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United States Environmental Protection Agency

EPA's Rapid Exposure and Dosimetry (RED) Project

January 23, 2018

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Chemical Regulation in the United States

- Park *et al.* (2012): At least 3221 chemicals in pooled human blood samples, many appear to be exogenous
- A tapestry of laws covers the chemicals people are exposed to in the United States (Breyer, 2009)
- Different testing requirements exist for food additives, pharmaceuticals, and pesticide active ingredients (NRC, 2007)

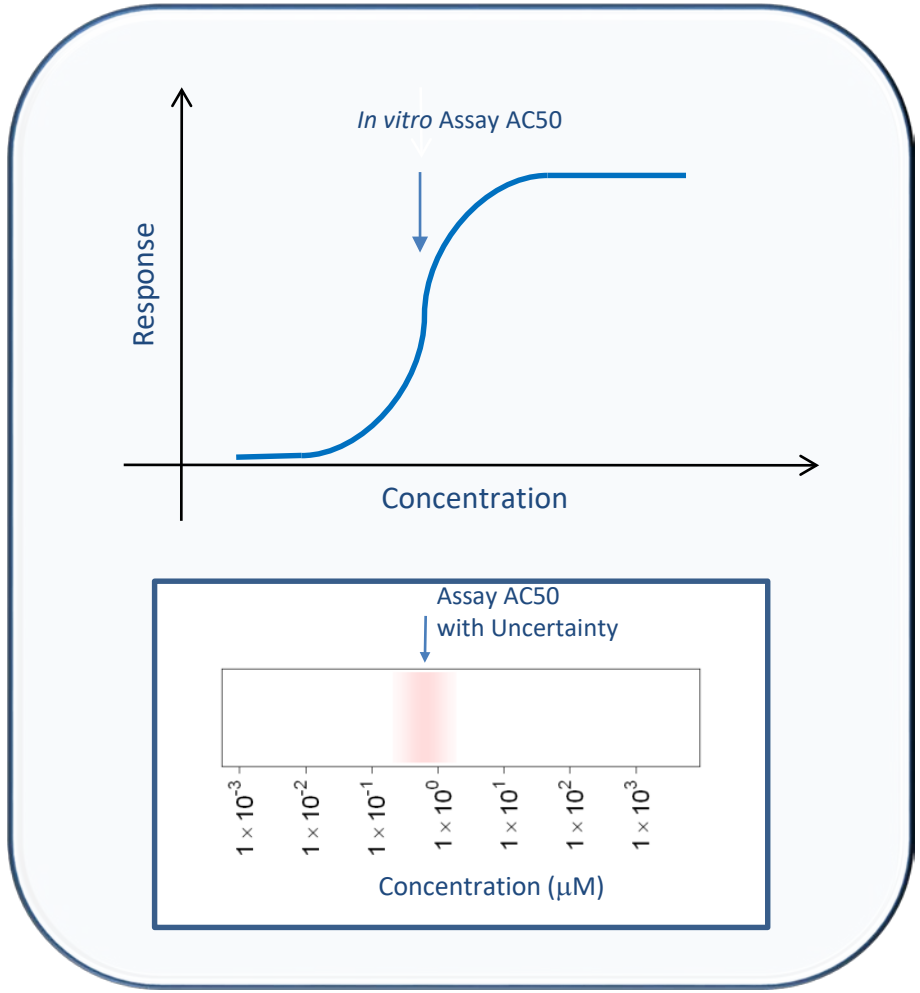
November 29, 2014

Chemical Regulation in the United States

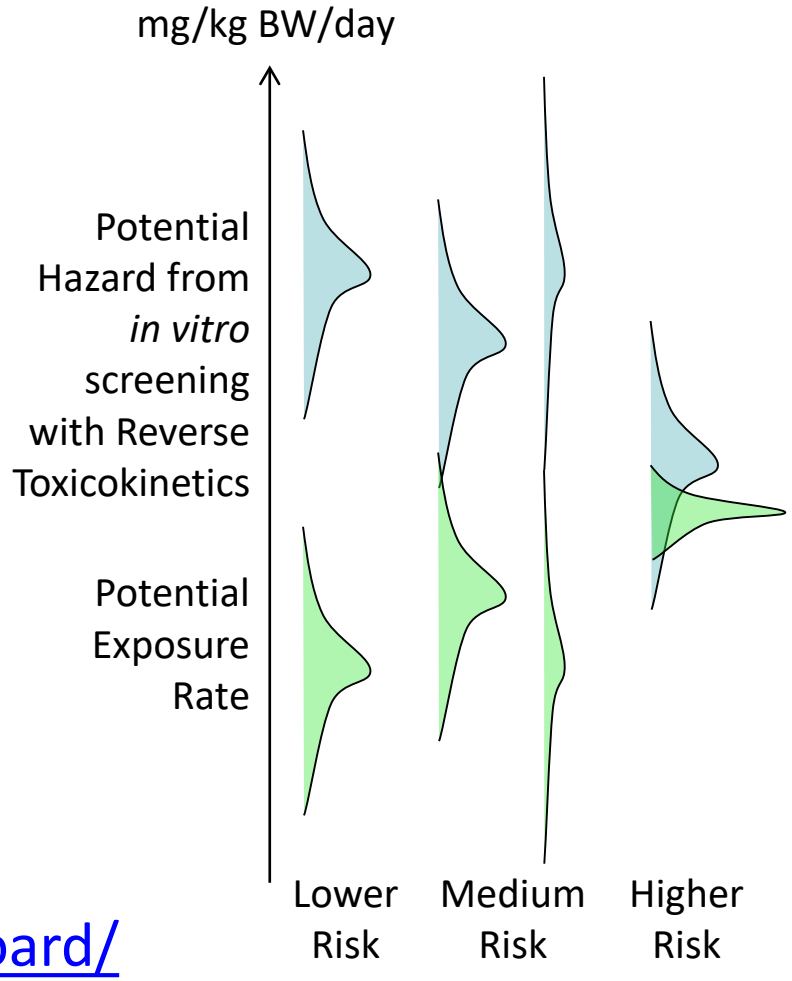
- Most other chemicals, ranging from industrial waste to dyes to packing materials are covered by the recently updated Toxic Substances Control Act (TSCA)
  - Thousands of chemicals on the market were either "grandfathered" in or were allowed without experimental assessment of hazard, toxicokinetics, or exposure
  - Thousands of new chemical use submissions are made to the EPA every year
  - **Methods are being developed to prioritize these existing and new chemicals for testing**

November 29, 2014

Chemical Risk = Hazard + Exposure

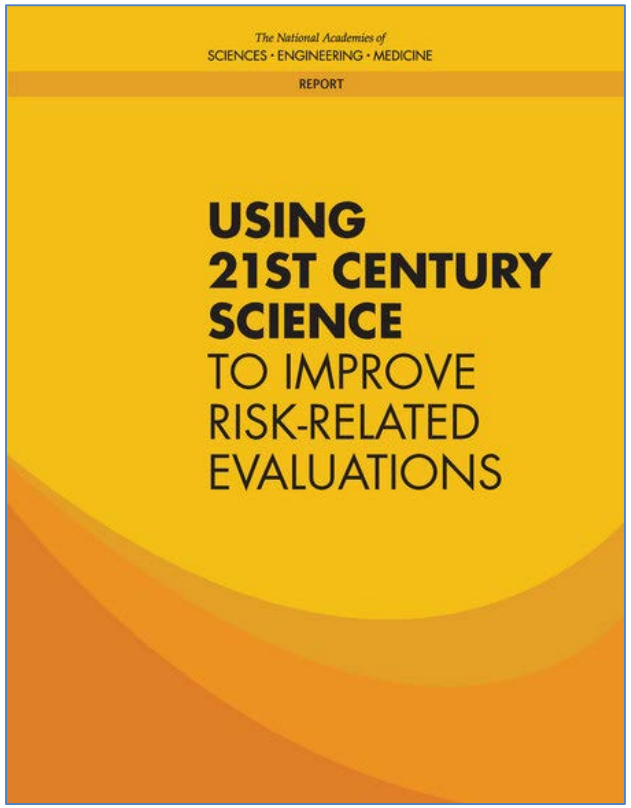


- "High Throughput" methods allow rapid assessment of potential hazard using "drug discovery" tools
- **Tox21**: Examining >10,000 chemicals using ~50 assays intended to identify interactions with biological pathways (Schmidt, 2009)
- **EPA Toxicity Forecaster (ToxCast)**: For a subset (>3000) of Tox21 chemicals run >1000 additional assay endpoints (Judson et al., 2010)



http://comptox.epa.gov/dashboard/

Exposure Based Priority Setting



National Academy of Sciences, January, 2017:
"Translation of high-throughput data into risk-based rankings is an important application of exposure data for chemical priority-setting. Recent advances in high-throughput toxicity assessment, notably the ToxCast and Tox21 programs… and in high-throughput computational exposure assessment… have enabled first-tier risk-based rankings of chemicals on the basis of margins of exposure…"

EPA Office of Research and Development

- The Office of Research and Development (ORD) is the scientific research arm of EPA
  - 655 peer-reviewed journal articles in 2016
- Research is conducted by ORD's three national laboratories, four national centers, and two offices
  - Includes **National Center for Computational Toxicology** and **National Exposure Research Laboratory**
- 14 facilities across the country and in Washington, D.C.
- Six research programs
  - Includes **Chemical Safety for Sustainability**
- Research conducted by a combination of Federal scientists; contract researchers; and postdoctoral, graduate student, and post-baccalaureate trainees

ORD Facility in Research Triangle Park, NC

EPA's Rapid Exposure and Dosimetry Project

Co-leaders Kristin Isaacs and John Wambaugh

We do exposure forecasting or "ExpoCast"

NCCT
Chris Grulke
Greg Honda
Richard Judson
Andrew McEachran
Robert Pearce
Ann Richard
Risa Sayre
Woody Setzer
Rusty Thomas
John Wambaugh
Antony Williams

NRMRL
Yirui Liang
Xiaoyu Liu

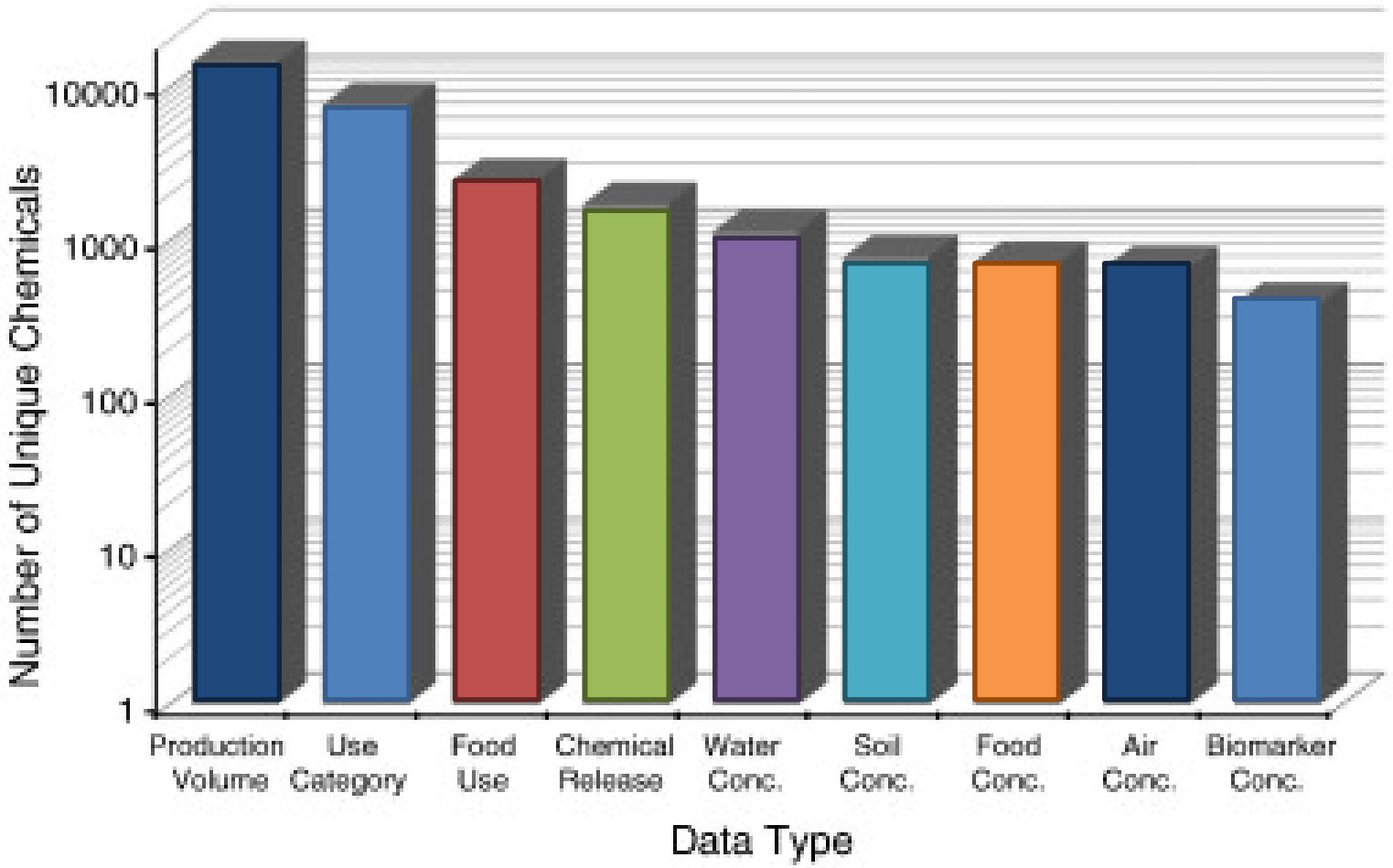
NHEERL
Linda Adams
Christopher Ecklund
Marina Evans
Mike Hughes
Jane Ellen Simmons

NERL
Craig Barber
Namdi Brandon
Peter Egeghy
Hongtai Huang
Brandall Ingle
Kristin Isaacs
Dawn Mills
Seth Newton
Katherine Phillips
Paul Price
Jeanette Reyes
Jon Sobus
John Streicher
Mark Strynar
Mike Tornero-Velez
Elin Ulrich
Dan Vallero
Barbara Wetmore

We develop exposure and toxicokinetic models, statistical methods, and chemical analyses of environmental samples including water, dust, blood, and household products

Chemical Safety for Sustainability (CSS)
Jeff Frithsen, Acting National Program Director
Lead CSS
Matrix Interfaces:
John Kenneke (NERL)
John Cowden (NCCT)

Limited Available Data for Exposure Estimations



- Most chemicals lack exposure data (Egeghy et al., 2012)

Forecasting Exposure is a Systems Problem

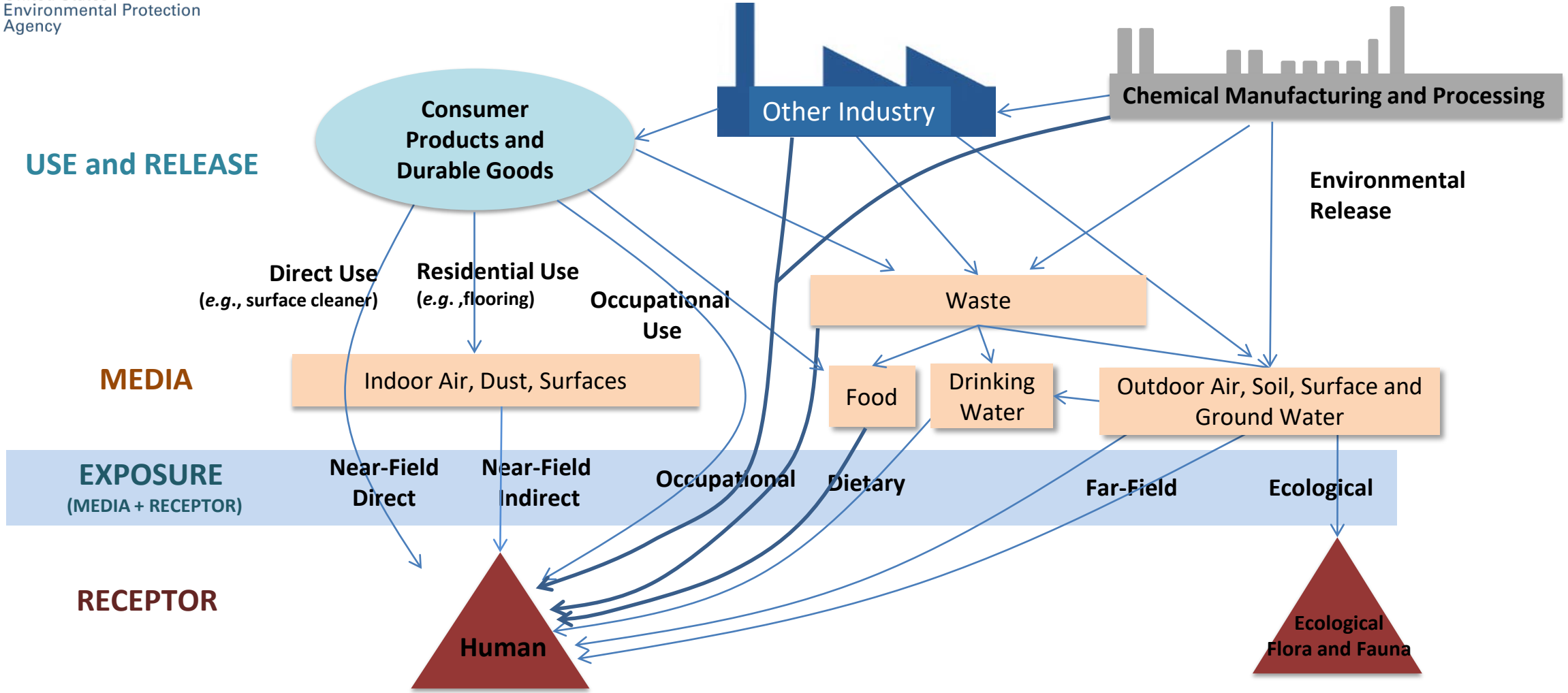


Figure from Kristin Isaacs

Forecasting Exposure is a Systems Problem

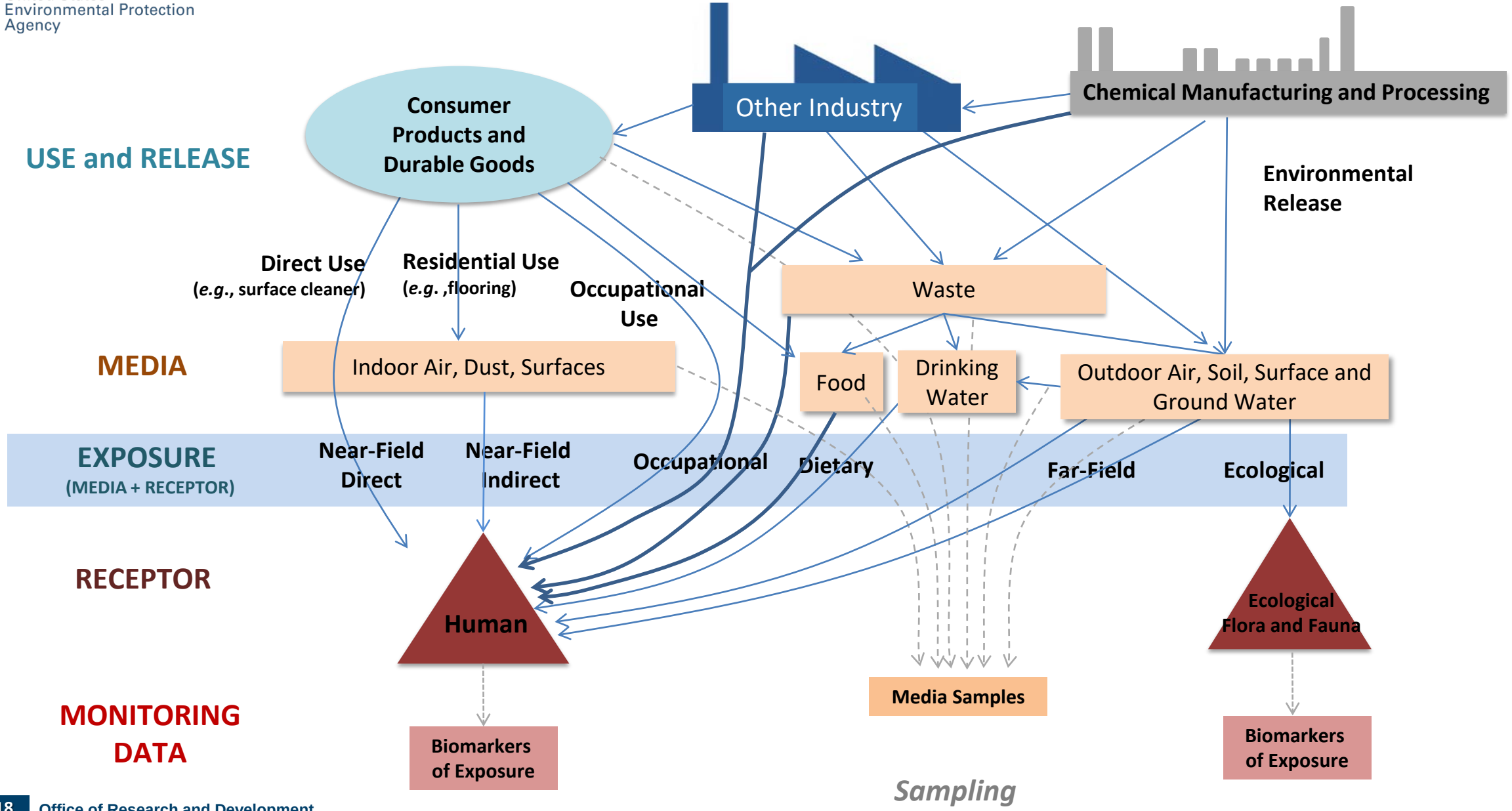


Figure from Kristin Isaacs

Consumer Pathways

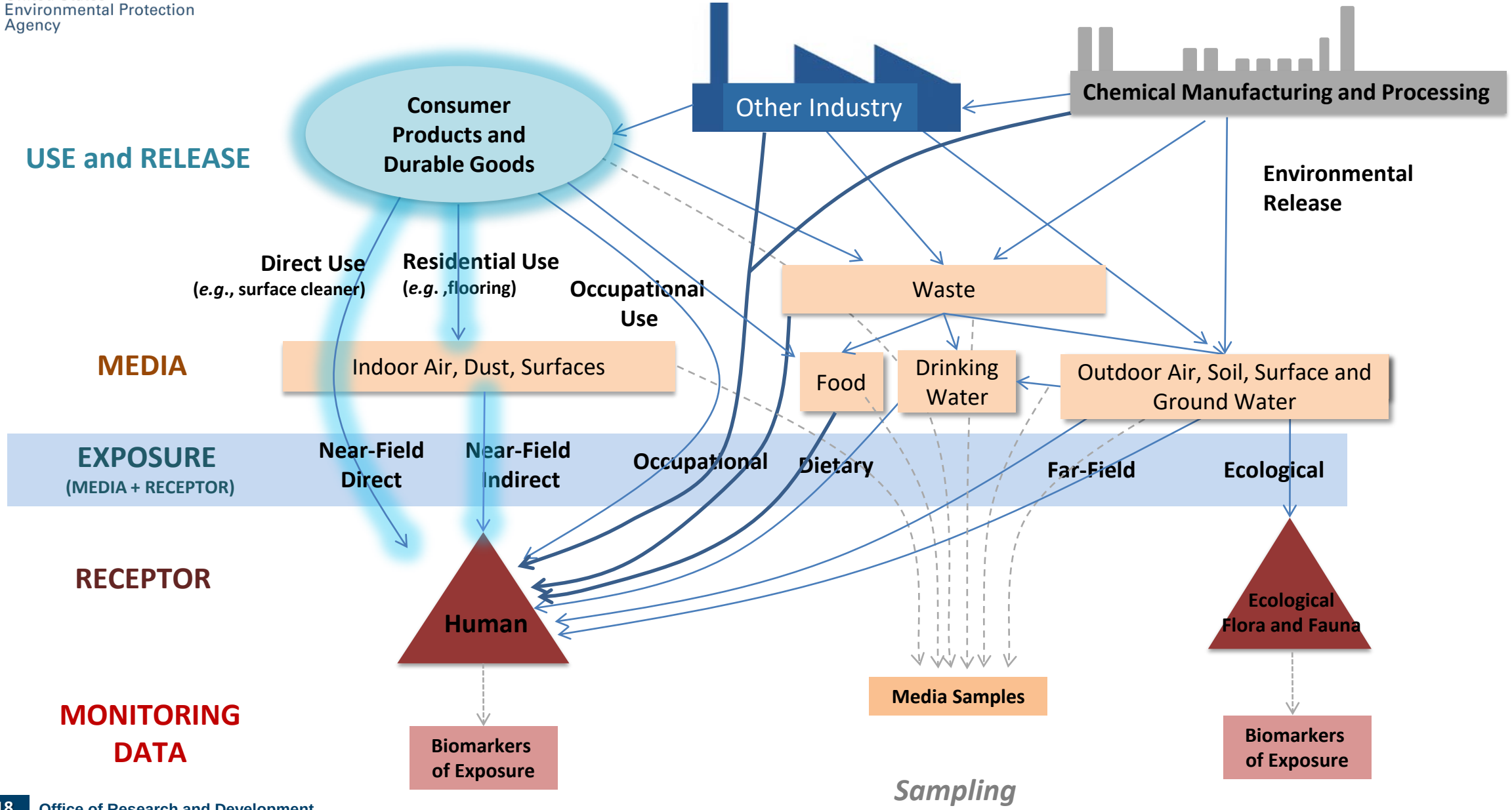
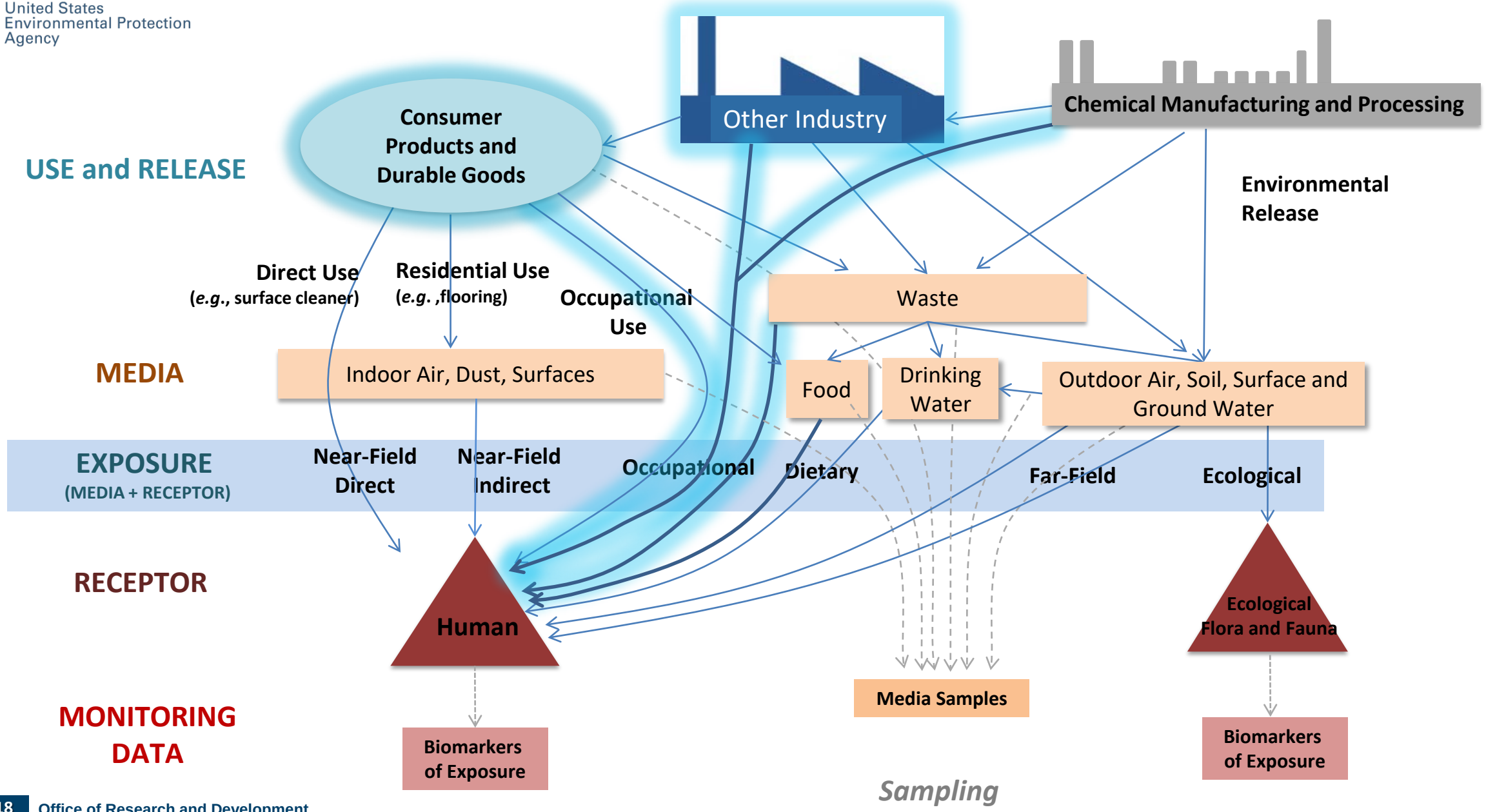


Figure from Kristin Isaacs

Occupational Pathways



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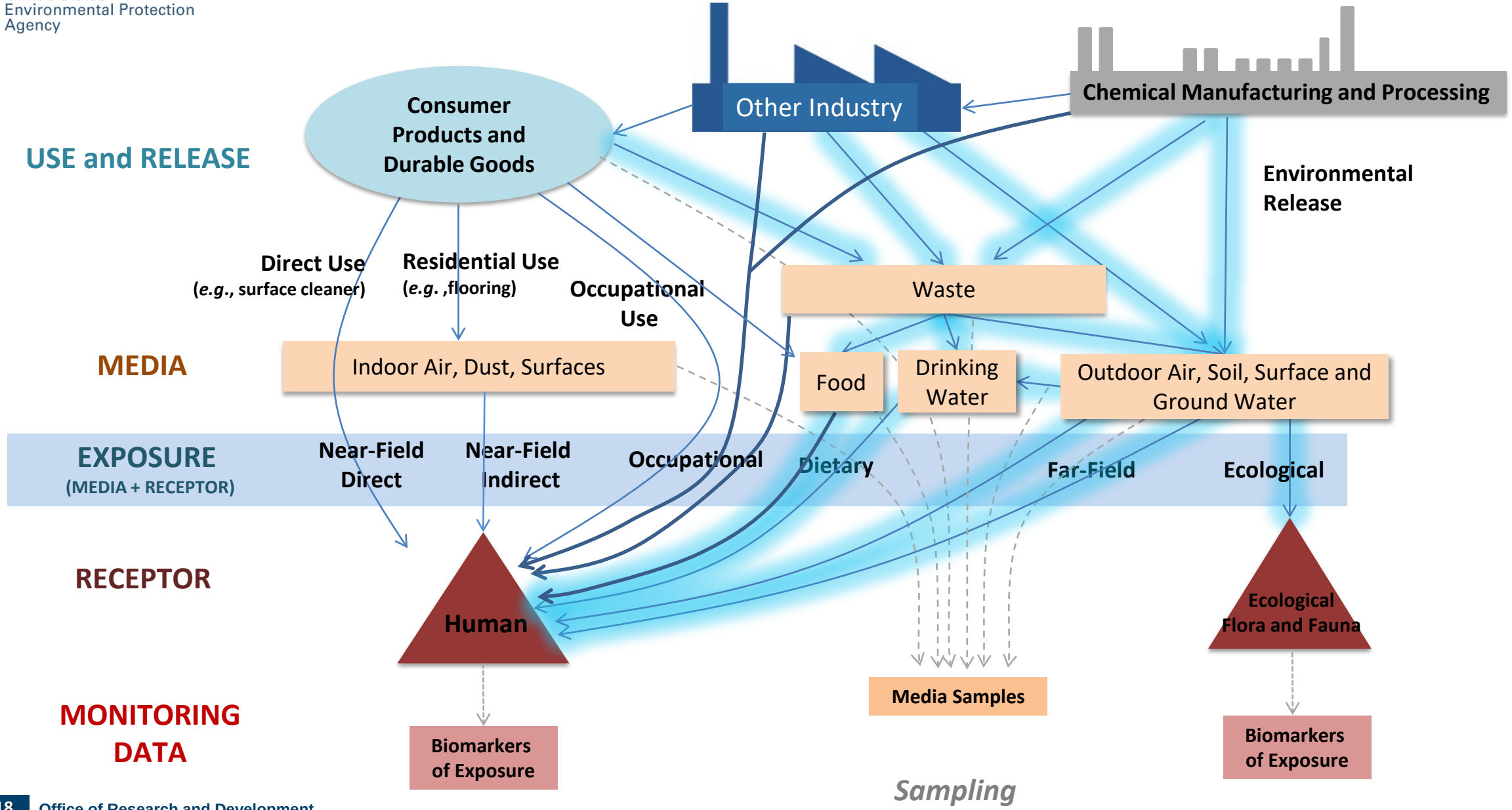
Ambient Pathways (Human and Ecological)



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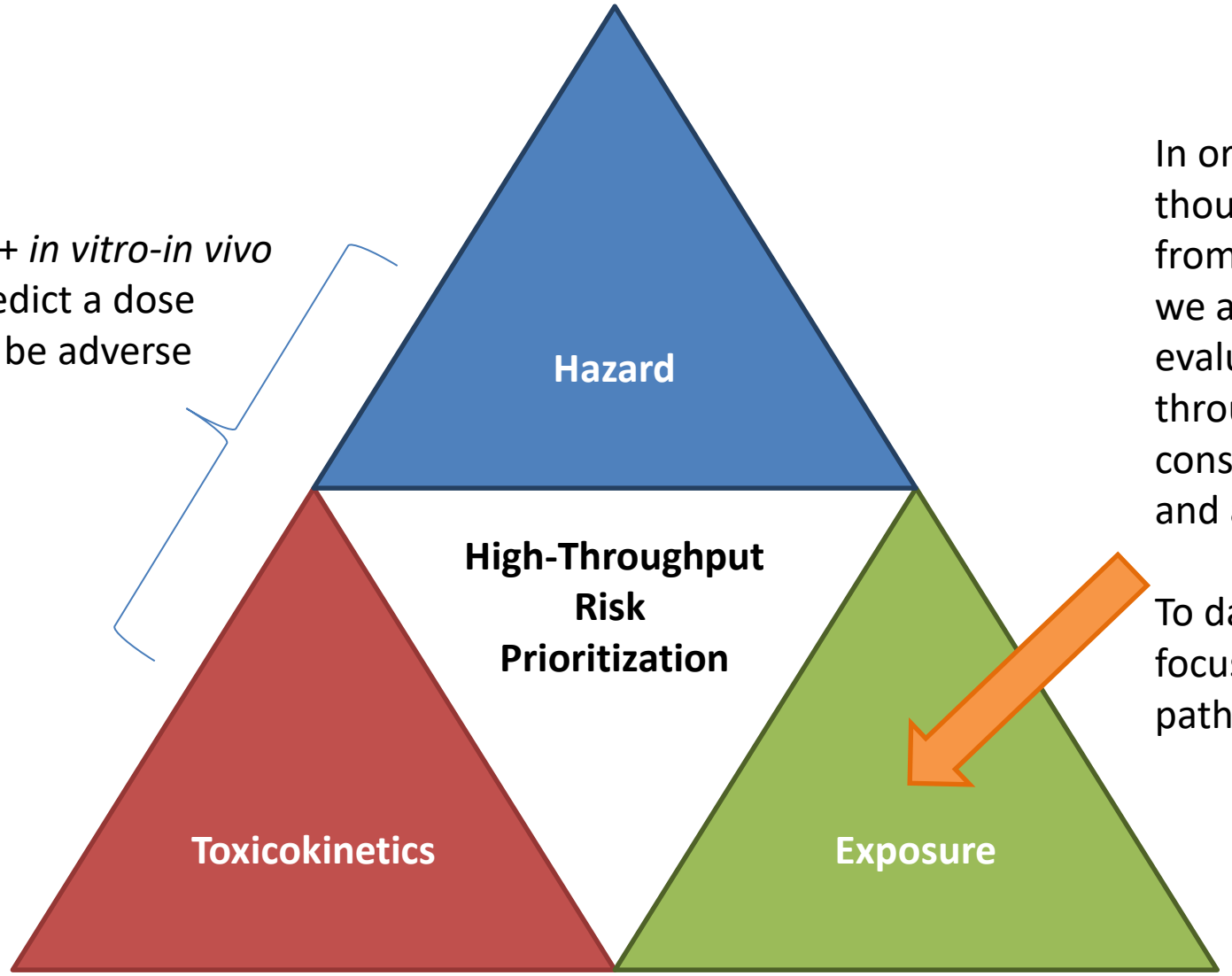
New Exposure Data and Models

High throughput screening + *in vitro-in vivo* extrapolation (IVIVE can predict a dose (mg/kg bw/day) that might be adverse



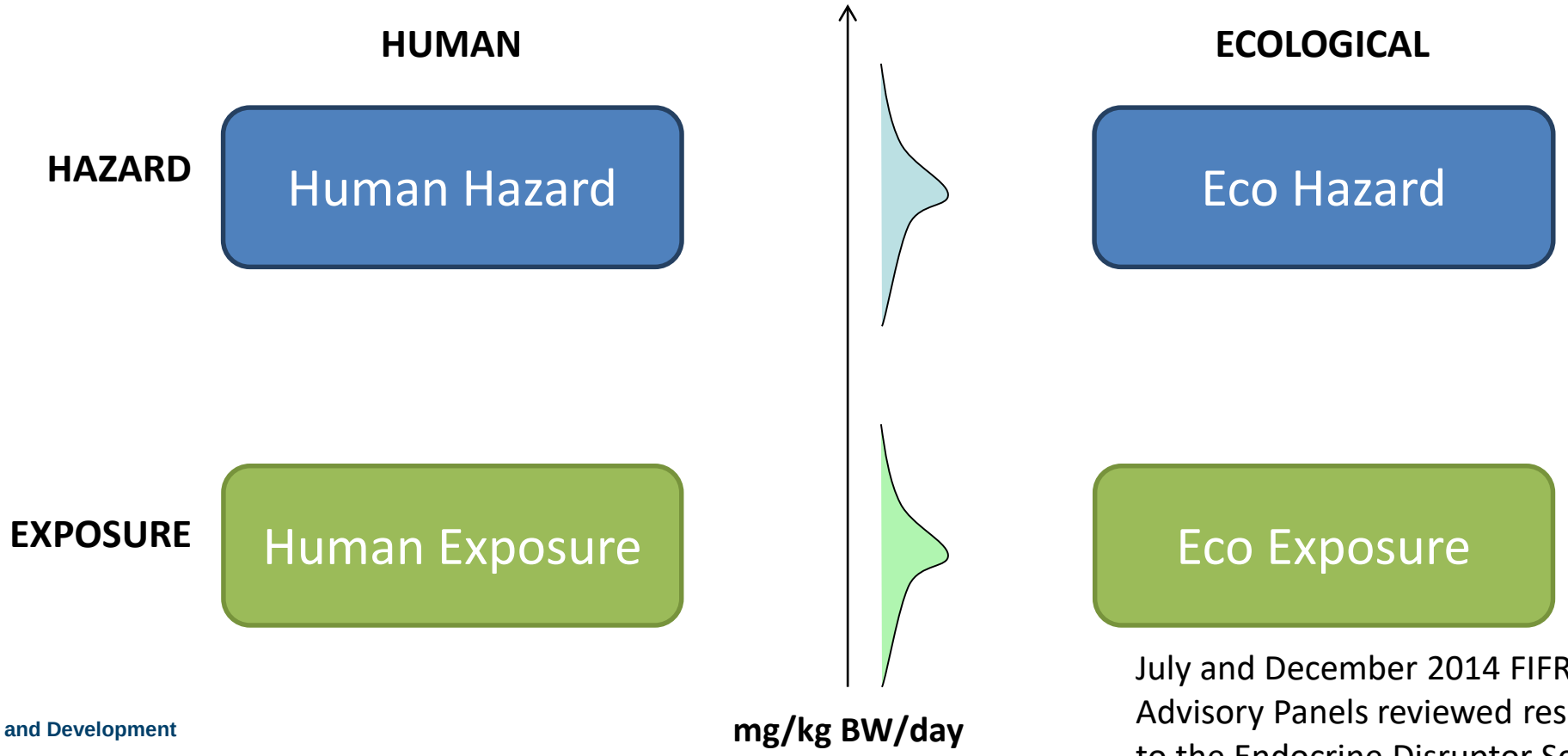
In order to address thousands of chemicals from limited information, we are working to evaluate and develop high throughput models for consumer, occupational, and ambient pathways

To date, most efforts have focused on consumer pathways

High Throughput Risk Prioritization in Practice

The Endocrine Disruptor Screening Program (EDSP) uses a two tiered approach to screen pesticides, chemicals, and environmental contaminants for their potential effect on estrogen, androgen and thyroid hormone systems.

All pesticide actives and chemicals in drinking water



July and December 2014 FIFRA Scientific Advisory Panels reviewed research as it applies to the Endocrine Disruptor Screening Program

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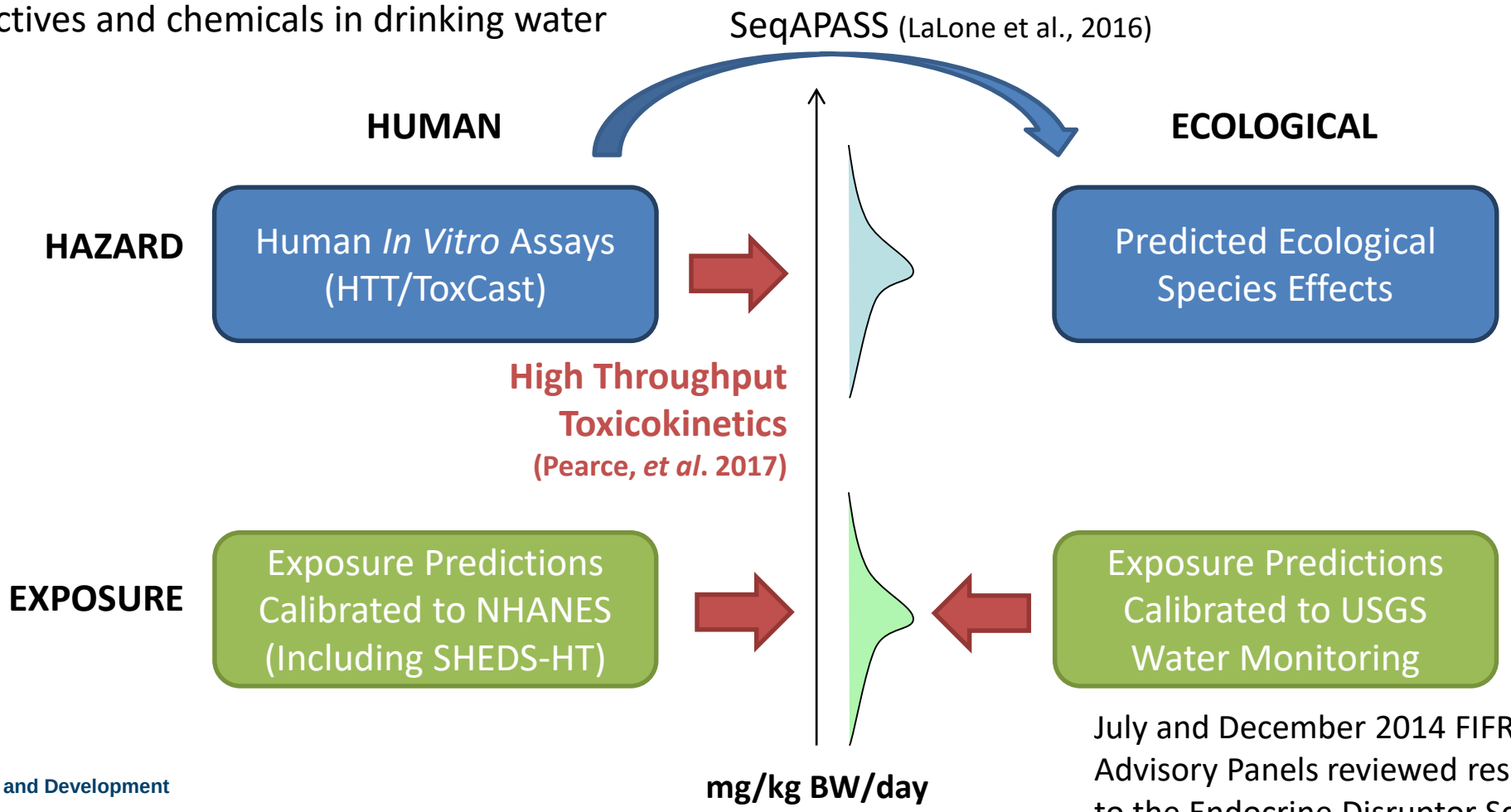

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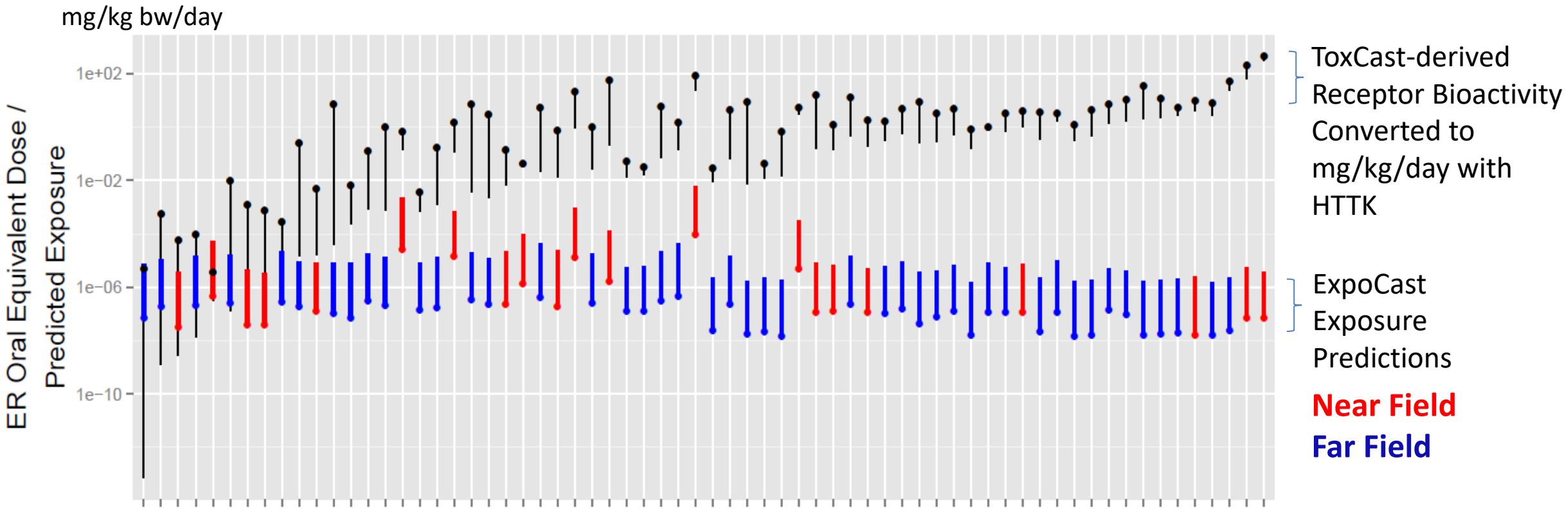
High Throughput Risk Prioritization in Practice



ToxCast Chemicals

Rapid exposure and dosimetry project helps establish exposure context for ToxCast high throughput screening

December, 2014 Panel:
"Scientific Issues Associated with Integrated Endocrine Bioactivity and Exposure-Based Prioritization and Screening"

Rapid Exposure and Dosimetry "ExpoCast" Research

- **Procurement and Mining of Exposure-Related Data for Support of Rapid Exposure Tools**
  - New Databases (such as CPdat)
  - Suspect screening and non-targeted analysis (SS/NTA)
- **High Throughput Toxicokinetics (HTTK) for Rapid Dosimetry**
- **Development and Evaluation of High-Throughput Human and Ecological Exposure Models**
  - SHEDS-HT: High Throughput Stochastic Human Exposure Dose Simulator
- **Statistical Methods for Model Evaluation and Calibration**
  - High throughput exposure models calibrated to exposure biomarker data (SEEM)
- **Application and Dissemination of Integrated Rapid Exposure Tools**
  - High throughput risk prioritization, as was done for Endocrine Disruptor Screening Program

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