

# An Update on the Implementation of the EPA's Endocrine Disruptor Screening Program

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# EDSTAC Recommendations-- Basis of the EDSP

- Estrogen, androgen and thyroid
- Human and ecological effects
- Priority setting for a broad universe of chemicals
- 2-Tiered Approach
  - Tier 1
    - *In vitro and in vivo screens*
    - *Detect potential to interact with endocrine system*
  - Tier 2
    - *Multi-generation studies covering a broad range of taxa*
    - *Provide data for hazard assessment*

# Tier 1 Assays

## Recommended by EDSTAC

- Primary recommendation:
  - Steroidogenesis (in vitro)
  - Estrogen / Androgen receptor binding and/or transcriptional activation assays (in vitro)
  - Uterotrophic
  - Hershberger
  - Pubertal female assay
  - Amphibian metamorphosis assay
  - Fish screen
- Potential alternative assays to validate:
  - Aromatase (in vitro)
  - Pubertal male assay
  - 14-Day adult male

# EDSP Implementation Activities



- **Assay Validation**
  - Development and validation of test assays (Tier 1 screening & Tier 2 testing)
- **Priority Setting**
  - Selecting chemicals to be screened
- **Procedures**
  - Developing procedures to require the data ED Screening Program (EDSP)

## Assay Validation

## Validation

- *Validation* -- Required by ICCVAM Authorization Act of 2000 and by FQPA Sec. 408p
- **Validation** is an assessment of the reliability and relevance of a test method for a particular purpose.
  - **Relevance**--The extent to which a test method will correctly predict or measure the biological effect of interest.
  - **Reliability**--The extent to which a test can be performed reproducibly within and among laboratories over time.

## Assay Validation

# Validation Criteria

1. Scientific and regulatory rationale
2. Relationship of endpoints to biological effect or toxicity
3. Formal detailed protocol
4. Assessment of variability
5. Assessment of performance with reference chemicals
6. Comparison of the performance of the replacement test to the original test or to data in the species of interest
7. Data quality/use of GLPs
8. Availability of data and independent scientific peer review

## Additional Criteria for Alternative Methods

- An alternative test method consists of two parts: the test system and a prediction model.
- A prediction model is an algorithm for converting in vitro data into a prediction of in vivo toxicity.
- Validation is a test or measure of the performance of the prediction model.
- The prediction model needs to be developed prior to validation to allow a prospective evaluation of the prediction model.
- The set of test chemicals used in validation should be different from the set used for model development.

# Validation of Ecotoxicity Test Methods

- New test method reproducibility measured across labs with limited number of chemicals (ring test).
- Relevance is assumed because an environmentally relevant species is selected for testing.
- No prediction model; direct observation of toxicity of interest (e.g., critical life processes).
- Standardized method is based on protocol assessment in ring test rather than prevalidation.

# OECD Guidance Document 34

- OECD recognized the need to update the Solna principles “ to provide practical guidance” on the validation of test methods. Result is GD 34.
- GD 34 recognized the need for flexibility in applying criteria:

The amount and kind of information needed and the criteria applied to a new test method depends on the type of test, its use, what is known about the test (mechanistic basis, history of use, etc)



## Assay Validation

# Validation Realities for the EDSP

- Tier I is for screening, i.e., detection of potential to interact with the endocrine system
- Battery of Tier I assays—assays compliment each other
- Assays are “new” assays, not replacements of existing screens or tests
- Limited number of reference chemicals available
- Practical limitations regarding numbers of tests that can be run during validation

## Assay Validation

# Reference Chemicals

- Challenge the assay with carefully selected benchmark chemicals
- Number of chemicals will vary with assay
  - 20-50 for *in vitro* screens
  - 5-15 for in vivo screens
  - 1-3 for in vivo Tier II
  - 10-25% of chemicals will be negatives (except Tier II)



**Assay Validation**

## Validation is a Characterization of Assay Performance

- Determine ability of labs to measure endpoints. Is variability satisfactory?
- Were expected results obtained with benchmark chemicals?
- EPA did not determine predictivity



## Assay Validation

# Validation Process

- Method development and preparation of Detailed Review Paper (DRP)
- Pre-validation
  - Demonstration of relevance
  - Development of standard optimized protocol
  - Determination of readiness for validation
- Validation in multiple laboratories
  - Demonstrate reliability across labs
- Independent scientific peer review of validation effort: Integrated Summary Report (ISR)
- Regulatory acceptance

## Assay Validation

# Validation Update on Tier 1 Assays Peer Review Status

■ Uterotrophic	Completed
■ Hershberger	Completed
■ Adult Male	Completed
■ Female Pubertal	Completed
■ Male Pubertal	Completed
■ AR Binding	Completed
■ Aromatase	Completed
■ Amphibian Metamorphosis	Completed
■ Fish Screen	Completed
■ Steroidogenesis	2008-Q1
■ ER Binding	2008-Q2

# SAP Meeting to Review EPA's Proposed Tier 1 Battery

- March 25-28, 2008
- Decision and Supporting Materials to be placed on SAP website: [www.epa.gov/scipoly/sap](http://www.epa.gov/scipoly/sap)
- Integrated Summary Reports
  - Peer Review Reports
  - Response to peer reviewer's comments
  - Battery Technical Support Document
- Additional information is available on the Endocrine Disruptor Screening Program website:  
[www.epa.gov/endo](http://www.epa.gov/endo)



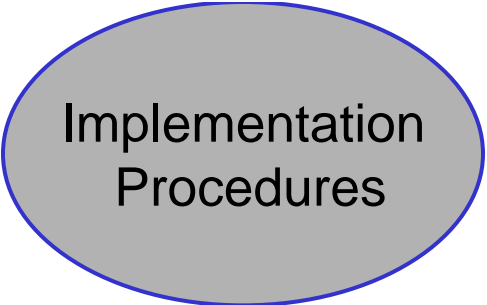
Priority Setting

# Priority Setting Approach

- Approach to selecting Chemicals for Initial Screening was established on Sept. 27, 2005, after considering comments.
- Based on potential human exposure
  - PAIs with food, water, residential, occupational exposure
  - HPV inerts in human and eco biomonitoring, water, air
- Based on chemicals found in multiple pathways

# Priority Setting: Draft List

- Issued the Draft List of Chemicals for Initial Screening on June 18, 2007
  - 64 Pesticide actives and 9 HPVs / pesticide inerts
  - Not a list of “known” or “likely” endocrine disruptors
- Comment period extended to February 11, 2008
- EPA will review comments on draft list and finalize list for Tier 1 screening by August 2008



Implementation  
Procedures

## EPA's Policy Goals:

- Fulfill FFDCA §408(p)(5) directive
  - Minimize duplicative testing
  - Promote fair and equitable cost sharing
  - Protect data from inappropriate public disclosure
  
- Minimize burden to the extent practical by building on existing procedures & infrastructures
  - Internally (EPA)
  - Externally (Affected Entities)

Implementation  
Procedures

# Policy & Procedures

- Draft Policy, Test Order Templates, & Information Collection Request issued on December 13, 2007
- Comment period extended to March 12.
- EPA will review comments and finalize by August 2008

Implementation  
Procedures

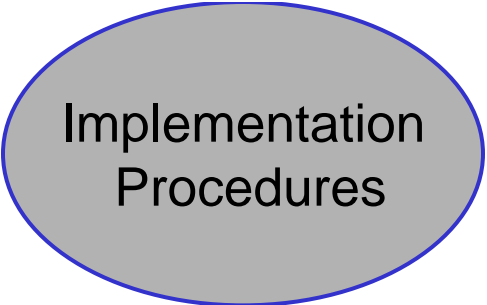
## Who Would Receive the EDSP Test Order?

- Pesticide Active Ingredients
  - Send test orders under FFDCA §408(p) & FIFRA §3(c)(2)(B) to technical registrants
  
- Inert Ingredients
  - Send test orders under FFDCA §408(p) to manufacturers/importers

Implementation  
Procedures

# How Should Recipients Respond to a Test Order?

- (1) *Read instructions*
- (2) *Plan activities*
- (3) *Submit an Initial Response to EPA within 90 days*
  - Indicates intentions
  - Uses Initial Response Form
- (4) *Read &, if appropriate, discuss the protocol w/ EPA*
- (5) *Generate the data/ participate in consortia*
- (6) *Compile & review the data for submission*
- (7) *Complete paperwork to assemble the submission package*
- (8) *Submit the data*
- (9) *Maintain records*



Implementation  
Procedures

## Summary of Basic Response Options

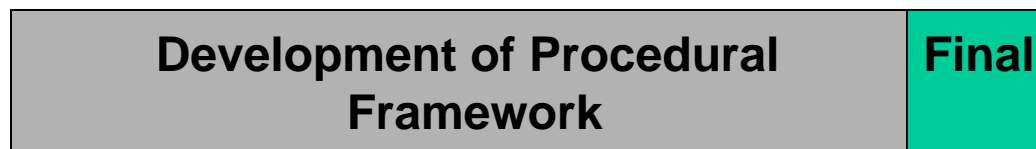
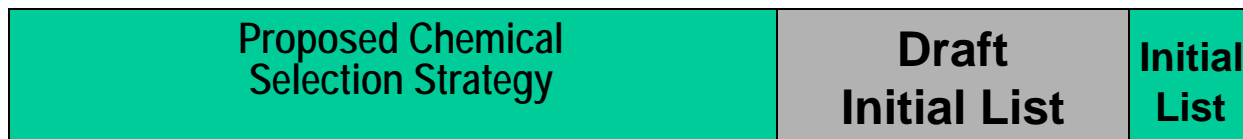
- (1) I will generate new data.
- (2) I have entered (or offered to enter) into an agreement to form a consortium to generate the data.
- (3) I am citing or submitting existing data.
- (4) I am not subject to the test order.
- (5) I request voluntary cancellation of my registration, I am applying to reformulate my product, or I commit to discontinue the manufacture and importation of the chemical.
- (6) I am claiming a formulators' exemption.

# Next Steps

Date	Assay Validation	Priority Setting	Implementation Procedures
Feb	Send EPA's Battery recommendation to SAP	Comment period for Draft List of Chemicals ends	
March	SAP Meeting to review Tier 1 Battery (Mar 25-28)	Begin developing final list	Comment period for Draft Policy Notice ends (Mar 12)
August 2008	FR Notice of Battery Selection	Issue Final List of Chemicals	Publish Final Procedures Issue Test Orders

# EDSP Timeline

2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010



# Review of Tier 1

- Review Tier 1 Screening Data
- Determine which chemicals must proceed to Tier 2 testing
- Review performance of Tier 1 battery by EPA and the SAP
- Review newly validated assays as potential replacements
- Modify Tier 1 battery as appropriate for subsequent screening



## Assay Validation

# Complete Validation of Tier 2 Assays

- Mammalian 2-generation – Complete
  - **Extended one-generation test** is being developed to replace most applications of the 2-gen mammalian test.
  
- Avian 2-generation – 2009/102626
  
- Amphibian Growth/Reproduction – 2009/10
  
- Fish 2-generation – 2009/10
  
- Mysid 2-generation – 2009/10

# Summary

- EPA will implement testing of the first group of 73 chemicals in August 2008
- First list based on simple exposure approach—no data showing potential endocrine effects or lack thereof was considered in listing
- EPA will continue to validate Tier 2 assays for ecotoxicity
- EPA is working with OECD to develop a test guideline for an improved 1-generation mammalian reproductive effects assay that may replace the current 2-gen in routine use.