

Overview of the EPA's Endocrine Disruptor Screening Program (EDSP)

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U.S. Endocrine Disruptor Screening Program

- Required by the Food Quality Protection Act (FQPA) of 1996
 - Must screen pesticides for estrogenic effects that may affect human health
 - Must use appropriate validated test systems or other scientifically relevant information
 - Can include other endocrine effects
- Safe Drinking Water Act (SDWA) Amendments of 1996:
 - Can screen drinking water contaminants to which substantial numbers of persons are exposed
- Testing will be the responsibility of registrants and manufacturers

Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC)

- Federal Advisory Committee ('96-'98)
- Stakeholder representation
- Provide design advice for a screening and testing program to identify endocrine disruptor chemicals
- 71 compelling and scientifically rigorous recommendations
- EPA adopted much of EDSTAC's advice

EDSTAC

General Recommendations

- Cover estrogen, androgen and thyroid
- Cover human and ecological effects
- Cover a broad universe of chemicals
- Tier 1
 - in vitro and in vivo screens
 - detect potential to interact with the endocrine system
- Tier 2
 - multi-gen studies covering a broad range of taxa
 - provide data for hazard assessment
 - mechanistic data

Current EDSP

1. Priority Setting of Chemicals
2. Regulatory Implementation
3. Validation of the Assays
 - Assay Validation
 - International coordination (OECD)
 - Inter-Agency coordination (ICCVAM)
 - Stakeholder input/expert advice: Endocrine Disruptors Methods Validation Advisory Committee (EDMVAC) (formerly EDMVS)

1. EPA's Chemical Selection and Priority Setting

- EPA concluded that it is not practical to sort and prioritize the universe of chemicals as defined by EDSTAC
- Selecting the first group of chemicals to be screened
 - December 30, 2002 notice proposed exposure – based approach for selecting 50-100 chemicals
 - Pesticide actives will be selected based on
 - Presence in food*
 - Presence in drinking water*
 - Residential use*
 - Occupational contact*

Priority Setting for First Group of Chemicals to be Screened

- HPV/Inerts to be selected based on
 - High production volume
 - Monitoring data that shows presence in human tissue, fish tissue, drinking water or indoor air
- Chemicals to be excluded for initial testing
 - “Positive Control” chemicals for validating Tier 1 Assays
 - Chemicals with low potential to cause endocrine disruption (e.g. strong mineral acids, certain FIFRA List 4 inerts)
 - Chemical mixtures*
 - Chemicals no longer produced or used in the US*

* May be addressed for future rounds of testing

2. Regulatory Implementation

- Federal Food, Drug, Cosmetic Act (FFDCA), Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), SDWA, Toxic Substances Control Act (TSCA)
- Intra-agency workgroup formed to:
 - examine a variety of chemical categories (pesticides, inerts...) and the authorities required for ED testing;
 - develop the procedures for invoking each authority or combination of authorities.

3. Validation of the Assays

Interagency Coordinating Committee On the Validation of Alternative Methods (ICCVAM) Validation Process

1. Method Development

- Comprehensive literature review
- Develop initial protocol

2. Prevalidation

- Demonstration of relevance
- Preliminary data on reliability
- Standardization of protocol

3. Validation in multiple laboratories

- Proof of relevance and reliability

4. Scientific Peer Review

5. Regulatory acceptance and implementation

Work Accomplished: Tier 1 Assays

<i>In vitro</i>	Detailed Review Papers	Pre-validation	Inter-lab
ER (rat cytosol)	•	•	○
hrER binding ^{OECD, a}	•	○	
AR (rat cytosol)	•	•	○
hrAR binding ^{OECD, a}	•		
Steroidogenesis - rat sliced testes	•	○	○
- H295R ^{OECD, a}	•	○	
Aromatase - placenta	•	•	○
- recombinant ^a	•	•	○

^a alternate ○ in progress • completed

Work Accomplished: Tier 1 Assays

<i>In vivo</i>	Detailed Review Papers	Pre-validation	Inter-lab
Hershberger ^{OECD}	•	•	◦
Uterotrophic ^{OECD}	•	•	•
Pubertal (female)	•	•	◦
Pubertal (male)	•	•	◦
Frog metamorphosis ^{OECD}	•		
Fish screen ^{OECD}	•	◦	
Adult Male (Industry)		•	

◦ in progress • completed

Work Accomplished: Tier 2 Assays

<i>In vivo</i>	Detailed Review Papers	Pre-validation	Inter-lab
Mammalian 2-gen ^{OECD}	-	○	
Avian 2-gen ^{OECD}	●	○	
Amphibian dev, repro ^{OECD}	●	○	
Mysid Lifecycle	●	○	
Fish lifecycle ^{OECD}	●	○	
<i>In utero/lactation -tier ?</i>	●	○	
Thyroid - ?	●	TBD	TBD

○ in progress ● completed

ED Methods Validation Advisory Committee (EDMVAC)

- ED Standardization and Validation Task Force (EDSVTF)
- ED Method Validation Subcommittee (EDMVS) to NACEPT under FACA –convened 9 public meetings in 2 years
- ED Methods Validation Advisory Committee (EDMVAC) under FACA - Chartered in May 2004
 - Scientific experts (in vitro, in vivo, multiple taxa)
 - Representing Industry, environmental groups, animal welfare, states, federal agencies, academia...
 - Purpose: to provide input and advice on the assays throughout validation process
 - Also emphasis on: replacing animals, reduction of animal use, refining procedures to decrease stress on animals (3 Rs)
 - First Public meeting of the 20 members is April 26 - 28, 2005

EDMVAC Role in Tier I & II Validation:

1. Detailed Review Documents (DRP) & Protocol(s)
→ *advice and Recommendations*
2. Pre-validation(s) in one laboratory
→ *advice and Recommendations*
3. Validation in multiple laboratories
→ *advice and Recommendations*
4. Review of Tier 1 battery
→ *advice and Recommendations on composition of assays for Tier 1 Screening*

Other EDMVAC considerations...

- Replacing animals
- Reduction of animal use
- Refining procedures to decrease stress on animals

- and, Provide advice on the composition of the Tier I screening battery

EDMVAC April Agenda

- Uterotrophic
- Steroidogenesis
- Fish Screen
- Amphibian Metamorphosis

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