

Building on Excellence to Tackle a Fundamental Scientific Challenge

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20 June 2018





What attracted me to the NTP?

- *Mission:*

- Evaluate agents of public health concern by developing and applying tools of modern toxicology and molecular biology.

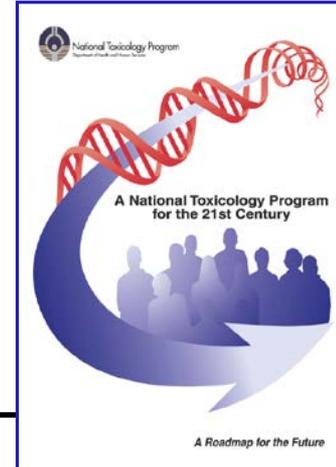
- *Goals:*

- Coordinate toxicological testing programs within the Department of Health and Human Services.
- Develop and validate improved testing methods that reduce, refine, or replace the use of animals.
- Develop approaches and generate data to strengthen scientific knowledge.
- Communicate information about potentially hazardous substances to the scientific, regulatory and public communities.





What attracted me to the NTP?



Mission

To evaluate agents of public health concern, by developing and applying tools of modern toxicology and molecular biology.

<http://ntp.niehs.nih.gov>; April 2015

21st Century Vision

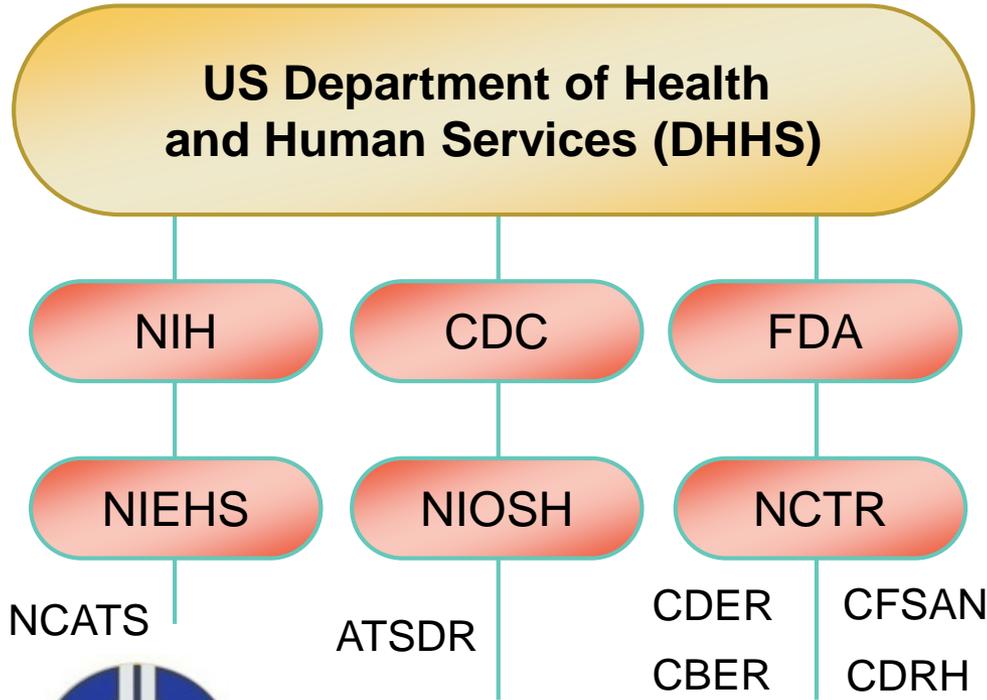
To support the evolution of toxicology from a predominately observational science at the level of disease-specific models to a predominately predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations.

A National Toxicology Program for the 21st Century, November 2004



What attracted me to the NTP?

NTP – A program of partnerships



National Toxicology Program
U.S. Department of Health and Human Services

<http://ntp.niehs.nih.gov>



Health and
Environmental
Sciences
Institute



International Agency
Research on Cancer



European Union Reference Laboratory
for Alternatives to Animal Testing

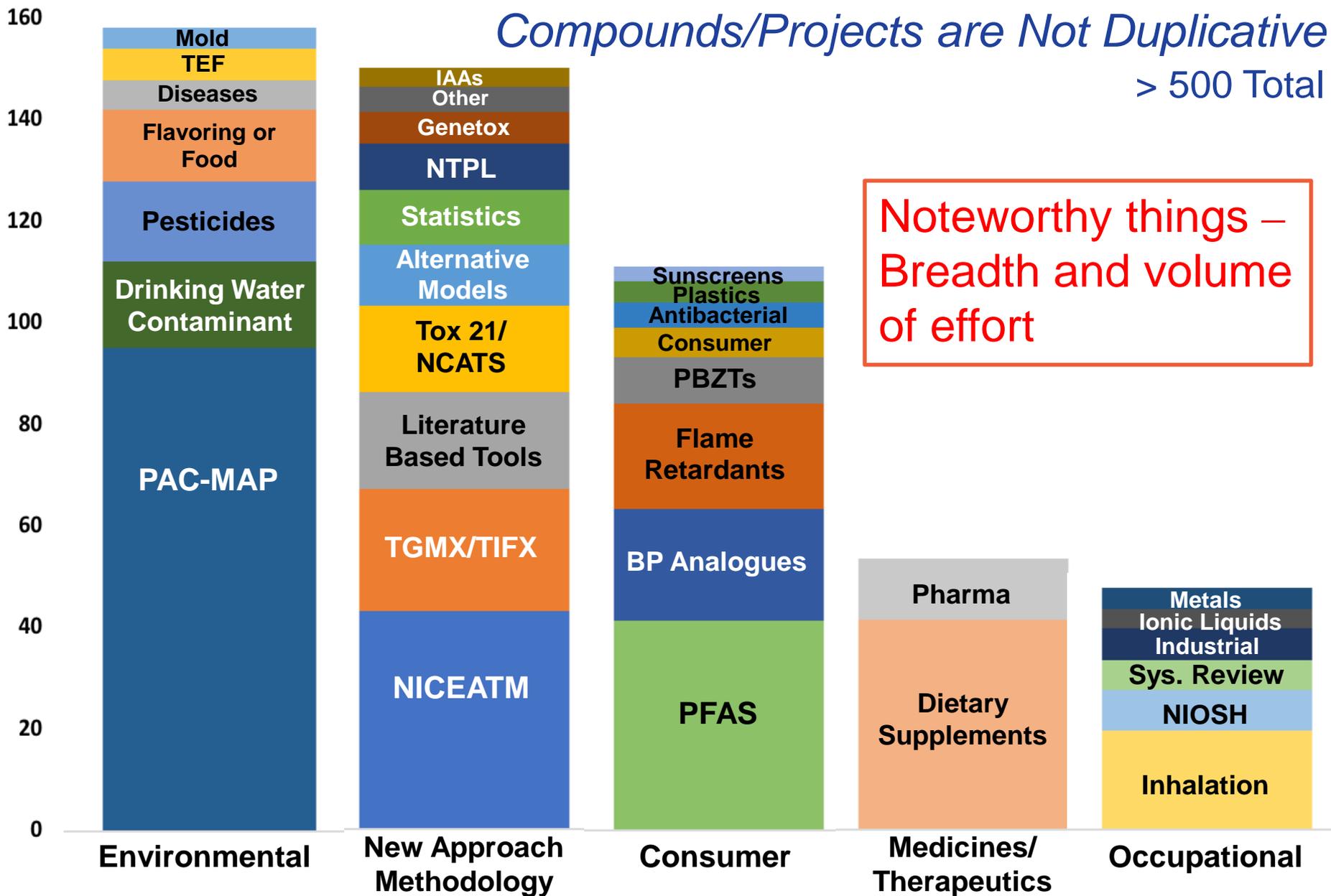


DNTP 2018 Portfolio Review Highlights

6 days X 3 hours/day = 18 hours of
presentation and discussion preceded
by countless hours of preparation



Ongoing Studies Grouped by Exposure

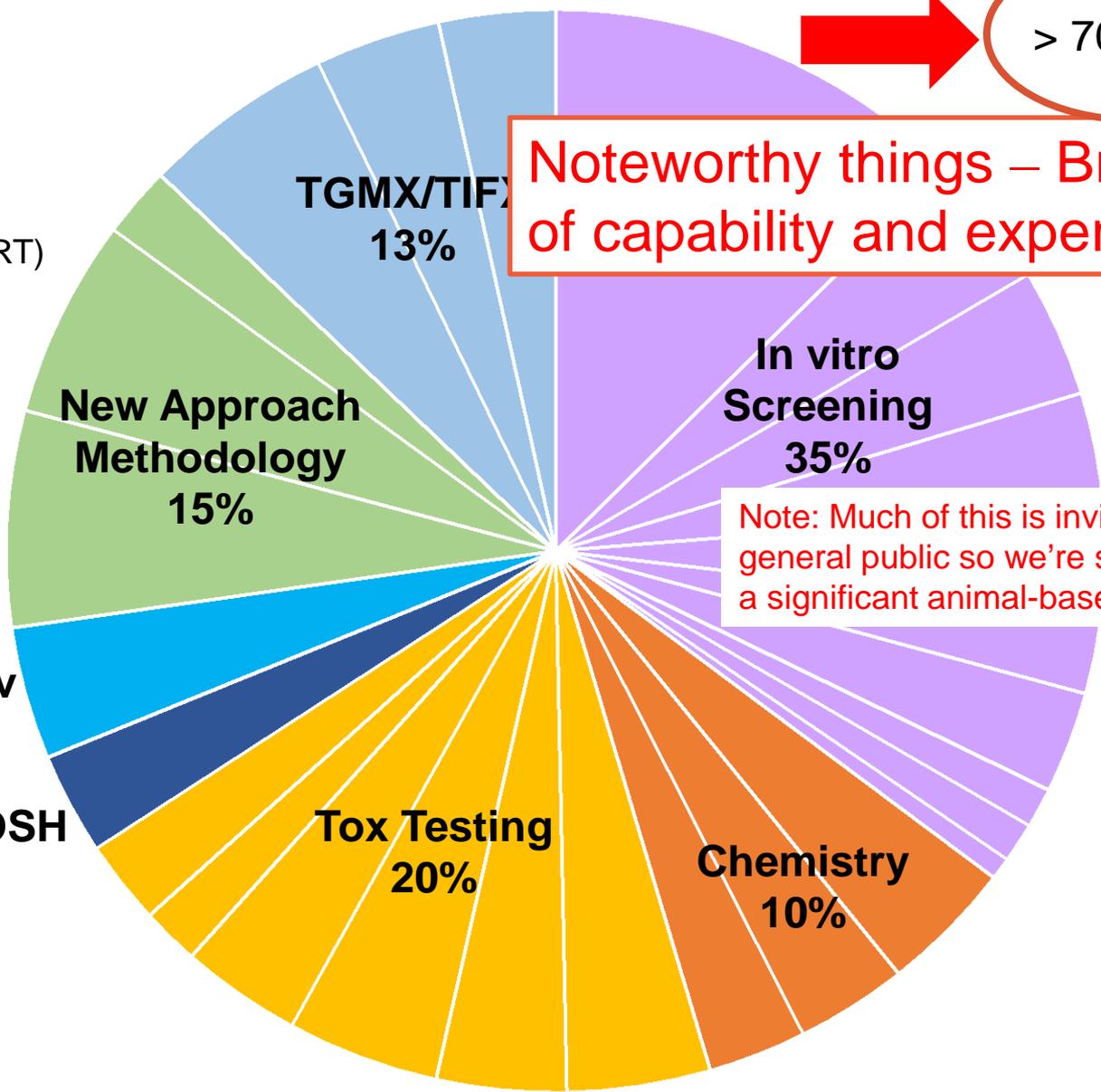




Ongoing Studies Grouped by Study Type

Test Agents May Appear in Multiple Categories, Ex:

- **BP Analogues**
- Chemistry
- Biosample
- Toxicokinetics (TK)
- Dev/Repro Toxicity (DART)
- 5-day
- Immuno Toxicity
- Chronic Toxicity (NCTR)
- Scoping/Sys Rev
- In vitro
- Zebrafish



> 700 Total

Noteworthy things – Breadth of capability and expertise

Note: Much of this is invisible to the general public so we're still seen as a significant animal-based program



NTP Products, Research Areas, Resources

ABSTRACTS



Developmental (Teratology) Abstracts

Evaluate the potential of chemicals to cause malformations and signs of toxicity during fetal development. [Go >](#)



Drinking Water Abstracts

Studies of water distribution by products provide their potential



Botanical Dietary Supplements



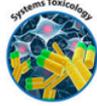
Chemical Effects in Biological Systems

View individual data and summaries from NTP studies. Use guided searches to find organ sites with neoplasia, publications, and more. [Go >](#)



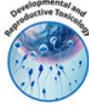
DrugMatrix

Access a comprehensive database of toxicogenomic studies for hundreds of compounds including drugs and environmental chemicals. [Go >](#)



Immunotoxicity Abstracts

The basic research program for the immunotoxicology studies conducted by NTP includes characterization of the potential for a substance to modulate immune function and



Reproductive

Evaluate exposure to reproductive systems



Glyphosate Formulations

NTP is conducting a series of



AIDS Therapeutics Toxicity Reports

Evaluate potential health effects of AIDS therapeutics in laboratory animals. [Go >](#)



Genetically Modified Model Reports

Characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected agents in laboratory animals that have been genetically modified. [Go >](#)



Polycyclic Aromatic Compounds

NTP is currently studying PACs to learn more about the toxicity of individual PACs and PAC mixtures. [Go >](#)



Sulfolane

NTP is performing a set of studies to evaluate sulfolane toxicity and its potential health impacts of exposure. [Go >](#)



Synthetic Turf/Recycled Tire Crumb Rubber

NTP is working to enhance the understanding of potential health impacts of chemicals released from synthetic turf. [Go >](#)



West Virginia Chemical Spill

NTP has completed the West Virginia chemical spill research program. NTP's Final Update, collective findings, and supporting files are now



Monographs

Assess evidence from the literature on substances in our environment that may cause adverse health effects. [Go >](#)



Report on Carcinogens

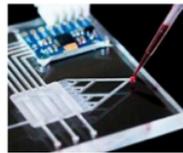
Identifies substances that may put people at increased risk for cancer. People can use the RoC to make informed decisions about their own health. Find [Scientific Review information](#) for substances evaluated since 1996. [Go >](#)

RESOURCES



NTP Archives

Request access to an extensive collection of research specimens and supporting data from over 2000 NTP studies. [Go >](#)



Alternative Toxicology

Gain access to research lists used to support methods development



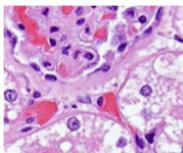
Research Reports

Provide results of NTP research and literature-analysis activities that do not fall under the scope of existing report series. [Go >](#)



Technical Reports

Describe long-term studies that characterize and evaluate the toxicologic potential of selected test articles in animals. [Go >](#)



Nonneoplastic Lesion Atlas

Search the atlas for high-quality images and descriptions of rodent nonneoplastic lesions. [Go >](#)



Tox21 Tool

Access useful tools for the Tox21 qHTS. [Go >](#)



Toxicity Reports

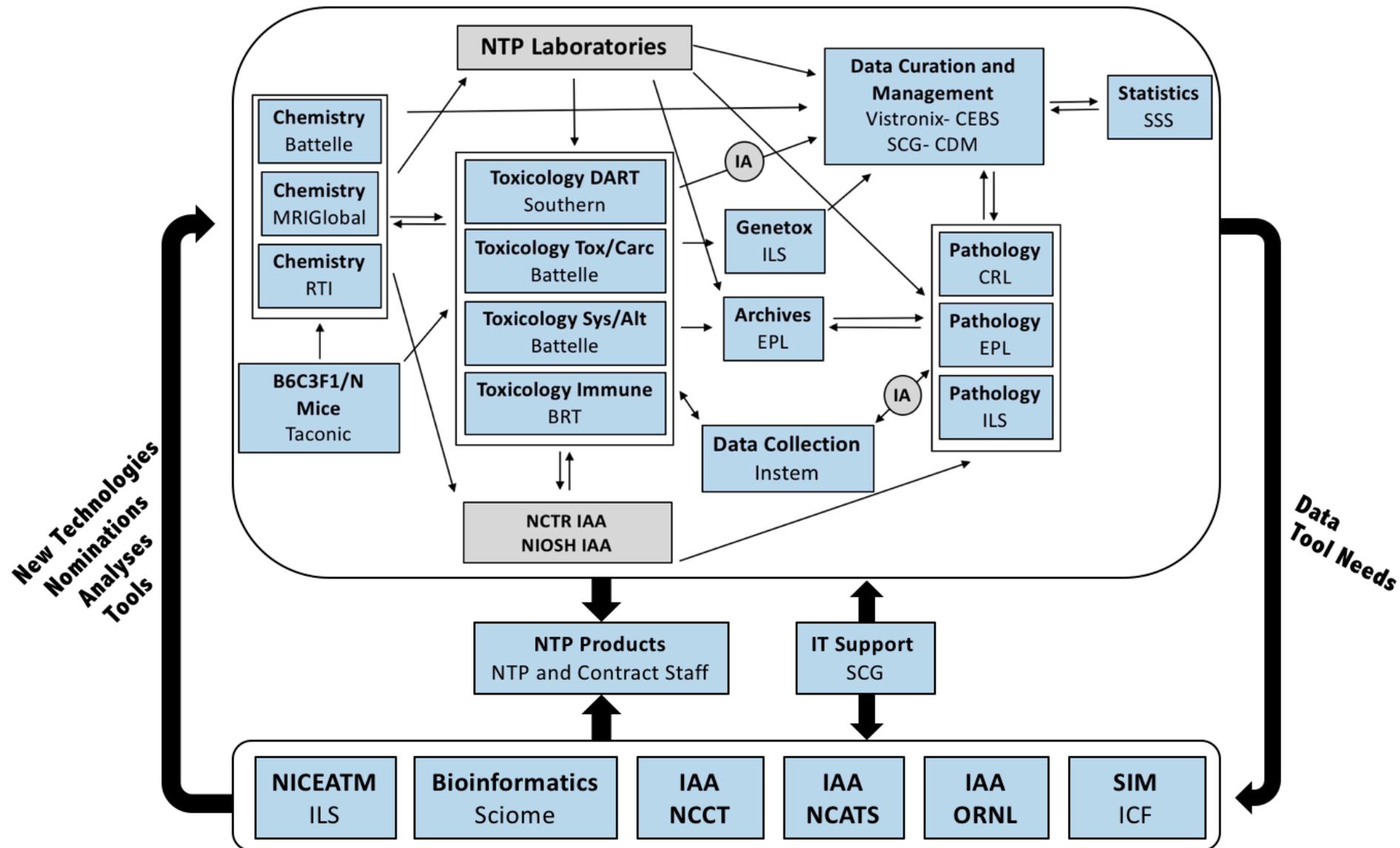
Describe short-term studies that characterize and evaluate the toxicologic potential of selected substances in laboratory animals. [Go >](#)

Noteworthy things – Breadth of products



Noteworthy things – Breadth of complexity

NTP Contract Support





- Multi-disciplinary expertise in toxicology
- Capabilities
 - General toxicology studies (with enablers like chemistry, TK/TD, etc.)
 - Repro/developmental
 - Immunotoxicity
 - Mechanistic/investigative toxicology
 - In vitro capabilities
 - Computational/in silico approaches
 - Literature/evidence-based assessments
 - Data management
- Taking on really hard problems!!!



- We can't animal study our way out of the growing need for insights into hazards from environmental exposures (chemical and non-chemical agents)
- Current non-animal approaches are better at producing data than enabling decisions
- The decision-making process of our stakeholders is still largely entrenched in the phenotypic outcomes of animal studies
- There is a gap in our ability to 'predict' human outcomes from higher throughput and more mechanistic *in silico* and *in vitro* assays
- Our resourcing is likely to remain relatively flat
- We've been too productive
- Our primary stakeholder (i.e., the public) is confused



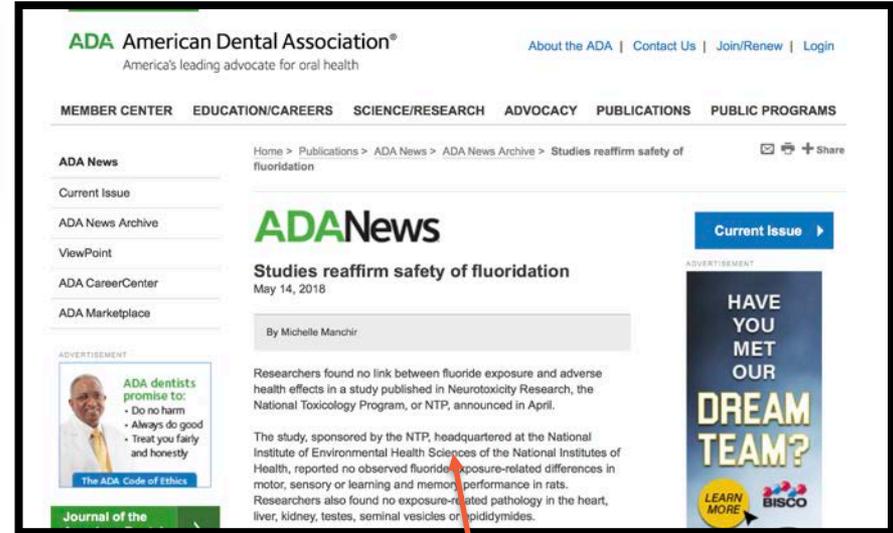
Solutions – Understand What Stakeholders Care About



They want us to help them understand hazards in their environment

Dear Secretary Azar and Director Linda S. Birnbaum:

I am writing today to implore you to direct the National Toxicology Program and the Agency for Toxic Substances and Disease Registry to conduct additional research into the link between exposure to polychlorinated biphenyls (PCBs) and cancer. It is important for us to fully understand the public health implications between PCBs and cancer in order to develop a plan to protect those who have been exposed to these dangerous chemicals.



They care about how we do the work



They look to us to affirm their decisions



Solutions – Align on a Vision

Translational Toxicology at NTP

Our impact



Our aims

Inform the present

- Engaging, informing and educating stakeholders
- Timely responses
- Contextualizing data

Innovate the future

- Build mechanistic understanding
- Capability innovation
- Train next generation of translational toxicologists

Our tools Literature analysis Animal studies In vitro systems In silico/computational analytics

Vision: Advancing public health and the discipline of toxicology through the use of innovative tools and strategies that are translatable, predictive, and timely.



Solutions – Align on a Vision

Translational Toxicology at NTP

Our impact

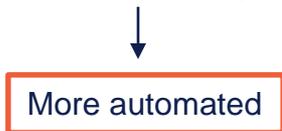


Our aims

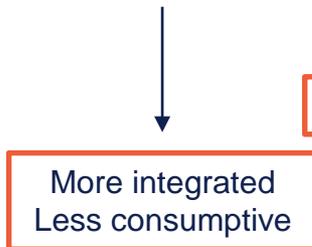


Our tools

Literature analysis



Animal studies



In vitro systems



In silico/computational analytics

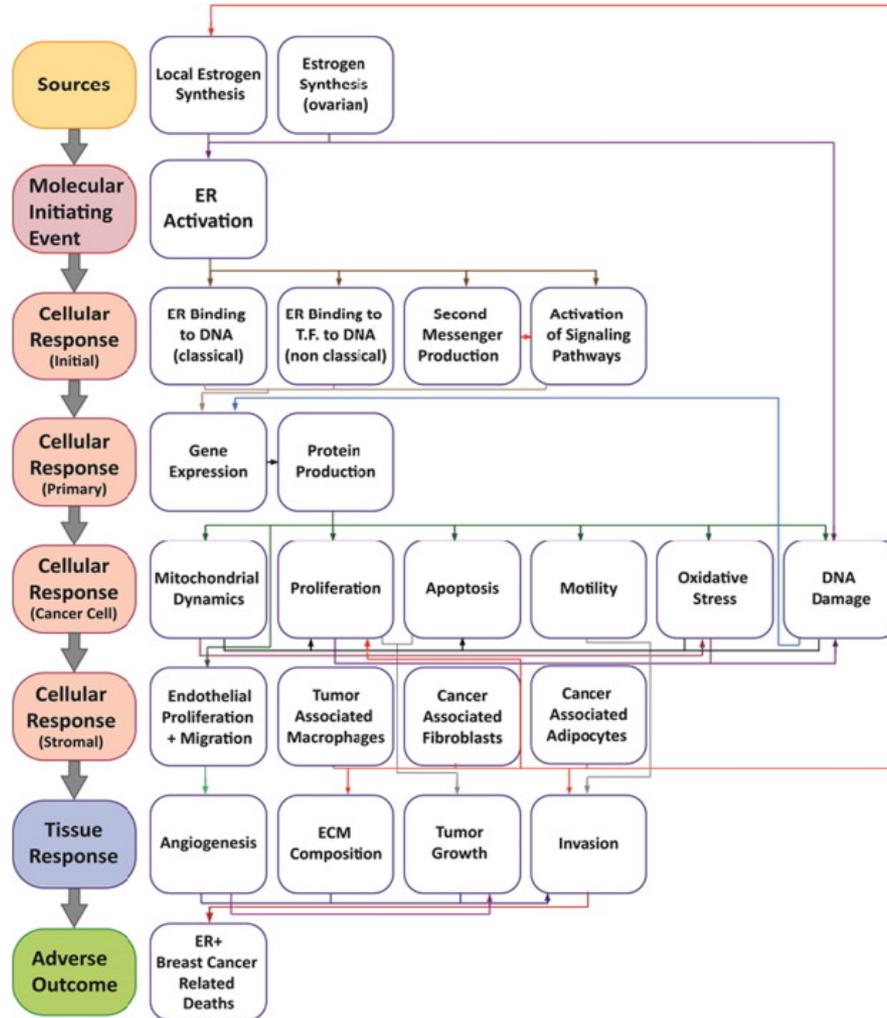


Vision: Advancing public health and the discipline of toxicology through the use of innovative tools and strategies that are translatable, predictive, and timely.



Solutions – Focus on a Fundamental Problem

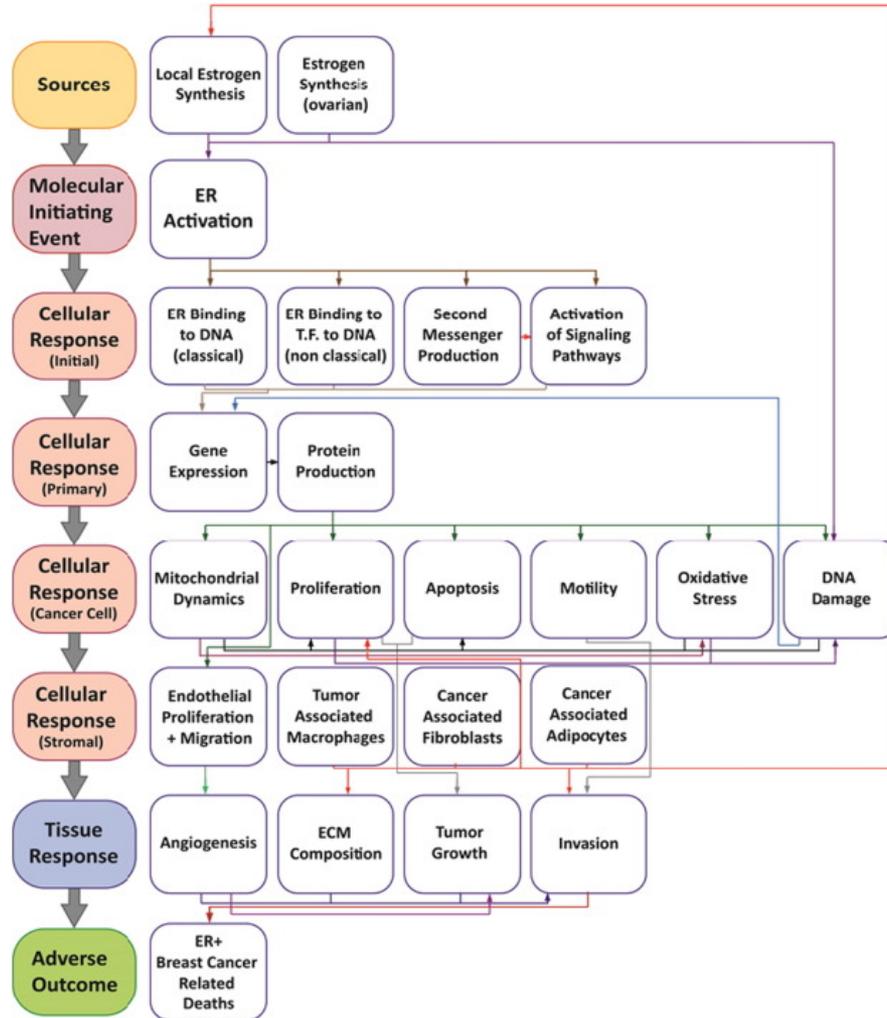
Estrogen Receptor (ER) pathway to breast cancer





Pathobiology – Predictive Toxicology Conundrum

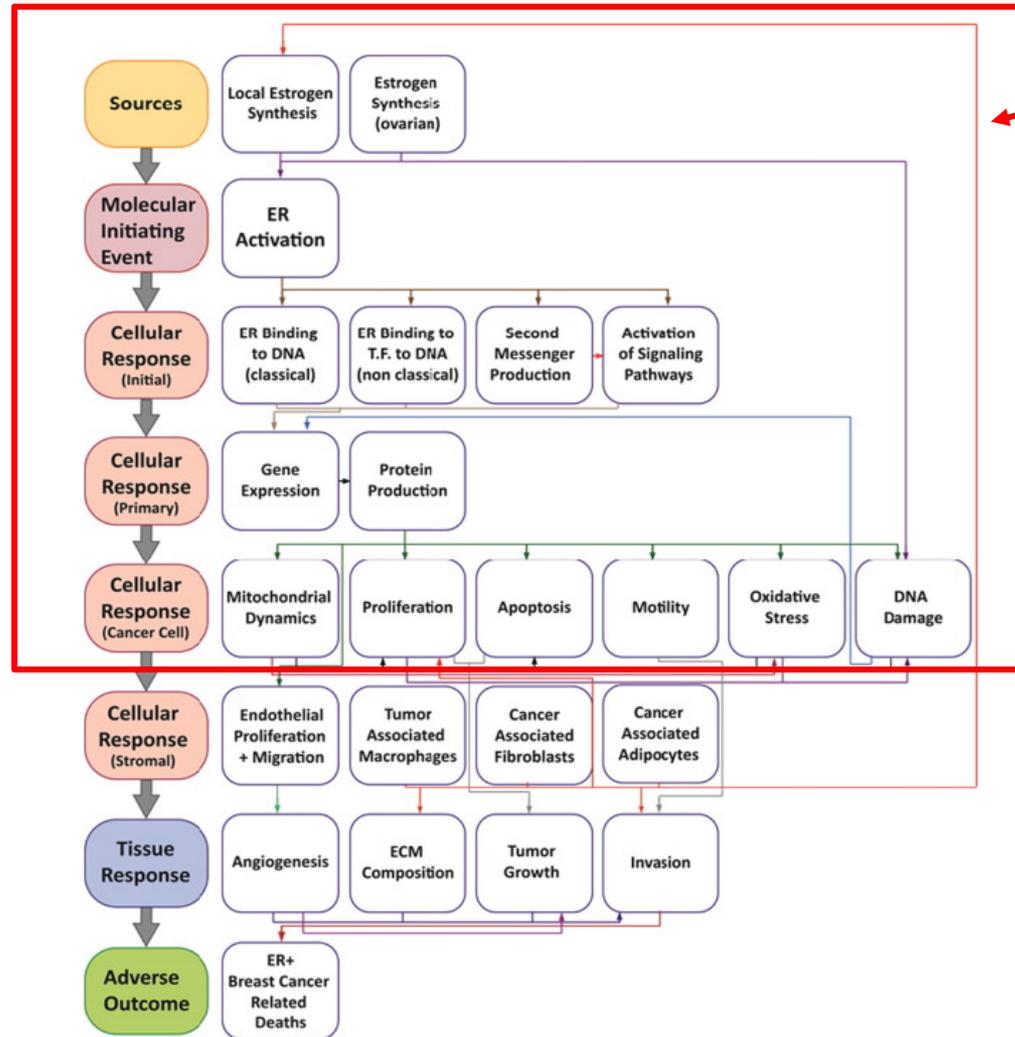
ER pathway to breast cancer





Pathobiology – Predictive Toxicology Conundrum

ER pathway to breast cancer

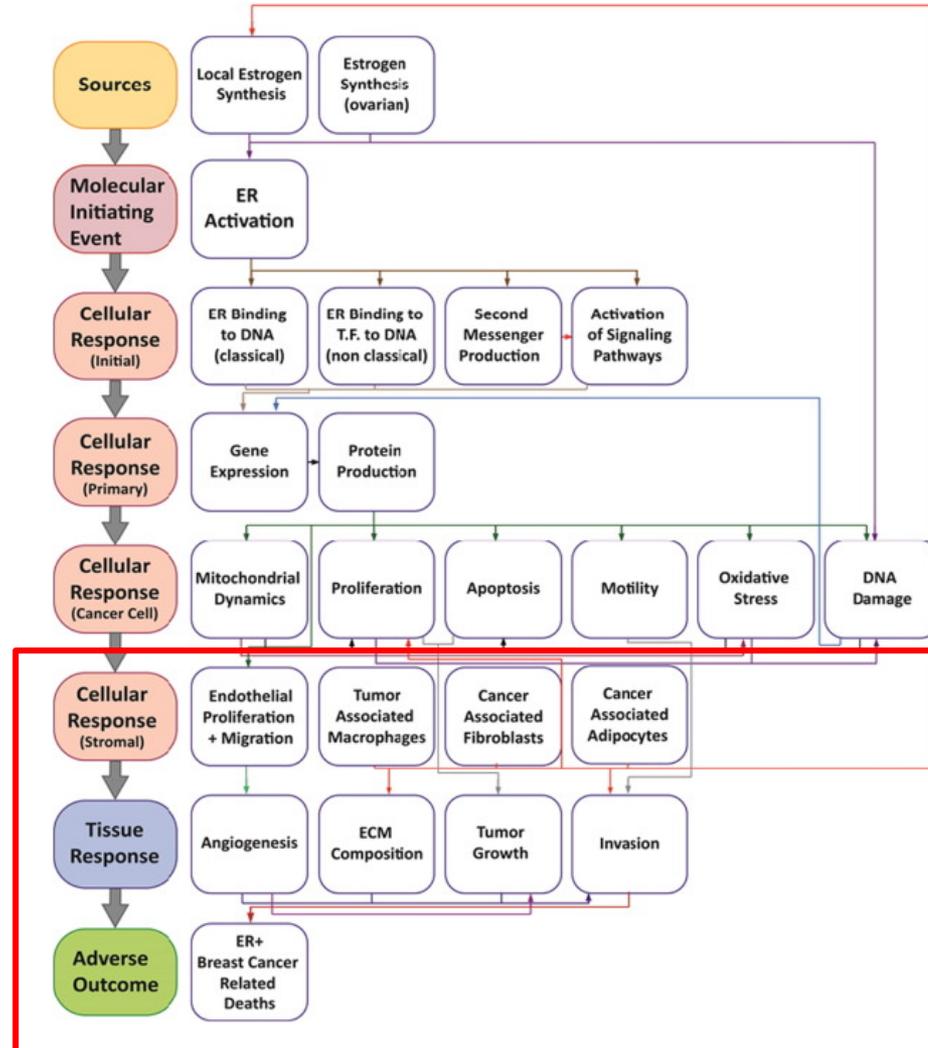


Normal adaptive biology



Pathobiology – Predictive Toxicology Conundrum

ER pathway to breast cancer



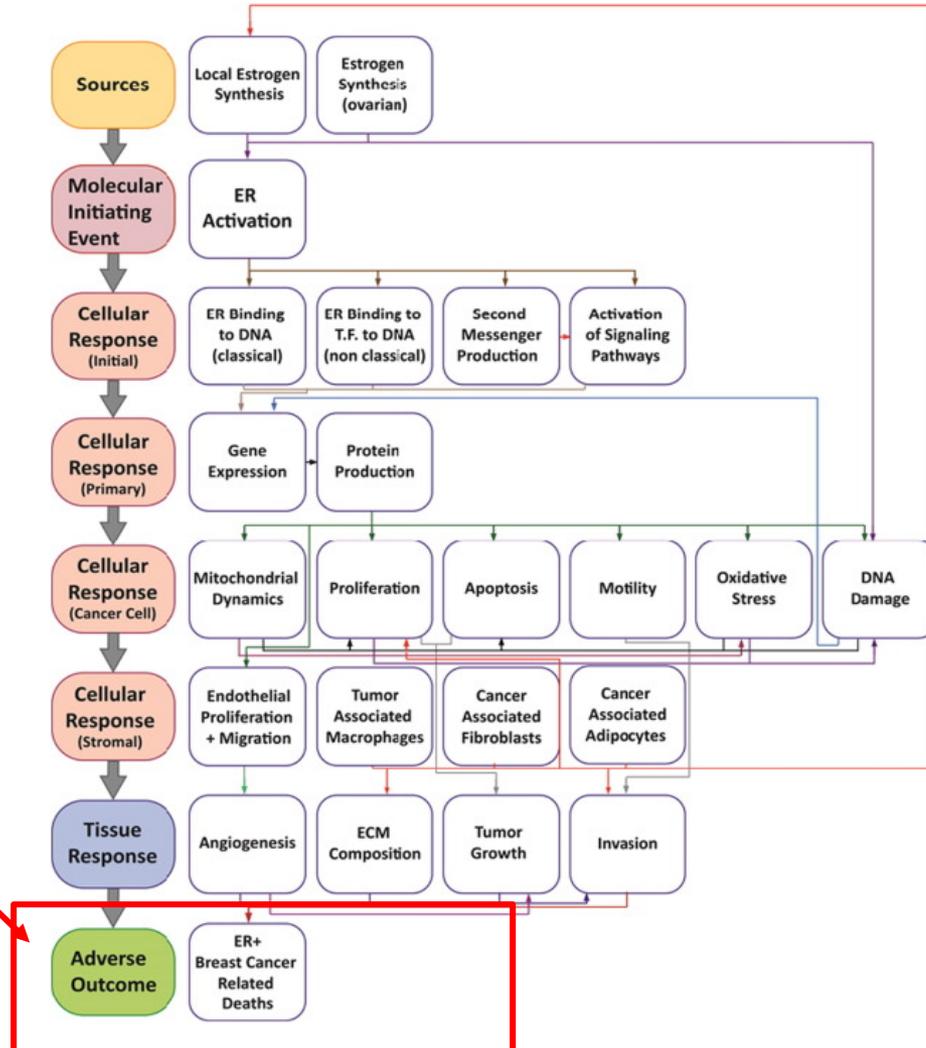
This is what we recognize to be bad.



Pathobiology – Predictive Toxicology Conundrum

ER pathway to breast cancer

This is what we traditionally model in observational ways.

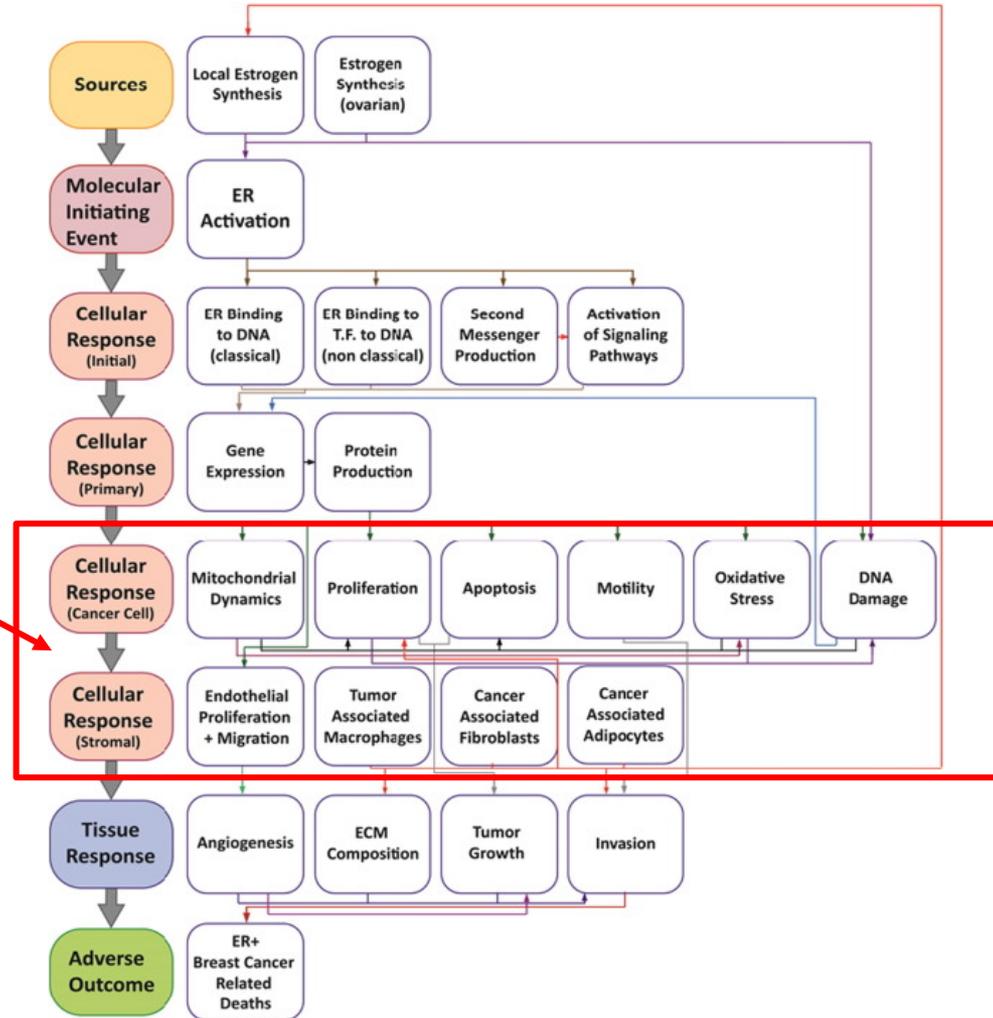




Pathobiology – Predictive Toxicology Conundrum

ER pathway to breast cancer

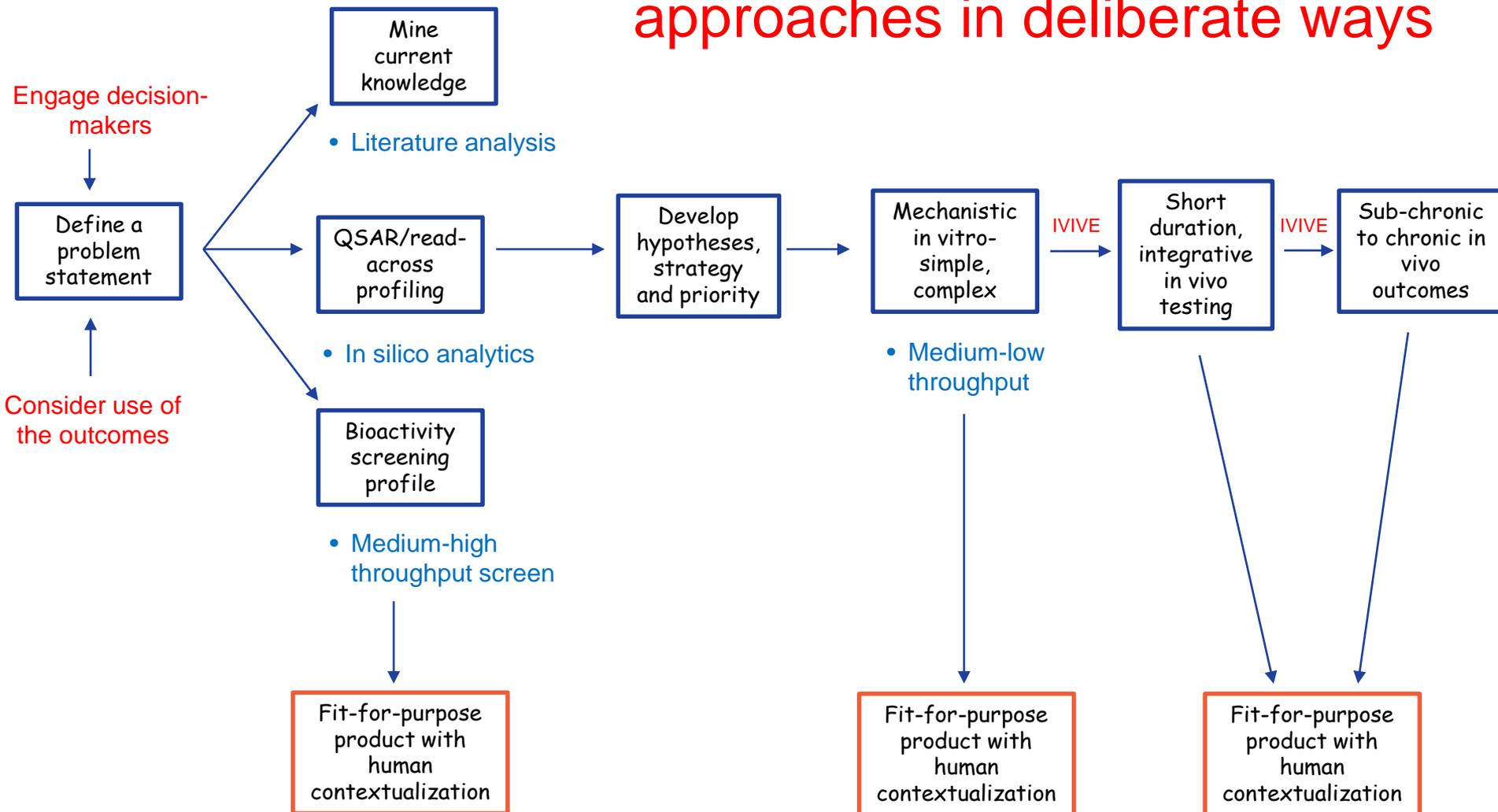
This is the inflection point we need to model since it represents the bridge between observation and prediction





NTP Translational Toxicology Pipeline

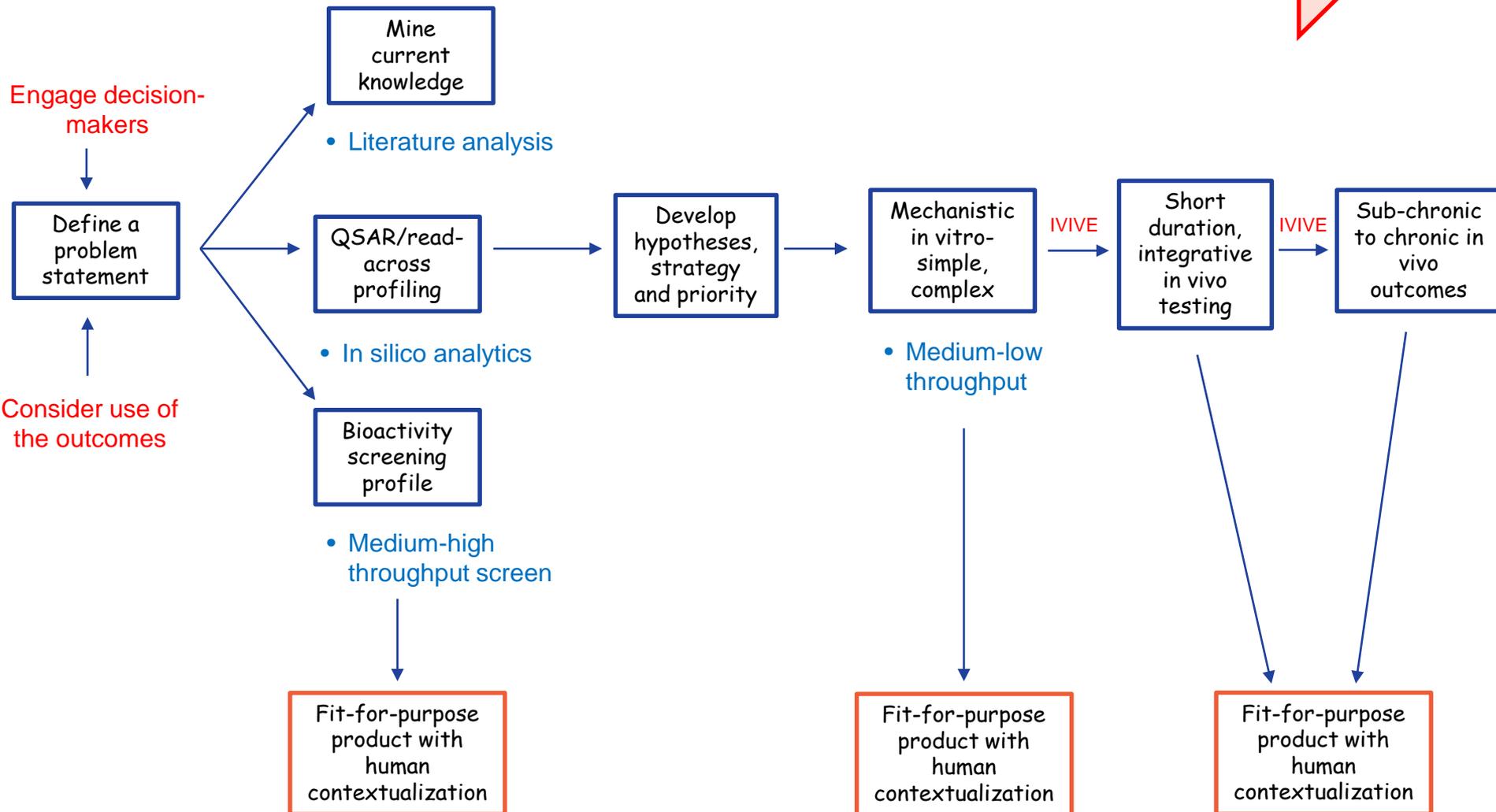
Apply our tools and approaches in deliberate ways





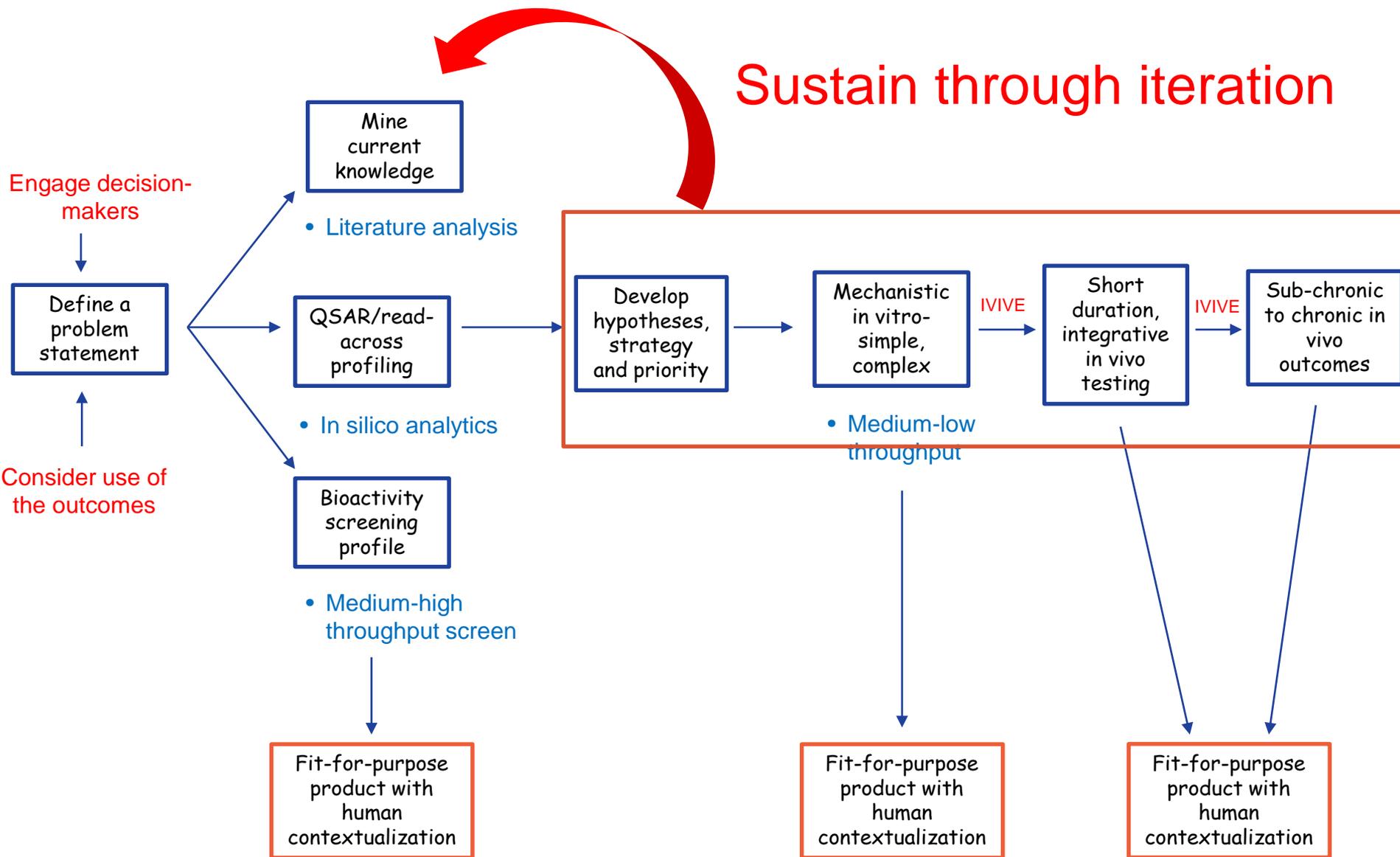
NTP Translational Toxicology Pipeline

Enable by informed progression



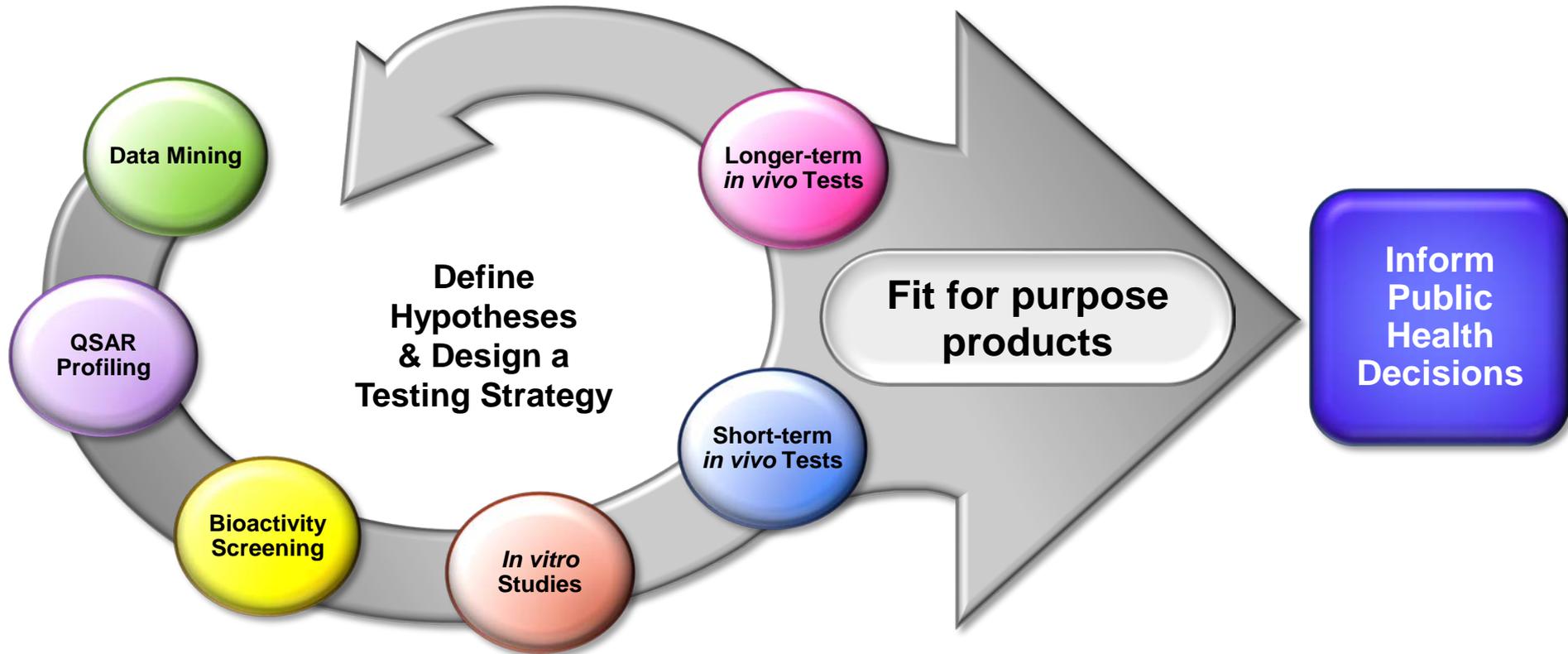


NTP Translational Toxicology Pipeline



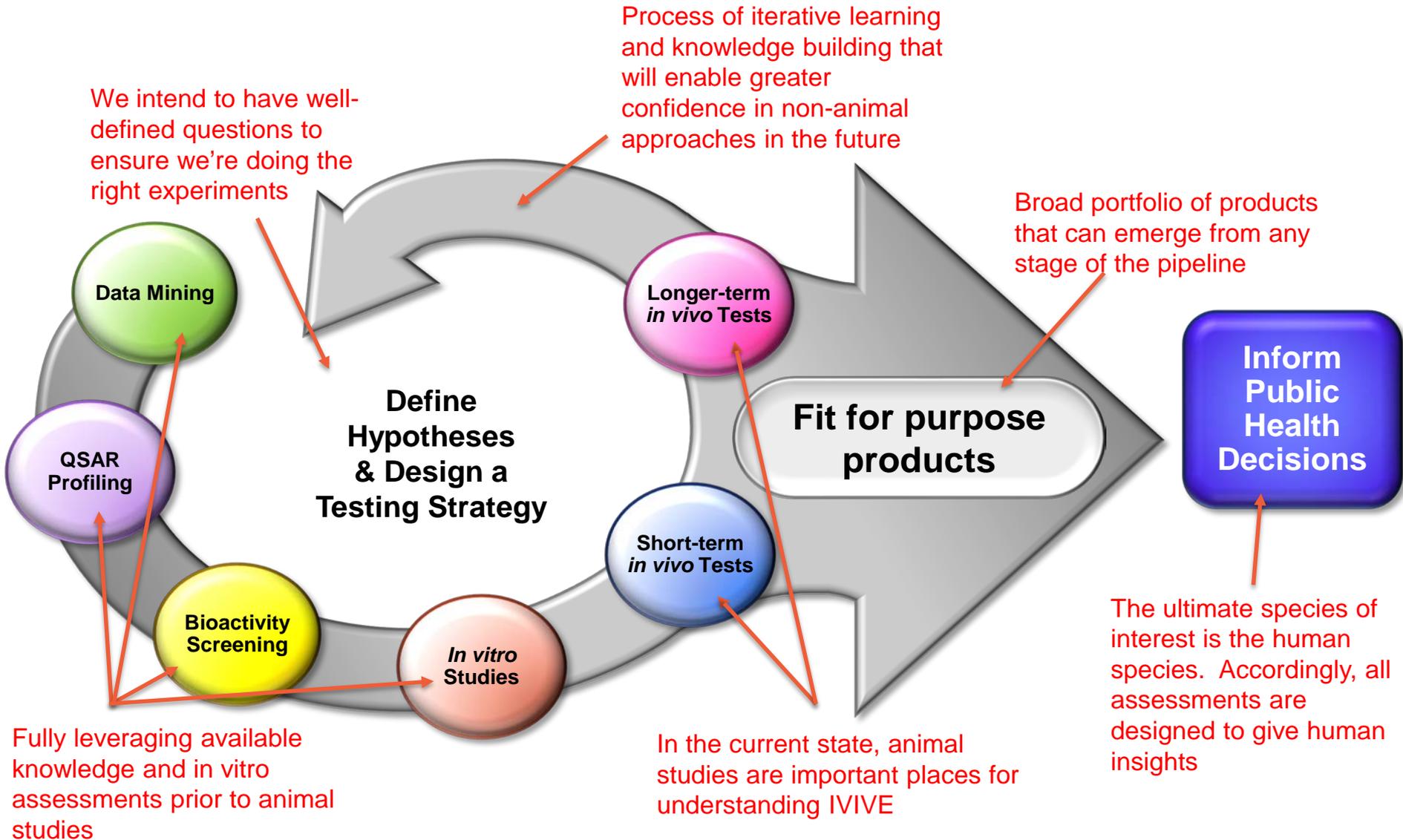


DNTP Translational Toxicology Pipeline Plan





DNTP Translational Toxicology Pipeline Plan





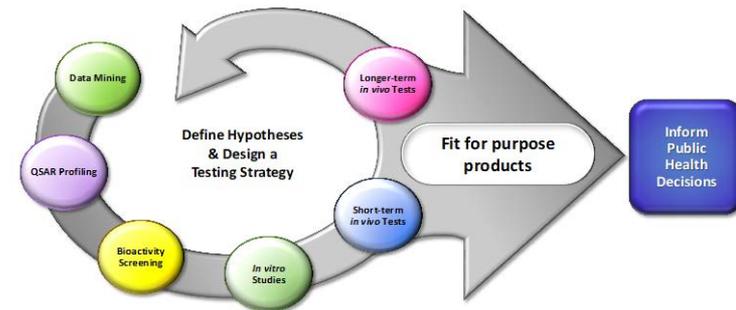
Solutions – Define Ways of Working

- Innovate at pace and for cause
- Leverage partnerships
- Leverage technology
- A portfolio that reflects contemporary needs and concerns
- Dynamic portfolio management
- Disciplined prioritization
- Judicious animal use
- Communication as a first intent
- Public engagement and education



NTP Portfolio Examples

- NTP Synthetic Turf/Recycled Tire Crumb Rubber Research
- Studies of Cell Phone Radiofrequency Radiation (RFR)
 - Report on March 26-28 2018 Peer Review of NTP Technical Reports
 - Follow-up Studies on RFR
- Activities on Bisphenols
 - CLARITY-BPA Research Program: Peer Review of Core Study and Next Steps
 - Evaluation of Bisphenol Analogues
- REACT Program for Per- and Polyfluoroalkyl Substances





Questions?