EPA
United States
Environmental Protection
Agency

Evolution of the CompTox Program at EPA

From Primitive Beginnings to Sophisticated Application

Global Chem
March 3, 2015

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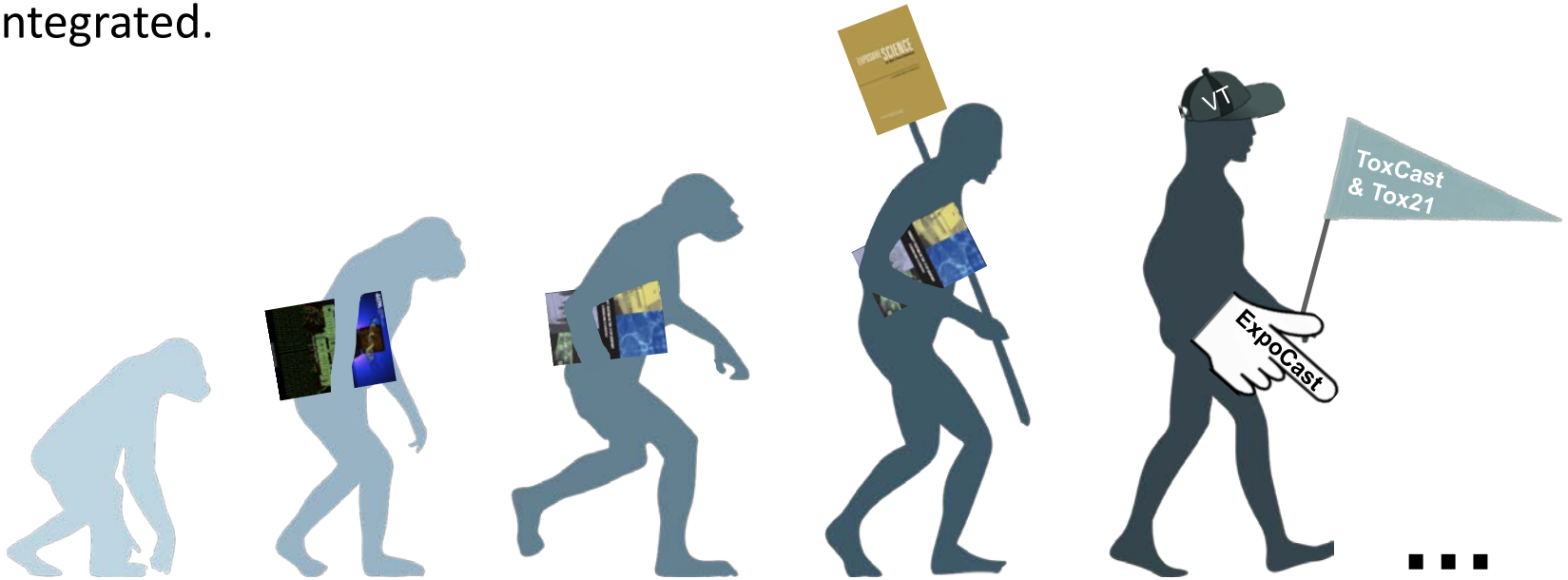
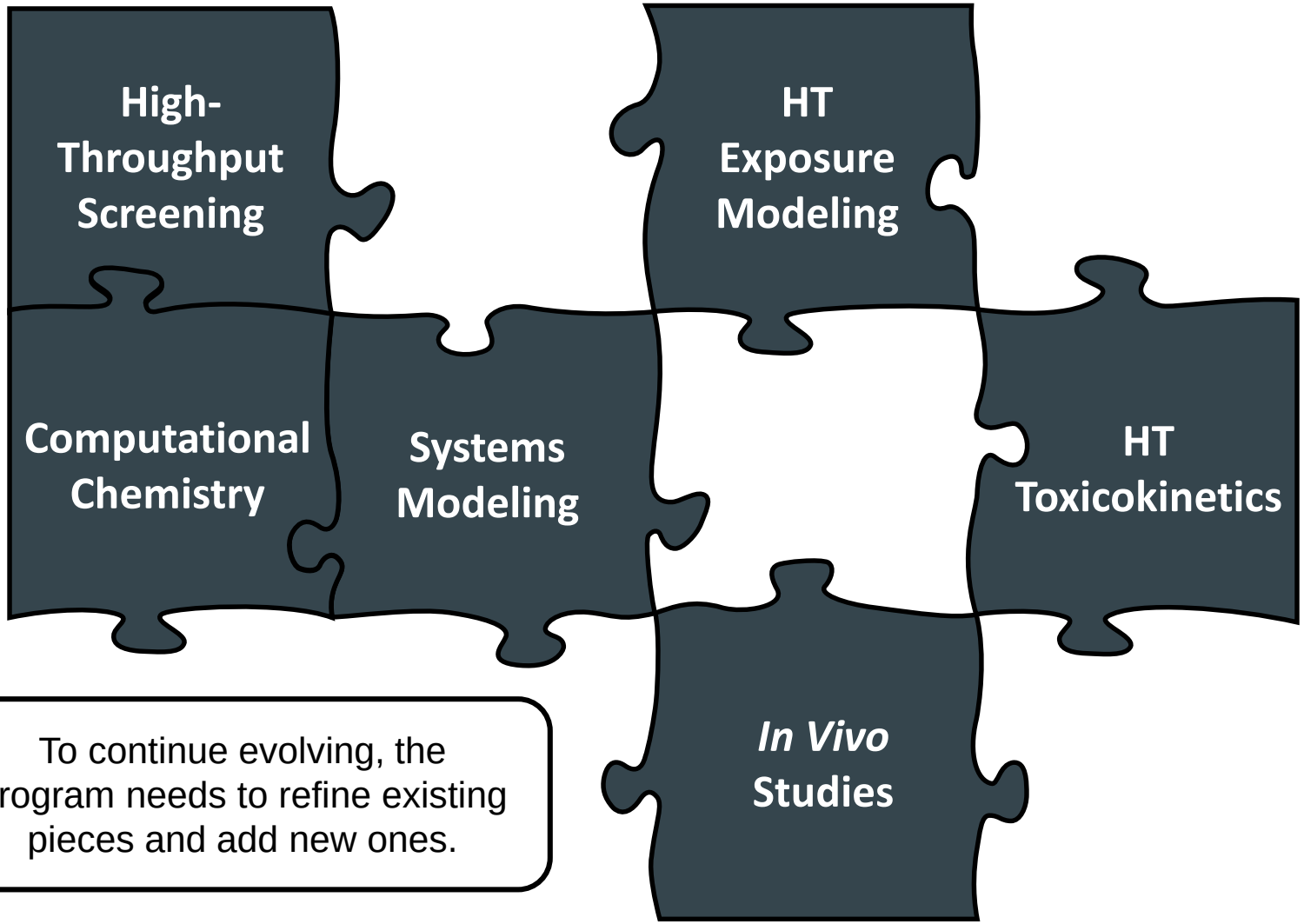
Introduction

- The CompTox program at the Agency and the field in general have undergone punctuated and rapid evolution since its inception
- Diverse regulatory needs, complex scientific challenges, large influx of data, and guidance from expert committees have provided significant selection pressure
- The research will be increasingly broad in scope, multi-disciplinary, and highly integrated.

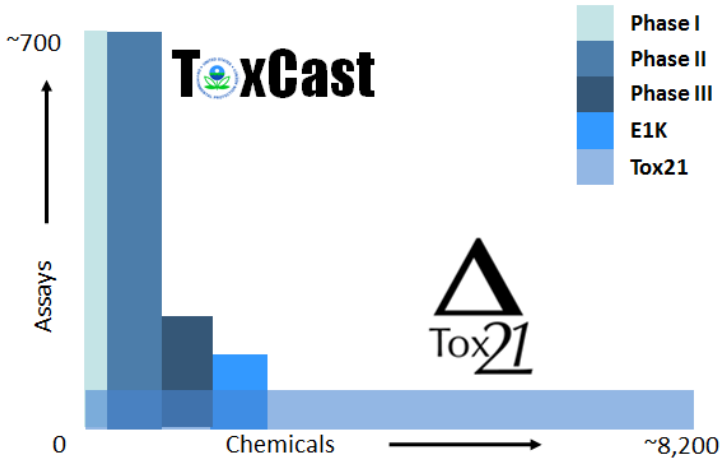


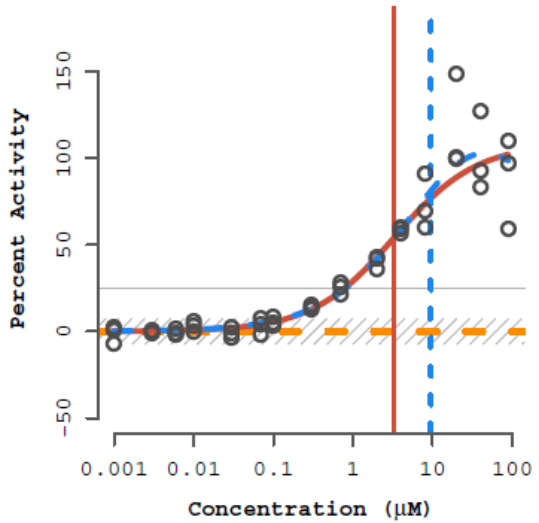
Continuing to Evolve



To continue evolving, the program needs to refine existing pieces and add new ones.

Evolution of High-Throughput Screening





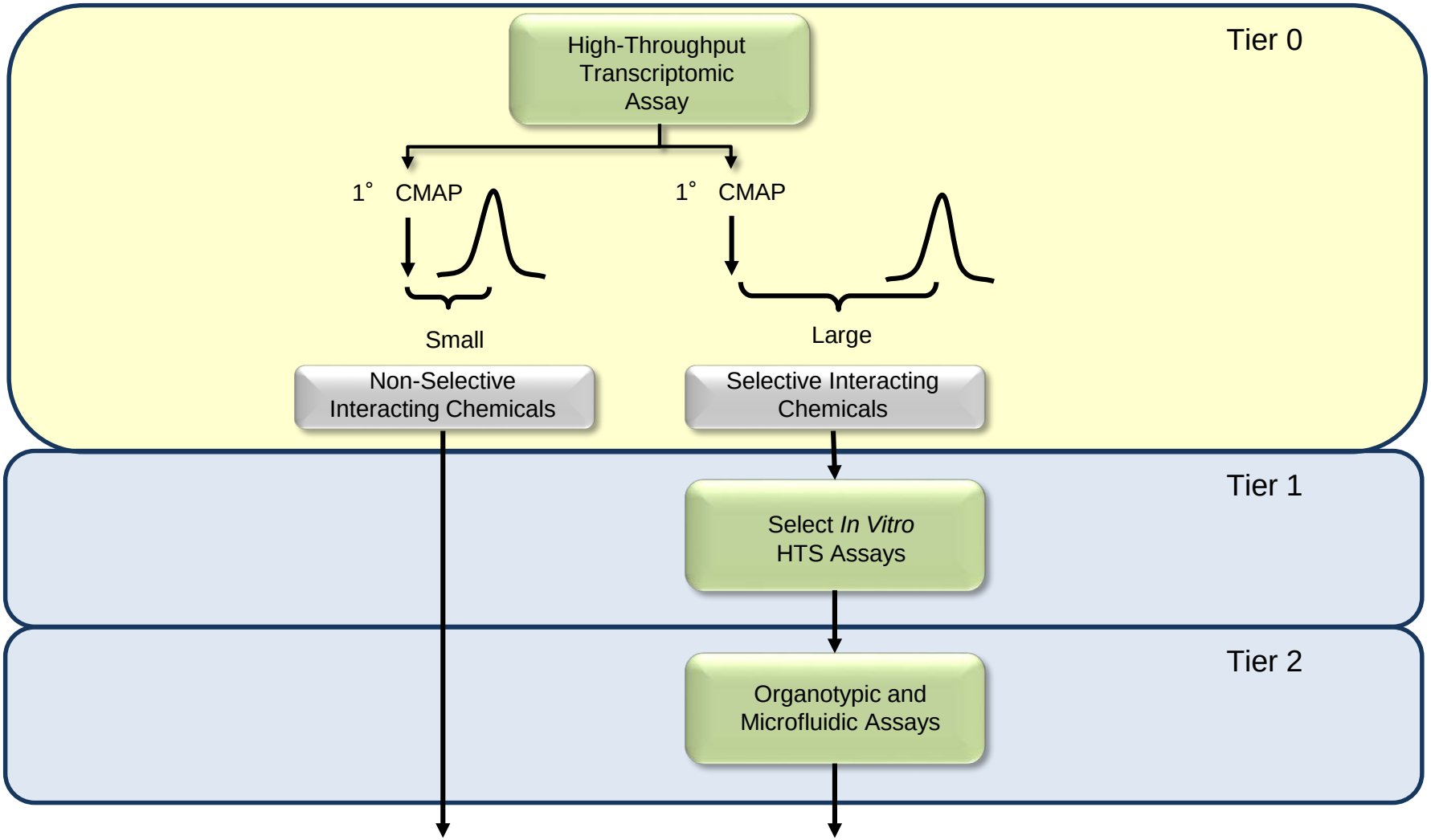
Present

- ToxCast has screened ~2,000 chemicals across ~700 assay endpoints
- Tox21 has screened ~8,200 chemicals across ~50 endpoints
- ToxCast assay coverage represents over 327 genes and 293 pathways

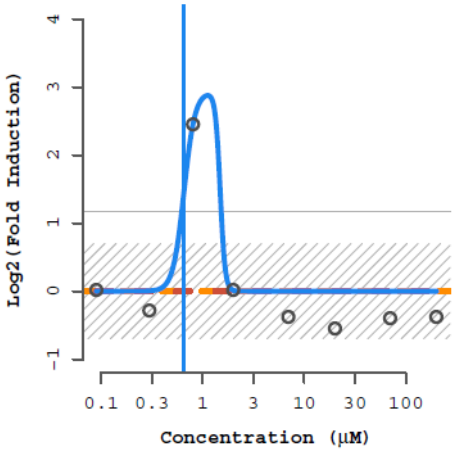
Planned

- Develop low cost, high-throughput global transcriptomic platform to screen across battery of cell types, concentration response, and time
- Capability to retrofit assays for metabolic competence
- Continue assay development for priority targets and complex organotypic cultures

Incorporating a Broad Biological Screening Platform



Efforts to Ensure HTS Data Quality and Increase Transparency




```
ASSAY:    AEID117 (ATG_ERa_TRANS)

NAME:     Thioglycolic acid
CHID:     26141    CASRN: 68-11-1
SPID(S): TX007664
L4ID:     420385

HILL MODEL (in red):
          tp          ga          gw
val:   3.1e-11     -2.15       0.416
sd:    NaN         NaN         NaN

GAIN-LOSS MODEL (in blue):
          tp          ga          gw          la          lw
val:   2.93        -0.184      8           0.173       18
sd:    3.56        0.334       9.48        5.82        814

          CNST        HILL        GNLS
AIC:   20.14       26.14       17.79
PROB:  0.23        0.01        0.76
RMSE:  0.92        0.92        0.32

MAX_MEAN: 2.45      MAX_MED: 2.45      BMAD: 0.233

COFF: 1.17    HIT-CALL: 1    FITC: 50    ACTP: 0.77
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```
FLAGS:
Only one conc above baseline, active
Borderline active
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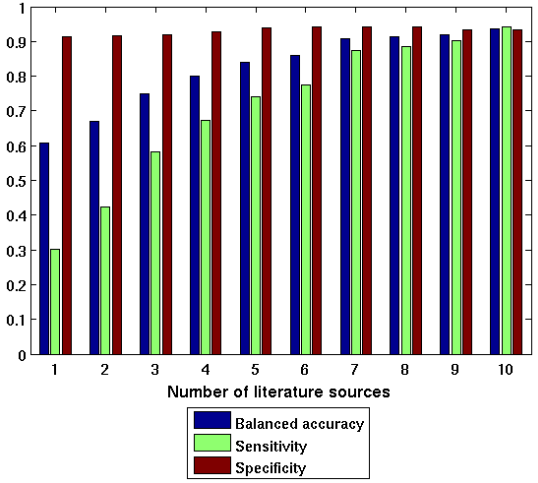
- Public release of Tox21 and ToxCast data on PubChem and EPA web site (raw and processed data)
- ToxCast data analysis pipeline has been completely revamped
  - More statistically rigorous and less prone to outliers
  - Data quality flags to indicate concerns with chemical purity and identity, noisy data, systematic assay errors, and activity in range of cytotoxicity
- Tox21 and ToxCast chemical libraries undergoing analytical QC and results will be publicly released
- Release of ToxCast “Owner’s Manual”
  - Chemical Procurement and QC
  - Data Analysis
  - Assay Characteristics and Performance
- External audit on ToxCast data and data analysis pipeline
- Continued offering of webinars and workshops to educate stakeholders on high-throughput screening data analysis and interpretation

Evolution of Computational Chemistry

Performance of Consensus ER QSAR Model with Literature Validation Set



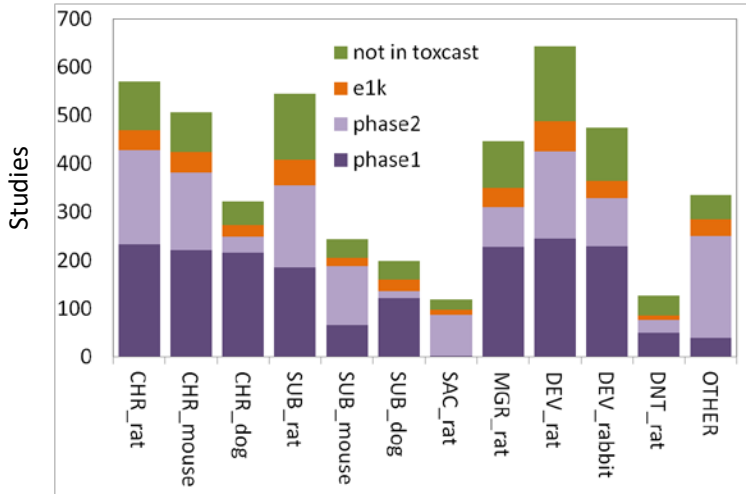
Present

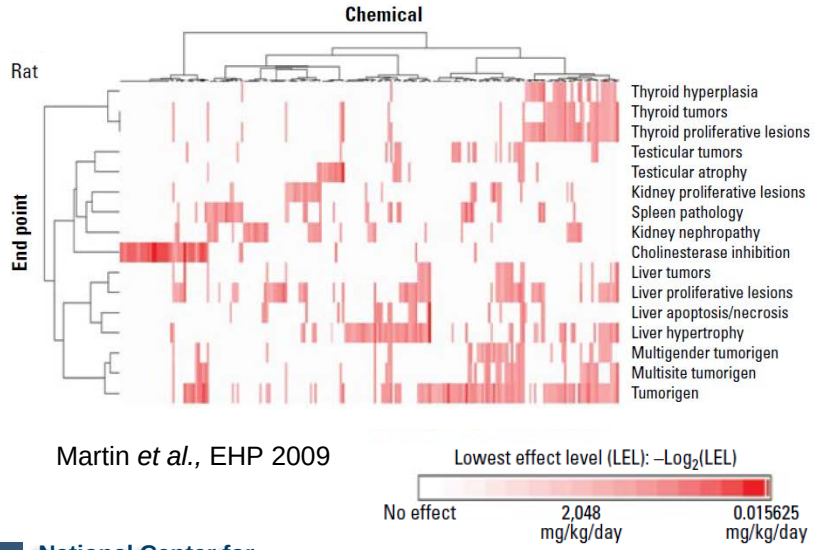
- High quality, curated chemical structure database of 22,000 molecules in DSSTox
- Development of an open-source KNIME workflow for automated structure processing and QC
- Community consensus QSAR models for endocrine-related bioactivity (ER and AR) with 17 international participants

Planned

- Increase curated chemical structure database to 150,000 molecules with addition of QC flags to indicate confidence in structural associations
- Chemical grouping and read-across effort that incorporates both chemical structure and bioactivity

Evolution of ToxRefDB





Martin *et al.*, EHP 2009

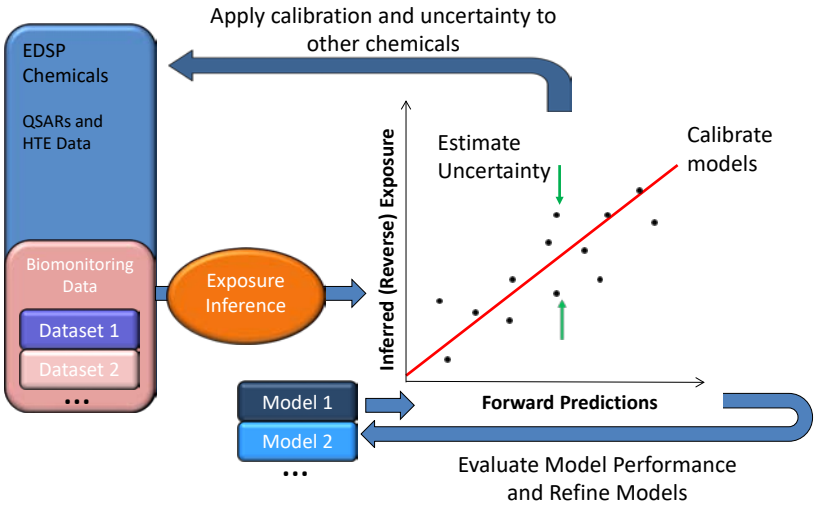
Present

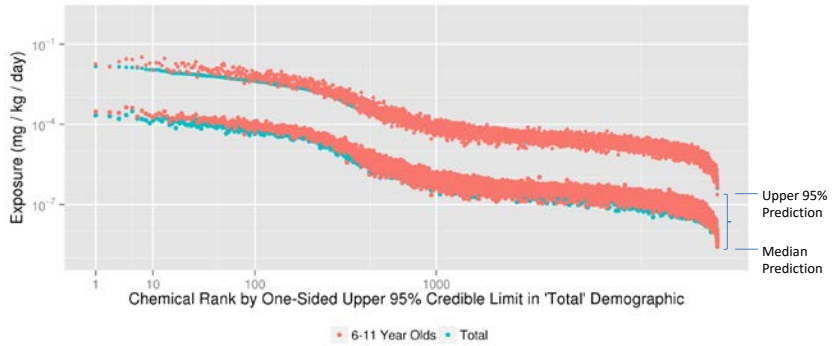
- *In vivo* endpoint data from 5,891 animal toxicology studies on ~1,110 unique chemicals
- A total of 654 chemicals (3311 studies) have LOAEL values, while 812 chemicals (2580 studies) have no adverse effect determination.
- Studies consist of chronic, subchronic, multigenerational, and developmental designs from DERs, NTP, open literature, and pharma

Planned

- Expand number of chemicals with critical effects and add quantitative dose-response data
- Add data from different sources (ECHA, E-Tox, Wignall et al.) and harmonize across databases
- Perform external QC review on ToxRefDB

Evolution of High-Throughput Exposure Modeling





Wambaugh *et al.*, EST 2014

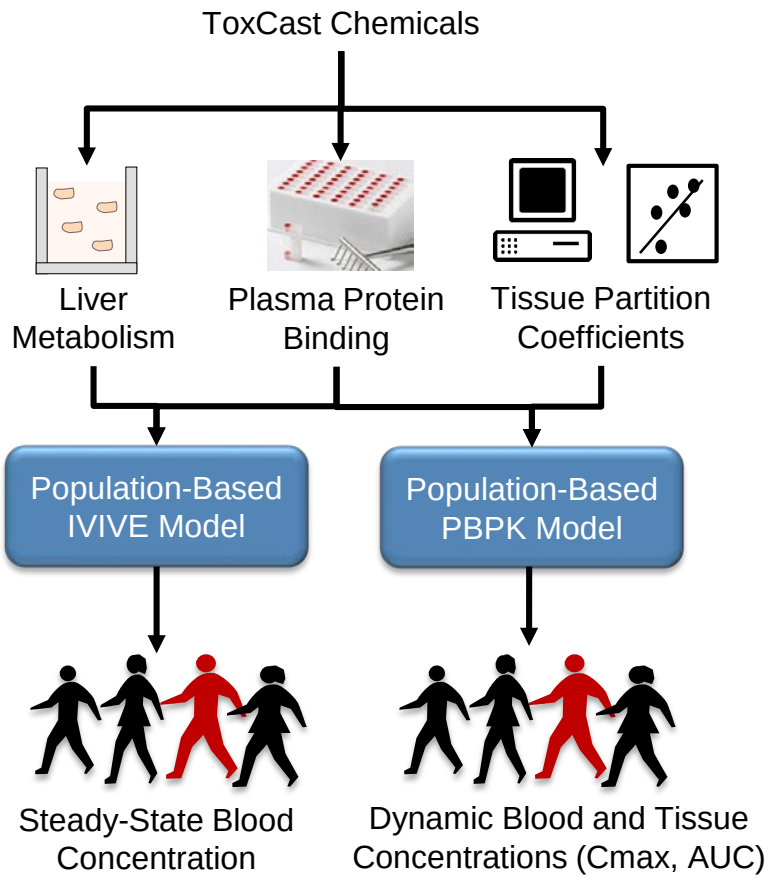
Present

- Computational exposure framework (SEEM) developed that provides exposure estimates for over 7,000 chemicals based on production volume and five chemical use categories
- A database of chemical-product categories (CPCat) that maps over 45,000 chemicals to ~8,000 product uses or functions

Planned

- Obtain additional biomonitoring data to expand domain of applicability
- Survey a range of consumer products and home goods for chemical ingredients and emissivity
- Incorporate SHEDS-HT into SEEM framework

Evolution of High-Throughput Toxicokinetics



Present

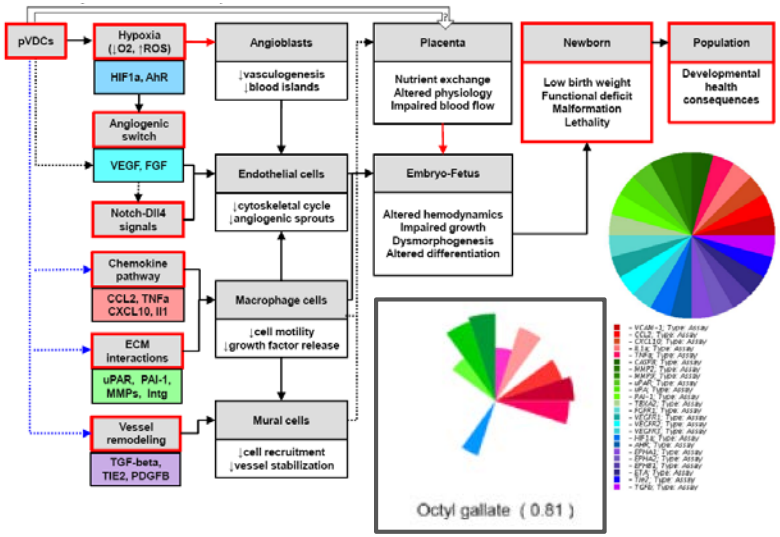
- Steady-state IVIVE models for hundreds of chemicals based on limited high-throughput *in vitro* assays
- Implemented structure-based methods to estimate tissue partitioning
- Developed HT-Physiologically-Based Pharmacokinetic (HT-PBPK) models for hundreds of chemicals

Planned

- Develop computational modeling framework to compare IVIVE with *in vivo* data and allow explicit estimates of uncertainty
- Separate chemical classes where we do either a good or poor job of predicting pharmacokinetics

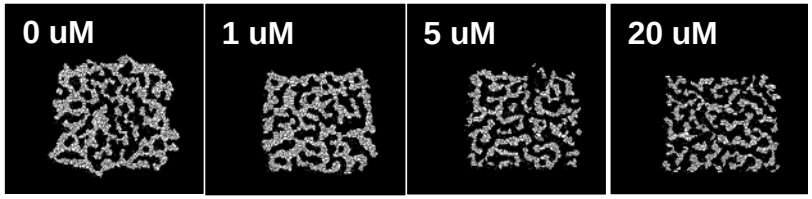
Evolution of Systems Modeling and Virtual Tissues

AOP for Developmental Vascular Disruption



Kleinstreuer *et al.*, PLoS Comp Bio, 2013

Model Simulations of Dev Vascular Disruption



Knudsen *et al.*, unpublished

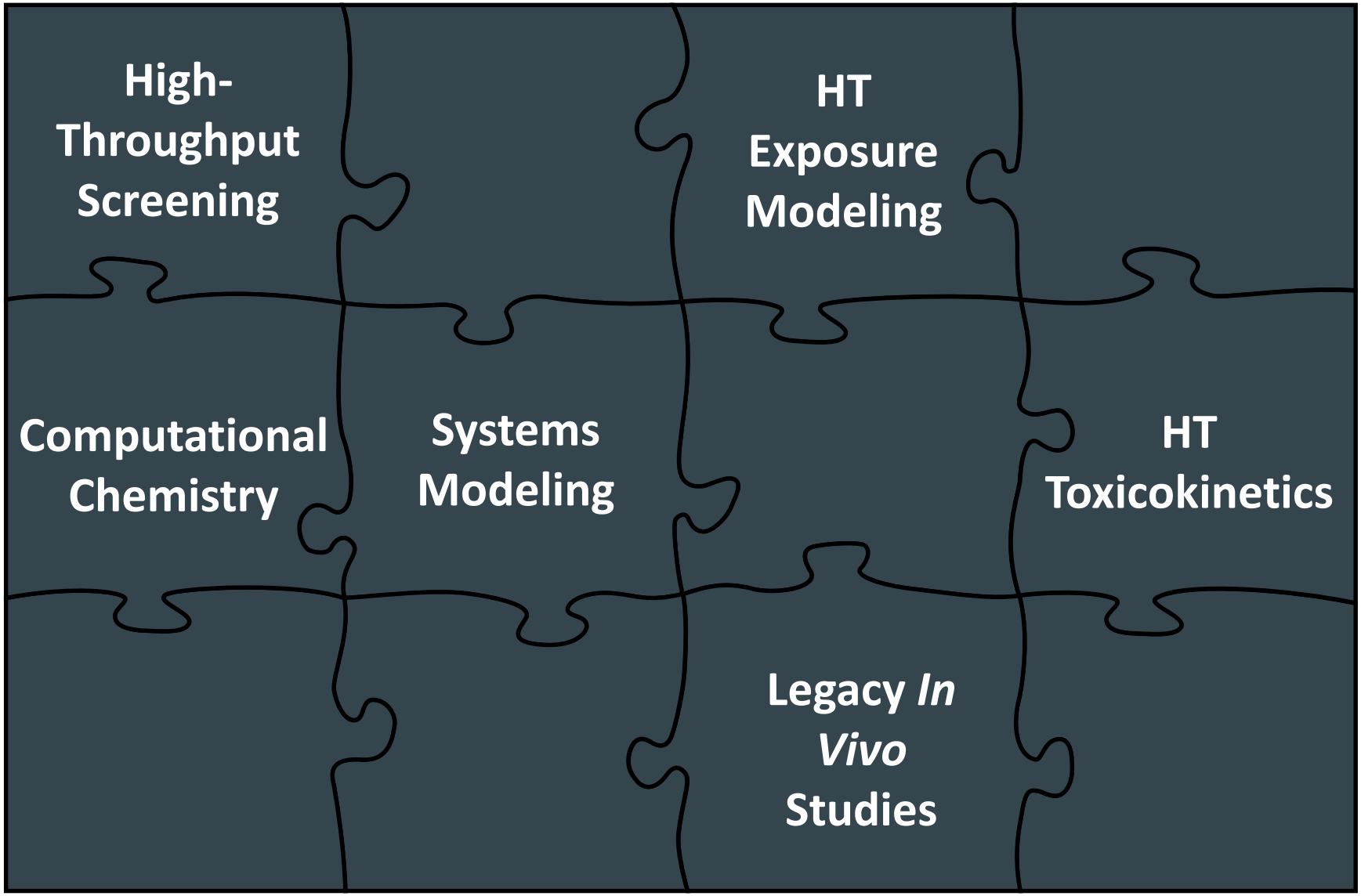
Present

- AOPs for embryonic vascular disruption, cleft palate, hypospadias, and limb (digit) defects
- Developed computational models for each AOP and used ToxCast data to parameterize models
- Validated model results with orthogonal organotypic assays and reference teratogens
- Developed first-generation methods for identifying cellular ‘tipping points’

Planned

- Refinement and validation of methods identifying concentration-dependent ‘tipping points’
- Evaluate impact of model assumptions on shape of the dose response curve and model potential sensitive populations

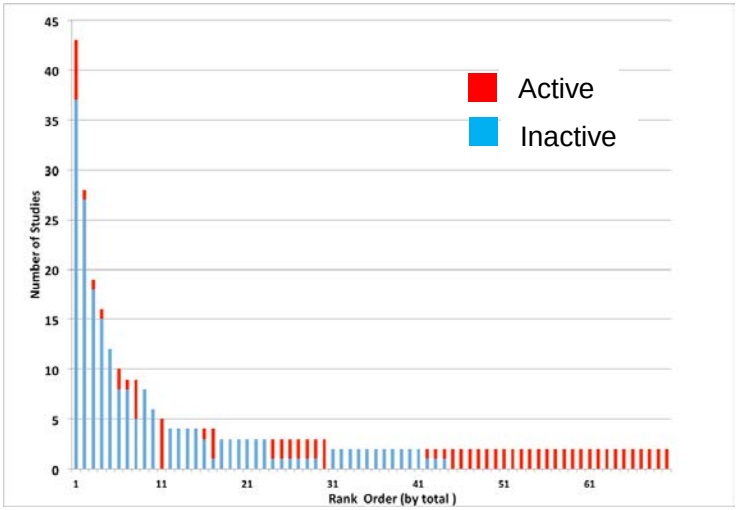
Fitting the Pieces Together for the Next Evolutionary Chapter

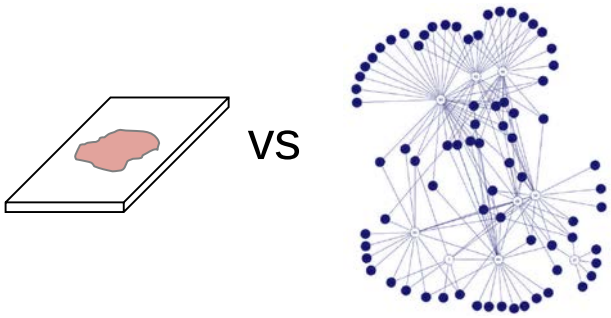


Fit-For-Purpose Agency Decisions

Challenges

Concordance of *In Vivo* Uterotrophic Studies





- Dealing with the "V" word
  - Defining a fit-for-purpose framework(s) that is time and resource efficient
  - Role of *in vivo* rodent studies
  - Incorporating the inherent uncertainty of the *in vivo* studies
- Moving from an apical to a molecular paradigm and defining adversity
- Predicting human safety vs. toxicity
- Integrating multiple data streams from the new approaches in a risk-based, weight of evidence assessment
- Ensuring a comprehensive screening and testing paradigm
- Quantifying uncertainty and variability
- Application to cumulative risk/mixtures

EPA United States Environmental Protection Agency

Questions?