Evolution from Traditional Data Requirements to Knowledge-based Requirements: EDSP21 Work Plan

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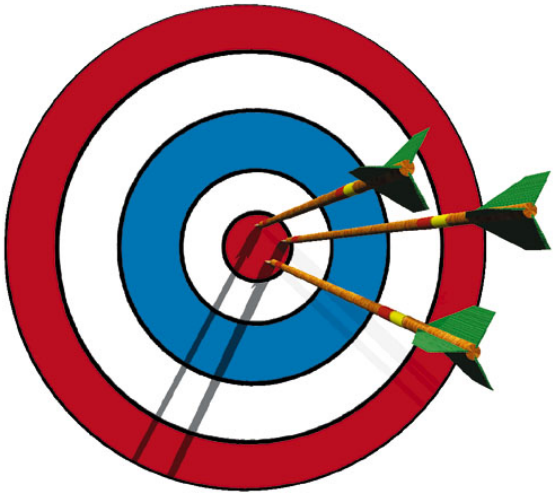
EDSP Targeted Mission



To protect public health and wildlife by screening and testing chemicals and taking appropriate actions for 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

Proposed EDSP Tier 2 Tests

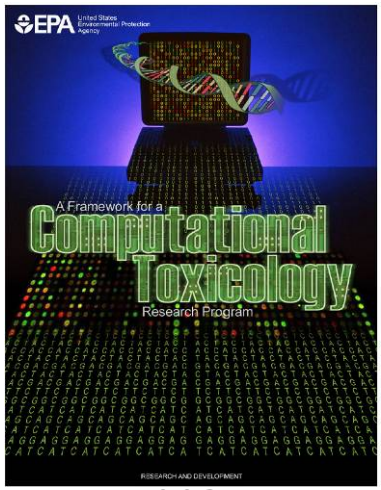
Mammalian Two-Generation Reproduction (Sprague Dawley rat) (may be replaced by Extended F1-Generation)
Avian Two-Generation Reproduction (Japanese quail)
Larval Amphibian Growth and Development (Xenopus laevis)
Fish Multi-Generation Reproduction (Medaka)
Invertebrate Multi-Generation Reproduction (Mysid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

The Future of Toxicology

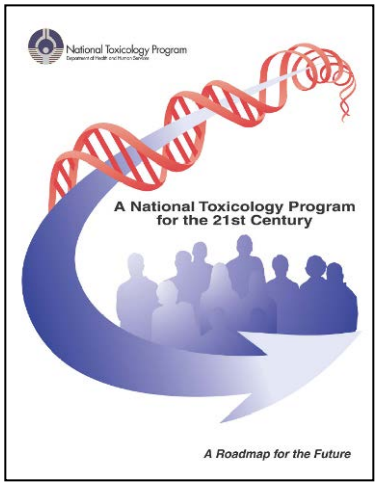
…the application of mathematical and computer models and molecular biological approaches to improve…prioritization of data requirements and risk assessments.

To support the evolution of toxicology from a predominantly observational science at the level of disease-specific models to a predominantly predictive science focused upon a broad inclusion of target specific, mechanism-based, biological observations.

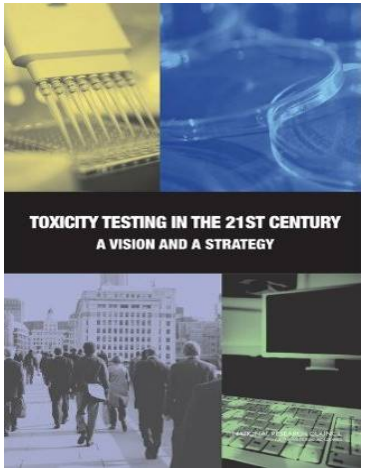
…a new toxicity-testing system that evaluates biologically significant perturbations in key toxicity pathways by using new methods in computational biology and a comprehensive array of in vitro tests based on human biology.



2003



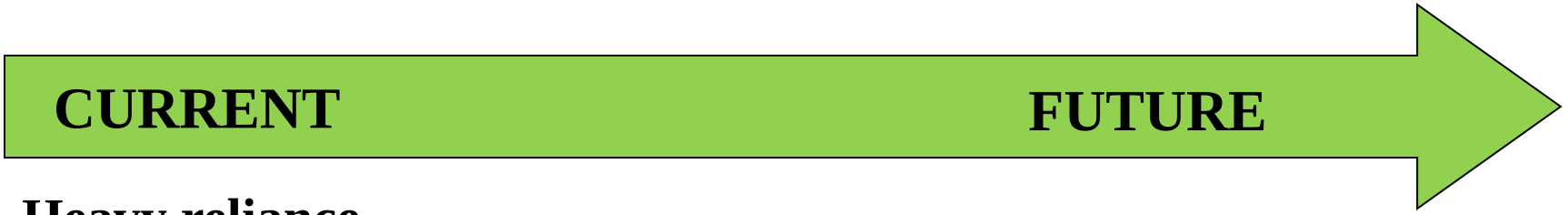
2004



2007

Tox21 Vision

Transition 21st century technologies, to enhance the efficiency and effectiveness of chemical risk management.



Heavy reliance on animal studies

Generate information for all possible outcomes

Based on traditional toxicity tests

Less reliance on animal studies

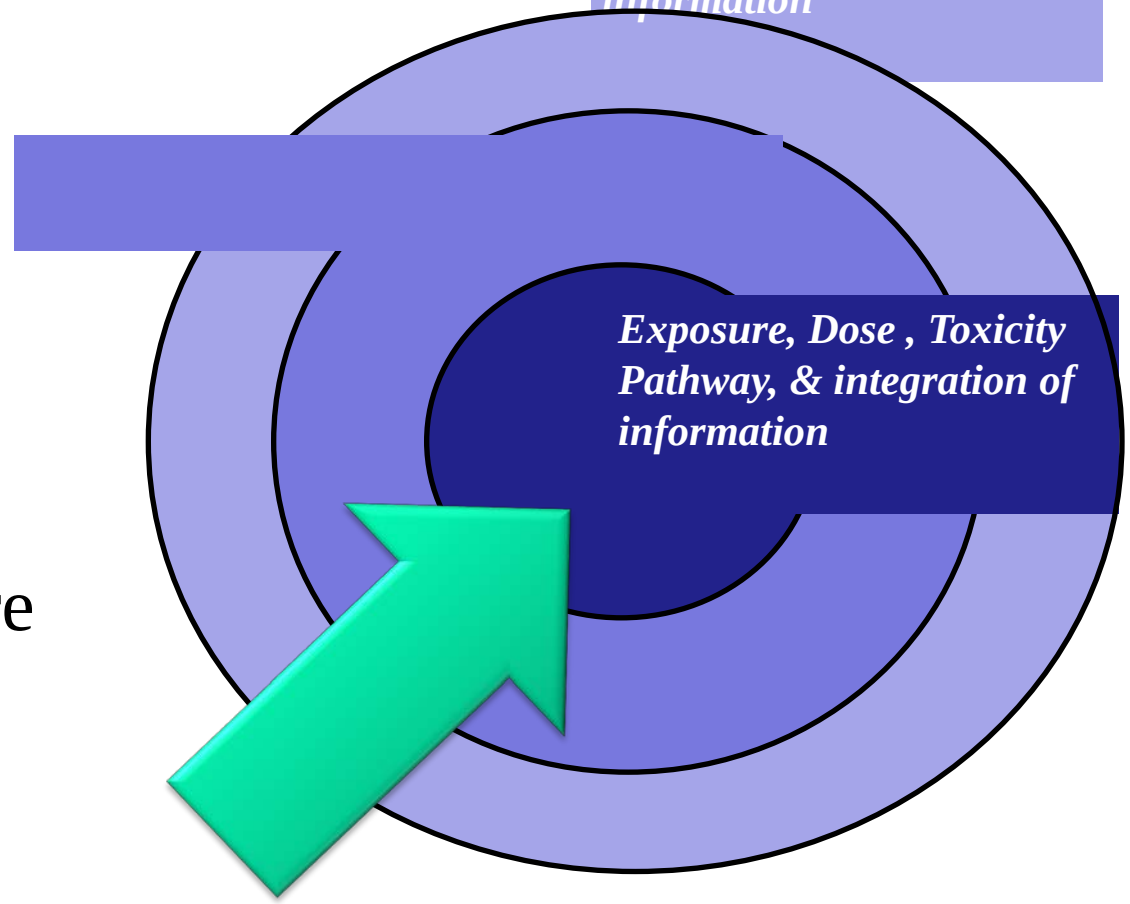
Tailor data generation

Based on understanding of toxicity pathways

Risk Management Decision-Based Approach

Less reliance on animal testing; more knowledge-based instead.

More detailed *in vitro* assays, enhanced exposure assessment, greater specificity of *in silico* models.



Greater certainty necessitates increased understanding, quantitative data, and greater integration at each level.

Adverse Outcome Pathway Concept

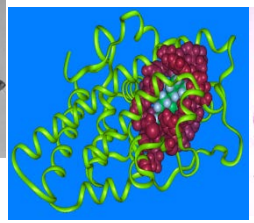
- Key to achieving goal.
- Framework that links the direct molecular initiating event to an adverse outcome at a level of biological organization relevant to risk assessment.
- Basis for
  - Integrating lower tier tests and non-animal models
  - Applying read across methods
  - Development of Expert Systems
- Consistent with Mode of Action analysis

Application to Levels of Organization Based on Source to Outcome

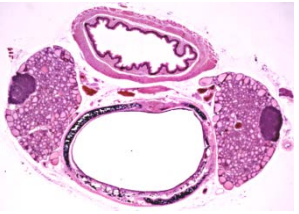
Source

Environmental Contaminant

Exposure



Molecular Initiating Event



Cellular Effects

Individual

Population

Community

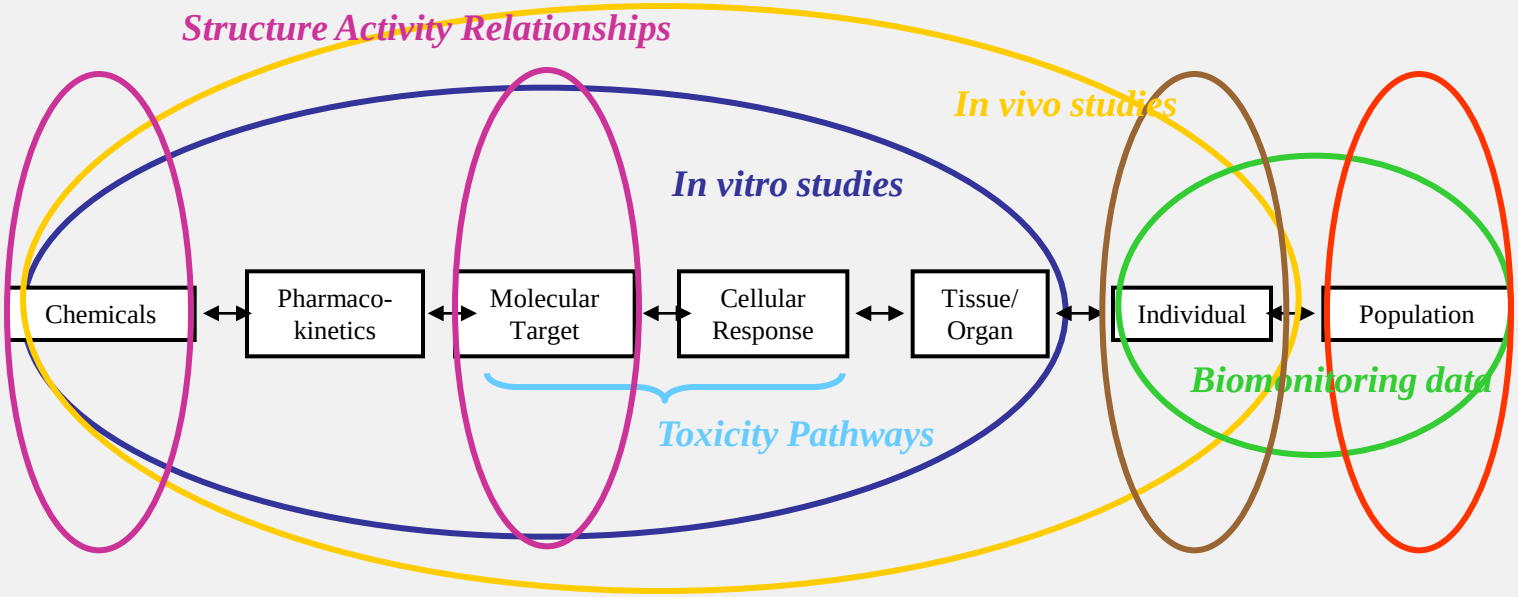
Toxicity Pathway

Mode of Action

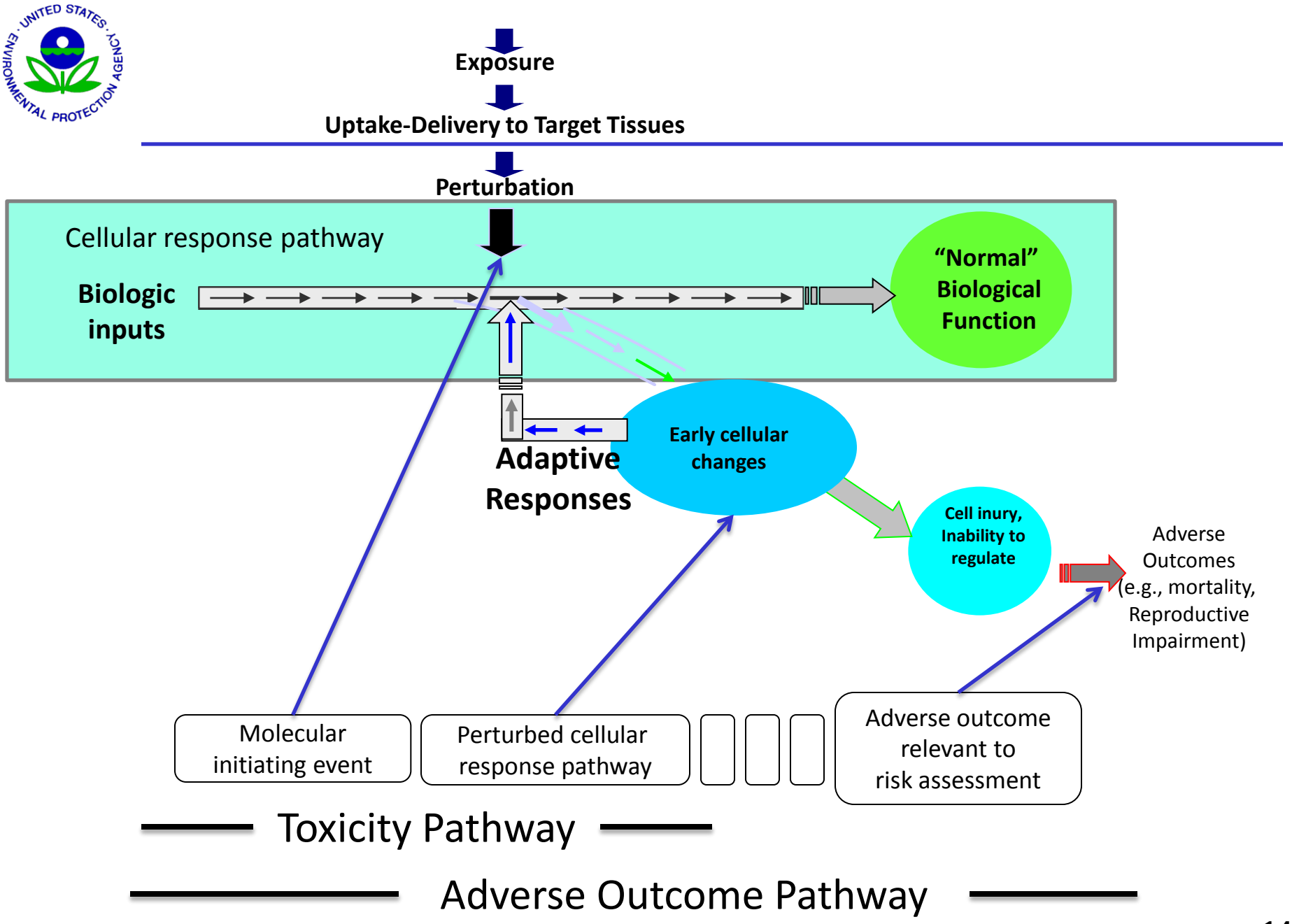
Adverse Outcome Pathway

Source to Outcome Pathway

Adverse Outcome Pathway and the Data Streams that Inform the Pathway



Adverse Outcome Pathways


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

EDSP21 Work Plan Summary (USEPA, September 2011)

www.epa.gov/endo

EDSP21 Objective

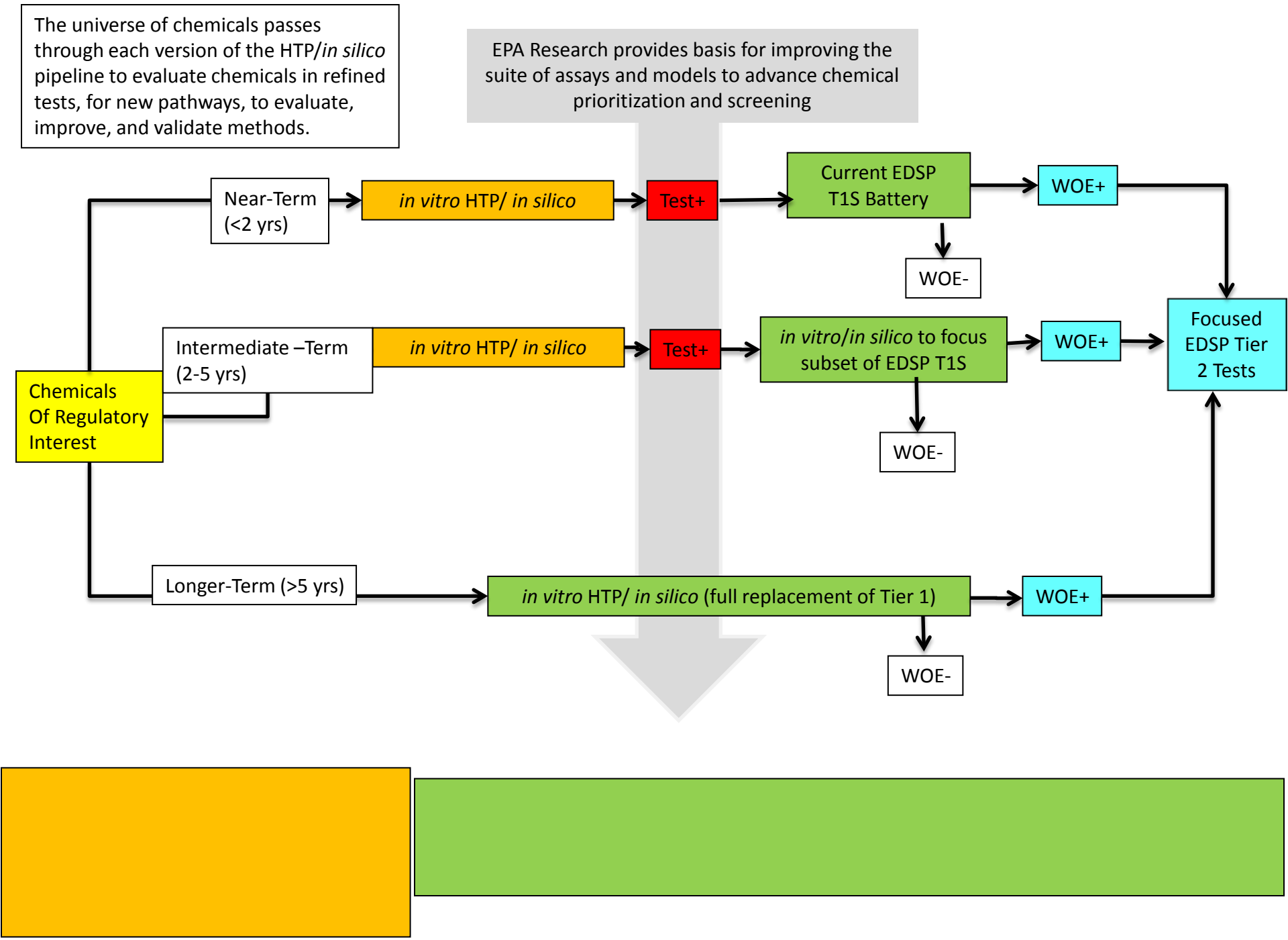
- Maximize use of existing data.
- Targeted *in vivo* toxicity screening.
- Use a variety of tools in a tiered testing and assessment framework.
- Systematically and *incrementally* incorporate new tools, methodologies.
- Advance understanding of key events in toxicity pathways.

Goals for Future EDSP Program

The EDSP21 Work Plan describes:
Multi-level and Integrated approach to determine whether a chemical has the potential to interact with E, A, or T.

Three main objectives:

(1) Prioritization - The near-term goal (<2 years)
(2) Screening - The intermediate-term goal (2-5 years)
(3) Data Replacement – The long-term goal (>5 years)


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
Chemicals Of Regulatory Interest
Near-Term (<2 yrs)
in vitro HTP/ *in silico*
Test+
Current EDSP T1S Battery
WOE+
WOE-
Intermediate –Term (2-5 yrs)
in vitro HTP/ *in silico*
Test+
in vitro/*in silico* to focus subset of EDSP T1S
WOE+
WOE-
Focused EDSP Tier 2 Tests
Longer-Term (>5 yrs)
in vitro HTP/ *in silico* (full replacement of Tier 1)
WOE+
WOE-

EDSP21 Work Plan

Pre-Prioritization

Develop science-based policy and tools for prioritization and screening

- Establish EDSP21 work group across EPA
- Develop and establish reference chemical library and EDSP21 database
- Develop a prioritization process with criteria to determine order for screening universe of non pesticide active ingredient chemicals
- Develop a validation process to evaluate *in silico* and *in vitro* HTP methods for screening
- Develop and evaluate exposure model

Short-term goal: use computational or *in silico* models and molecular-based *in vitro* high-throughput (HTP) screening assays to prioritize chemicals for EDSP Tier 1 screening.

Prioritization

Determine the order of chemicals for screening

- Identify the universe of chemicals
- Identify *in silico* models and *in vitro* HTP assays for EAT
- Prioritize based on re-registration, existing exposure and effects information, and results from *in silico* and *in vitro* HTP methods
- Establish list of chemicals for screening
- Send orders for Tier 1 screening to determine potential to interact with E, A, or T

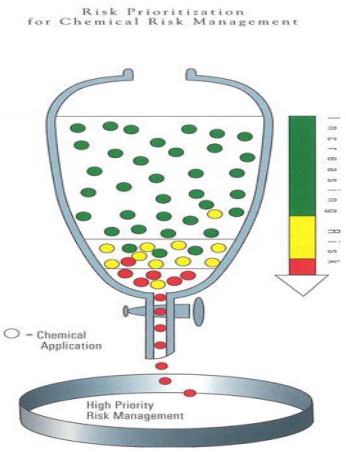
Screening

Optimize Tier 1 screening to determine the need for Tier 2 testing

- Compare EAT information from prioritization to results of Tier 1 screening for E, A or T
- Utilize Tier 1 screening results as a step in validation process for using HTP assays to screen for the potential to interact with E, A or T
- Integrate valid HTP assays into Tier 1 screening
- Allow for public comment and peer review before regulatory acceptance

Intermediate-term goal: incorporate computational or *in silico* models and molecular-based *in vitro* high-throughput (HTP) screening assays into EDSP Tier 1 screening.

Chemical Prioritization



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

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

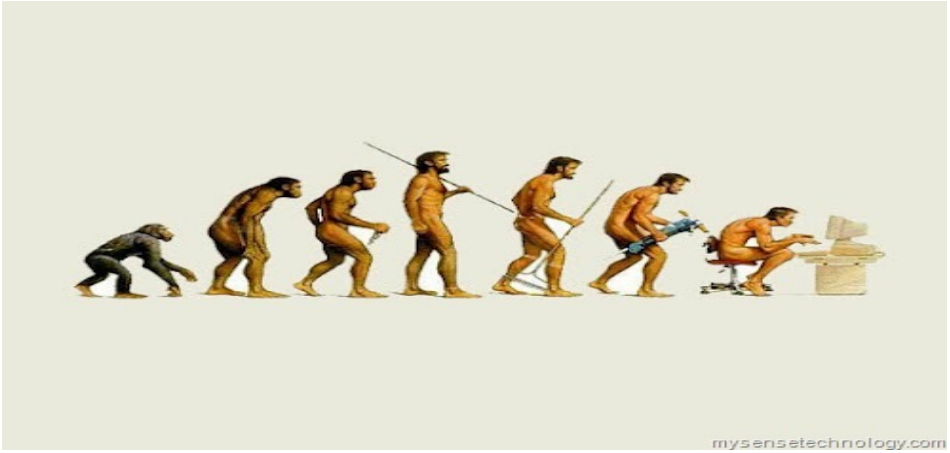
OECD (Q)SAR Validation Principles

- Defined Endpoint
- Unambiguous Algorithm
- Defined Domain of Applicability
- Appropriate Measures of Goodness-of-fit, Robustness and Predictivity
- Defined Biological Mechanism of Action, if possible

Key considerations for implementation of EDSP21

- Ensure clarity of programmatic goal
- Define application and regulatory decision contexts
- Build transparent strategy with sound scientific basis
- Determine scientific validity
- Ensure public outreach

Evolution of Computational Tools



The transition from traditional empirical data to computational tools must evolve slowly in incremental steps, with strong confidence and adequate assurance that no single apical health endpoint will be left behind.