U.S. Environmental Protection Agency Endocrine Disruptor Screening Program (EDSP)

Steven Knott, M.S.
Exposure Assessment Coordination and Policy Division
Office of Science Coordination and Policy
Office of Chemical Safety and Pollution Prevention
United States Environmental Protection Agency
knott.steven@epa.gov

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PESTICIDE PROGRAM DIALOGUE COMMITTEE MEETING
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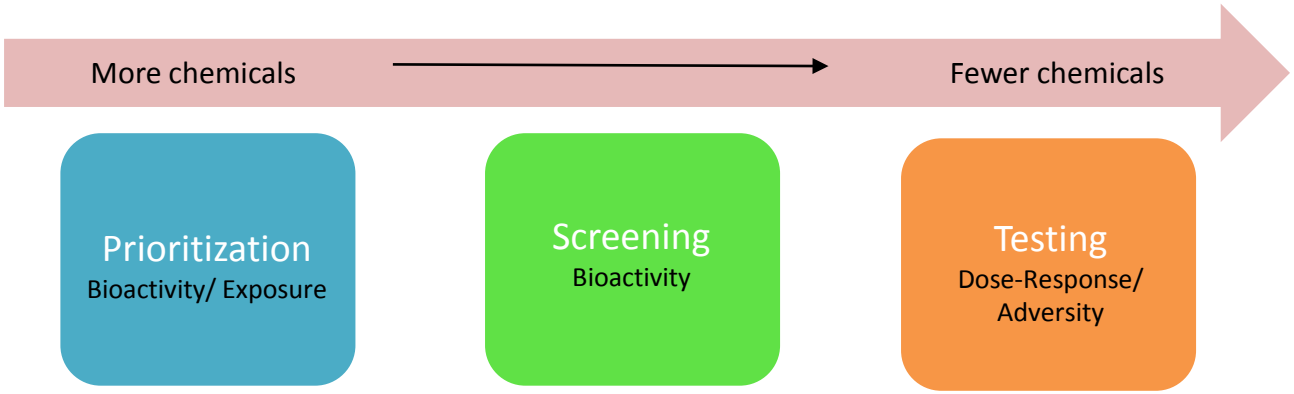
Endocrine Disruptor Screening Program (EDSP)

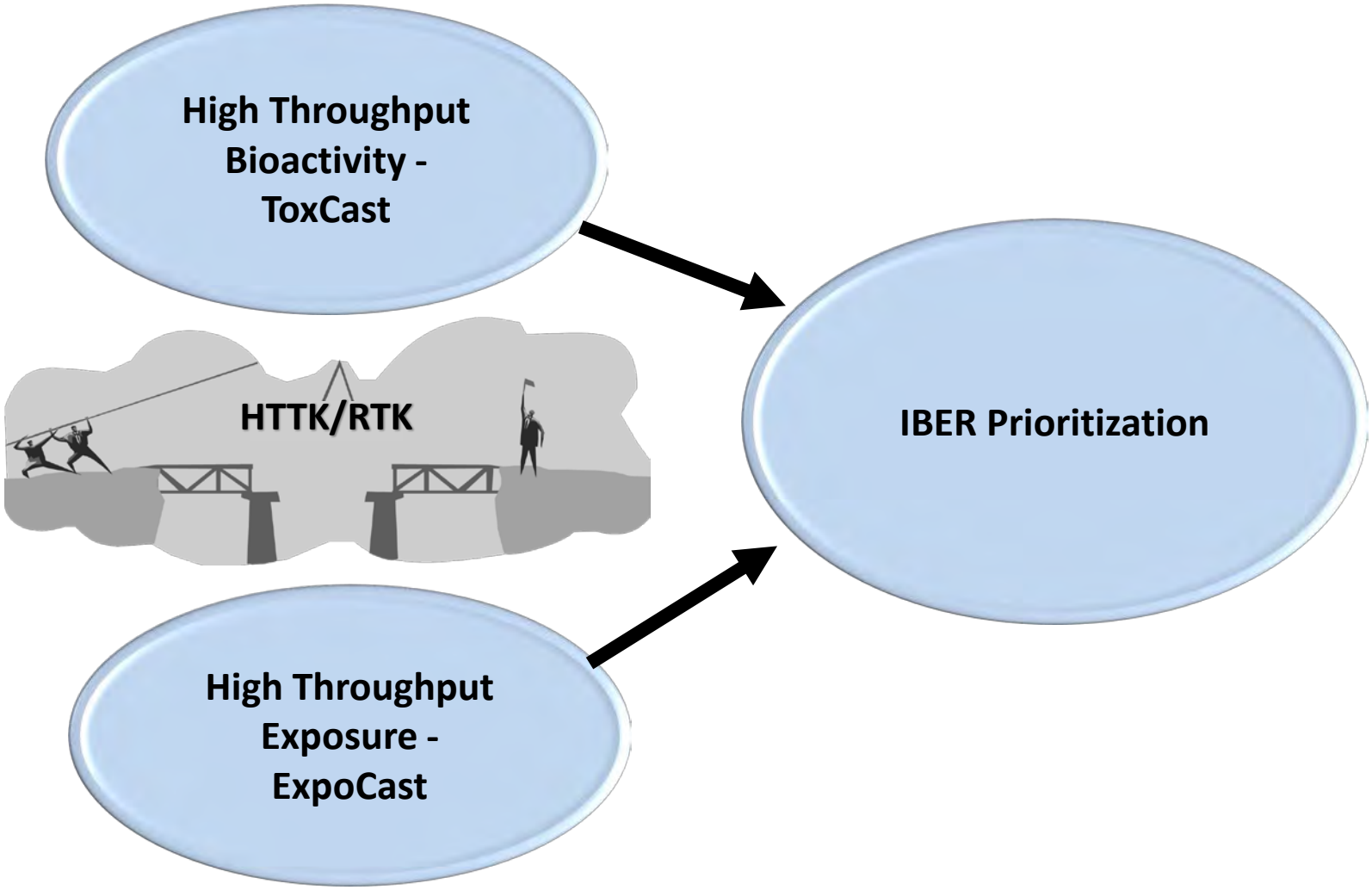
- Established in 1998
- Protection of human health and wildlife
- Includes estrogen, androgen and thyroid pathways
- Approach
  - Prioritization based on exposure and high throughput bioactivity

    "Data resulting from HTPS [HTS] will be combined with exposure-related information, and with any other effects-related information that is available, for each chemical for the purpose of setting priorities for T1S [screening]" (EDSTAC 1998)

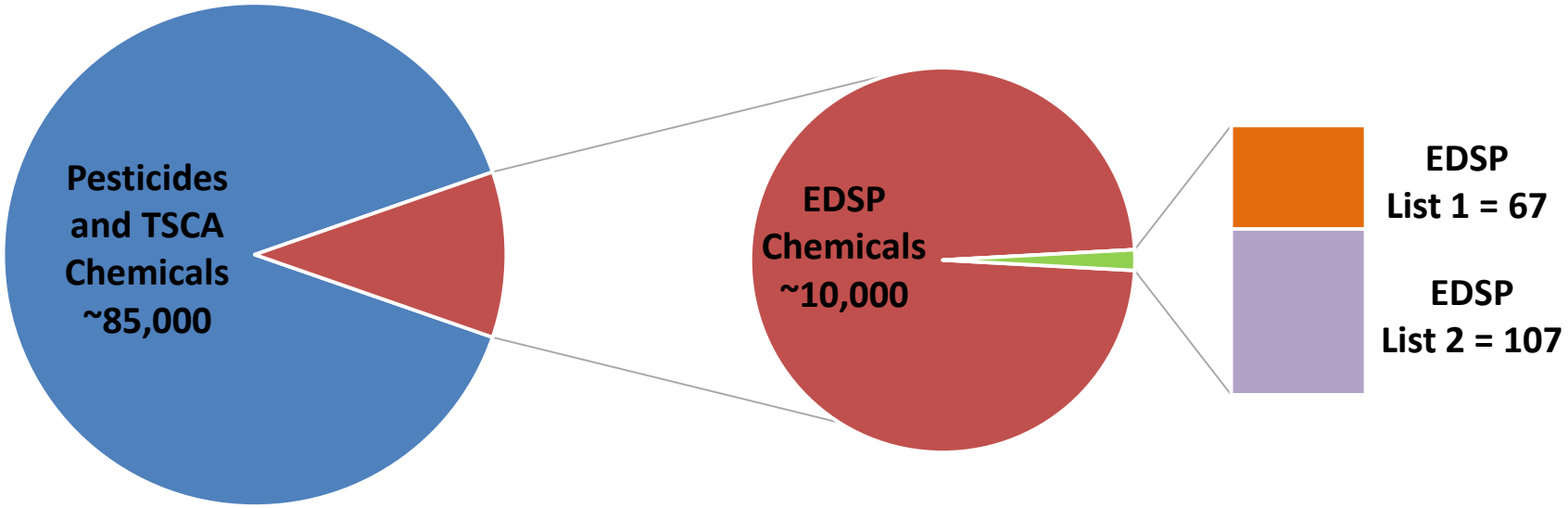
    (Now the Integrated Bioactivity Exposure Ranking or IBER)
  - Screening for bioactivity
  - Testing for dose-response and adverse effects



What is the Integrated Bioactivity-Exposure Ranking (IBER) Prioritization Approach?

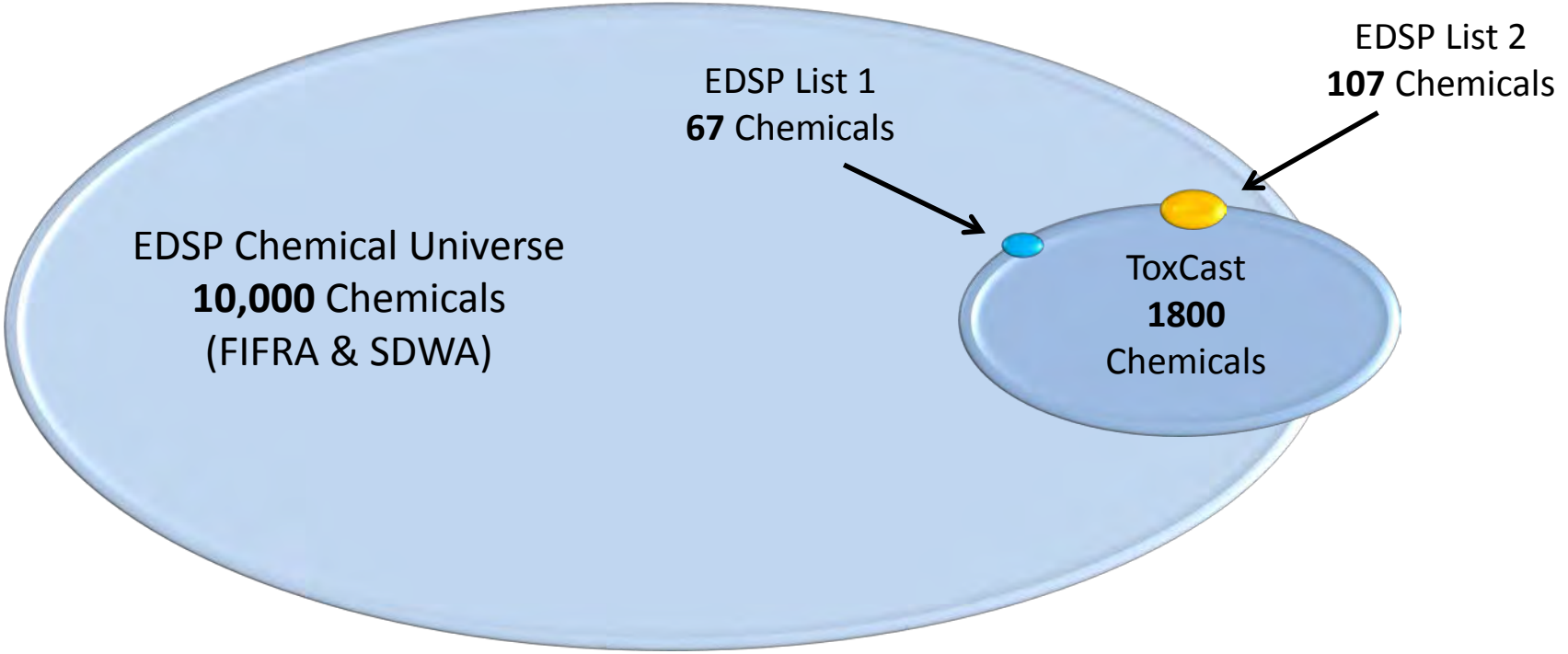


Why Integrated Bioactivity – Exposure Based Prioritization?



- **Limited existing and available data for many chemicals (next to nil for new substances)**
- **IBER can help establish priorities for targeted data collection and further assessment**

Why Integrated Bioactivity – Exposure Based Prioritization in the EDSP?



- **Lists 1 and 2**
  - Based primarily on exposure considerations
  - Not presumed to interfere with the endocrine systems of humans or other species

- **<u>Other chemicals could have higher priority for EDSP screening and testing if bioactivity considerations are joined with exposure considerations in an integrated approach</u>**

Evolution of the EDSP

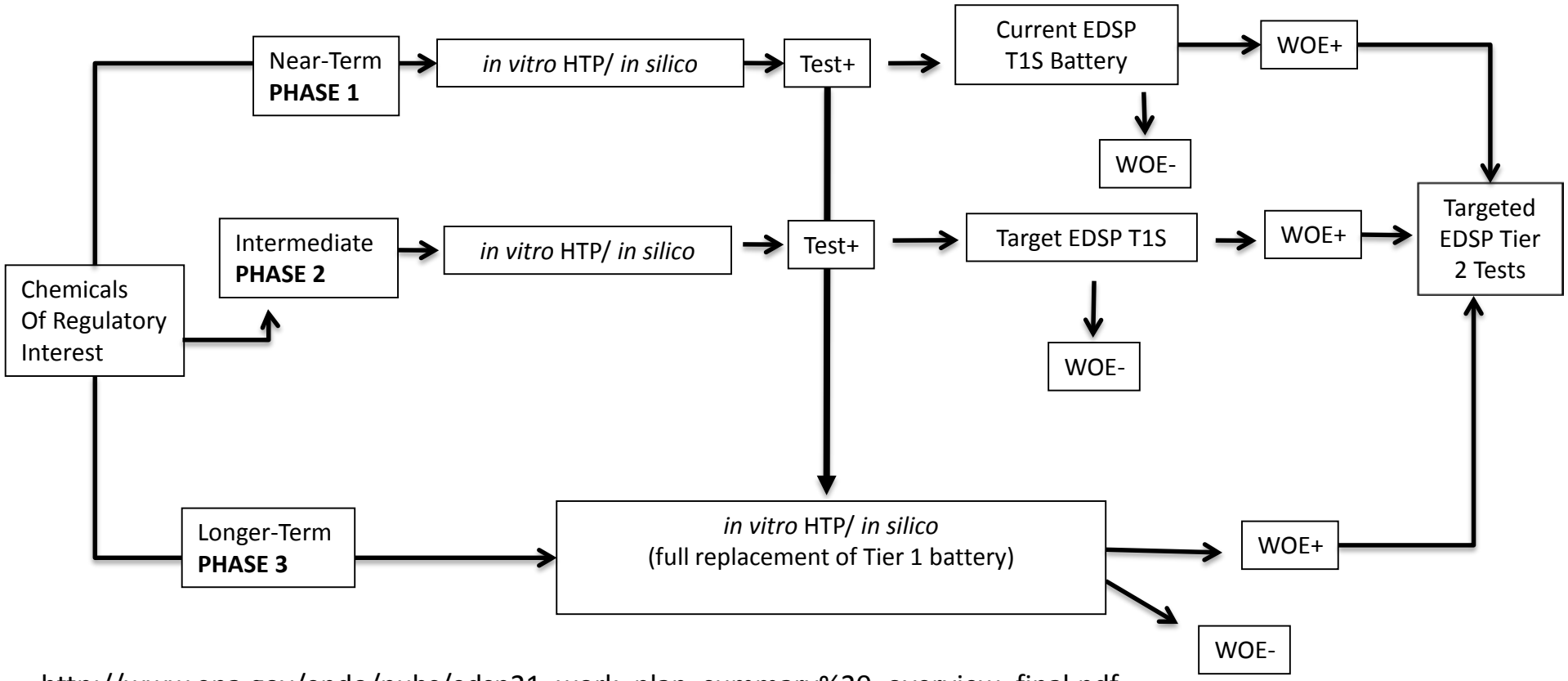
- Based on current pace it could take decades to screen all 10,000 chemicals for potential to interact with the endocrine system

- To address thousands of chemicals for potential to interact with the endocrine system, we must implement a more strategic approach to prioritize chemicals for targeted screening

- Recent advances in computational toxicology herald an important “evolutionary turning point” and an accelerated pace of screening and testing

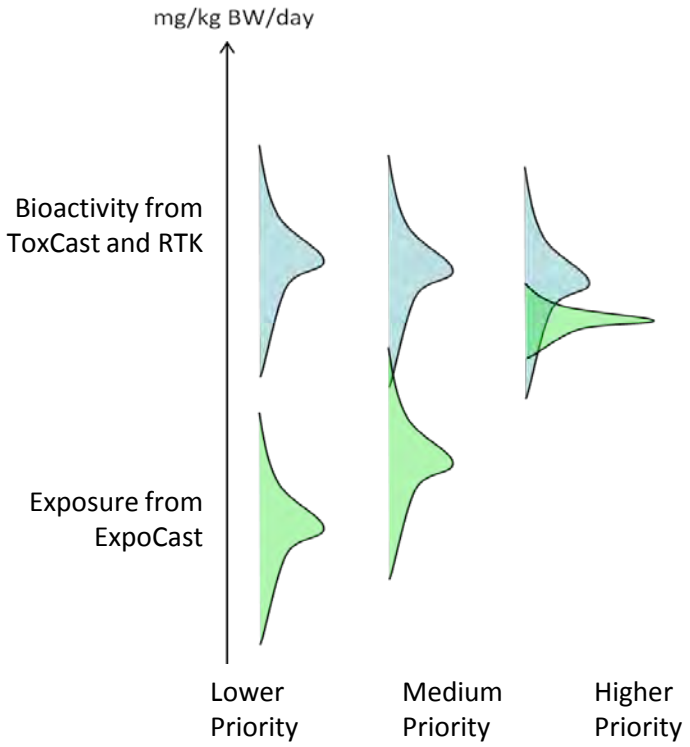
EDSP21 Workplan (2011)

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



http://www.epa.gov/endo/pubs/edsp21_work_plan_summary%20_overview_final.pdf

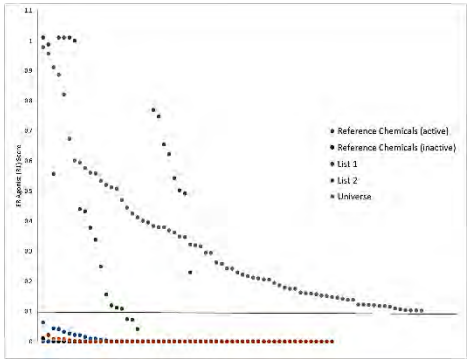
Integrating Bioactivity and Exposure



- *in vitro* chemical dose-response HTP bioactivity data are used to identify potential biological targets
- RTK methods are then employed to determine the human dose needed for each chemical to activate these targets *in vivo*
- putative bioactive doses are then directly compared to HTE predictions to estimate likelihood of exposures that cause bioactive doses

Chemicals where the putative human bioactive dose is comparable to HTE predictions become targets for further investigation

Integrated Bioactivity Exposure Ranking (IBER) Method



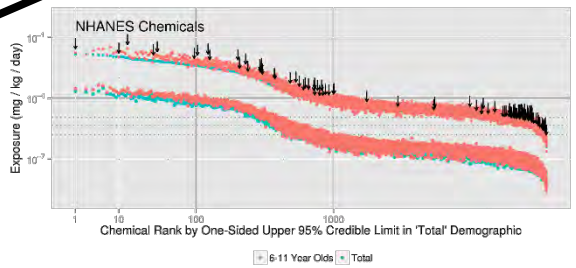
Bioactivity
ToxCast

1800
Chemicals

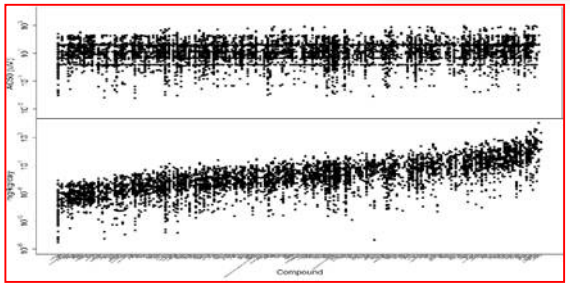
HTTK

7968
Chemicals

Exposure
ExpoCast



IBER



239
Chemicals

Prioritization

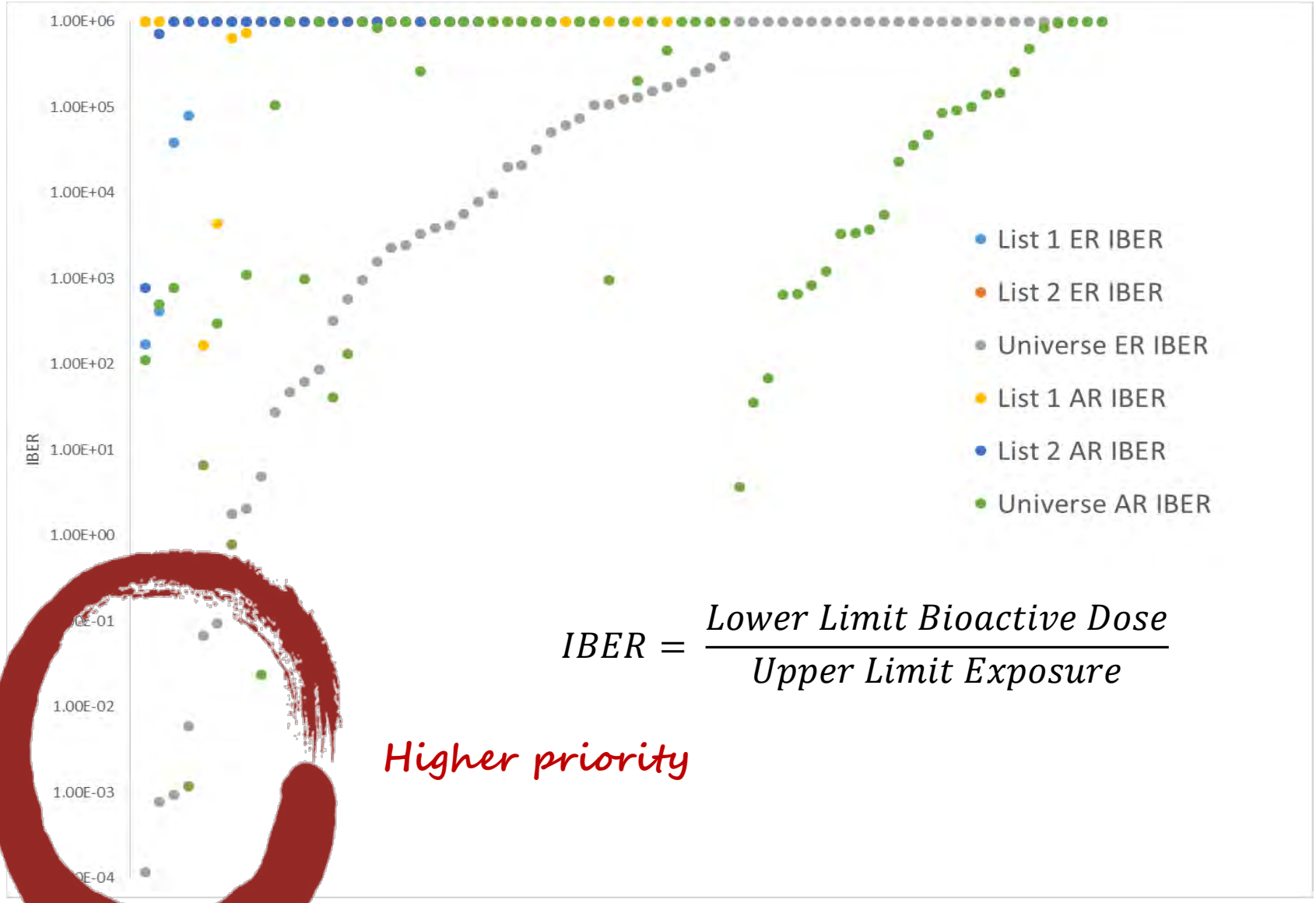
Screening

Testing

Some or All
EDSP Tier 1 Assays

Some or All
EDSP Tier 2 Assays

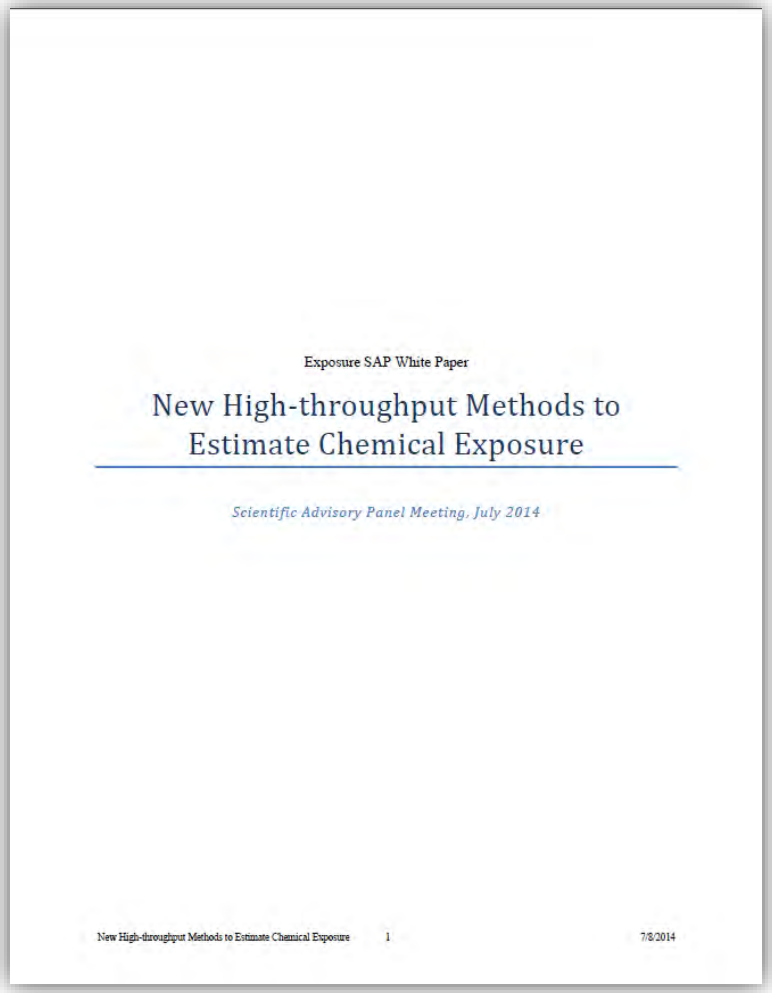
Integrated Bioactivity Exposure Ranking (IBER) Method



$$IBER = \frac{Lower\ Limit\ Bioactive\ Dose}{Upper\ Limit\ Exposure}$$

Higher priority

Building Scientific Confidence – Peer Review

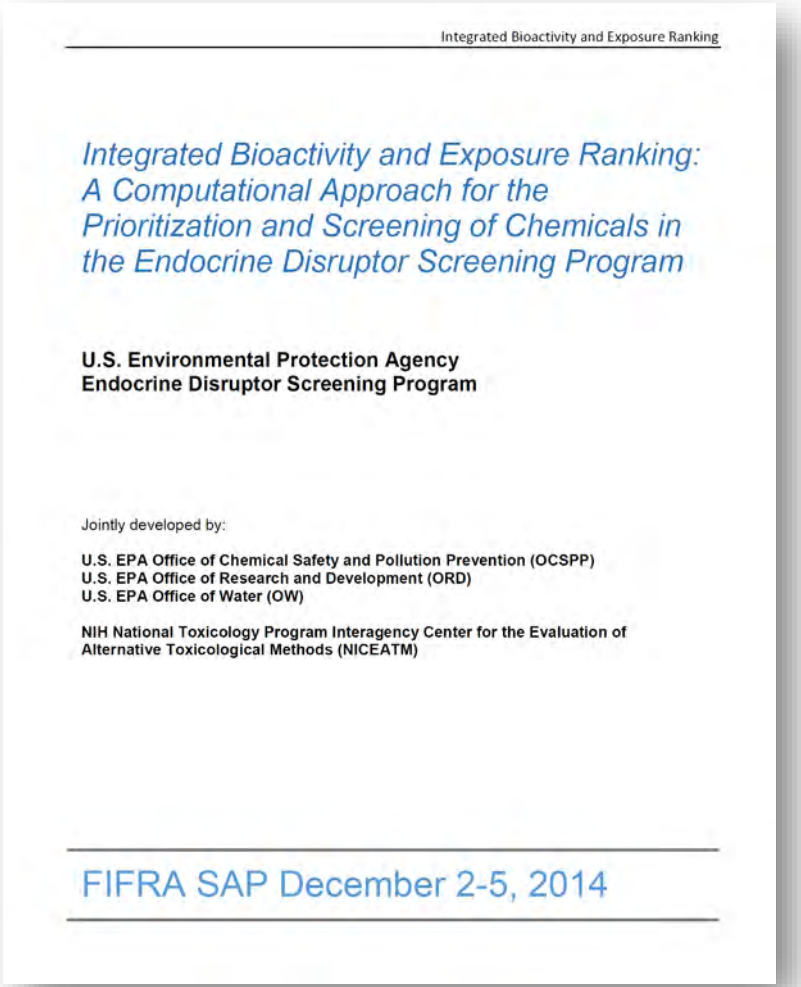


Exposure SAP White Paper

New High-throughput Methods to Estimate Chemical Exposure

Scientific Advisory Panel Meeting, July 2014

New High-throughput Methods to Estimate Chemical Exposure 1 7/8/2014



Integrated Bioactivity and Exposure Ranking

Integrated Bioactivity and Exposure Ranking: A Computational Approach for the Prioritization and Screening of Chemicals in the Endocrine Disruptor Screening Program

U.S. Environmental Protection Agency
Endocrine Disruptor Screening Program

Jointly developed by:

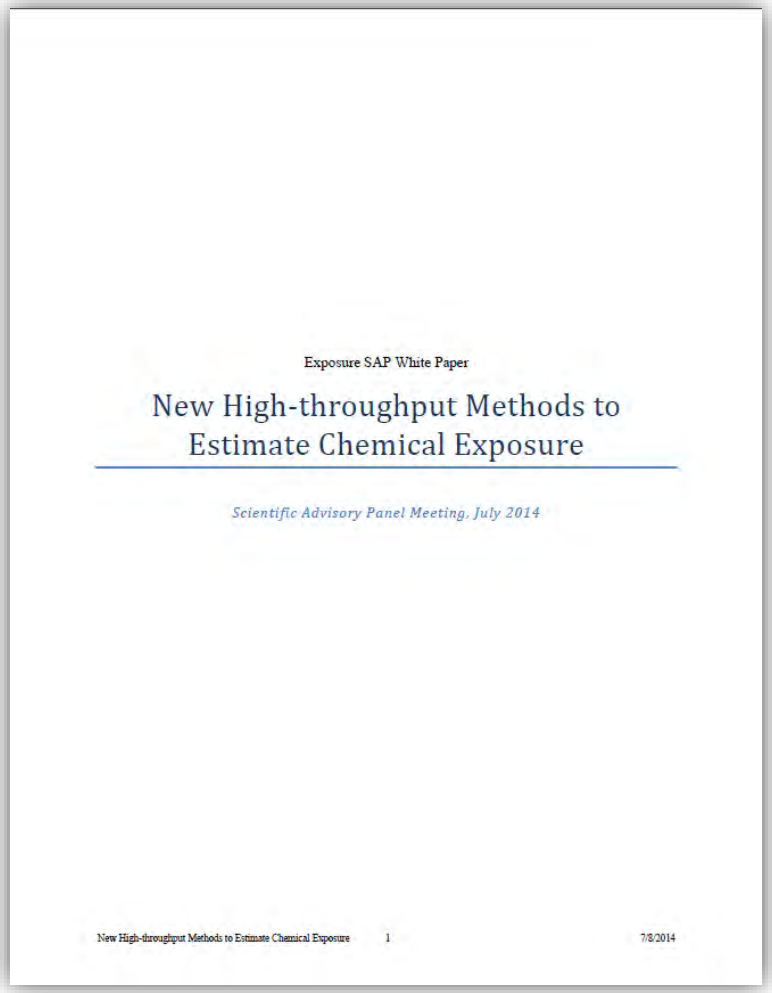
U.S. EPA Office of Chemical Safety and Pollution Prevention (OCSPP)
U.S. EPA Office of Research and Development (ORD)
U.S. EPA Office of Water (OW)

NIH National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

FIFRA SAP December 2-5, 2014

http://www.epa.gov/scipoly/sap/meetings/2014/index.html

The July 2014 FIFRA SAP was charged with advising the Agency in the following 3 topic areas:


Exposure SAP White Paper

New High-throughput Methods to Estimate Chemical Exposure

Scientific Advisory Panel Meeting, July 2014

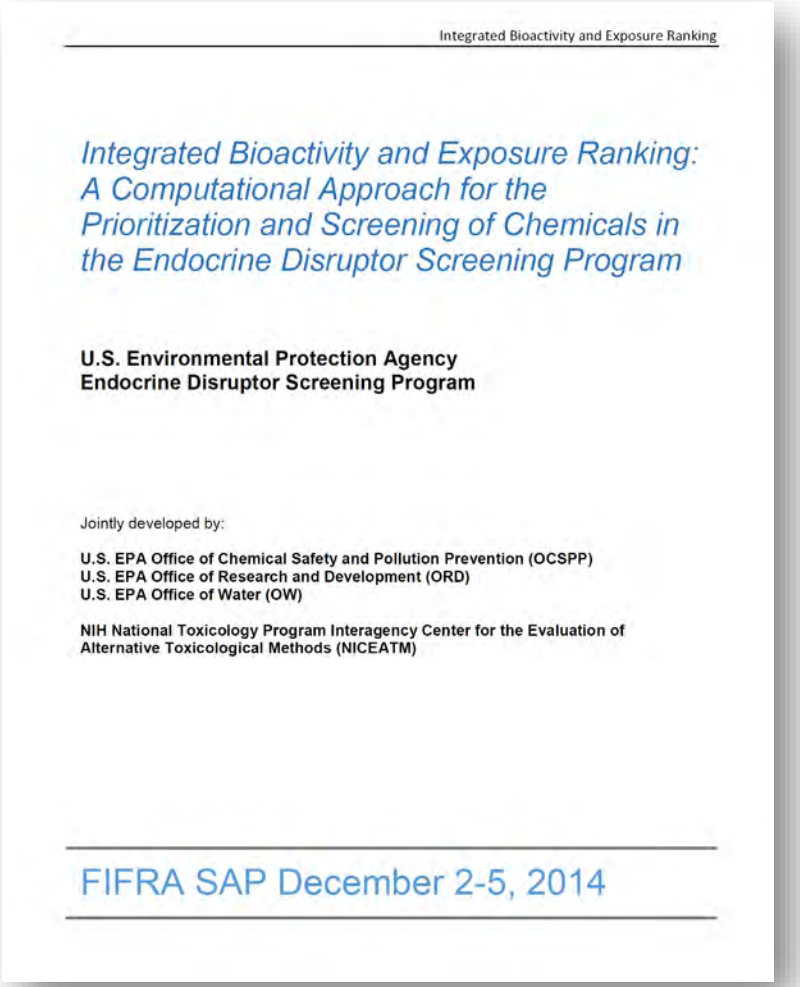
New High-throughput Methods to Estimate Chemical Exposure 1 7/8/2014

- **The Systematic Empirical Evaluation of Models (SEEM) Framework for Exposure**
- **High Throughput Toxicokinetics (HTTK) and Reverse Toxicokinetics (RTK)**
- **Future Direction**

July 2014 FIFRA SAP - Highlights from Panel Comments and Recommendations

- SEEM appears scientifically sound and suitable for high throughput exposure (HTE) methods to assess relative risks of chemical exposure for diverse groups of chemicals.
    - Further effort in measuring and minimizing uncertainty within the SEEM framework is needed prior to implementation in the EDSP or other Programs.
- With respect to RTK, the main Panel conclusions were that the EPA is going in the right direction and that there were no other existing viable approaches.
    - Effort should be focused on understanding the failure of the model to better predict the *in vivo* Css.
    - *In vivo* data for additional chemicals should be generated to assist in the calibration.
    - There was no consensus on whether the predictive approach could be used for prioritization and/or screening.

The December 2014 FIFRA SAP was charged with advising the Agency in the following 3 topic areas:



- **Estrogen receptor (ER) bioactivity model**
- **Androgen receptor (AR) bioactivity model**
- **Integrated Bioactivity Exposure Ranking (IBER) approach**

December 2014 FIFRA SAP - Highlights from Panel Comments and Recommendations on IBER

Strengths

- Agency captured "worst-case scenarios" aimed to account for uncertainty and variability in both chemical bioactivity and population exposure.
- Model is complex enough to capture potential sources of variability yet simple enough to allow for straightforward scientific interpretation, model validation, and further development.
- "Good starting point" (need to further address variability and uncertainty).

Limitations

- Need further model development to account for sources of uncertainty and variability and model them jointly
- Exposure dataset was more limited than data available for bioactivity.
- Concerned that specific human populations such as agricultural workers, chemical formulators and pregnant women, who may have the highest exposure levels for specific compounds were not always taken into account.

Future Direction / Path Forward

Recommendations from FIFRA SAP Peer Reviews are under consideration; path forward includes:

- Next generation models that include:
  - new exposure models and data (e.g., SHEDS-HT),
  - additional sources of exposure (e.g., ground water and drinking water),
  - dermal and inhalation routes of exposure,
  - exposures other than steady state, and
  - extrapolations to ecological species (e.g., fish)

- Work to expand # of chemicals with biomonitoring data

- Work to expand # of chemicals with reverse toxicokinetic data

Acknowledgements

- US EPA Office of Chemical Safety and Pollution Prevention
- US EPA Office of Research and Development
- US EPA Office of Water
- National Institutes of Health
  - National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)