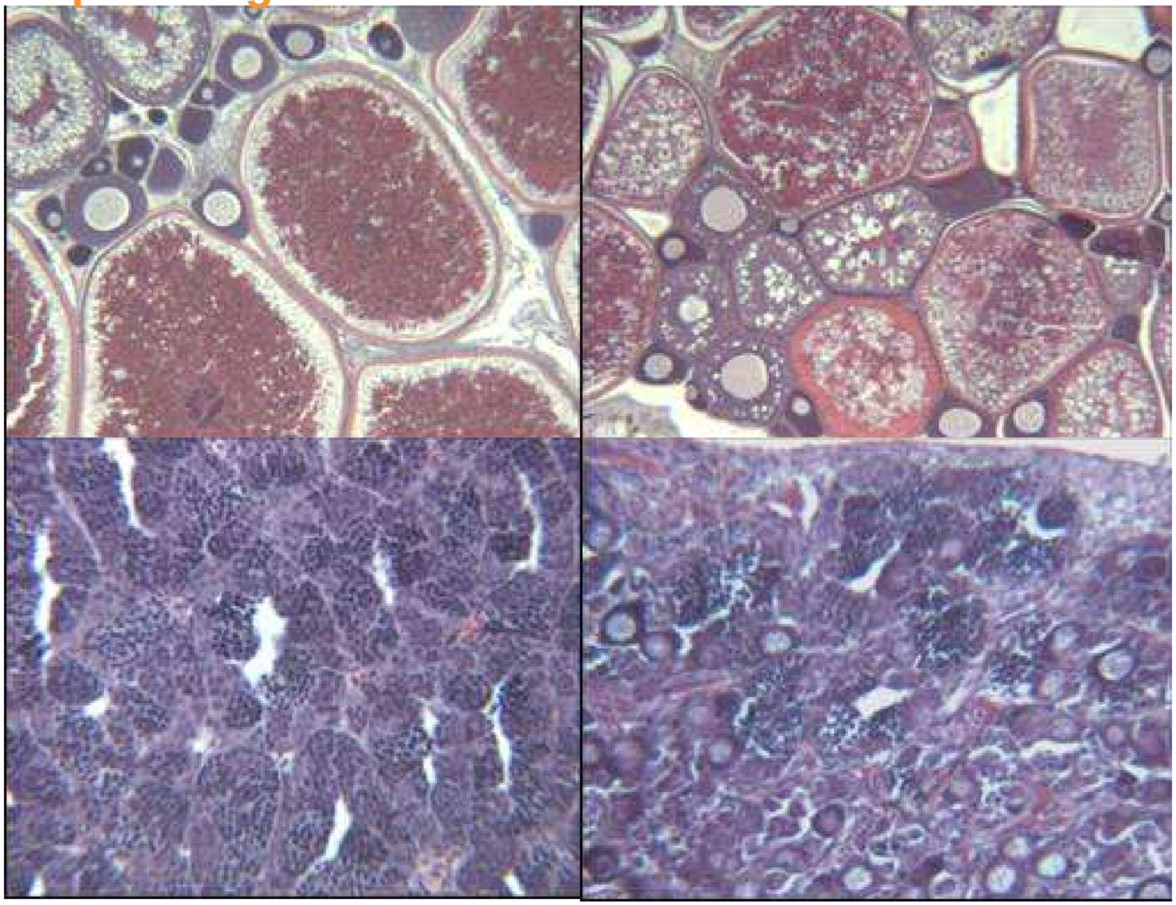
What We Think We Know

Ecological Effects –Tissue Level

2003 Histopathological Results Fathead Minnow Ovaries and Testis

A

B



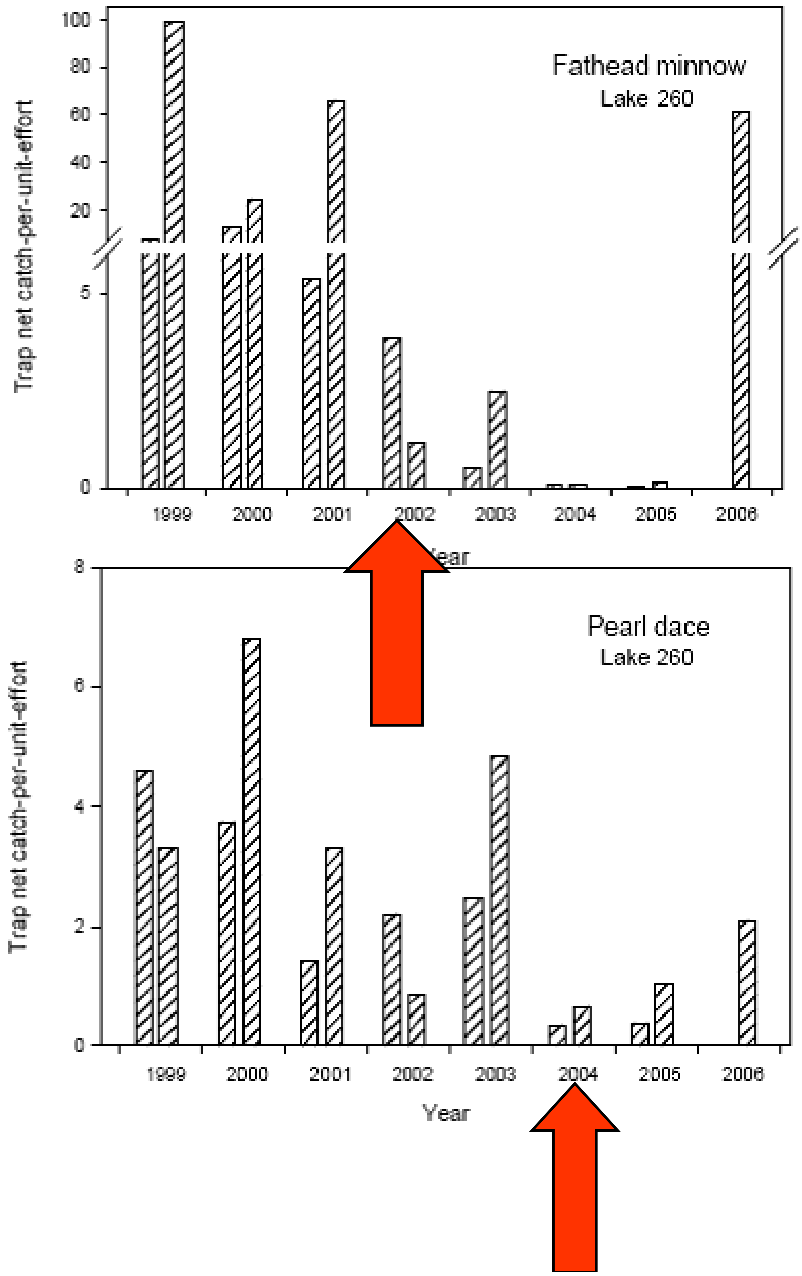
C

D

(Kidd et al)

A) Reference Lake 442 ovary B) Ovary from treated Lake 260
C) Reference Lake 442 testis; D) Testis from Lake 260 demonstrating inter-sex

What We Think We Know



Ecological Effects – Population level

Fathead minnow & Pearl Dace catch results pre-dose 1999-2000,

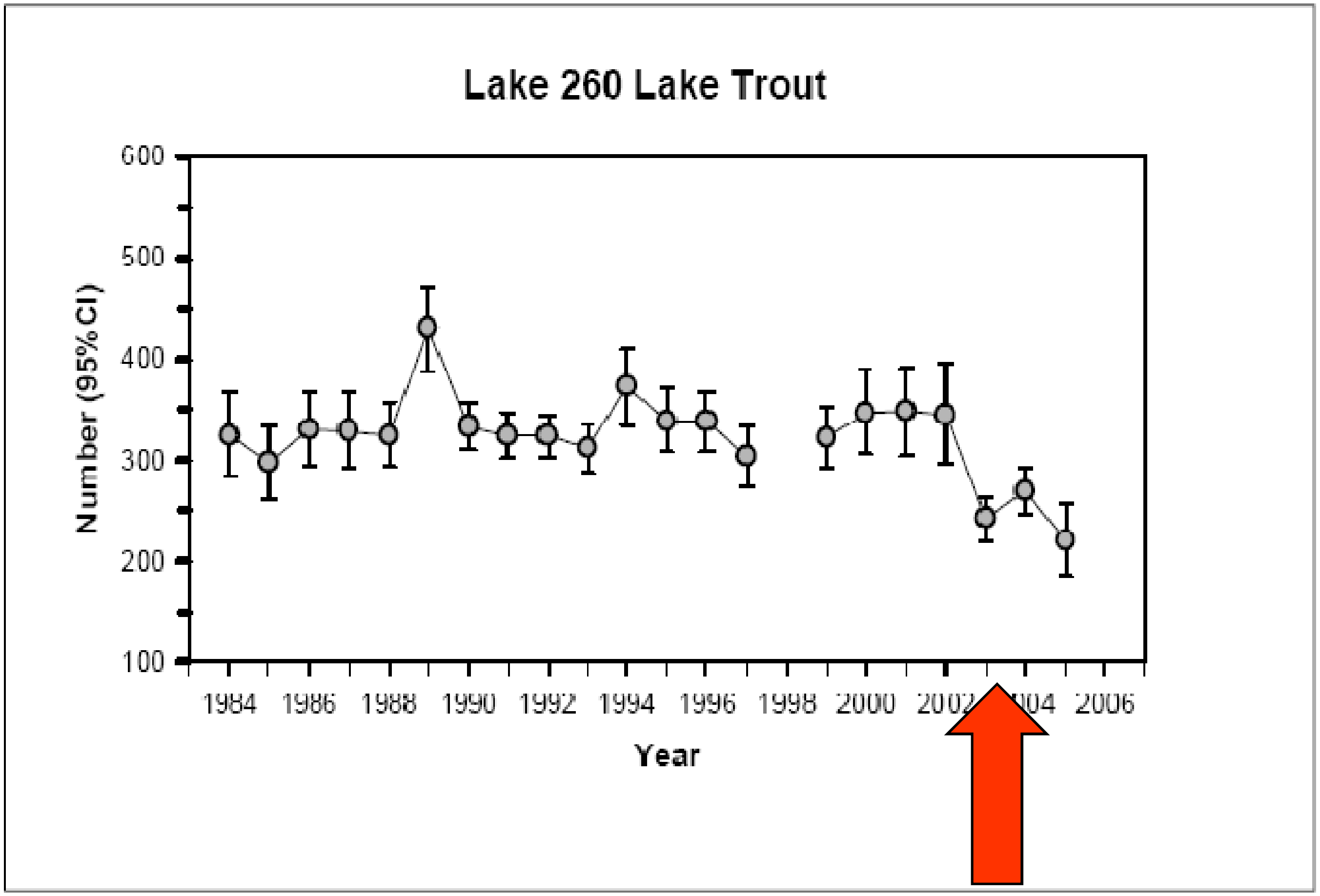
During Dosing 2001-2003

and Post Dosing 2004-2005

K Mills – FW Inst

What We Think We Know

Ecological Effects – Population level



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What We Think We Know

Human Exposure and Exposure Pathways

U.S.

Pharmaceuticals have been detected in finished drinking water and their concentrations tend to be near the limit of detection (less than 1-10 ppt). A few in the range of hundreds of ng/L (sub-ppb), such as: carbamazepine (258 ng/L).

USGS provide information on the occurrence of pharmaceuticals in source waters water at drinking water intakes) for 25 ground-water and 49 surface-water intakes across the nation, serving populations as great as over 8 million.

Measured sulfonamide antimicrobials in six domestic wells located near a confined animal feeding operation in Idaho.

In Other Countries

Korea - pharmaceuticals were detected in finished drinking water and differences in performance of various treatment alternatives were identified.

Germany - carbamazepine, a carbamazepine-related metabolite, and primidone were detected in finished drinking water.

Canada - carbamazepine, cotinine, and caffeine were detected in finished drinking but ozone treatment was found to significantly reduced concentrations.

United States Environmental Protection Agency

Ecological Exposure Research Division

What We Think We Know

Pharmaceutical Detections in Perspective

Human Health Effects

Compound	Finished Water Maximum Conc (ng/ L)	Single Dose (mg)	Volume to Consume Single Dose (L)	**Time to Consume Single Dose (years)**	Ref
Caffeine	119	100	840,336	**1151**	2
Carbamazepine	258	200	775,194	**1062**	2
Codeine	58.7	10	170,358	**233**	1
Fluoxetine	5.4	10	1,851,852	**2537**	1
Sulfamethoxazole	59.2	1000	16,891,892	**23,140**	1
Warfarin	73.4	2	27,248	**37**	1

[1]Kinney et al *Environmental Toxicology and Chemistry*, 2006

[2]Stackelberg et al *Science of the Total Environment*, 2006

What We Think We Know

Human Health Effects

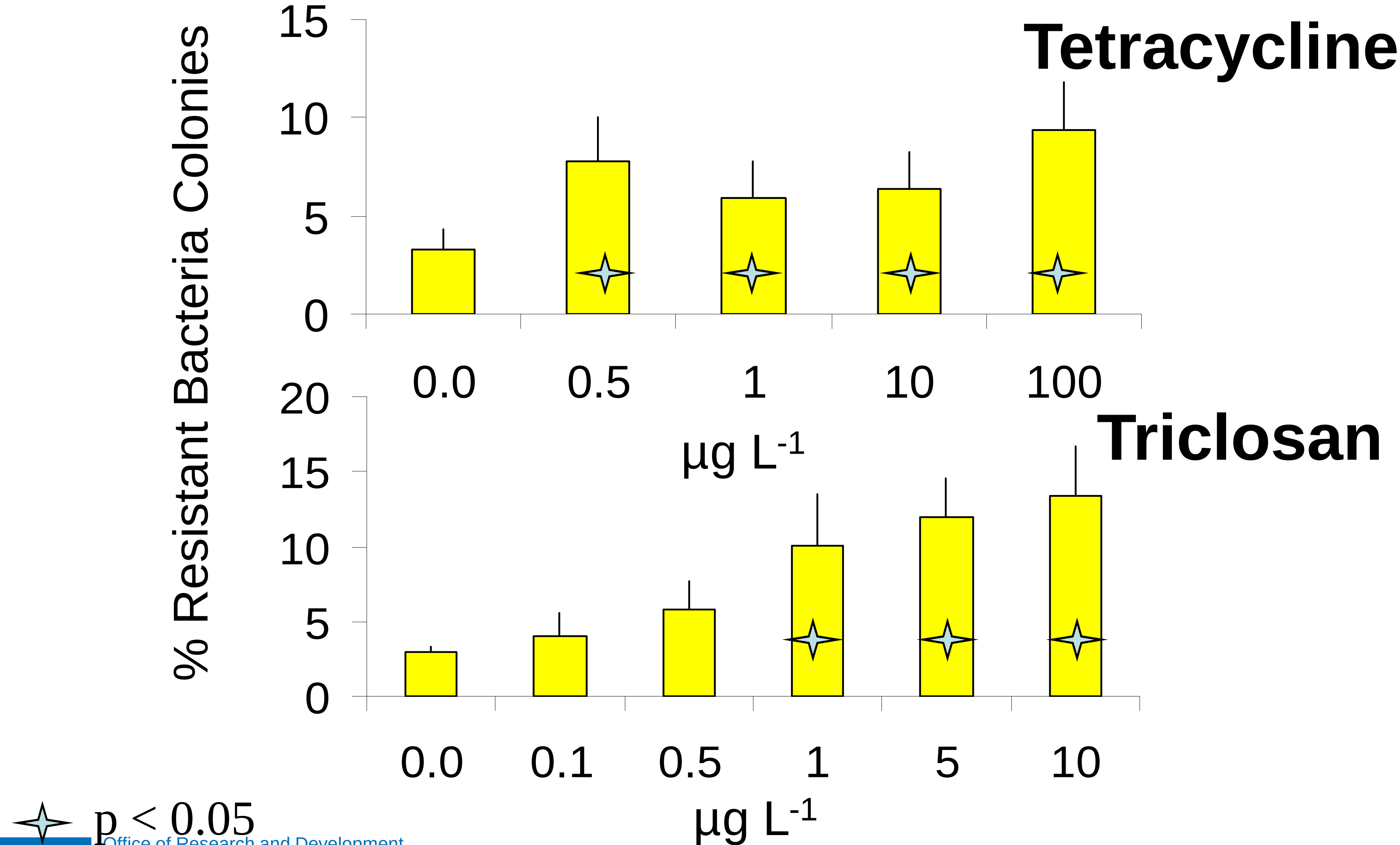
Antimicrobial Resistance and the Environment

The term antimicrobial resistance is used herein to define in the broadest sense pharmaceuticals used to destroy or inhibit the growth of pathogenic microorganisms (bacteria, viruses, fungi and protozoa). Different medications are used to treat these infections, antibiotics (antibacterials), antifungals, antivirals, and antiparasitics.

Although spread of antimicrobial resistance is usually considered in the context of people and animals given therapeutic doses of antimicrobials, environmental release of antimicrobials, antimicrobial resistant microbes, and antimicrobial resistance genes from human and animal sources may be important to the spread and maintenance of antimicrobial resistance.

Chemicals with antimicrobial properties also are found in nature and can produce natural pressures for selection of antimicrobial resistance.

Antibiotic Resistance



What We Need to Know

1) How can we identify and prioritize relevant analytes (including metabolites and byproducts) and Mode of Action (MoA) for research and assessments?

2) What are the capabilities and limitations of 'state of the art' analytical methods for relevant analytes in environmental samples? Limit Of Quantification (LOQs)?

3) Types and numbers of analytes? Matrix issues (water, sediment, tissue, soil)?

4) What are the factors that may effect bioavailability of Pharmaceuticals?

5) Relevant level of organization: molecules vs. cells vs. tissues vs. organisms vs. populations?

6) How do chemical mixtures and other stressors affect dose response?

What We Need to Know

7) How do dose responses vary among taxa?

8) What do relevant dose response curves look like? Shape? Linear? Sigmoid? U? J? Slope?

9) What is a 'safe' dose single pharmaceutical (Eco) multiple or mixture matrix of pharmaceuticals (Eco & Human)?

10) Are there any risks from Long-term (chronic) low-level exposures (Eco & Human)?

11) Are some first order effects (i.e. repro) more dangerous than others?

12) How do effects propagate between species (i.e. effects through altered community structure)?