Using Alternative Approaches to Prioritize Testing for the Universe of Chemicals with Potential for Human Exposure

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WC9, Prague, August 2014

EDSP – Driver of Prioritization

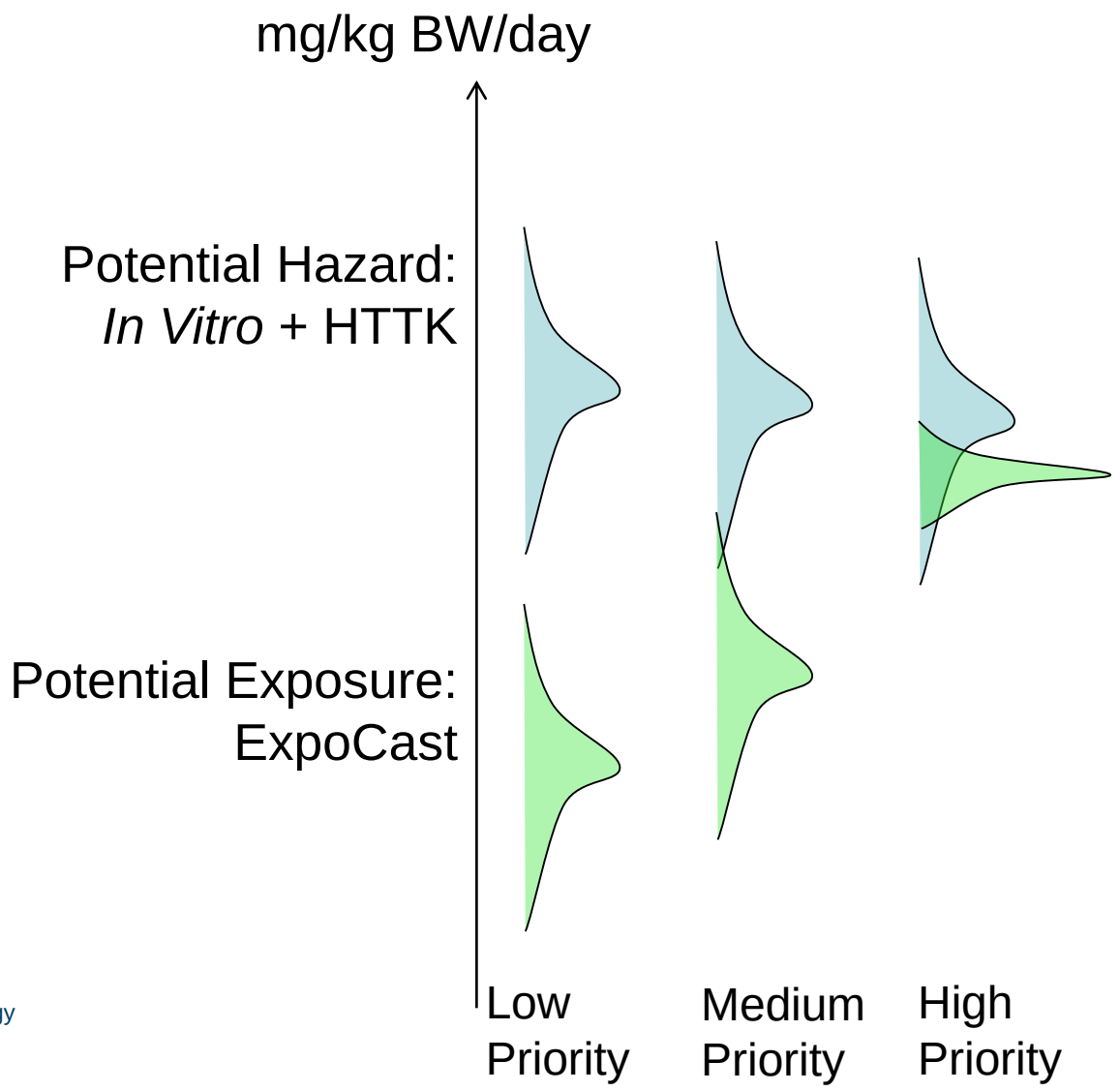
- Endocrine Disruptor Screening Program

- Tier 1: Battery of 11 *in vitro* and *in vivo* assays
  - $1,000,000 per chemical
  - 5000-10000 chemicals
  - 50-100 years to complete
  - This is just the start – Tier 1 positives go into Tier 2

- Use Risk-based Prioritization
  - Potential for Hazard (estrogen, androgen or thyroid)
  - Potential for Exposure

- *In Vitro* assays: Bioactivity Concentration
- Need Bioactivity Dose to compare with exposure
- Convert using High Throughput Toxicokinetics (HTTK)

Semi-quantitative *In Vitro* to *In Vivo* Approach

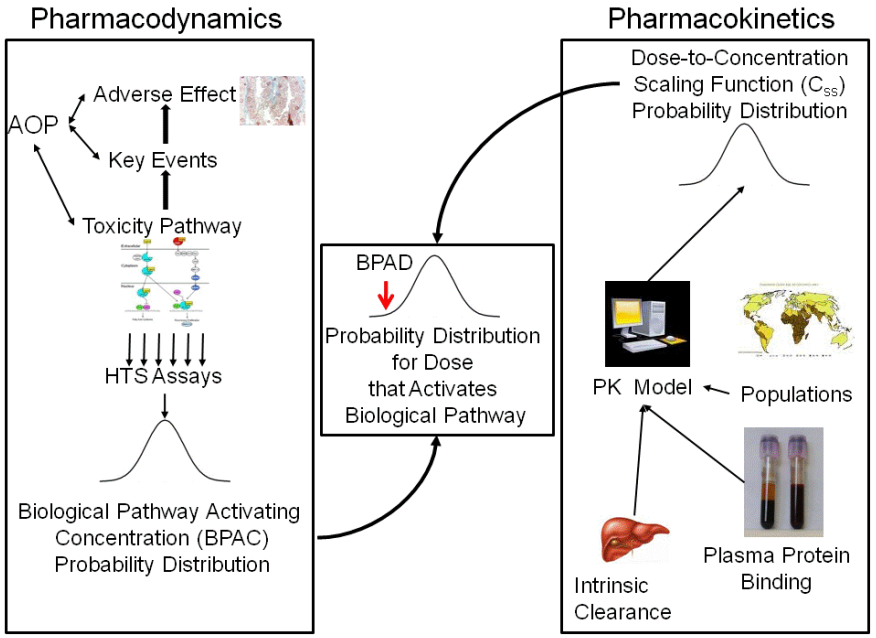


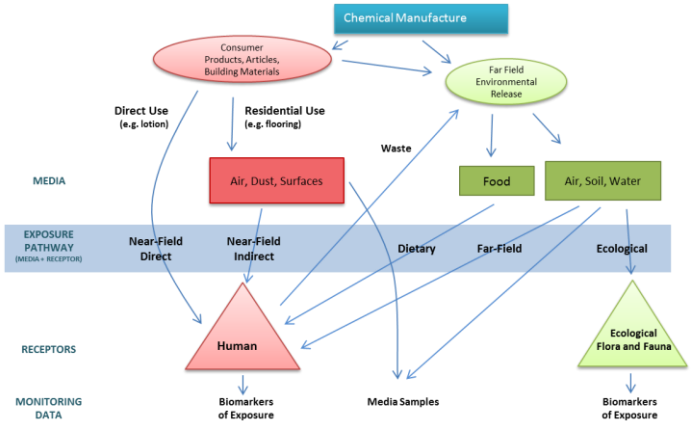
HTRA – High-Throughput Risk Assessment

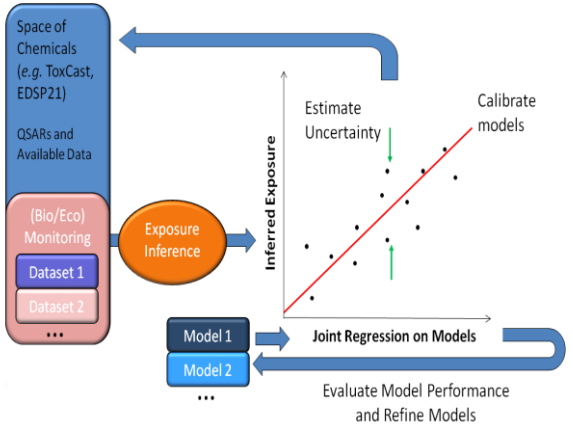
High-throughput Hazard and Kinetics

+

High-throughput Exposure







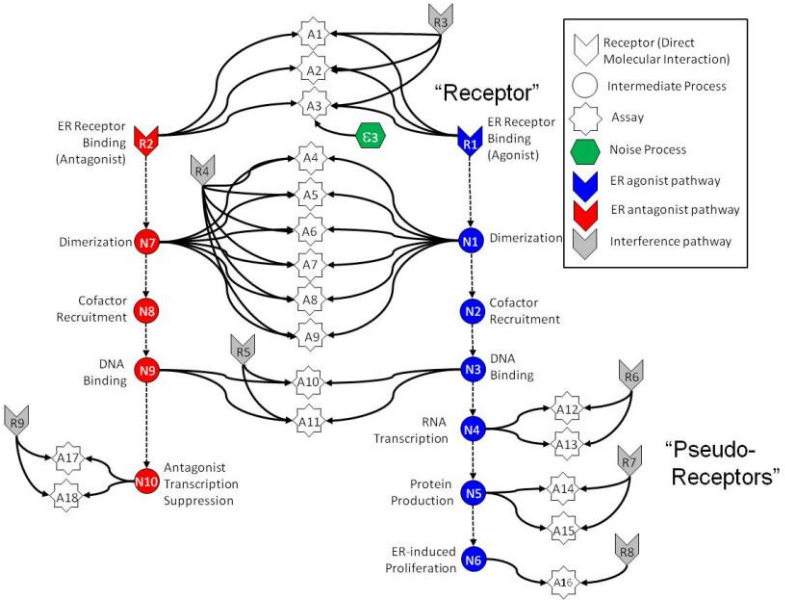
Chemicals for Prediction: The Human Exposure Universe

- Estimate universe of man-made chemicals with potential for exposure
  - EDSP Universe (10K)
  - Chemicals with known use (40K)
    - From Chemical and Product Category DB (CPCat)
    - http://actor.epa.gov/cpcat
  - Canadian Domestic Substances List (DSL) (23K)
  - EPA DSSTox – structures of EPA/FDA interest (15K)
  - ToxCast and Tox21 (In vitro ER data) (8K)
- Unique set of structures: ~32K

In Vitro hazard: ER as Example

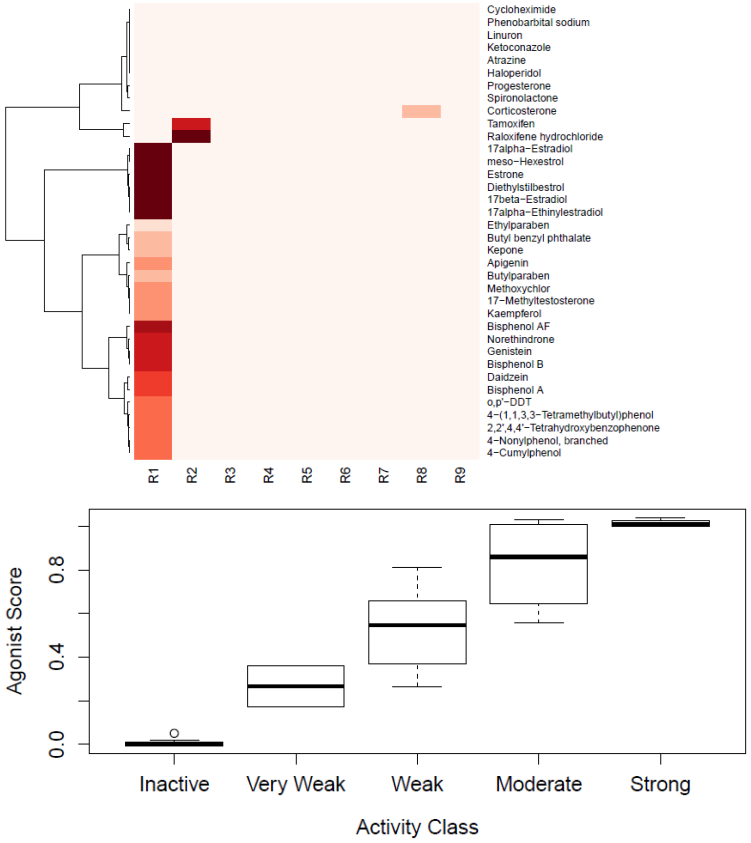
Combines results from multiple in vitro assays

- Use multiple assays per pathway
  - Different technologies
  - Different points in pathway
- No assay is perfect
  - Assay Interference
  - Noise
- Use model to integrate assays
- Evaluate model against reference chemicals



ER Model Results

Appropriate Results for Reference Chemicals



Results For EDSP Universe Chemicals

1431 EDSP chemicals run *in vitro*
71 (5%) have a significant ER score

Mostly known chemical classes:

- Phenols
- Steroids
- Parabens
- Phthalates
- Organo-chlorides

Uses:

- Pesticides
- Pharmaceuticals
- Plastics
- Dyes
- Industrial Intermediates

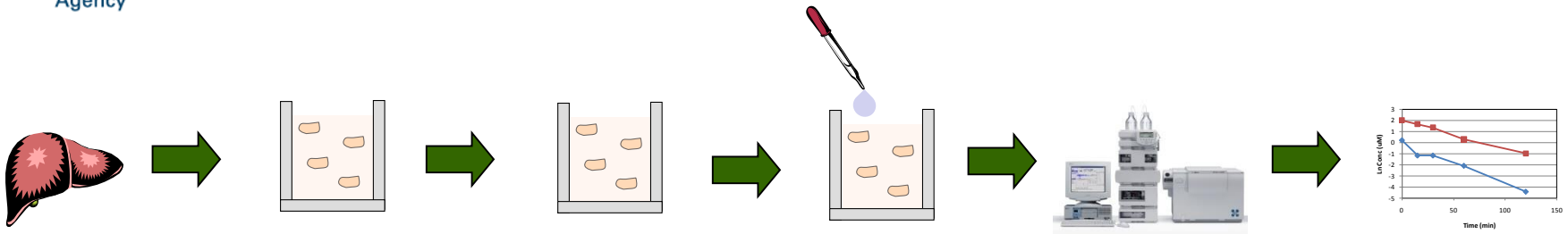
What chemicals to run *in vitro* next?
Use QSAR to select

10-15% Predicted ER Positive

- CERAPP: Collaborative Estrogen Receptor Activity Prediction Project
  - Crowd-sourced Science: 17 groups in U.S. and Europe
  - Each uses the ER model results to train QSAR models
  - Predict the Human Exposure Universe (includes EDSP Universe)
  - Evaluate with independent data set from the literature
  - Run positive *in vitro* to confirm

Models	Training set	All predicted	opt_score
DTU_1	873	16063	0.80
DTU_2	737	13442	0.75
EPA_NCCT	1529	32463	0.78
FDA_NCTR_DBB	1529	32464	0.84
Helmholtz_ISB	1512	31629	0.80
ILS_EPA	1506	31318	0.79
IRCCS_CART	1529	32442	0.77
IRCCS_Ruleset	1383	28958	0.77
JRC_Ispra	1465	30801	0.74
LockheedMartin_EPA_1	1529	32464	0.75
LockheedMartin_EPA_2	1529	32464	0.70
NIH_NCATS	1528	32184	0.67
NIH_NCI_GUASAR	1529	32455	0.84
NIH_NCI_PASS	1465	30800	0.76
RIFM	1529	32463	0.69
UMEA	1529	32430	0.76
UNC_MML_1	1529	32464	0.73
UNIBA	750	15178	0.80
UNIMIB_Michem_1	1529	32464	0.68
UNIMIB_Michem_2	531	11832	0.85
UNISTRA_InfoChim	1529	32464	0.73

Adding Pharmacokinetics: High-Throughput ToxicoKinetics (HTTK)



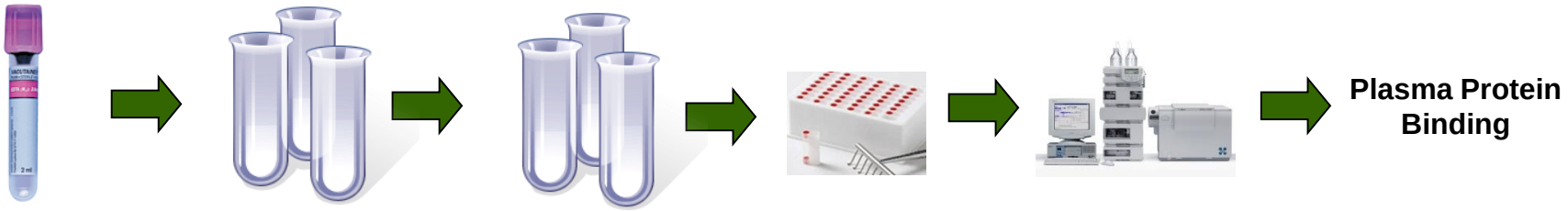
Human Hepatocytes (10 donor pool)

Add Chemical (1 and 10 μM)

Remove Aliquots at 15, 30, 60, 120 min

Analytical Chemistry

Hepatic Clearance



Human Plasma (6 donor pool)

Add Chemical (1 and 10 μM)

Equilibrium Dialysis

Analytical Chemistry

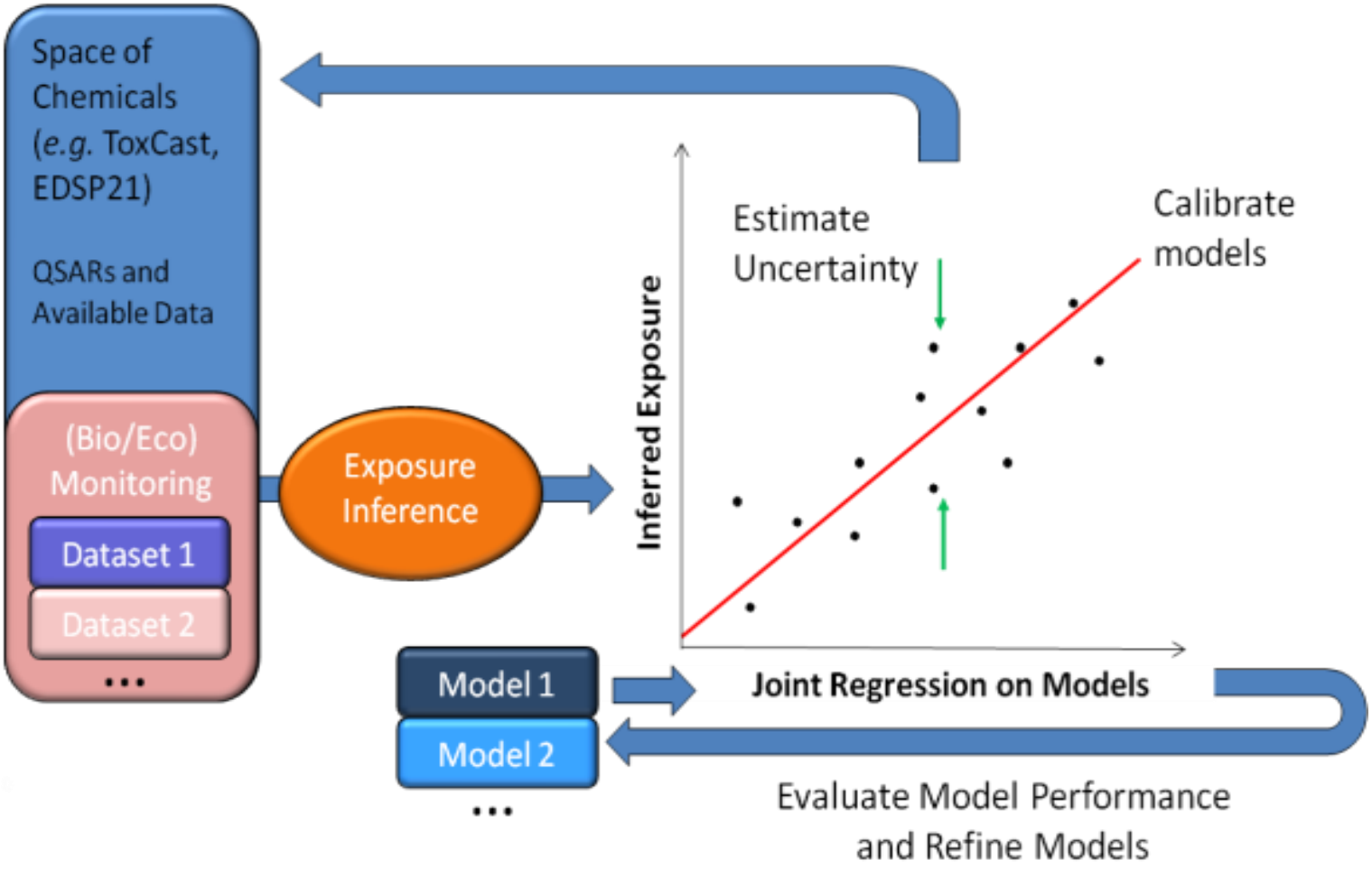
Plasma Protein Binding

Combine experimental data w/ PK Model to estimate dose / concentration scaling

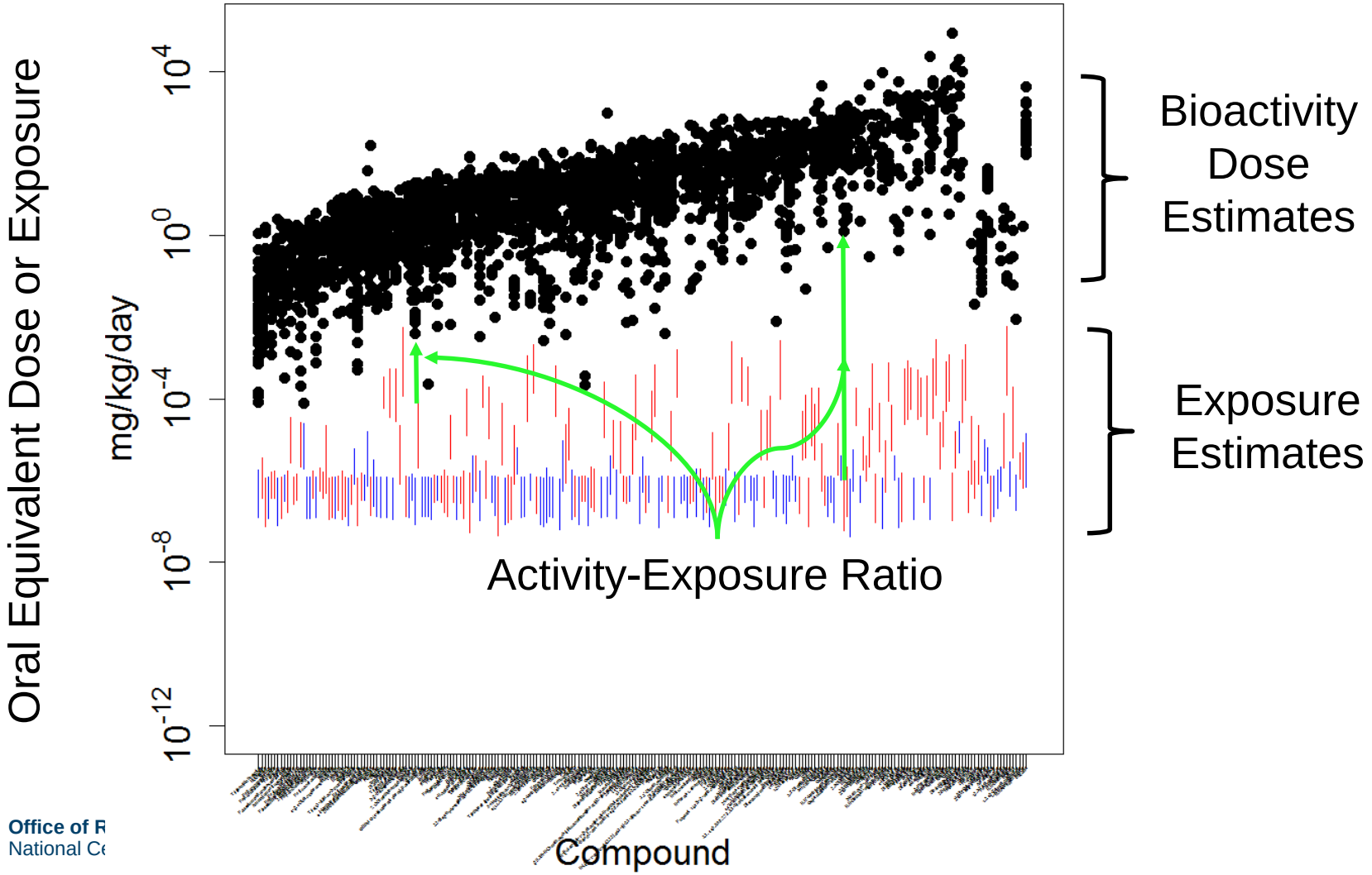
Bioactivity Dose = Bioactivity Concentration / Css

ExpoCast Exposure Modeling

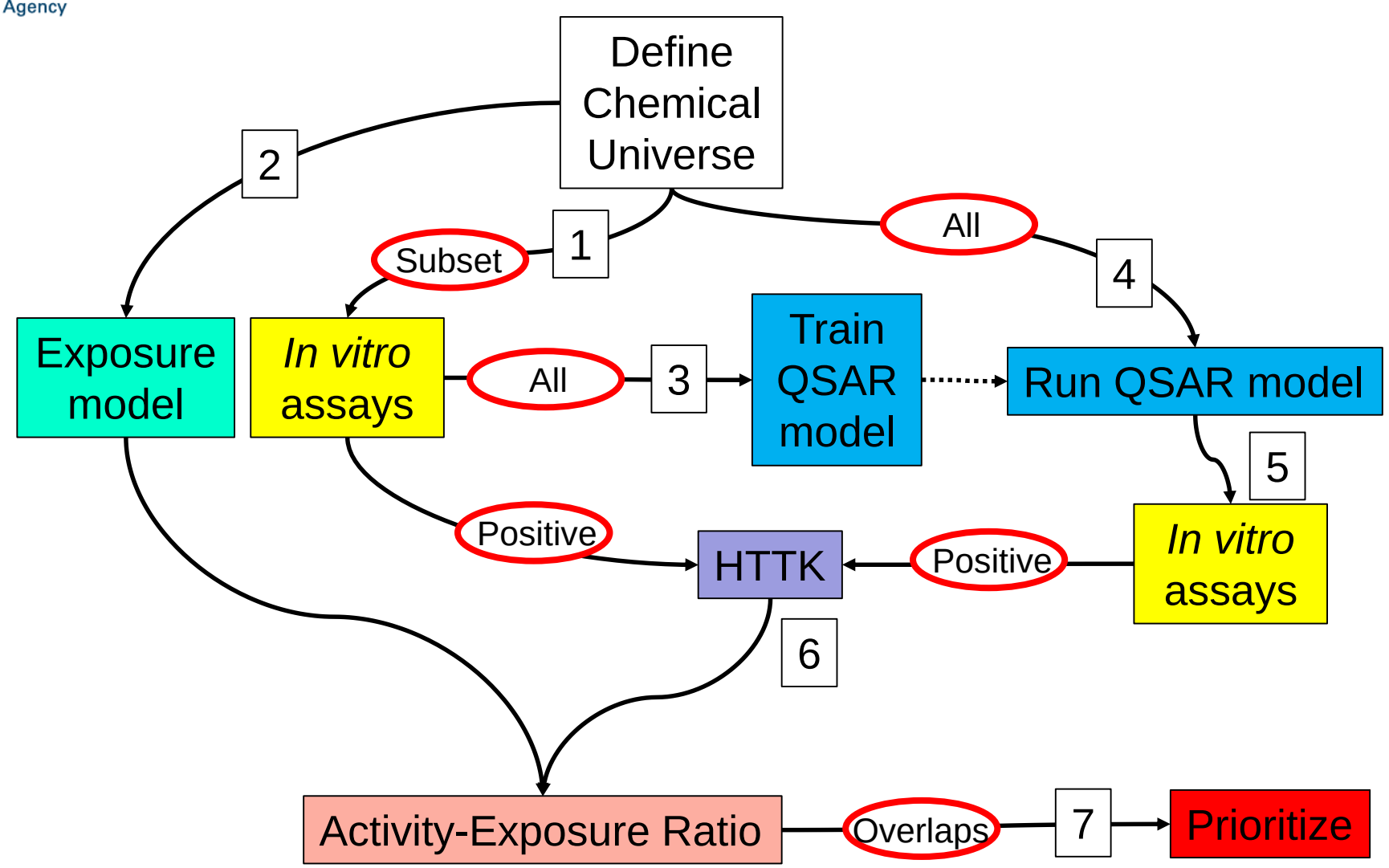
Output: Estimate of exposure (w/ confidence interval)



Combine Hazard, HTTK Dose, Exposure
Output: "Activity Exposure Ratio (AER)"



Summary: Overall Prioritization Scheme



Acknowledgements

EPA NCCT
Rusty Thomas
Kevin Crofton
Keith Houck
Ann Richard
Richard Judson
Tom Knudsen
Matt Martin
Woody Setzer
John Wambaugh
Monica Linnenbrink
Jim Rabinowitz
Steve Little

EPA NCCT
Nancy Baker
Jeff Edwards
Dayne Filer
Jayaram Kancherla
Parth Kothiya
Jimmy Phuong
Jessica Liu
Doris Smith
Jamey Vail
Hao Truong
Sean Watford
Indira Thillainadarajah
Christina Baghdikian

Agnes Forgacs
Jill Franzosa
Chantel Nicolas
Bhavesh Ahir
Nisha Sipes
Lisa Truong
Max Leung
Kamel Mansouri
Eric Watt
Corey Strope

EPA Collaborators
Kathie Dionisio
Kristin Isaacs
Peter Egeghy
David Dix
Alan Dixon
Scott Lynn
Patience Brown
Don Bergfelt
Les Touart
Rocky Goldsmith

NIH/NCATS
Menghang Xia
Ruili Huang
Anton Simeonov

Others
Alicia Frame (Dow)
Alan Liddell (NCSU)

NTP
Warren Casey
Nicole Kleinstreuer
Mike Devito
Dan Zang
Ray Tice

CERAPP

DTU/food: Technical University of Denmark/ National Food Institute
EPA/NCCT: U.S. Environmental Protection Agency / National Center for Computational Toxicology
FDA/NCTR/DBB: U.S. FDA / National Center for Toxicological Research/Division of Bioinformatics and Biostatistics
FDA/NCTR/DSB: U.S. FDA / National Center for Toxicological Research/Division of Systems Biology
ILS&EPA/NCCT: ILS Inc & EPA/NCCT
IRCSS: Istituto di Ricerche Farmacologiche “Mario Negri”
JRC_Ispra : Joint Research Centre of the European Commission, Ispra.
LockheedMartin&EPA : Lockheed Martin IS&GS/ High Performance Computing
NIH/NCATS : National Institutes of Health/ National Center for Advancing Translational Sciences
NIH/NCI : National Institutes of Health/ National Cancer Institute
RIFM : Research Institute for Fragrance Materials, Inc
UMEA/Chemistry: University of UMEA/ Chemistry department
UNC/MML: University of North Carolina/ Laboratory for Molecular Modeling
UniBA/Pharma: University of Bari/ Department of Pharmacy
UNIMIB/Michem: University of Milano-Bicocca/ Milano Chemometrics and QSAR Research Group
UNISTRA/Infochim: University of Strasbourg/ ChemoInformatique
Helmholtz/ISB: Helmholtz Zentrum Muenchen/Institute of Structural Biology