

CLA and RISE 2018 Regulatory Conference

State of Toxicology Assessment in Human Health Risk Assessments: EPA's Endocrine Disruptor Screening Program (EDSP) “Pivot” Implements 21st Century Toxicology

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Statutory Mandates

- Food Quality Protection Act 1996 amended
 - Federal Food, Drug, and Cosmetic Act
 - Safe Drinking Water Act

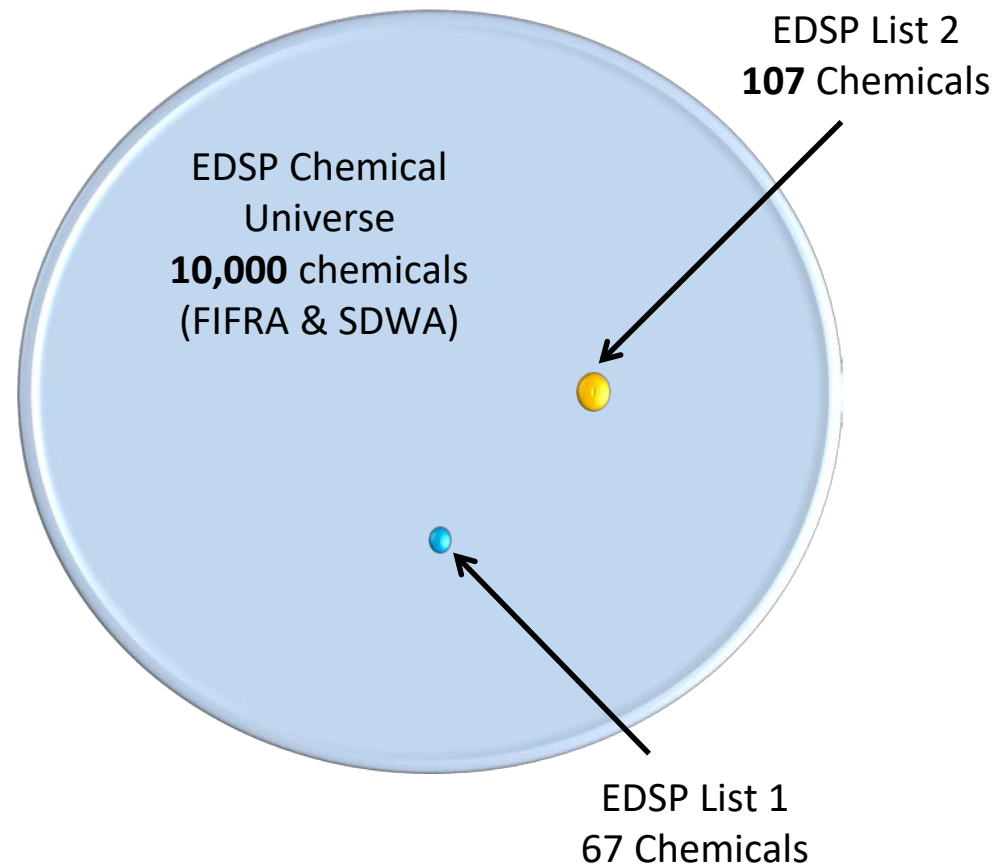
Requires EPA to:

“...develop a screening program, using appropriate validated test systems and other scientifically relevant information to determine if certain substances may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen...”

Endocrine Disruptor Screening Program (EDSP)

- Established following recommendations of:
 - The Endocrine Disruptor Screening and Testing Advisory Committee
 - Public comment
 - EPA's Science Advisory Board & FIFRA Scientific Advisory Panel
- Evaluates:
 - Estrogen, androgen and thyroid hormones
 - Human, fish and wildlife
 - Pesticides, commercial chemicals and environmental contaminants
- Two-Tiered Approach
 - Tier 1 battery – identify potentially endocrine bioactive substances
 - Tier 2 testing – evaluate dose-response relationship and if substance is endocrine bioactive

Evolution of EDSP - the “Pivot”



- Based on current pace it could take decades to screen all 10,000 chemicals in EDSP Universe
- High-throughput assays can reduce costs, animal use, and testing time required, and allow efficient prioritization protocols

EDSP Goals for Using Computational Toxicological Approaches

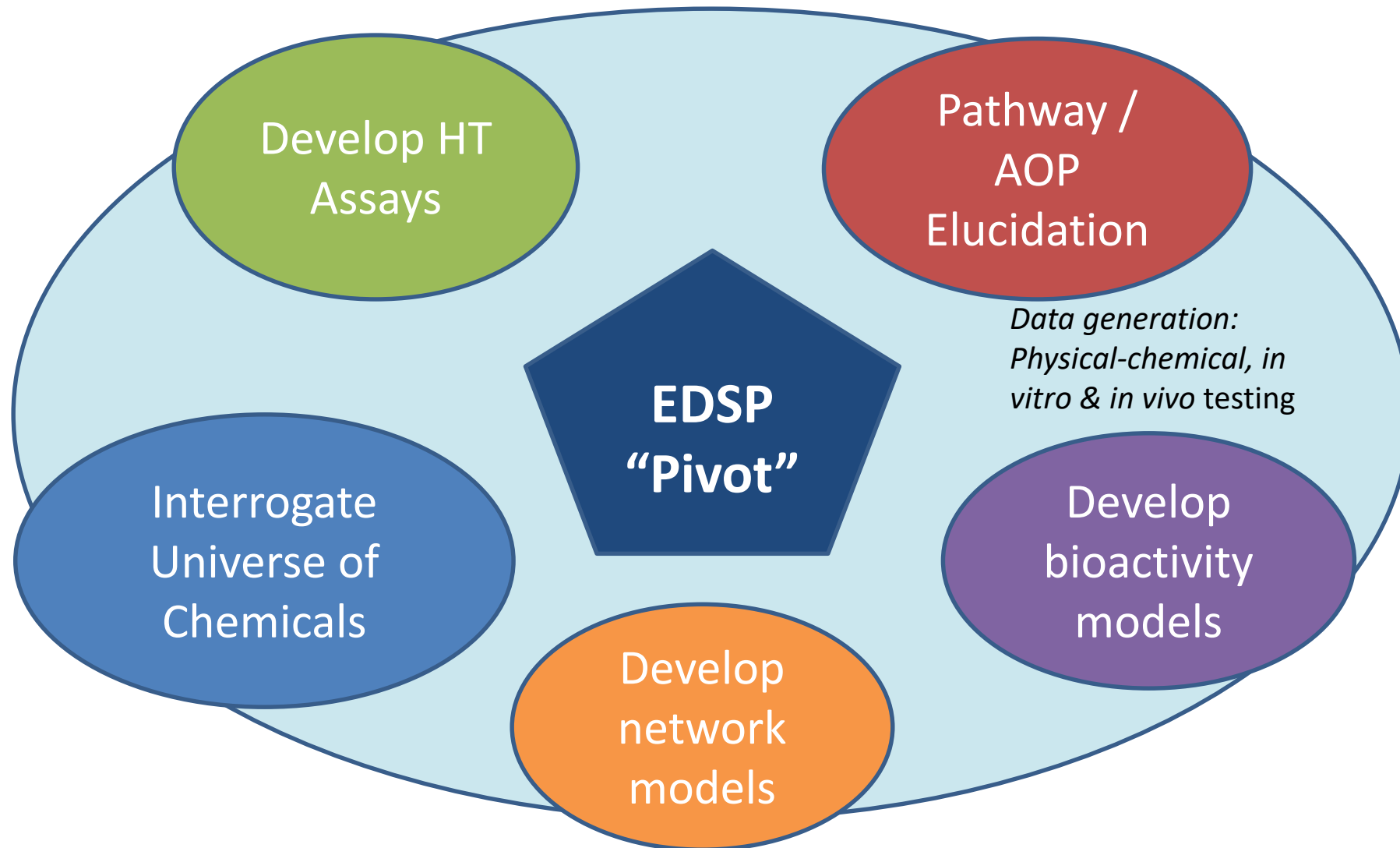
- Use computational tools and models in the EDSP framework to:
 - Rapidly **screen** chemicals in the EDSP Universe for endocrine bioactivity
 - **Contribute** to the weight of evidence screening level determination of a chemical's potential bioactivity
 - Provide **alternative** data for specific endpoints in the EDSP Tier I battery



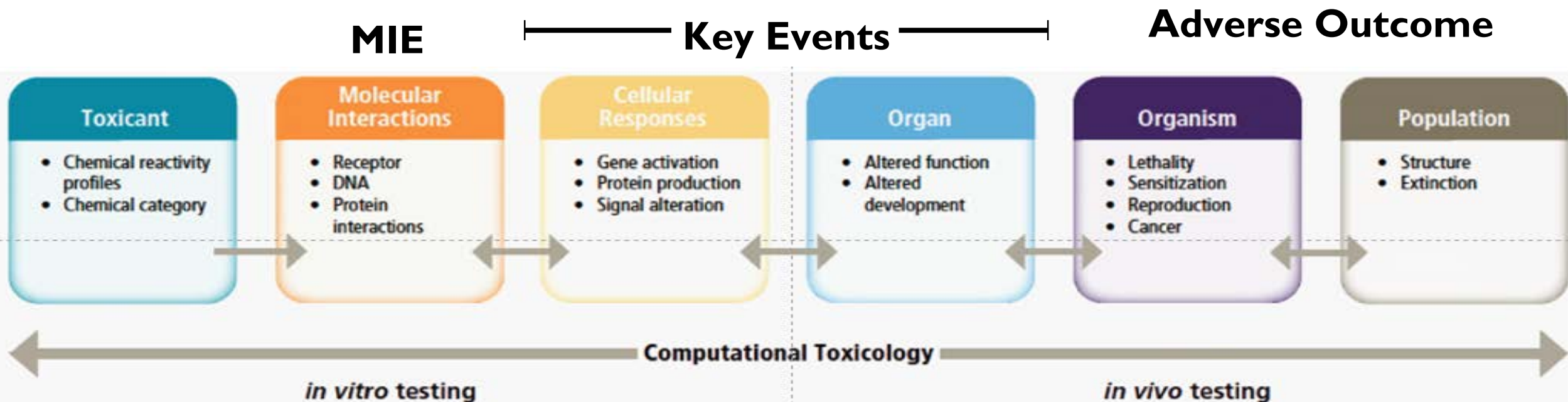
Developing Alternative EDSP Assays

EDSP Tier 1 Battery of Assays (current)	High-Throughput Assays and Computational Model Tier 1 Battery Alternatives
<i>Estrogen Receptor (ER) Binding</i>	<i>ER Model (alternative)</i>
<i>Estrogen Receptor Transactivation (ERTA)</i>	<i>ER Model (alternative)</i>
<i>Uterotrophic</i>	<i>ER Model (alternative)</i>
<i>Androgen Receptor (AR) Binding</i>	<i>AR Model (Proposed)</i>
<i>Hershberger</i>	<i>AR/STR Model (Future)</i>
<i>Aromatase</i>	<i>STR Model (Future)</i>
<i>Steroidogenesis</i>	<i>STR (Proposed)</i>
<i>Female Rat Pubertal</i>	<i>ER, STR, THY Models (Future)</i>
<i>Male Rat Pubertal</i>	<i>AR, STR, THY Models (Future)</i>
<i>Fish Short Term Reproduction</i>	<i>ER, AR, STR Models (Future)</i>
<i>Amphibian Metamorphosis</i>	<i>THY Model (Future)</i>
EDSP Tier 2 Tests	High-Throughput Assays and Computational Model Tier 2 Tests Alternatives
<i>Rat 2-gen/EOGRT</i>	<i>ER, AR, STR, THY (Future)</i>
<i>Medaka Extended 1-Gen Reproduction</i>	<i>ER, AR, STR (Future)</i>
<i>Larval Amphibian Growth & Development</i>	<i>THY (Future)</i>
<i>Avian Multi-Generation Reproduction</i>	<i>ER, AR, STR, THY (Future)</i>

Implementation of EDSP's Pivot



Adverse Outcome Pathway (AOP) Based Approach



An **adverse outcome pathway (AOP)** is a concept that provides a framework for organizing knowledge about the progression of toxicity events across scales of biological organization that lead to **adverse outcomes** relevant for risk assessment.

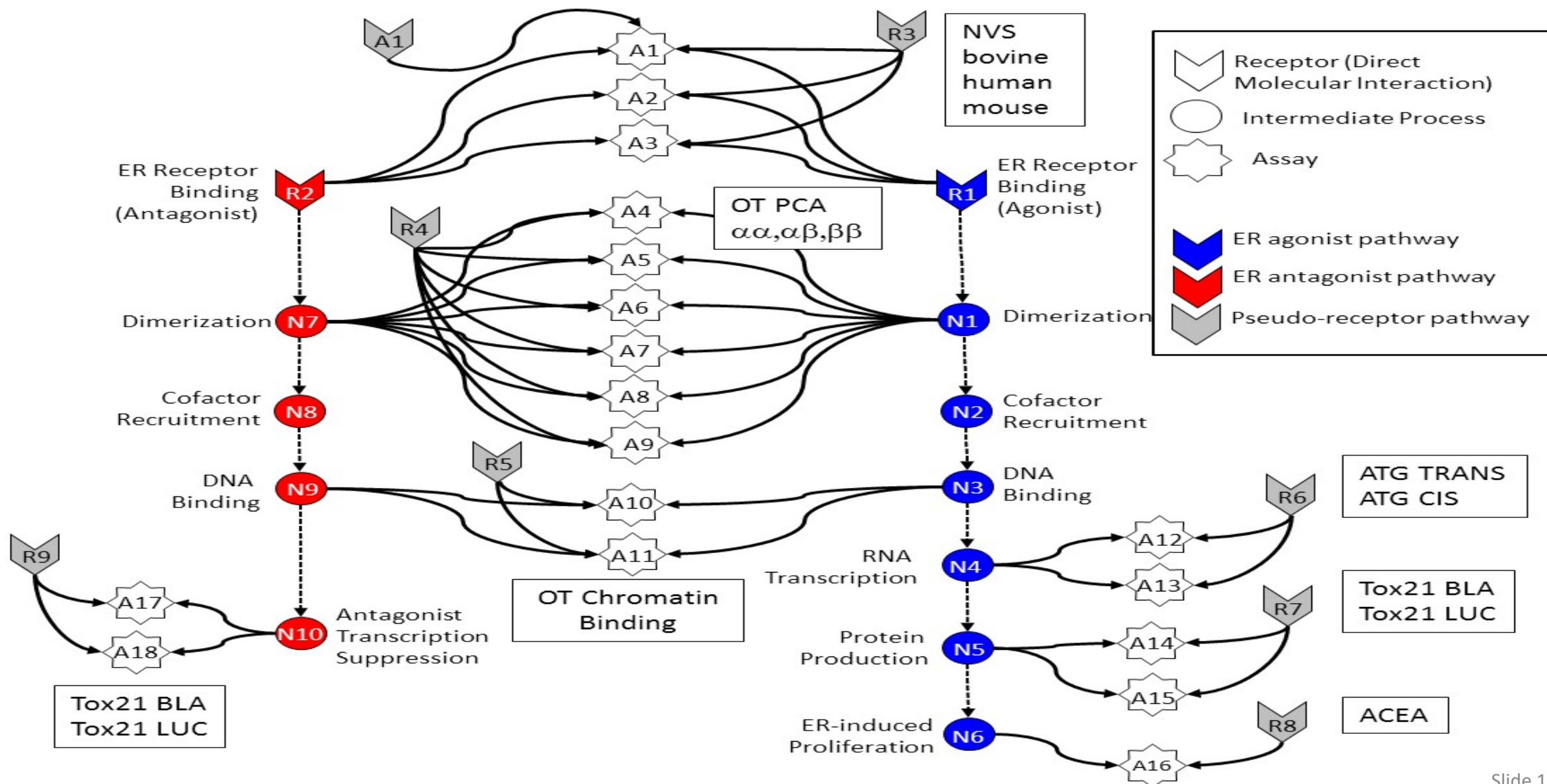
Performance-Based Approach

- Focuses on the end result
- Allows diverse methodology within the same use-context
- Uses performance-based acceptance criteria for relevance, reliability, and transparency to establish confidence in results
- Allows the quick adoption of scientific innovations

Estrogen Receptor Pathway Model

- Prioritization of chemicals for EDSP testing
- Alternative to the LT ER binding assay, LT ER transactivation assay, and uterotrophic assay

ER Pathway Model Schematic: 18 assays



ER Pathway Model Next Steps

- Minimal assay set for model predictions can be obtained from 4 orthogonal assays
- Development of performance-based test guidance
- Advantages of the ER Pathway Model
 - Covers more of the biological pathway than the *in vitro* assays, useful for mechanistic information
 - Useful for rapid prioritization
 - Reduces animal use
 - Potential saving of money, time, and resources

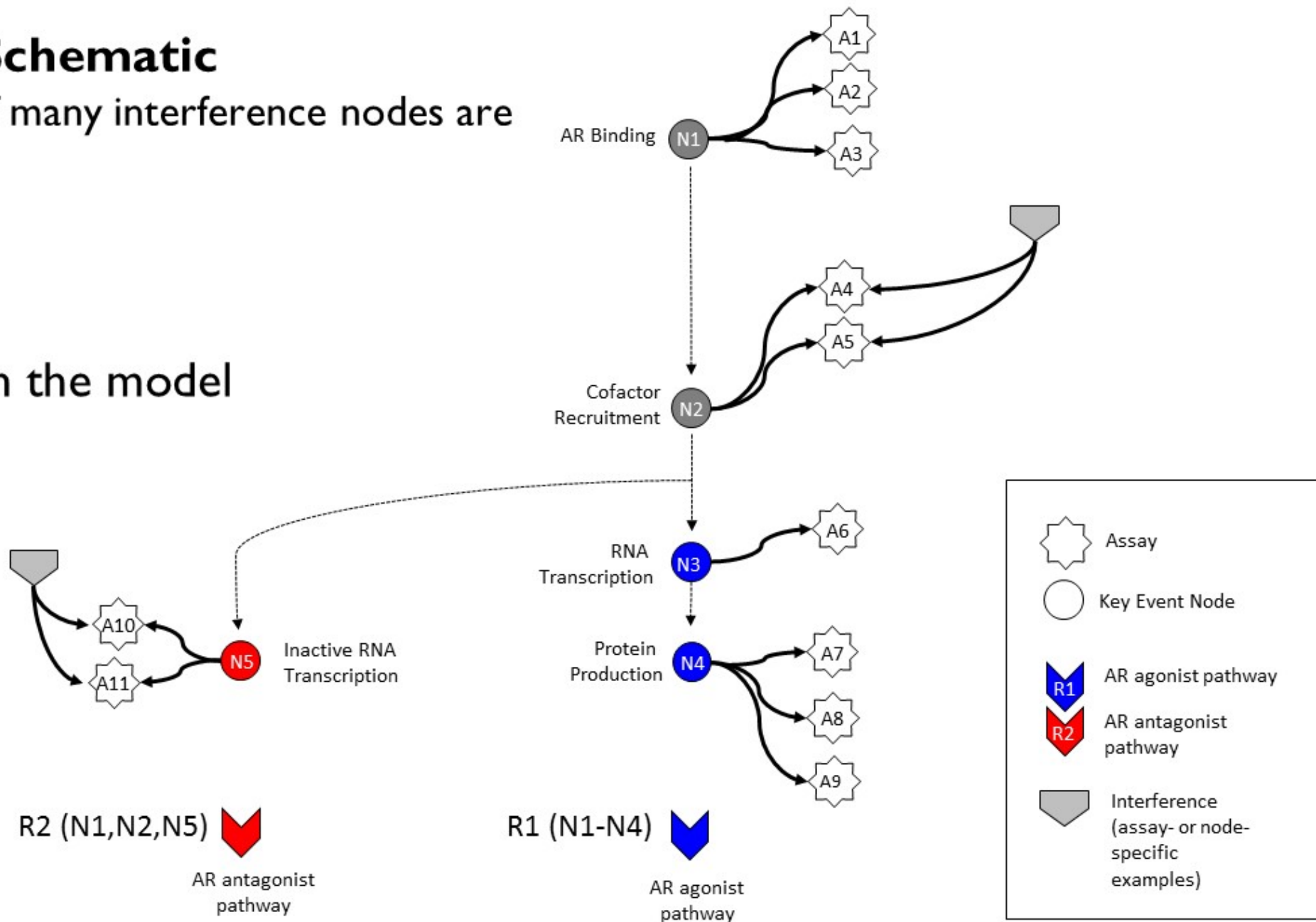
Androgen Receptor Pathway Model

- Prioritization of chemicals for EDSP testing
- Alternative to the LT AR binding assay

AR Pathway Schematic

Note: Only two of many interference nodes are shown

Assays in the model



AR Pathway Model Next Steps

- Revision and addition of phenotypic assay data to pathway model
- Evaluation of model predictions to determine minimal assay set
- Development of performance-based test guidance
- Advantages of the AR Pathway Model
 - Covers more of the biological pathway
 - Useful for rapid prioritization
 - Reduces animal use
 - Potential saving of money, time, and resources

Future EDSP “Pivot” Work

- Steroidogenesis Pathway
- Thyroid Pathway
- Incorporating exposure
- Incorporating metabolism
- Performance-base Test Guidelines (PBTG)
- Systematic Review of Chemicals for Development of Alternative Assays

EDSP Partners



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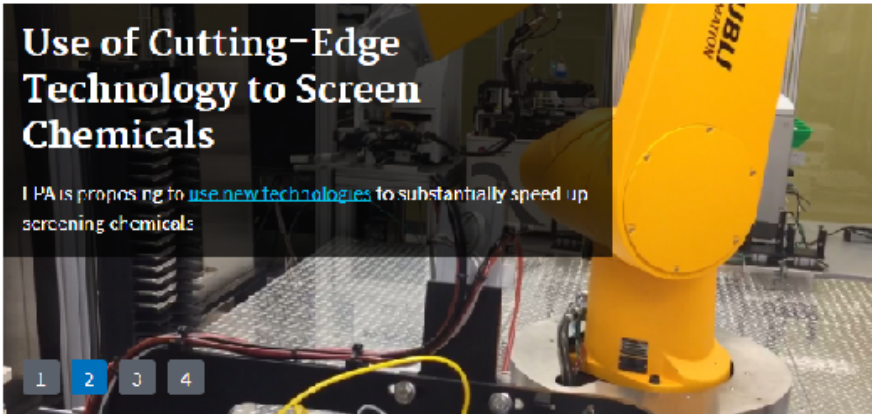


Endocrine Disruption

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Use of Cutting-Edge Technology to Screen Chemicals

EPA is proposing to [use new technologies](#) to substantially speed up screening chemicals.



Highlights:

- [Use of New Screening Technology](#)
- [Guidelines for Screening and Testing Chemicals](#)
- [EDSP Status of Orders](#)
- [EDSP Dashboard](#)

Stay Informed:

- [Join the EDSEPL server](#)

EPA implements screening, testing and research programs to gather information the Agency uses to evaluate possible endocrine effects associated with the use of a chemical. EPA takes appropriate steps to mitigate any related risks to ensure protection of public health and the environment.

U.S. Environmental Protection Agency

- Office of Chemical Safety and Pollution Prevention
 - Office of Science and Coordination Policy
 - Office of Pesticide Programs
 - Office of Pollution Prevention and Toxics
- Office of Research and Development
- Office of Water

U.S. Department of Health and Human Services: National Institutes of Health

- National Center for Advancing Translational Sciences (NCATS)
- NIEHS/NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)