

PNWS AWWA Annual Conference

Endocrine Disrupting Chemicals (EDCs) Research Program of U.S. EPA – An Engineer's Peer-Review Perspective

May 8, 2009
Salem, Oregon



Glen R. Boyd, PhD, PE
Professional Associate

425.450.6391 Glen.Boyd@hdrinc.com

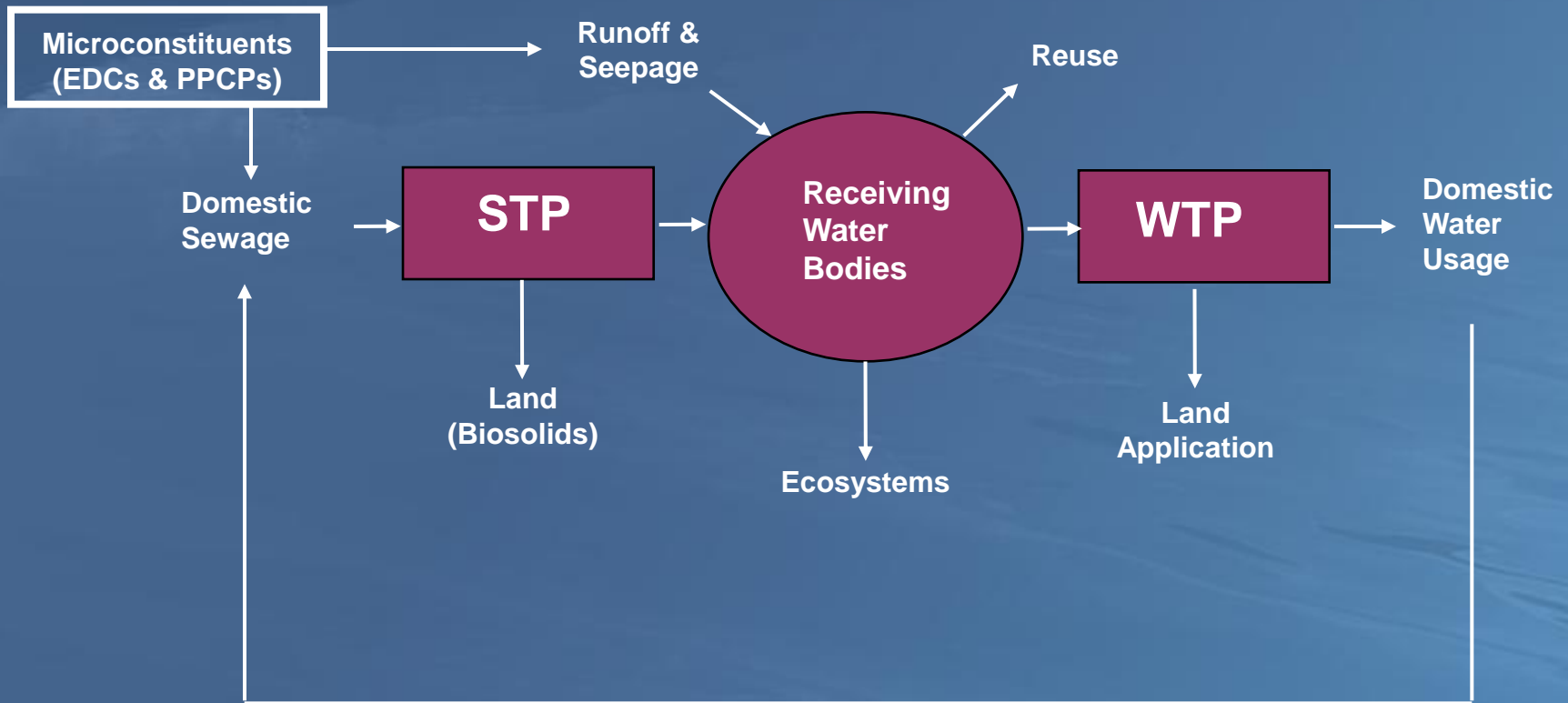


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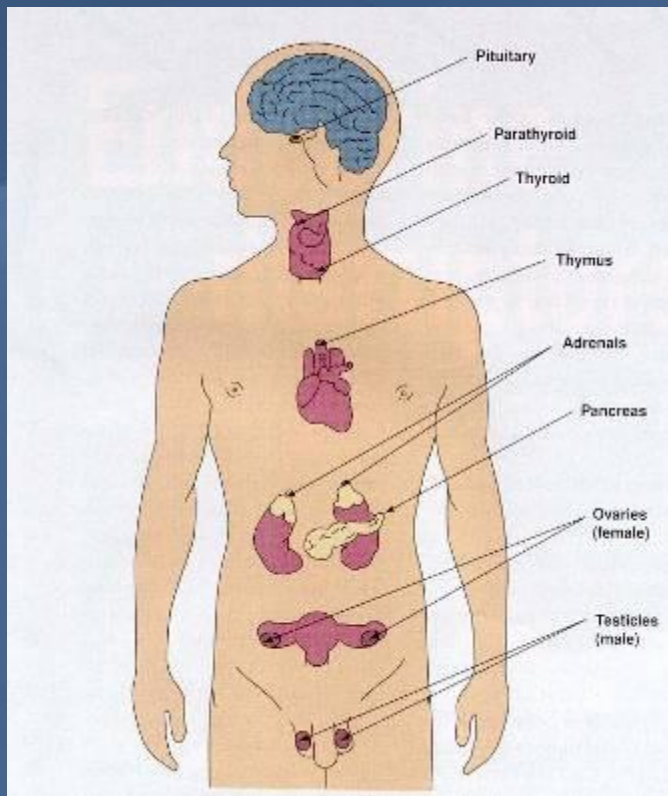
500 108th Avenue NE, Suite 1200
Bellevue, Washington 98004

425-450-6200
www.hdrinc.com

Concept



Endocrine Disrupting Chemicals (EDCs)



Trussel, R. 2001. *JAWWA* 93(2):58-65

Endocrine Disruptor – an exogenous substance or mixture that alters functions of the endocrine system and consequently causes adverse health effects.

Dose-Response Relationship

- EDCs mimic or antagonize natural hormones
- Low-dose effects - controversial
- Timing of exposure is critical

WHO. 2002. *Global Assessment of EDCs*.

EDCs – US Regulatory Issues

- **1996 amendments required USEPA to consider EDC effects**
 - Safe Drinking Water Act Amendments
 - Food Quality Protection Act
 - and in support of other regs (FIFRA, TSCA, FFDCA)
- **Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) – August 1998 Final Report**
 - **Priority Setting – universe of chemicals and initial sorting**
 - On hold - Polymers (approx. 20,000-25,000 compounds)
 - Tier 1 Screening (approx. 62,000 compounds)
 - Tier 2 Testing (approx. 500-600 compounds)
 - Hazard Assessment – sufficient data (~50-100 compounds)

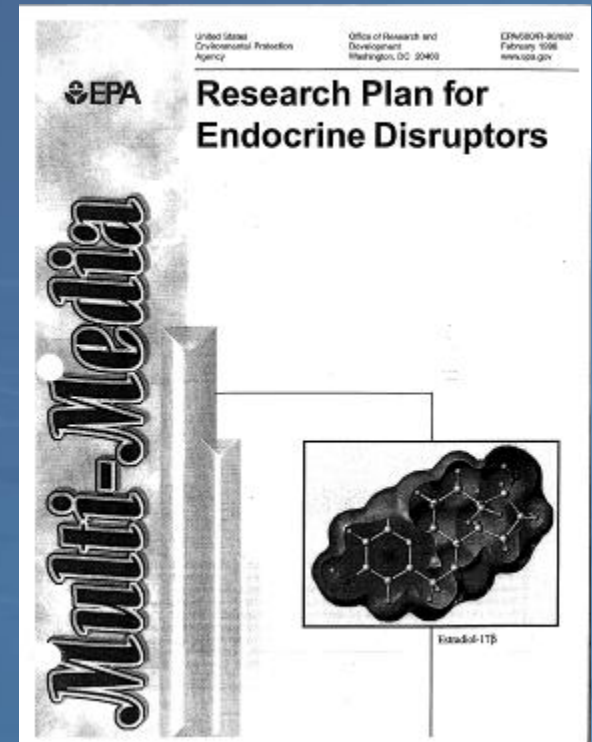
EDCs – US Regulatory Issues

- **Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) – August 1998 Final Report**
 - **Tier 1 Screening**
 - ***In Vitro***
 - Estrogen receptor binding/transcriptional activation assay
 - Androgen receptor binding/transcriptional activation assay
 - Steroidogenesis assay with minced testis
 - ***In Vivo***
 - Rodent 3-day uterotrophic assay
 - Rodent 20-day pubertal female assay with thyroid
 - Rodent 5-7 day Hershberger assay
 - Frog metamorphosis assay
 - Fish gonadal recrudescence assay
 - **Other possible alternative *in vitro* and *in vivo* assays**
 - **Tier 2 Testing**
 - **Mammalian tests (2-generation reproduction or other)**
 - **Non-mammalian multi-generation tests (avian, fish, mysid, amphibian)**

EDCs – US Regulatory Issues

USEPA Multi-Year Plan for EDCs (2000-2012)

- LTG1 – Provide a better understanding of the science underlying the effects, exposure, assessment, and risk management of EDCs
- LTG2 – Determine the extent of the impact of EDCs on humans, wildlife, and the environment
- LTG3 – Support EPA's screening and testing program



2004 EDC Program Review

U.S. Environmental Protection Agency (EPA) Office of Research and Development (ORD) Board of Scientific Counselors (BOSC) Endocrine Disruptors Program Review Subcommittee (8 members)

- 5 Academia (Pub Health; Vet Sci; Math & Comp Sci; Biology; Engineering)
- 1 Industry (chem/pharms & products)
- 1 Consultant (toxicology)
- 1 Government research (USGS)

Aug thru Dec 2004



2004 EDC Program Review

Charge Questions (CQ) Regarding MYP

CQ1 – Program Design

- Are goals & priorities appropriate?
- Has Program been implemented appropriately?
- Has the public benefit been articulated?
- Are collaborations underway?
- Is a schedule in place?
- Is MYP sufficiently flexible?

CQ2 – Program Relevance

- Responsiveness to agency & stakeholders?

CQ3 – Program Progress

- Addressing LTGs?
- Meeting annual goals?

CQ4 – Scientific Leadership

- Contribution to advancing science on EDCs?

CQ5 – Resource Allocation

- Allocation across LTGs?
- Is funding appropriate?

2004 EDC Program Review Subcommittee's Findings

Overall – LTGs and science questions in EDC Program are appropriate and represent a combination of problem-driven and core research

- LTG1 – provides a solid foundation for risk assessment & risk management decisions
- LTG2 – showed greater progress on ecological effects compared to human health effects of EDCs
- LTG3 – two mammalian tests through validation and soon available for use



**PROGRAM REVIEW
OF THE
ENDOCRINE DISRUPTORS
RESEARCH PROGRAM**

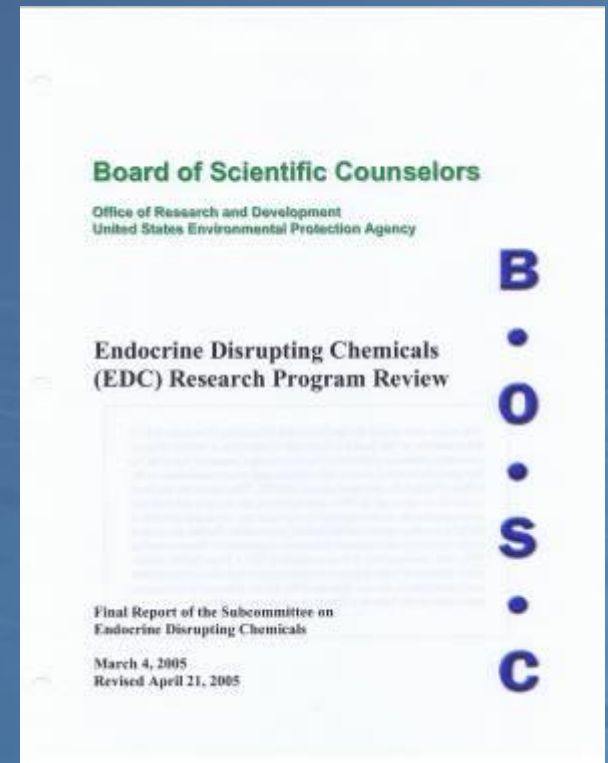


Research Triangle Park, NC

December 13-15, 2004

2004 EDC Program Review Subcommittee's Recommendations

- Expedite validation of EDSTAC tests
- Continue dependable funding of EDC Research Program
- Strengthen expertise in wildlife toxicology
- Take leadership role in application of “omnics” technologies for evaluating environmental & health effects of EDCs
- Continue to sponsor multidisciplinary research and interagency collaborations



2007 EDC Program Mid-Cycle Review

Mid-Cycle Review of ORD's EDC Research Program at U.S. EPA Subcommittee Members (4)

3 Academia

(Env. Health Sci.; Vet Sci.; Biology)

1 Consultant (Engineering)

Sep to Nov 2007

3 conference calls

1 face-to-face meeting



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University of Tennessee

Vice Chair
Rogene F. Henderson, Ph.D.
Lovelace Respiratory Research
Institute

George P. Daston, Ph.D.
Proctor & Gamble

Kenneth L. Demerjian, Ph.D.
State University of New York

Clifford S. Duke, Ph.D.
Ecological Society of America

Henry Falk, MD, M.P.H.
Centers for Disease Control and
Prevention

John P. Giesy, Ph.D.
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Emory University

Deborah L. Swackhamer, Ph.D.
University of Minnesota

Carol H. Weiss, Ph.D.
Harvard University

May 2, 2008

Dr. George Gray
Assistant Administrator
Office of Research and Development
U.S. Environmental Protection Agency
Washington, D.C. 20460

Dear Dr. Gray:

The Board of Scientific Counselors (BOSC) has completed a Mid-Cycle Review of ORD's Endocrine Disrupting Chemicals Research Program (EDCRP). This review focuses on the Agency's efforts and progress following a detailed BOSC subcommittee review of the EDCRP conducted in 2004 and subsequent BOSC report provided to ORD in April 2005. Drawing from the original review subcommittee, a four-member BOSC subcommittee (including one new member) was charged to conduct the mid-cycle review. The Subcommittee was chaired by Dr. Deborah Swackhamer, a member of the BOSC Executive Committee. The Subcommittee conducted teleconference review of ORD provided information and presentation materials in the fall of 2007 with a face-to-face meeting with EDCRP researchers and management in September 2007. The Mid-Cycle report was delivered for BOSC Executive Committee approval in April 2008. This report has been vetted by the BOSC and appropriately clarified, revised, and approved for transmittal to ORD.

The purpose of the mid-cycle review is to provide general feedback on ORD's progress to date and, as appropriate, responsiveness to previous BOSC recommendations to assist in addressing issues and opportunities surrounding continued development of the Endocrine Disrupting Chemicals Research Program's Multi-Year Plan. Specific charge questions guided the BOSC Subcommittee in accomplishing the analysis of the materials prepared for the review process and in preparing the final report itself. Each of the charge questions has been addressed by detailed response in the BOSC Subcommittee review.

The summary findings of the mid-cycle review point to a program that exceeds expectations in progress to address concerns of the previous 2004 program review. The EDCRP provides a logical and structured multi-year planning framework for identifying priority research to meet regulatory

A Federal Advisory Committee for the U.S. Environmental Protection Agency's Office of Research and Development

2007 Mid-Cycle EDC Program Review Charge Questions (CQ) for Subcommittee

CQ1 – Responsiveness

How responsive has the EDC Research Program been to the 2004 BOSC recommendations?

CQ2 – Updated MYP

Does the updated MYP provide a coherent framework and rationale for addressing priority research needs?

CQ3 – Performance Metrics

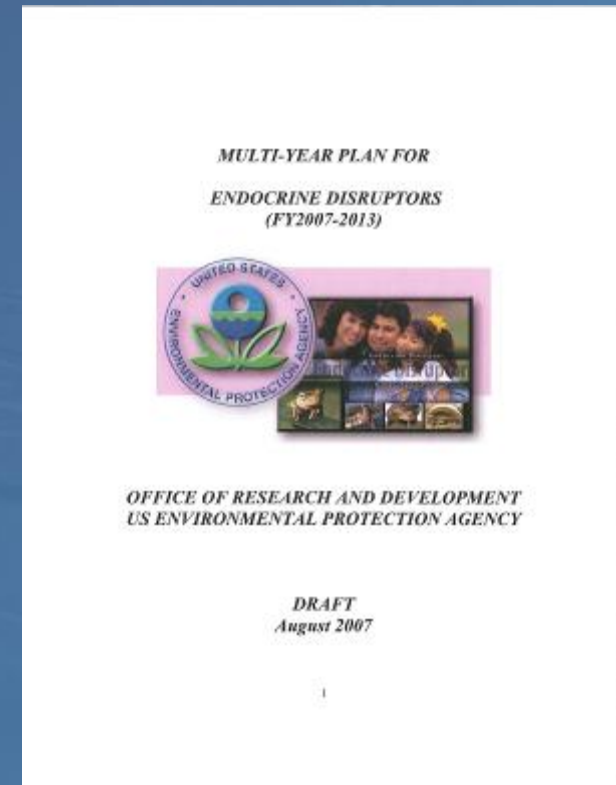
Are there performance metrics that the EDC Research Program should use in addition to current indicators?

CQ4 – Advice

What advice can BOSC provide to EDC Research Program given evolution and budget impacts?

CQ5 – Rating

Rate the progress made by the EDC Research Program in response to 2004 BOSC Recommendations.

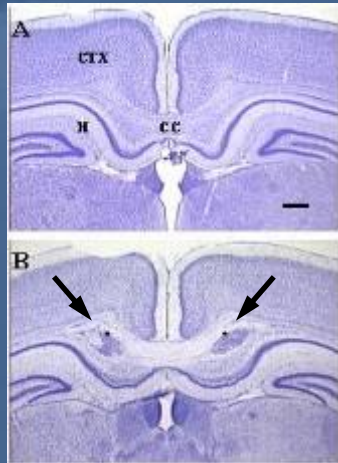


LTG1 – Understand Science

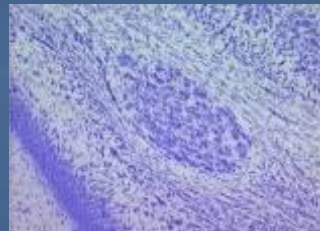
Example Project: Low-Dose Effects

Brain Malformation Induced by Prenatal Thyroid Hormone Insufficiency

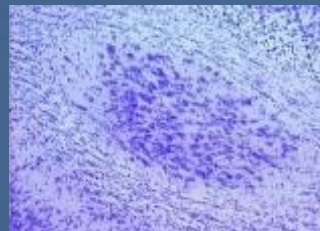
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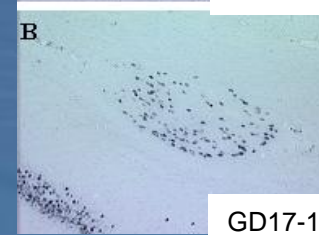
Only seen in TH-deficient offspring



Incidence and size are dose dependent



Cells are neuronal phenotype, not injury response



Cells are born late gestation ~ mid-pregnancy in humans

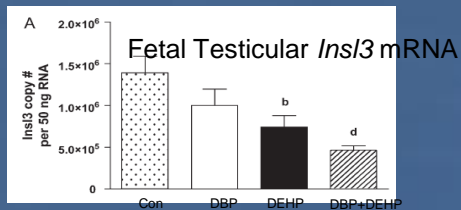
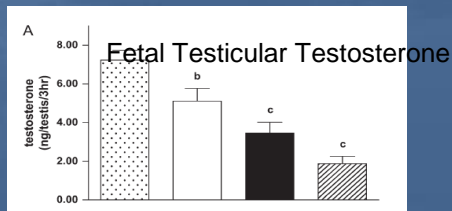
Goodman and Gilbert, Endocrinology, 2007

Gilbert, M.E. 2007. Long Term Goal 1, Washington DC, Sep 14.

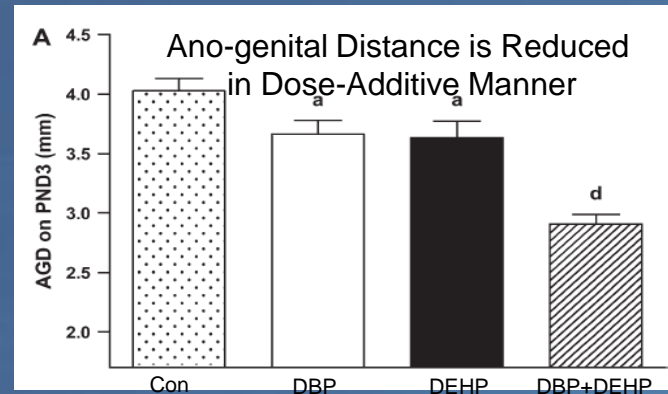
LTG1 – Understand Science

Example Project: Mixtures of EDCs

Binary Mixtures of Phthalates Induce Dose-Additive Effects



Both phthalates reduce testicular hormone production and expression of genes critical for steroidogenesis.



Several androgen-dependent endpoints of male reproductive tract development interact in dose-additive manner as predicted by common mechanism of toxicity during sexual differentiation.

Howdeshell et al., Toxicological Sciences, 2007

Gilbert, M.E. 2007. Long Term Goal 1, Washington DC, Sep 14.

LTG1 – Understand Science

Example: Exposure & Risk Mgmt

Analytical Methods Development For Ecologically Relevant Pharmaceuticals & Metabolites/Degradation Products

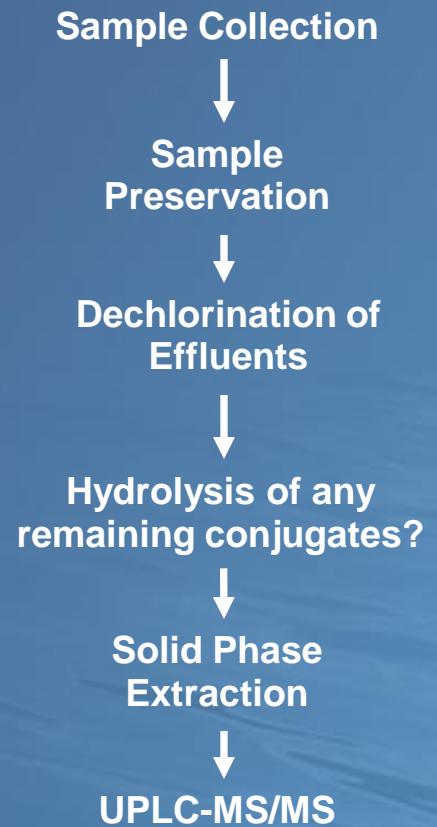
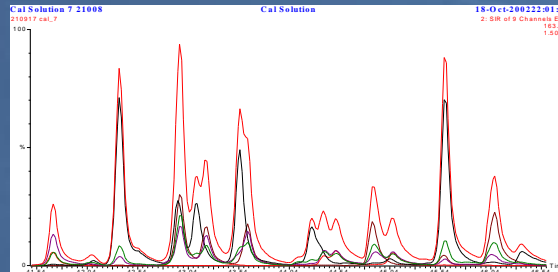
USEPA-ORD-NERL-Cincinnati

Objective:

Develop methods for waters, sediment, and tissues to conduct fate and occurrence studies. Target analytes were identified using the bioinformatics approach and Program office priorities.

Impact:

Assist the Program Offices, Regions, industry, and scientific community in designing and implementing exposure monitoring and assessment programs for selected emerging contaminants



Mills, M.A. 2007. Long Term Goals 1 and 2, Washington DC, Sep 14.

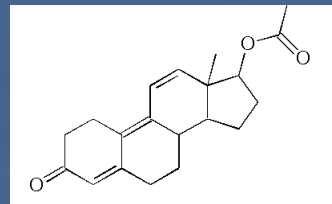
LTG1 – Understand Science

Example: Exposure & Risk Mgmt

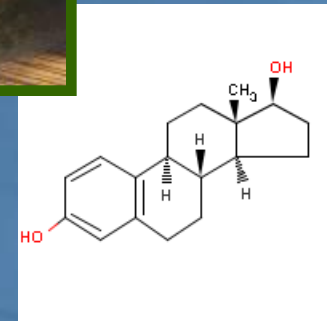
Assessment of the Occurrence and Potential Risks of EDCs in Discharges from Concentrated Animal Feeding Operations
EPA-ORD NHEERL, NERL, NRMRL, NCEA, Academic Co-operators



Trenbolone Acetate



Estradiol



- **Science Questions:**
- Determine how and to what degree human and wildlife populations are exposed to EDCs.
- Determine what effects are occurring in exposed human and wildlife populations.
- Determine what are the major sources and environmental fates of EDCs.
- Determine how unreasonable risk can be managed.

Mills, M.A. 2007. Long Term Goals 1 and 2, Washington DC, Sep 14.

LTG1 – Understand Science

Example: Exposure & Risk Mgmt

Evaluation of Drinking Water Treatment Technologies for Removal of Endocrine Disrupting Chemicals (EDCs)

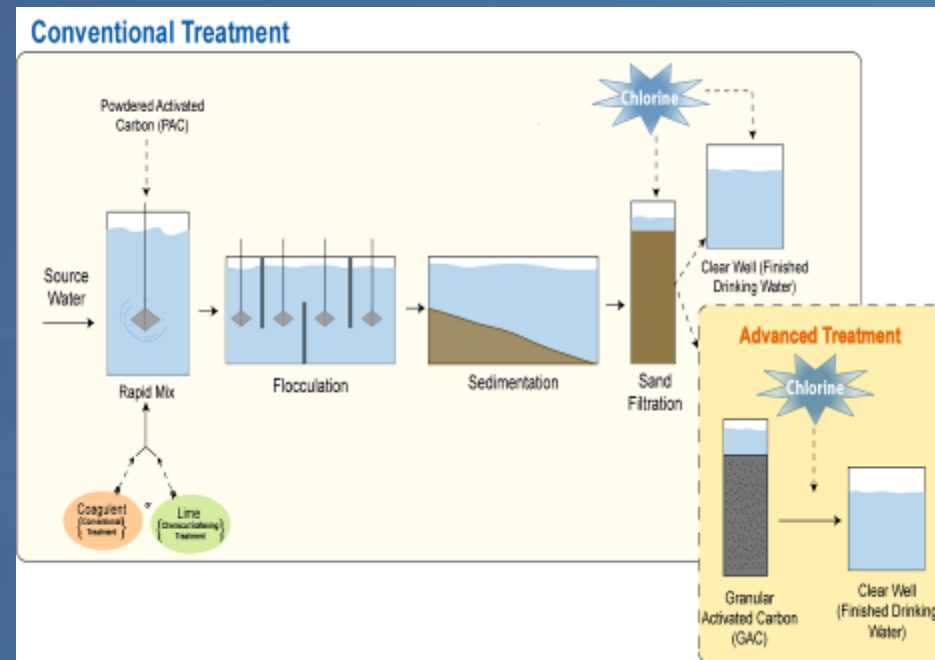
EPA-ORD-NRMRL

Objective:

Determine the ability of conventional and advanced drinking water treatment processes to remove EDCs from source waters

Project Design:

- Develop appropriate analytical methods
- Evaluate the applicability of a bioassay .
- Conduct bench-scale evaluations of various drinking water treatment processes



Mills, M.A. 2007. Long Term Goals 1 and 2, Washington DC, Sep 14.

LTG1 – Understand Science

Example: Exposure & Risk Mgmt

Strategies to Suggest Substitutes for Endocrine Active Substances

EPA-ORD-NRMRL, Academia

Objectives:

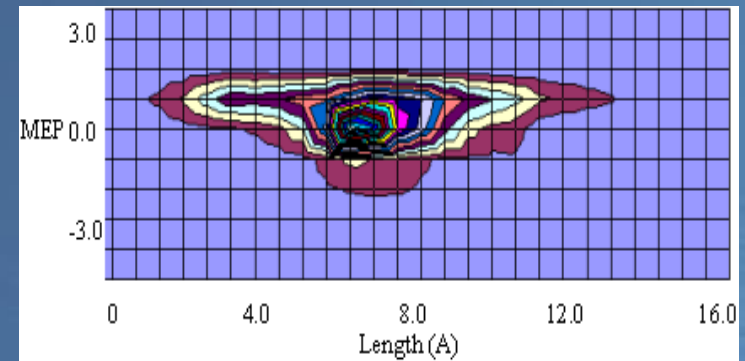
- Substitutes for existing EDCs require:
 - Chemical properties that maintain desirable performance
 - Significantly lower undesirable endocrine activity
- Computational approach developed
 - Methodology tested with alkylphenol ethoxylate surfactants
 - Satisfactory substitute found

Impact:

- Process may be used by EPA and industry to suggest suitable chemical substitutes for replacing endocrine active compounds

Status:

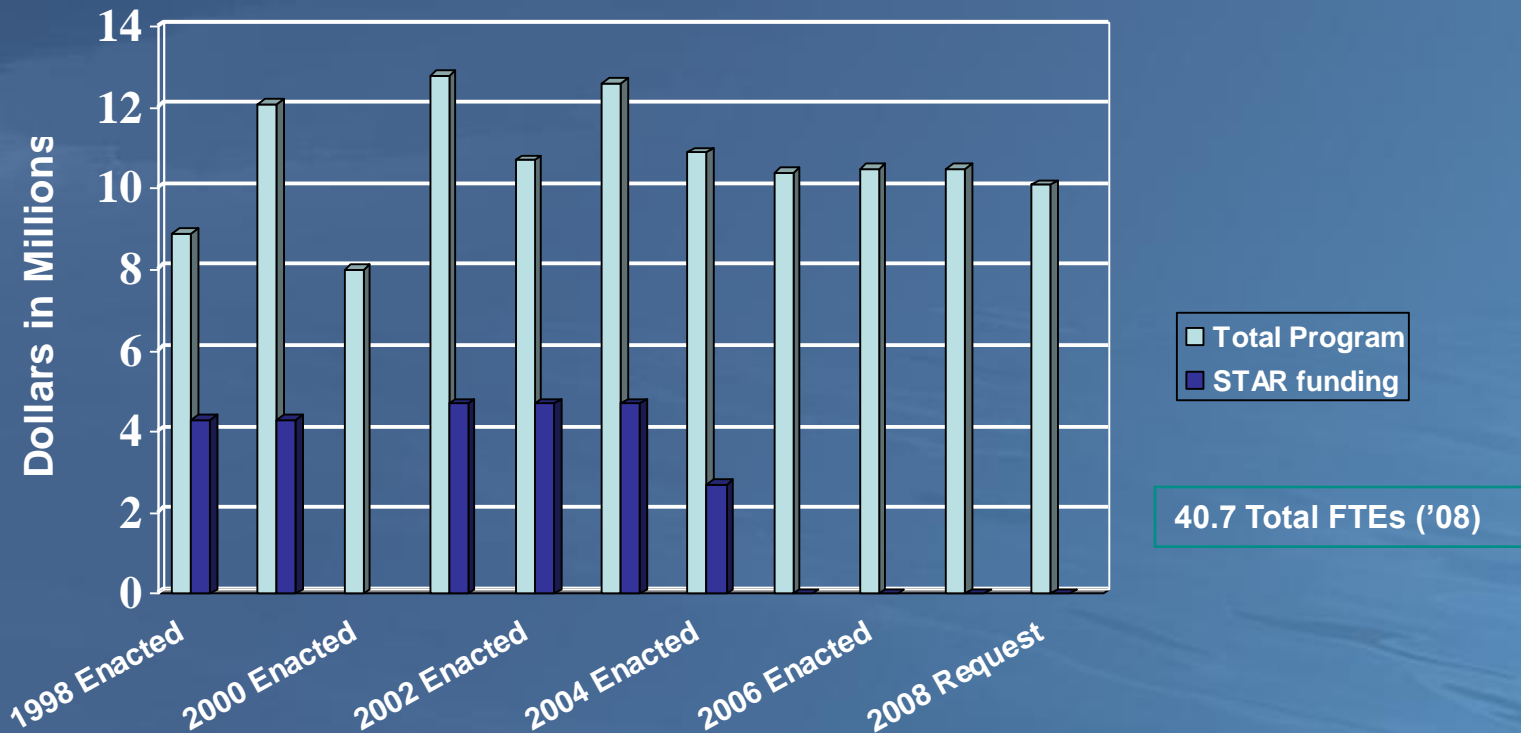
- Research has been discontinued under EDC MYP due to funding limits



Mills, M.A. 2007. Long Term Goals 1 and 2, Washington DC, Sep 14.

EPA Endocrine Disruptors Research Budget

1998 - 2008



Francis, E. 2007. ED Res Program: Overall Progress Review, Washington, DC, Aug 21.

2007 Mid-Cycle EDC Program Review Subcommittee's Findings

Charge Question	Findings
CQ1 – Responsiveness	V. resp. to 2004 BOSC recommendations; Some not implemented - budget constraints
CQ2 – Updated MYP	Very logical; provides coherent framework for EDC priority research needs
CQ3 – Performance Metrics	Apply new metrics to assess (a) advancements to science, etc & (b) collaborations
CQ4 - Advice	No gaps; cont. ongoing research; enhance EPA's leadership in risk management
CQ5 - Rating	Exceeds expectations; Remarkable accomplishments w/ diminishing resources

2007 Mid-Cycle EDC Program Review Subcommittee's Findings

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Enhance EPA's Leadership in Risk Management

- Compile & synthesize what is known about occurrence and exposure.
- Advise water, wastewater & reuse industries on EDC priorities.
- Strengthen relationships with prof orgs, private res foundations, academia & industry to identify res funding & EDC research needs.
- Strengthen relationships with other national & international agencies
- Build & strengthen outreach with stakeholders & public



Regulation of EDCs under SDWA

- EPA statutory framework to identify & address EDCs
- Known or suspected endocrine disrupting drinking water contaminants being considered in the Contaminant Candidate Listing (CCL) process
 - Draft CCL3 (2/08) - 73 chemicals for initial Tier 1 testing (not known or suspected endocrine disruptors)
 - Draft implementation policies & procedures (FR-12/07)
- May or may not lead to regulatory determination

Francis, E. 2007. Overview of Regulatory Activities: Endocrine Disruptors, ASCE EWRI, Tampa, FL, May 15.

Next Steps

2009 EDC Program Review

- **New Subcommittee (9 members)**
 - 4 Academia (biol; vet sci; physiol & pharmacol; and neuroscience)
 - 2 Government research (ecol; human health)
 - 1 consultant (engineering)
 - 2 nonprofit research (comp biol; policy & mgt)
- **June thru August 2009**
 - 2 conference calls
 - 1 face-to-face