Endocrine Disruptors Screening Program: U.S. perspective

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EDSP Mission

To protect public health and wildlife by screening and testing chemicals and taking appropriate actions with respect to those chemicals that are found to have endocrine effects.

Endocrine Disruptor Screening Program Legislative Mandate

- **1996 Federal Food, Drug and Cosmetic Act, section 408(p)**
  Requires the U. S. EPA to develop a screening program using appropriate validated test systems and other scientifically relevant information to determine whether certain substances may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effect as the Administrator may designate.

- **1996 Safe Drinking Water Act Amendments, section 1457**
  Testing of chemical substances that may be found in sources of drinking water, if substantial human populations may be exposed.

1998 Endocrine Disruptor Screening and Testing Advisory Committee

1998 EDSTAC Recommendations:

- **Protect Human Health and Wildlife**
- **Include Estrogen, Androgen and Thyroid pathways**
- **Develop a two-tiered screening and testing program:**

Tier 1 Screening

potential to interact with the estrogen, androgen or thyroid hormone systems

Tier 2 Testing

if endocrine-mediated adverse effects then quantify dose-response

EDSP Tier 1 Screening Battery

In vitro
Estrogen Receptor (ER) Binding
Estrogen Receptor Transcriptional Activation Assay (ERTA)
Androgen Receptor (AR) Binding
Steroidogenesis
Aromatase
In vivo
Uterotrophic (rat)
Hershberger (rat)
Pubertal Female (rat)
Pubertal Male (rat)
Amphibian Metamorphosis Assay (frog)
Fish Short-Term Reproduction Assay

Endocrine Disruptor Screening Program
Tier 1 Screening Assays

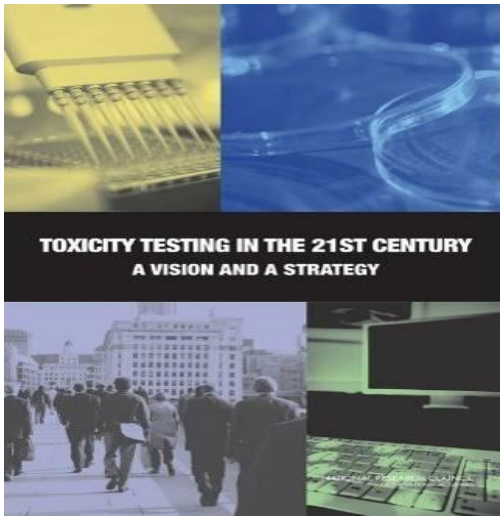
					Steroid	Synthesis		
	E	E-	A	A-	T	E	HPG	HPT
In vitro								
ER Binding	X	X						
ER Transcriptional Activation	X							
AR Binding			X	X				
Steroidogenesis (H295R)					X	X		
Aromatase (Recombinant)						X		
In vivo								
Uterotrophic	X							
Hershberger			X	X				
Pubertal male			X	X	X		X	X
Pubertal female	X	X				X	X	X
Fish Reproductive Screen	X	X	X	X	X	X	X	
Amphibian Metamorphosis								X

EDSP Tier 2 Tests

Mammalian Two-Generation Reproduction (Sprague Dawley rat) (may be replaced by Extended F1-Generation)
Avian Two-Generation (Japanese quail)
Larval Amphibian Growth and Development (Xenopus laevis)
Fish Multi-Generation (Medaka)
Invertebrate Multi-Generation (Mysid and Copepod)

EDSP in 21st Century

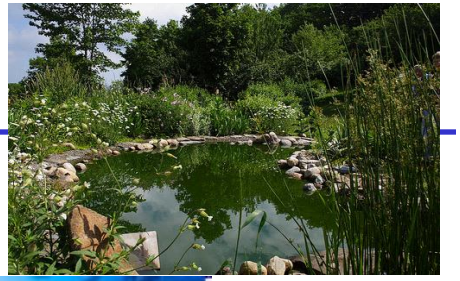
Hypothesis Driven, Targeted Testing Strategy



EDSP21 Objectives

- Maximize use of existing data.
- Targeted *in vivo* toxicity screening.
- Use a variety of tools in a tiered testing and assessment framework.
- Systematically and *incrementally* incorporate HTP, *in silico* tools and methodologies.
- Advance understanding of key events in toxicity pathways.

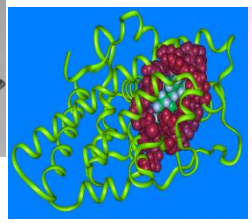
Application to Levels of Organization Based on Source to Outcome

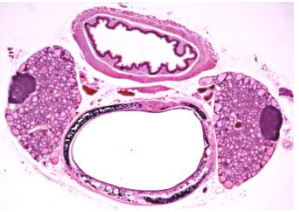


Source

Community

Environmental Contaminant





Population

Exposure

Molecular Initiating Event

Cellular Effects

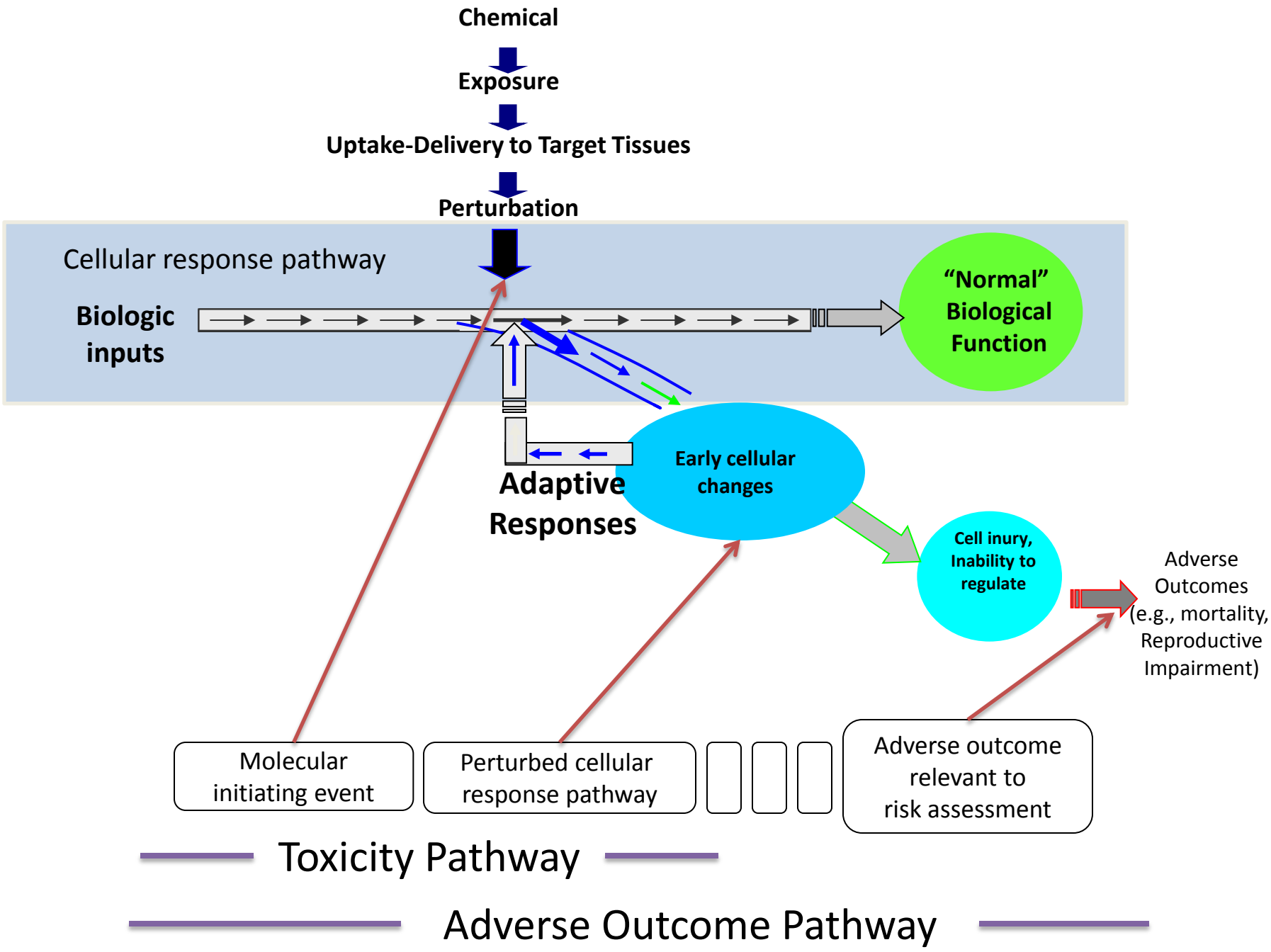
Individual

Toxicity Pathway

Mode of Action

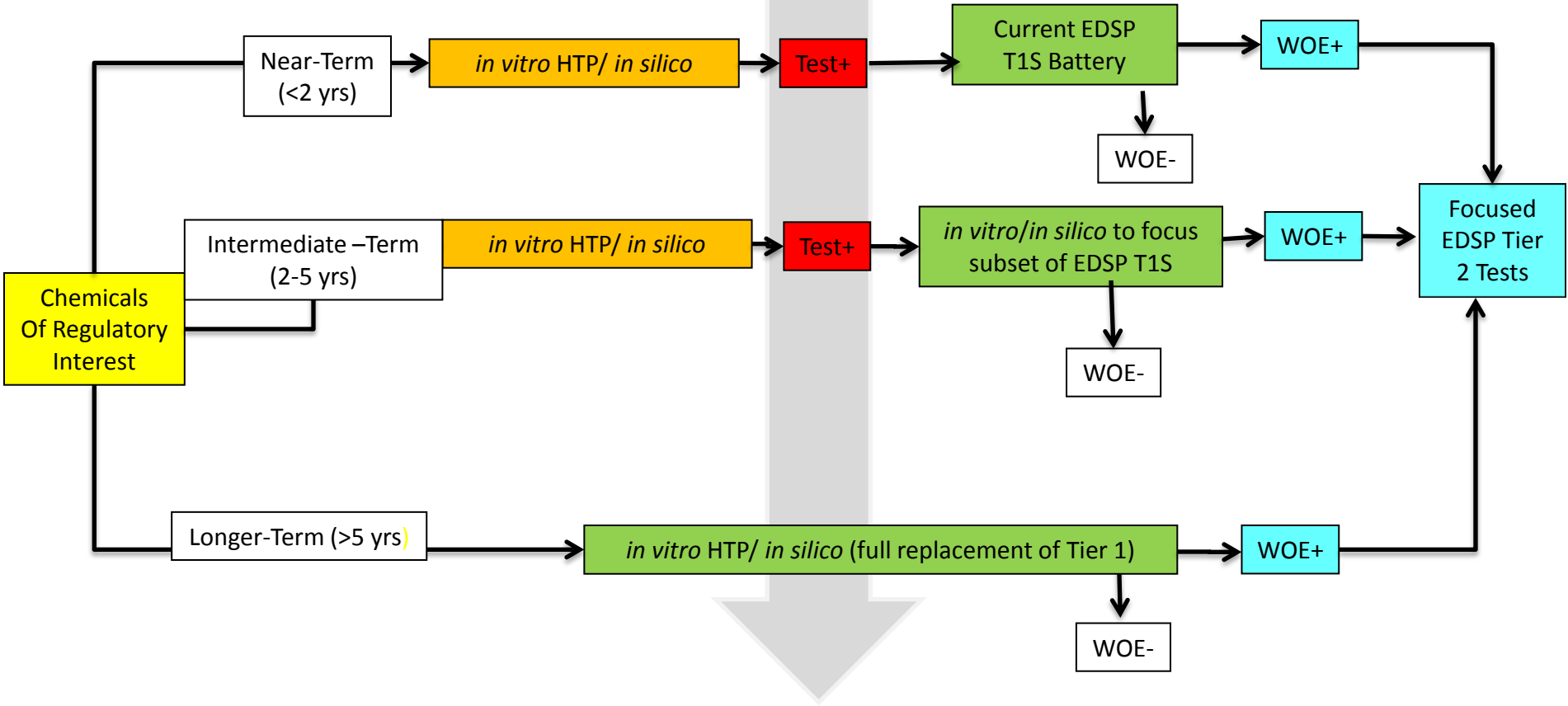
Adverse Outcome Pathway

Source to Outcome Pathway


Chemical
Exposure
Uptake-Delivery to Target Tissues
Perturbation
Cellular response pathway
Biologic inputs
"Normal" Biological Function
Adaptive Responses
Early cellular changes
Cell inury, Inability to regulate
Adverse Outcomes (e.g., mortality, Reproductive Impairment)
Molecular initiating event
Perturbed cellular response pathway
Adverse outcome relevant to risk assessment
Toxicity Pathway
Adverse Outcome Pathway

The universe of chemicals passes through each version of the HTP/*in silico* pipeline to evaluate chemicals in refined tests, for new pathways, to evaluate, improve, and validate methods.

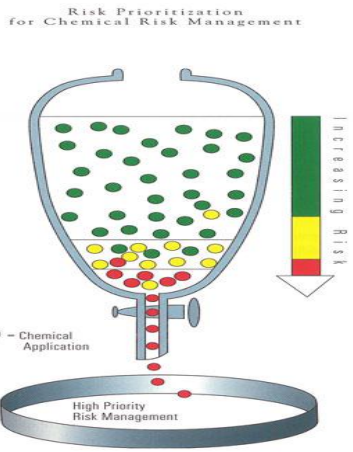
EPA Research provides basis for improving the suite of assays and models to advance chemical prioritization and screening



Chemical Prioritization
Includes , registration review timeline, physico-chemical properties, exposure estimates, *in vitro* assays and computer models (QSAR, expert systems, systems biology models).

Screening Decisions
Near-Term: Incorporates HTP/*in silico* prioritization methods
Intermediate-Term: Run subset of current T1S assays indicated by HTP and *in silico* predictions
Longer-Term: Full replacement of EDSP T1S Battery

EDSP Chemical Prioritization



- Consideration of multiple data streams:
  - HTP assays for estrogen, androgen and thyroid pathways
  - Inherent chemical properties (pKa, LogP, etc.)
  - Data from structural analogs (read across and chemical categories)
  - Modeling predictions (e.g., QSAR and ER expert systems)
  - Toxicity pathway anchored by biological mechanistically based understanding

*Figure taken from *1996, Chemical Maufacturers Association Product Risk Management Strategy Overview*

Key considerations for implementation of EDSP21

- Ensure clarity of programmatic goal
- Define application and regulatory decision contexts
- Build transparent strategy with sound scientific basis – Multiple tools
- Determine scientific validity
- Ensure external peer review and public outreach

Questions?

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