EPA
United States
Environmental Protection
Agency

Computational Environmental Sciences and Toxicology

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BIO592
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April 15, 2019

The views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the U.S. EPA

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EPA Office of Research and Development

- The Office of Research and Development (ORD) is the scientific research arm of EPA
  - 562 peer-reviewed journal articles in 2018
- Research is conducted by ORD's three national laboratories, four national centers, and two offices organized to address:
  - Hazard, exposure, risk assessment, and risk management
- 13 facilities across the United States
  - Largest facility in Research Triangle Park
- Research conducted by a combination of Federal scientists (including uniformed members of the **Public Health Service)**; contract researchers; and postdoctoral, graduate student, and post-baccalaureate trainees

ORD Facility in Research Triangle Park, NC

Chemical Regulation in the United States

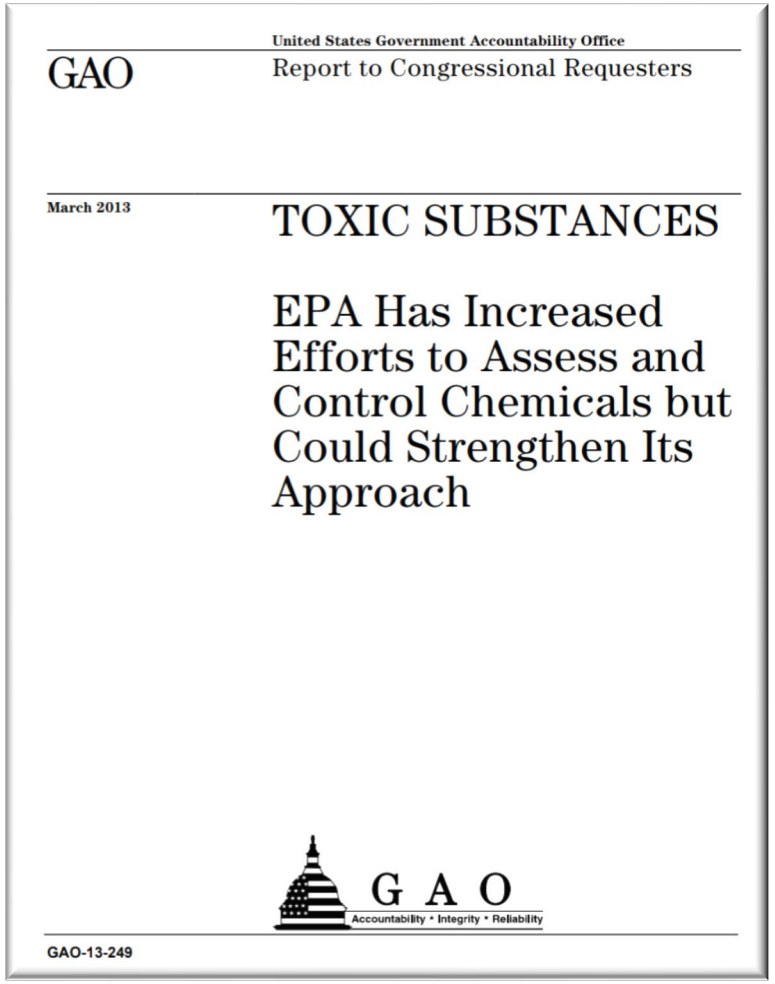
- Park *et al.* (2012): At least 3221 chemical signatures in pooled human blood samples, many appear to be exogenous
- A tapestry of laws covers the chemicals people are exposed to in the United States (Breyer, 2009)
- Different testing requirements exist for food additives, pharmaceuticals, and pesticide 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 Toxic Substances Control Act (TSCA)
  - Thousands of chemicals on the market were either "grandfathered" or were allowed without experimental assessment of hazard, toxicokinetics, or exposure (Judson et al. (2009), Egeghy et al. (2012), Wetmore et al. (2015))

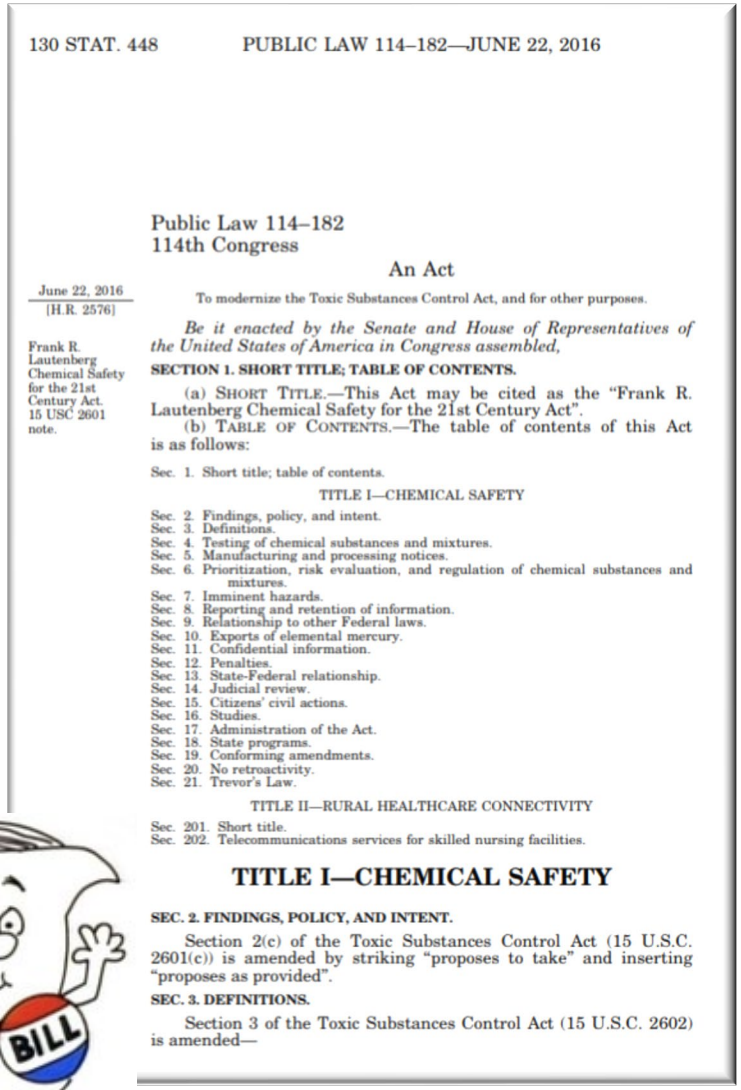
"Tens of thousands of chemicals are listed with the Environmental Protection Agency (EPA) for commercial use in the United States, with an average of 600 new chemicals listed each year."
U.S. Government Accountability Office



March, 2013

Chemical Regulation in the United States

- TSCA was updated in June, 2016 to allow more rapid evaluation of chemicals (Frank R. Lautenberg Chemical Safety for the 21st Century Act)
  - New approach methodologies (NAMs) are being considered to inform prioritization of chemicals for testing and evaluation
  - "Strategic Plan to Promote the Development and Implementation of Alternative Test Methods Within the TSCA Program" (June 22, 2018)



130 STAT. 448 PUBLIC LAW 114–182—JUNE 22, 2016

Public Law 114–182
114th Congress

An Act

To modernize the Toxic Substances Control Act, and for other purposes.

June 22, 2016
[H.R. 2576]

Frank R. Lautenberg Chemical Safety for the 21st Century Act.
15 USC 2601 note.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE; TABLE OF CONTENTS.

(a) SHORT TITLE.—This Act may be cited as the "Frank R. Lautenberg Chemical Safety for the 21st Century Act".

(b) TABLE OF CONTENTS.—The table of contents of this Act is as follows:

Sec. 1. Short title; table of contents.

TITLE I—CHEMICAL SAFETY

Sec. 2. Findings, policy, and intent.
Sec. 3. Definitions.
Sec. 4. Testing of chemical substances and mixtures.
Sec. 5. Manufacturing and processing notices.
Sec. 6. Prioritization, risk evaluation, and regulation of chemical substances and mixtures.
Sec. 7. Imminent hazards.
Sec. 8. Reporting and retention of information.
Sec. 9. Relationship to other Federal laws.
Sec. 10. Exports of elemental mercury.
Sec. 11. Confidential information.
Sec. 12. Penalties.
Sec. 13. State-Federal relationship.
Sec. 14. Judicial review.
Sec. 15. Citizens' civil actions.
Sec. 16. Studies.
Sec. 17. Administration of the Act.
Sec. 18. State programs.
Sec. 19. Conforming amendments.
Sec. 20. No retroactivity.
Sec. 21. Trevor's Law.

TITLE II—RURAL HEALTHCARE CONNECTIVITY

Sec. 201. Short title.
Sec. 202. Telecommunications services for skilled nursing facilities.

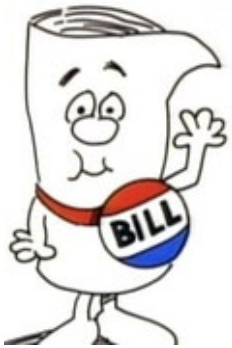
TITLE I—CHEMICAL SAFETY

SEC. 2. FINDINGS, POLICY, AND INTENT.

Section 2(c) of the Toxic Substances Control Act (15 U.S.C. 2601(c)) is amended by striking "proposes to take" and inserting "proposes as provided".

SEC. 3. DEFINITIONS.

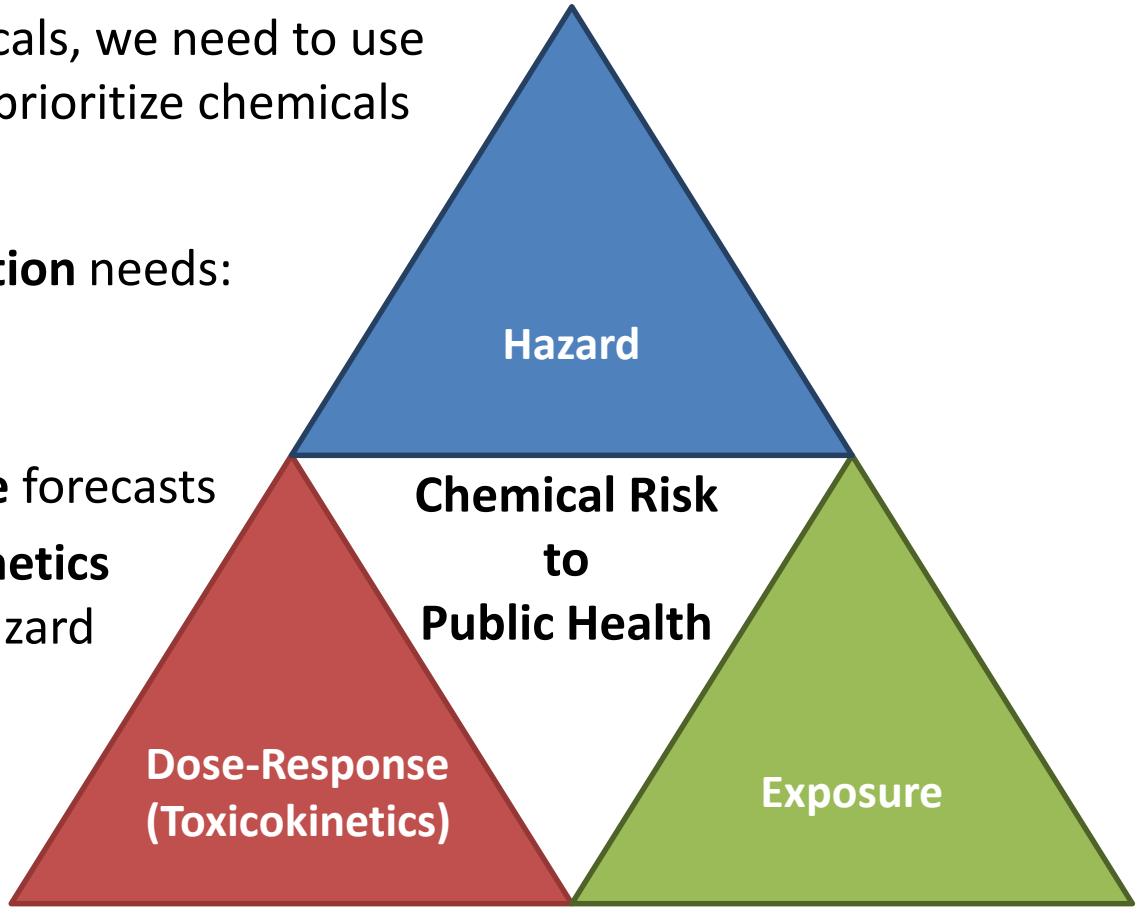
Section 3 of the Toxic Substances Control Act (15 U.S.C. 2602) is amended—



June 22, 2016

Chemical Risk = Hazard x Exposure

- National Research Council (1983) identified chemical risk as a function of both inherent hazard and exposure
- To address thousands of chemicals, we need to use "high throughput methods" to prioritize chemicals for additional study
- **High throughput risk prioritization** needs:
  1. high throughput **hazard** characterization
  2. high throughput **exposure** forecasts
  3. high throughput **toxicokinetics** (*i.e.*, dosimetry) linking hazard and exposure



High-Throughput Risk Prioritization

High throughput screening (HTS) for *in vitro* bioactivity potentially allows characterization of thousands of chemicals for which no other testing has occurred

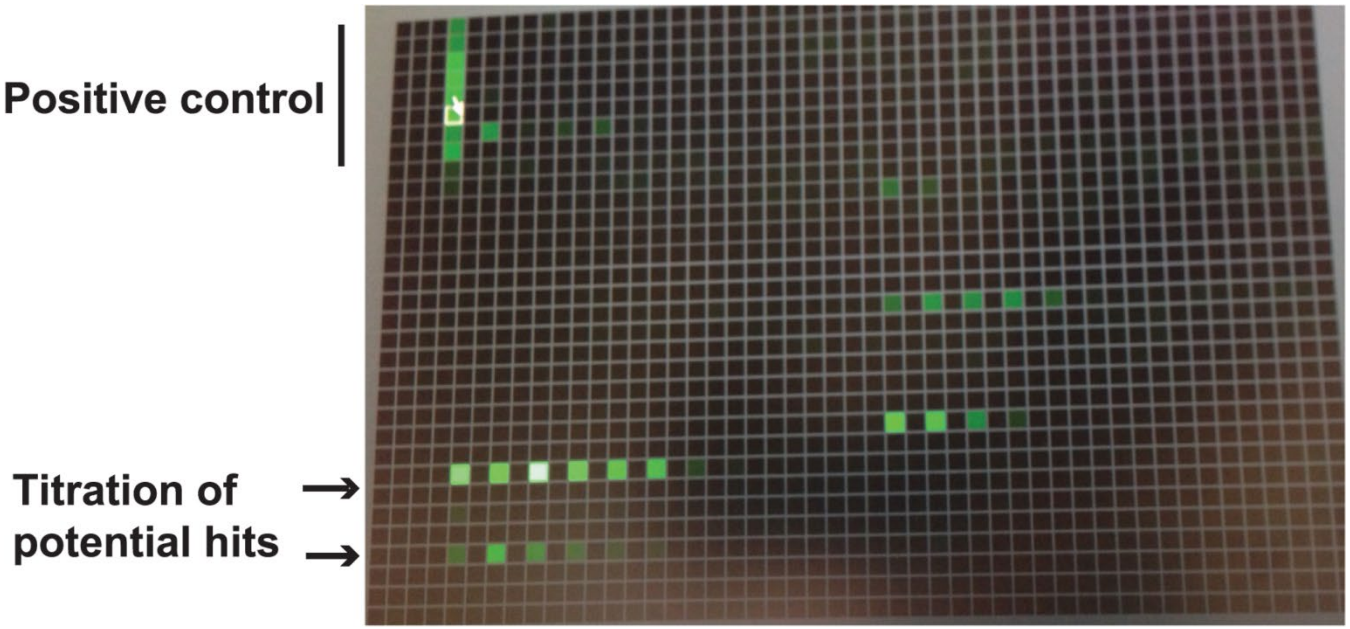
High-throughput Screening

Hertzberg and Pope (2000):

- "New technologies in high-throughput screening have significantly increased throughput and reduced assay volumes"

- "Key advances over the past few years include new fluorescence methods, detection platforms and liquid-handling technologies."

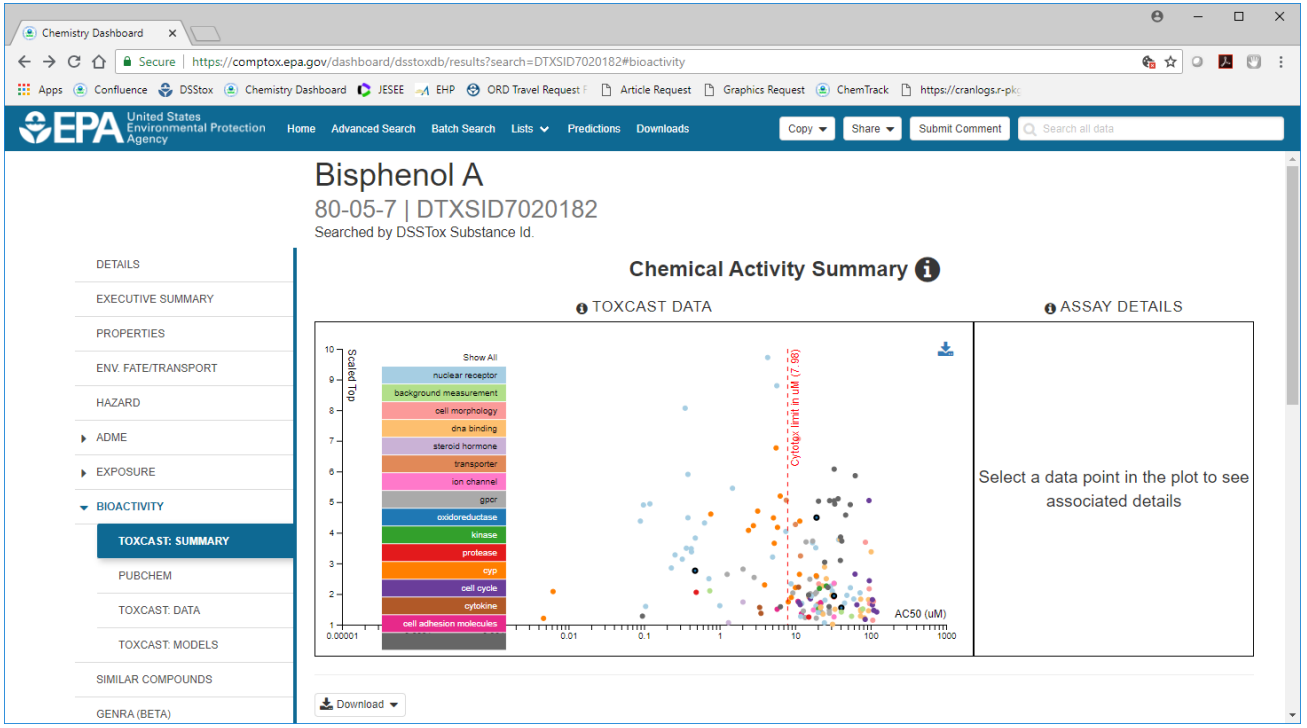
Kaewkhaw et al. (2016)



Toxicity Testing in the 21st Century

- **Tox21**: Examining >8,000 chemicals using ~50 assays intended to identify interactions with biological pathways (Schmidt, 2009)

- **ToxCast**: For a subset (>2000) of Tox21 chemicals ran >1100 additional assays (Kavlock *et al.*, 2012)



https://comptox.epa.gov/dashboard/

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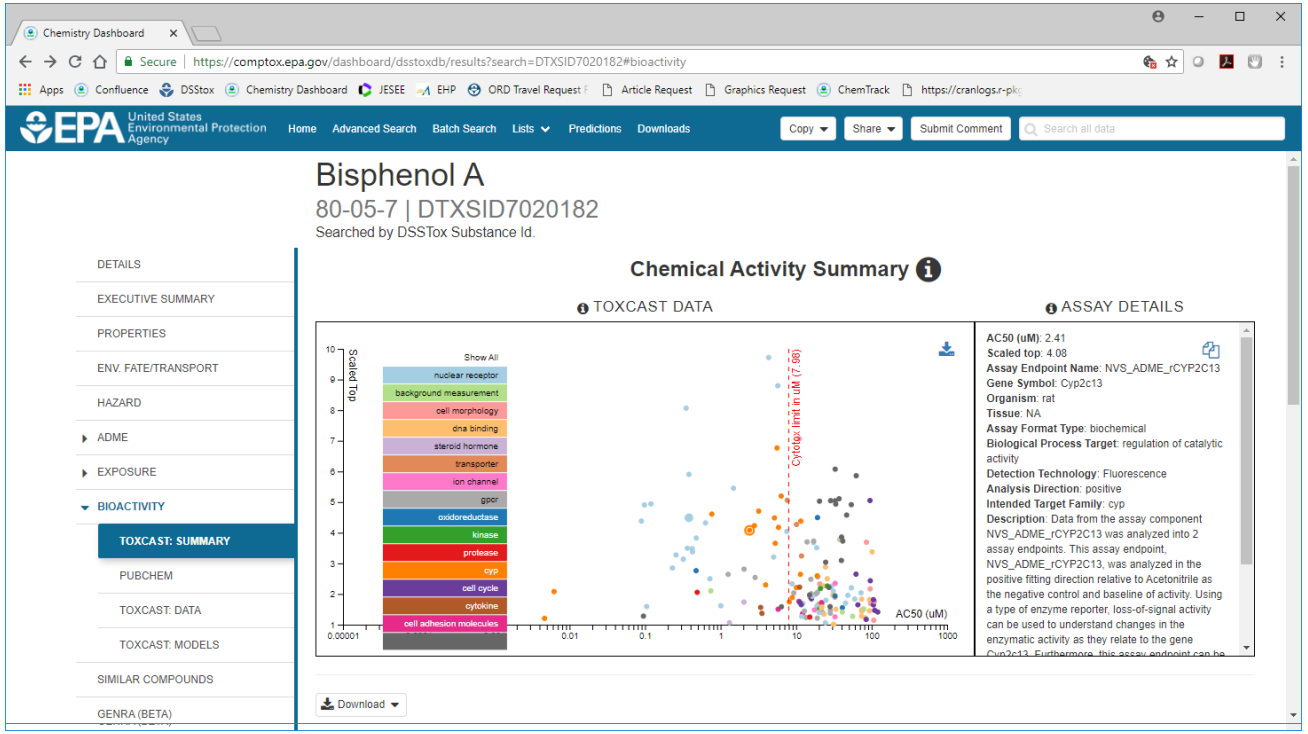

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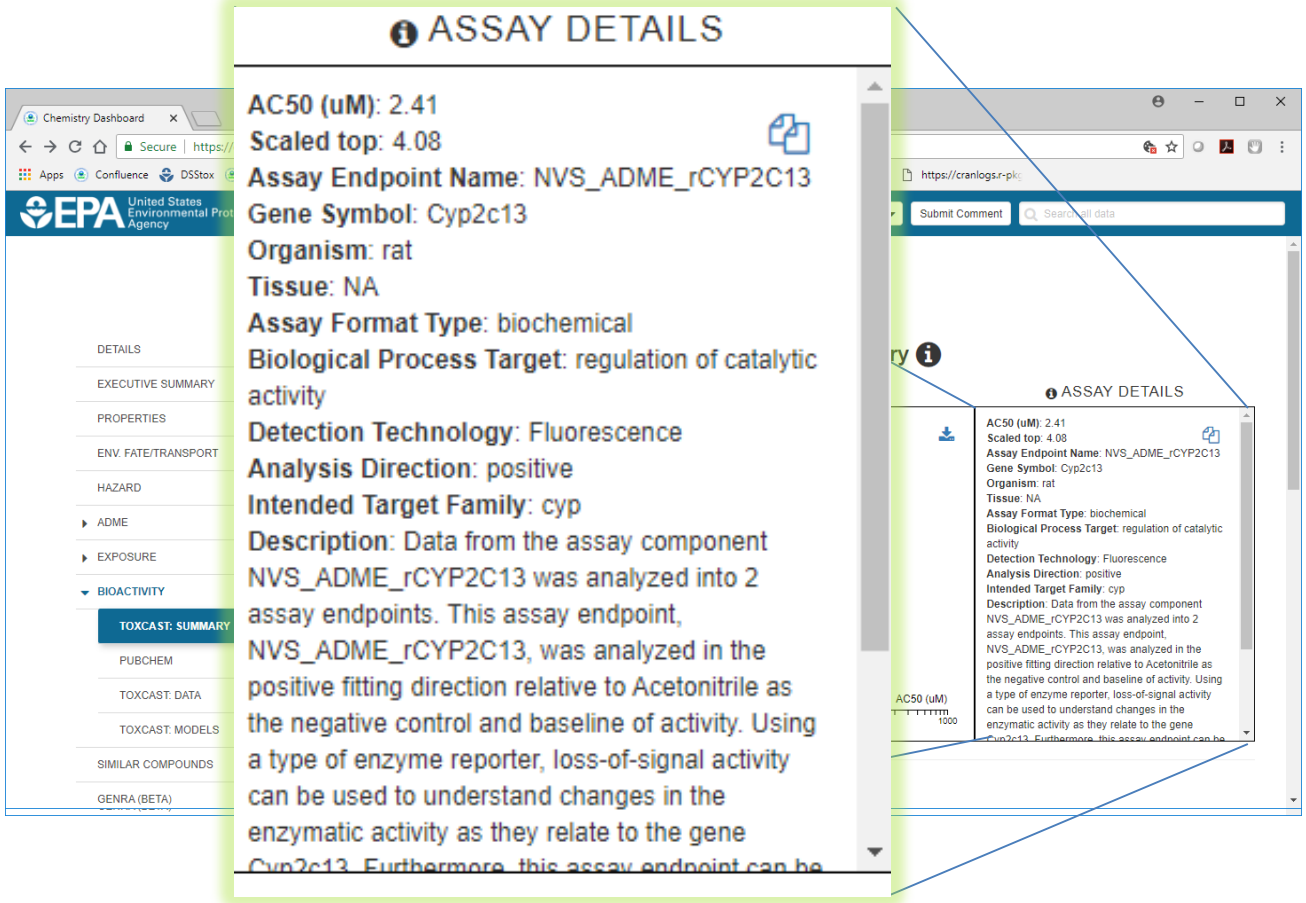
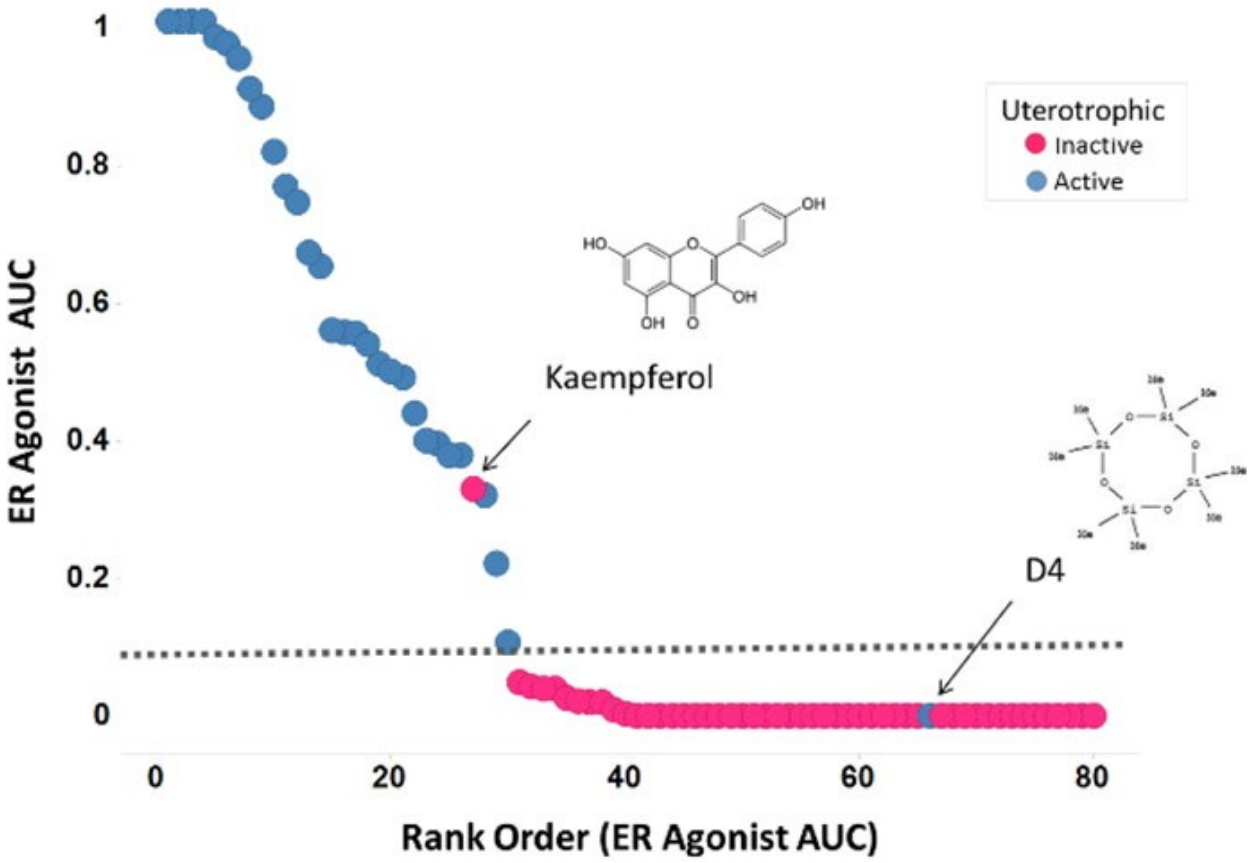


https://comptox.epa.gov/dashboard/

Can also download data as Excel, MySQL, CSV…

New Approach Methodologies

- New approach methodologies (NAMs) are being considered to inform prioritization of chemicals for testing and evaluation (Kavlock et al., 2018)
- *In vivo* uterotrophic assay has been replaced with in vitro assays to screen chemical for endocrine disruption (EPA, 2015)



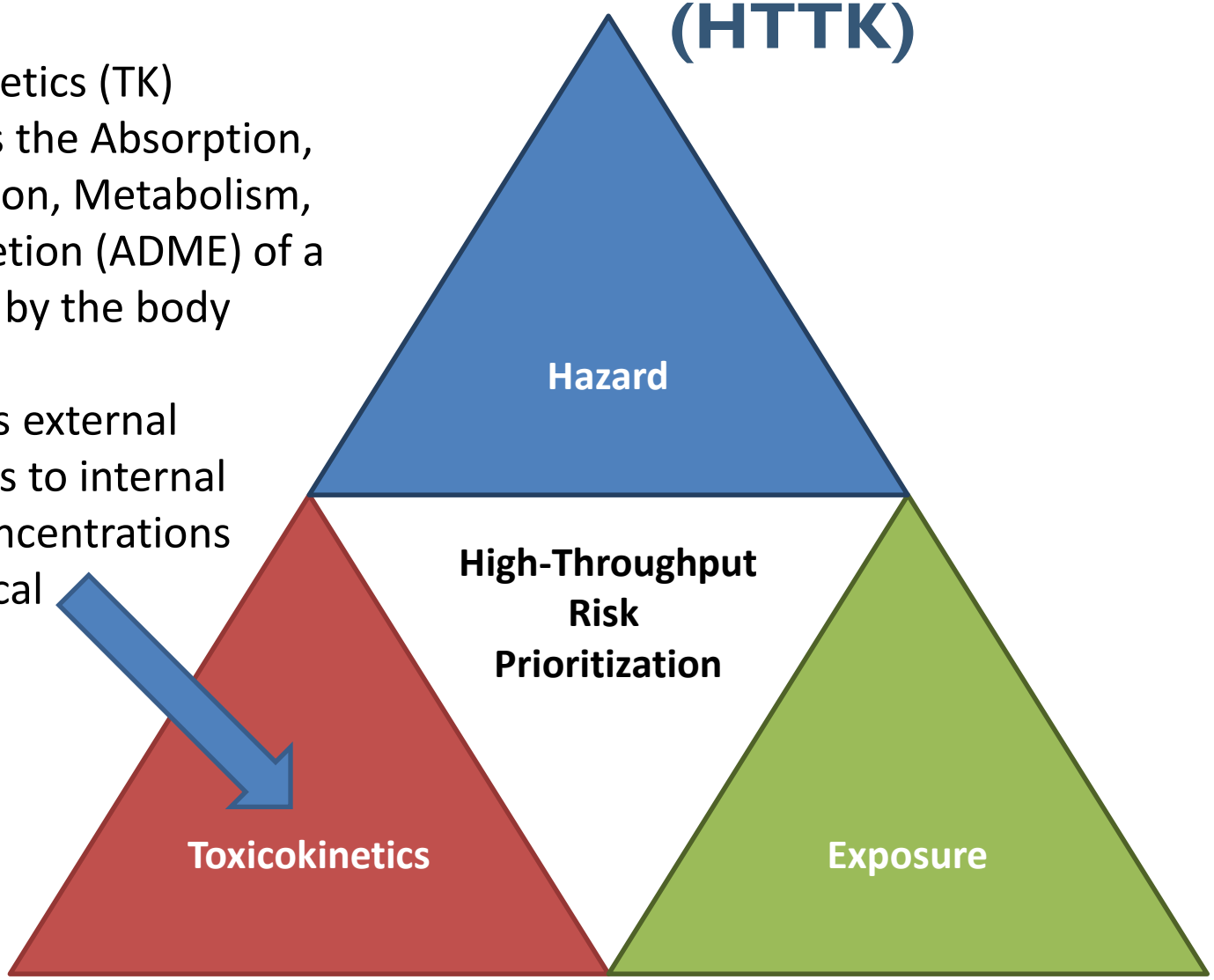
- EPA has released a "A Working Approach for Identifying Potential Candidate Chemicals for Prioritization" (EPA, 2018)

Browne et al. (2015)

High Throughput Toxicokinetics (HTTK)

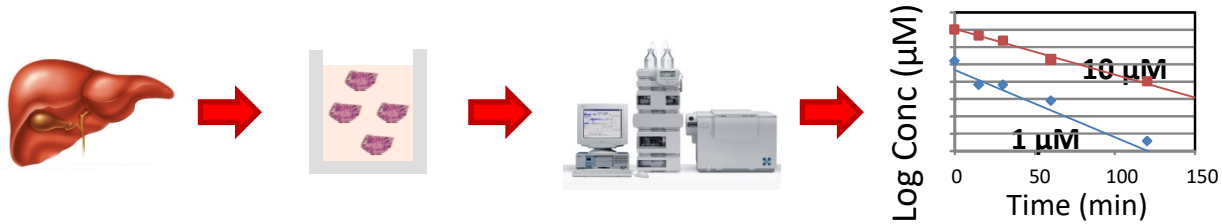
Toxicokinetics (TK) describes the Absorption, Distribution, Metabolism, and Excretion (ADME) of a chemical by the body

TK relates external exposures to internal tissue concentrations of chemical



High-Throughput Toxicokinetics (HTTK)

- **Most chemicals do not have TK data** – we use *in vitro* HTTK methods adapted from pharma to fill gaps
- In drug development, HTTK methods estimate therapeutic doses for clinical studies – predicted concentrations are often within 3-fold of clinical trials (Wang, 2010)



Human Hepatocytes (10 donor pool)

4h Incubation Shibata et al. (2002)

Intrinsic Hepatic Clearance (Cl_{int})

Figure modified from original by Barbara Wetmore

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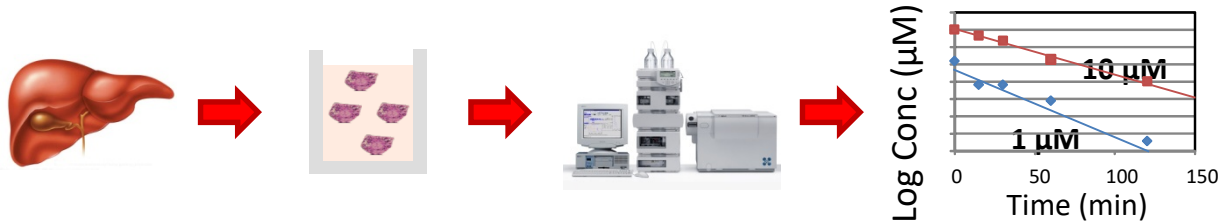

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Free fraction in Plasma (f_{up})

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In Vitro – In Vivo Extrapolation

Predicted Plasma Concentrations

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Both measurements require chemical-specific chemical analysis methods for concentration

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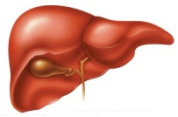

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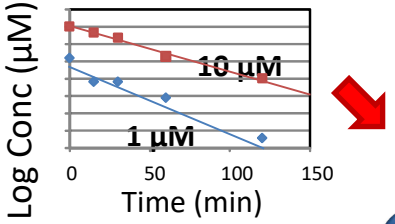

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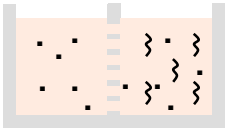

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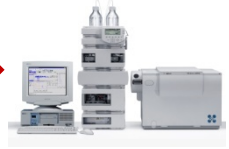


Free fraction in Plasma (f_{up})

In Vitro – In Vivo Extrapolation

Predicted Plasma Concentrations

Rotroff et al. (2010) 35 chemicals
Wetmore et al. (2012) +204
Wetmore et al. (2015) +163
Wambaugh et al. (in prep) + 496

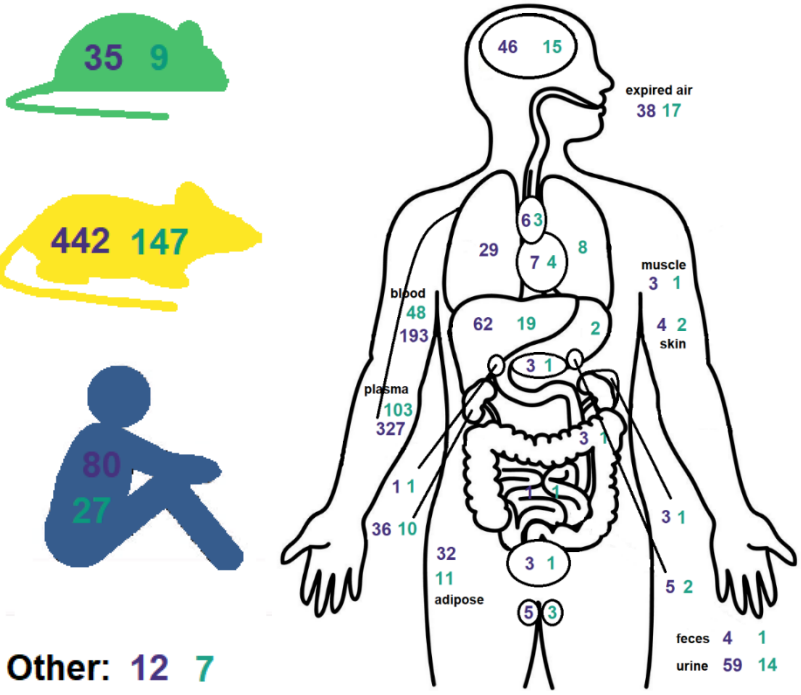
Figure modified from original by Barbara Wetmore

Building Confidence in HTTK: The Need for Data

- EPA is developing a public database of concentration vs. time data for building, calibrating, and evaluating TK models

- Curation and development ongoing, but to date includes:
  - 198 analytes (EPA, National Toxicology Program, literature)
  - Routes: Intravenous, dermal, oral, sub-cutaneous, and inhalation exposure

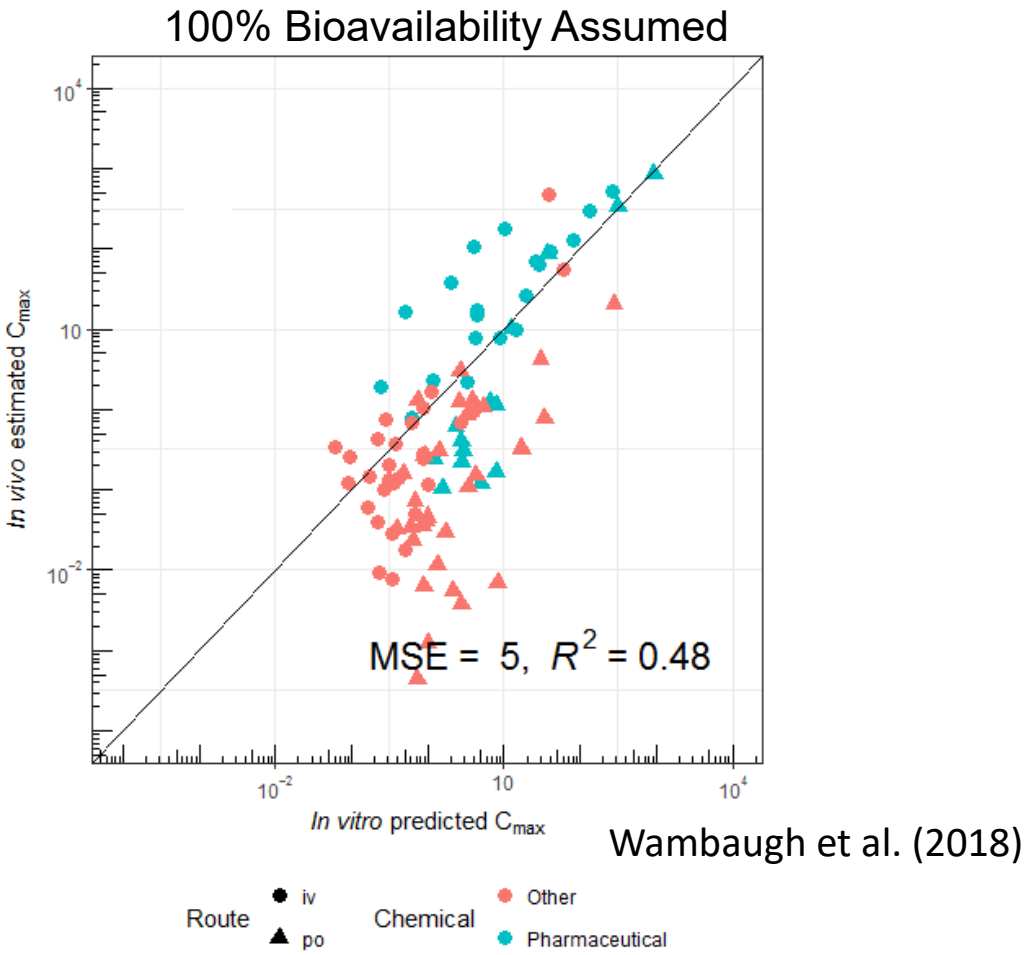
- Database will be made available through web interface and through the “httk” R package



- Standardized, open source curve fitting software invivoPKfit used to calibrate models to all data: https://github.com/USEPA/CompTox-ExpoCast-invivoPKfit

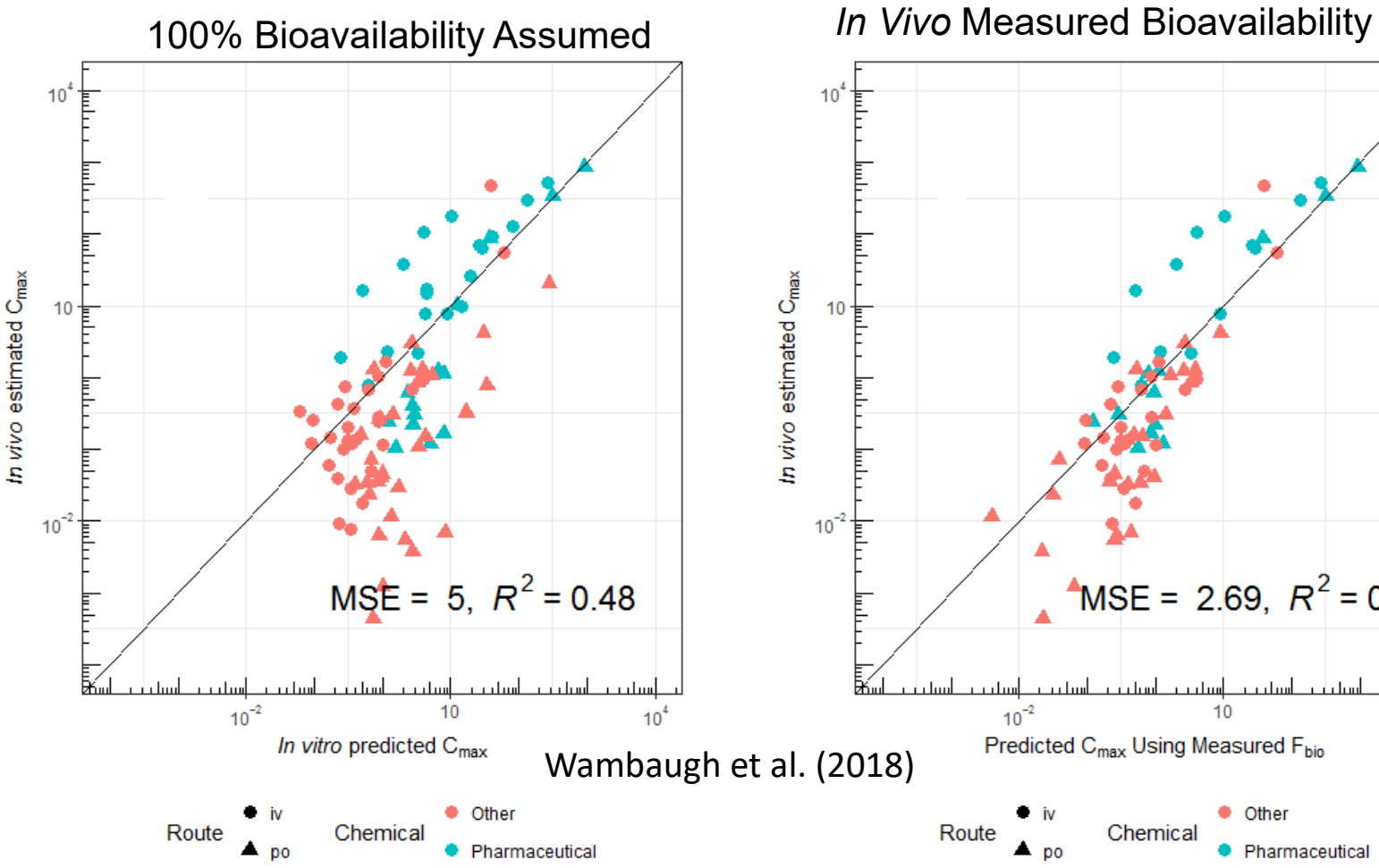
Sayre et al. (in preparation)

Evaluating HTTK



Wambaugh et al. (2018)

Evaluating HTTK



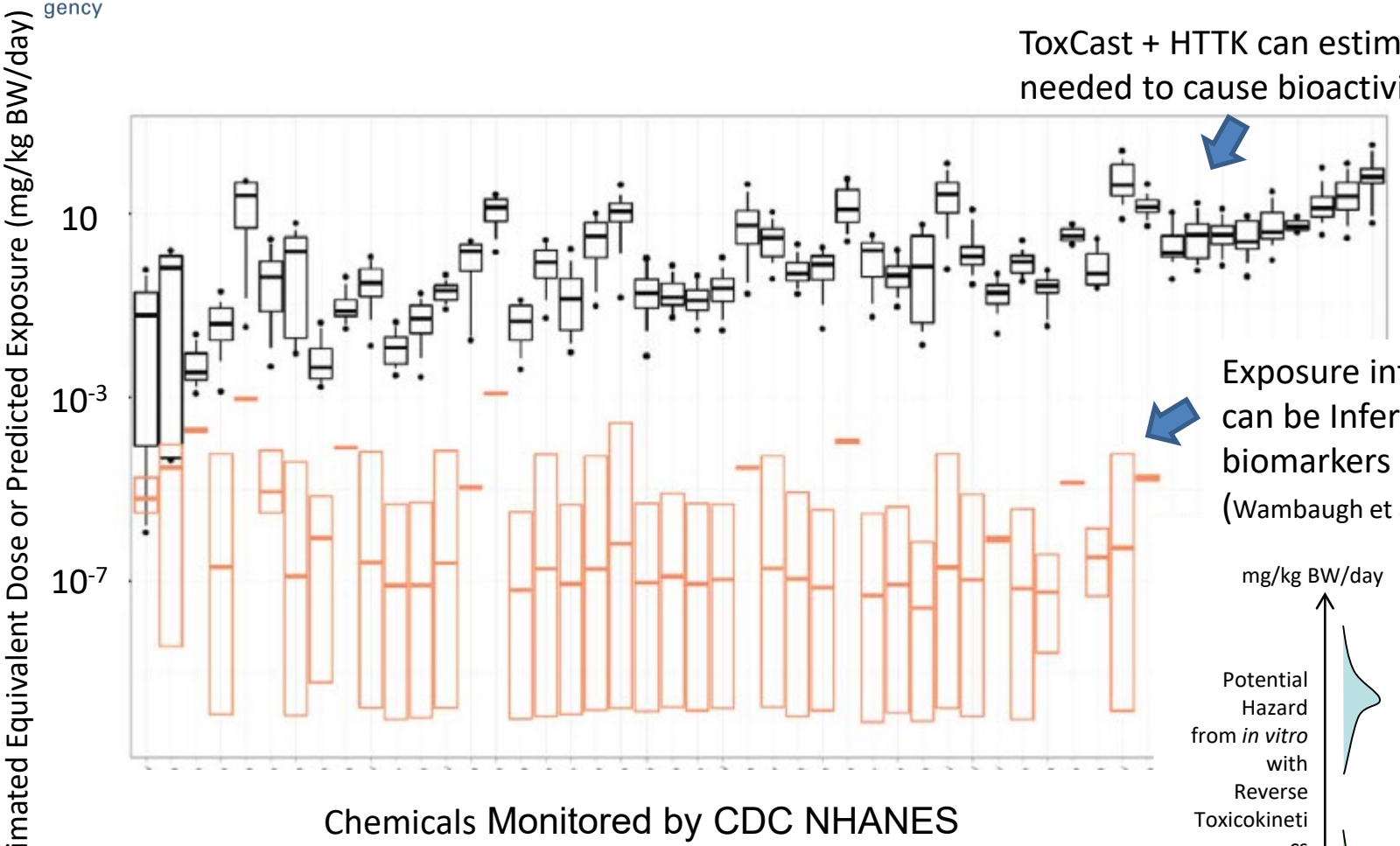
Wambaugh et al. (2018)

Here, we find that need to predict oral absorption

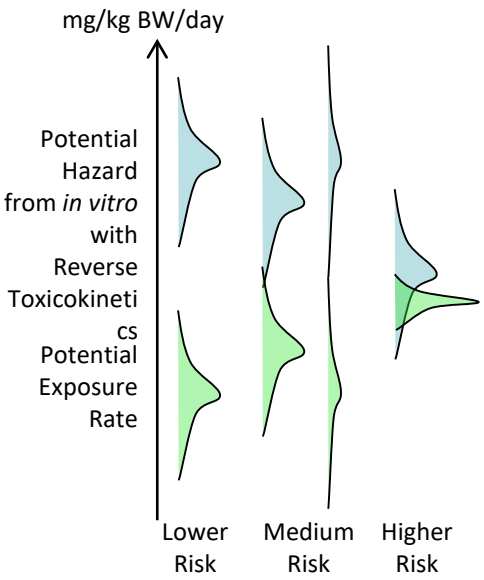
Honda et al. (in preparation)

High Throughput Risk Prioritization

ToxCast + HTTK can estimate doses needed to cause bioactivity



Exposure intake rates can be Inferred from biomarkers (Wambaugh et al., 2014)

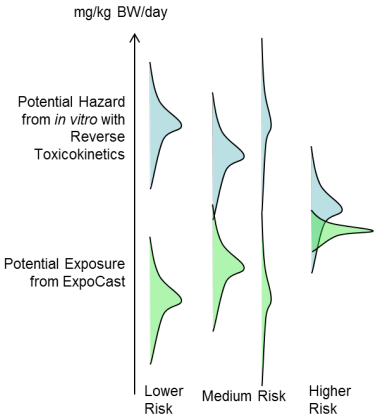


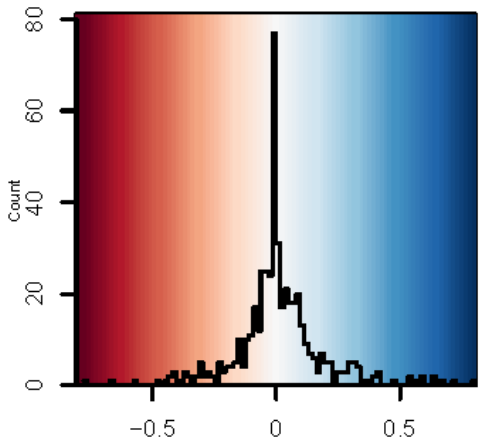
National Health and Nutrition Examination Survey (NHANES) is an ongoing survey that covers ~10,000 people every two years

Ring *et al*. (2017)

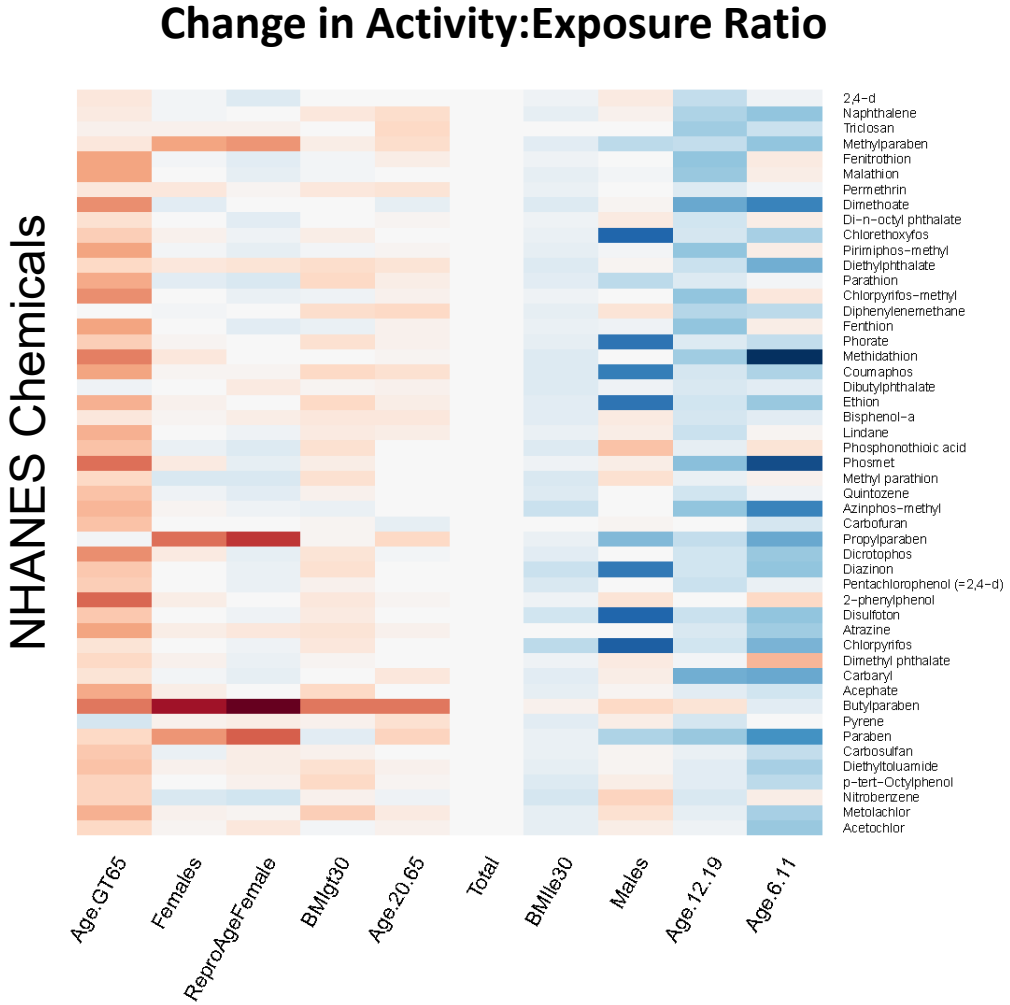
Life-stage and Demographic Specific Predictions

- Can calculate margin between bioactivity and exposure for specific populations



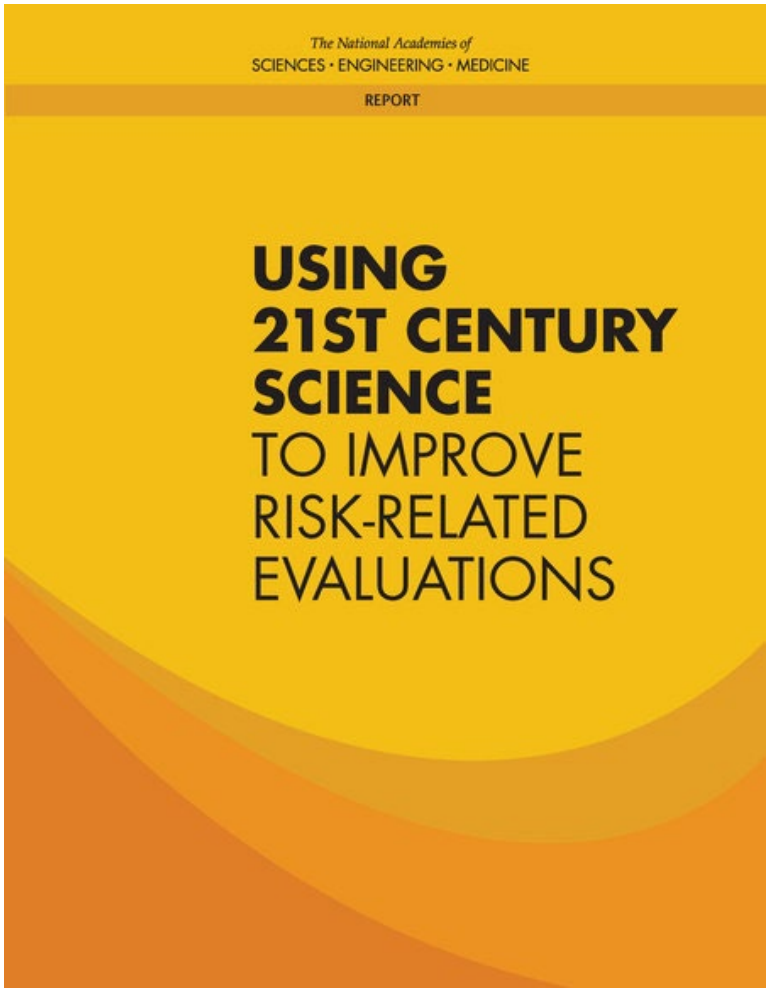


Change in Risk Relative to Total Population



Ring *et al*. (2017)

Risk Assessment in the 21st Century

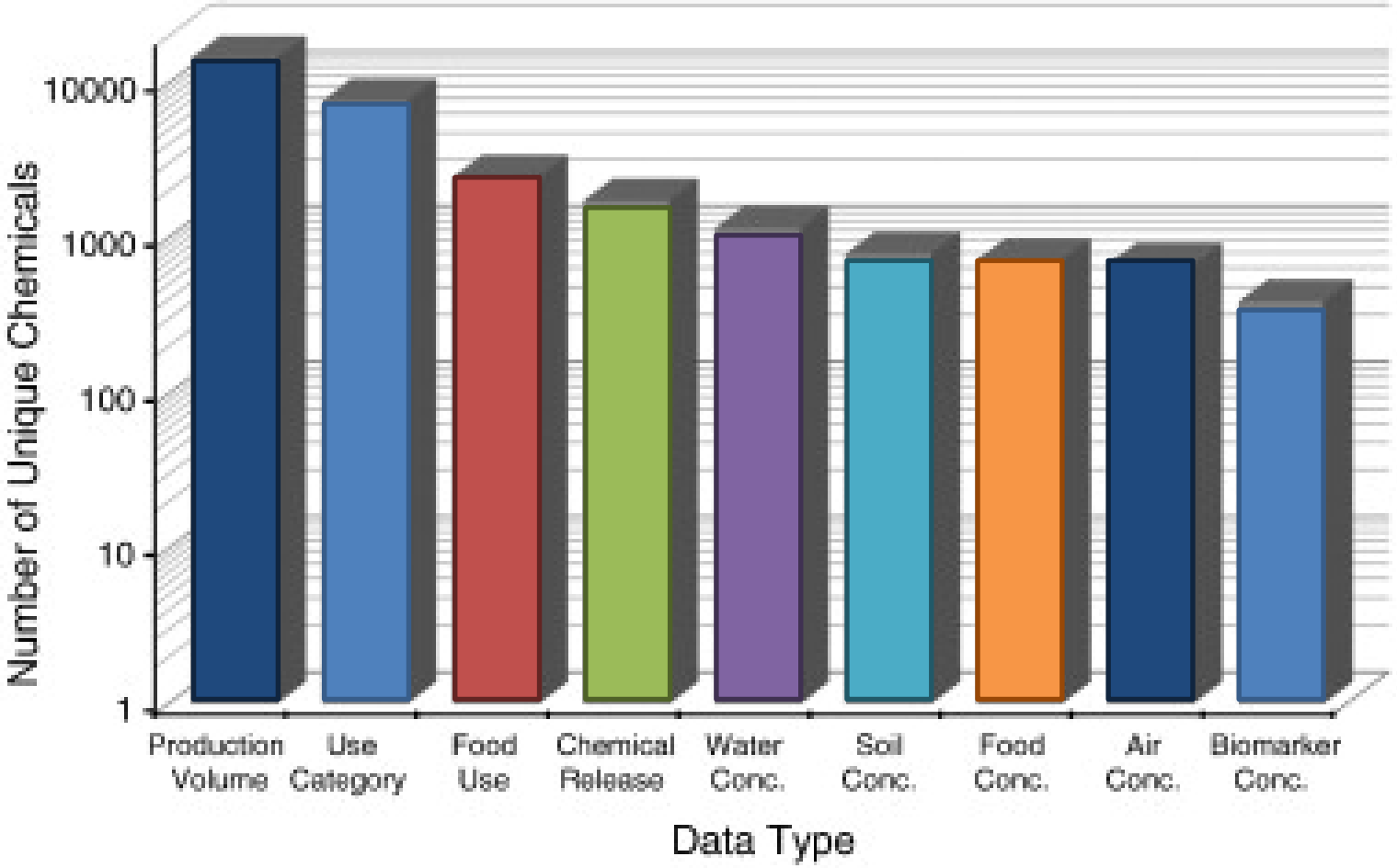


"Translation of high-throughput data into risk-based rankings is an important application of exposure data for chemical priority-setting. Recent advances in high-throughput toxicity assessment, notably the ToxCast and Tox21 programs… and in high-throughput computational exposure assessment… have enabled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

"…The committee sees the potential for the application of **computational exposure science** to be highly valuable and credible for comparison and **priority-setting among chemicals in a risk-based context**."

Limited Available Data for Exposure Estimation

Most chemicals lack public exposure-related data beyond production volume (Egeghy et al., 2012)



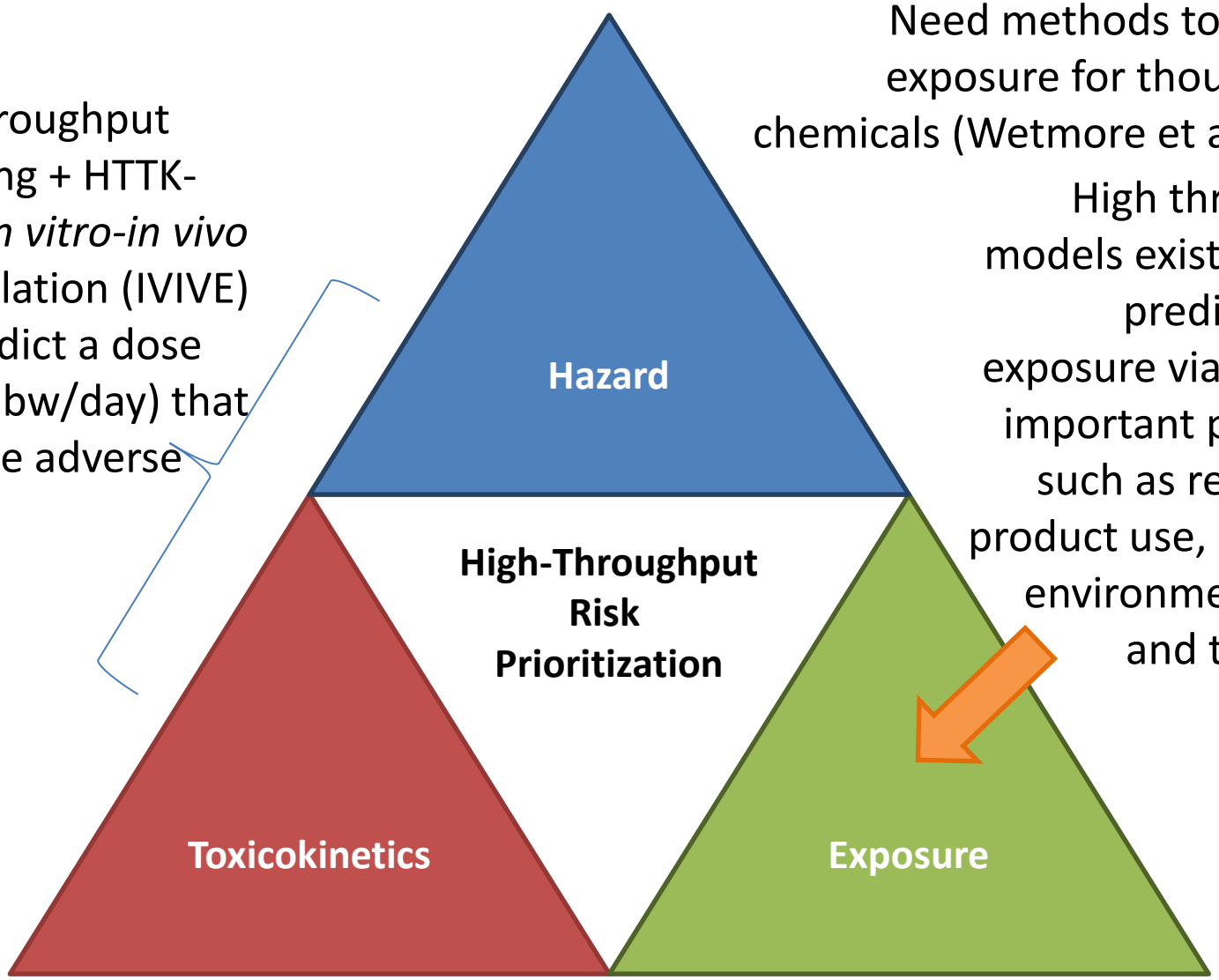
Can we use models to generate the exposure information we need?

New Exposure Data and Models

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

Need methods to forecast exposure for thousands of chemicals (Wetmore et al., 2015)

High throughput models exist to make predictions of exposure via specific, important pathways such as residential product use, diet, and environmental fate and transport



What Do We Know About Exposure? Exposure Models

- Human chemical exposures can be coarsely grouped into "**near-field**" sources that are close to the exposed individual (consumer or occupational exposures) '**far-field**' scenarios wherein individuals are exposed to chemicals that were released or used far away (ambient exposure) (Arnot *et al.*, 2006).

- A model captures knowledge and a hypothesis of how the world works (MacLeod *et al.*, 2010)

- EPA's EXPOsure toolBOX (EPA ExpoBox) is a toolbox created to assist individuals from within government, industry, academia, and the general public with assessing exposure
  - Includes many, many models

  https://www.epa.gov/expobox

"Now it would be very remarkable if any system existing in the real world could be exactly represented by any simple model. However, cunningly chosen parsimonious models often do provide remarkably useful approximations… The only question of interest is 'Is the model illuminating and useful?'" George Box

Forecasting Exposure is a Systems Problem

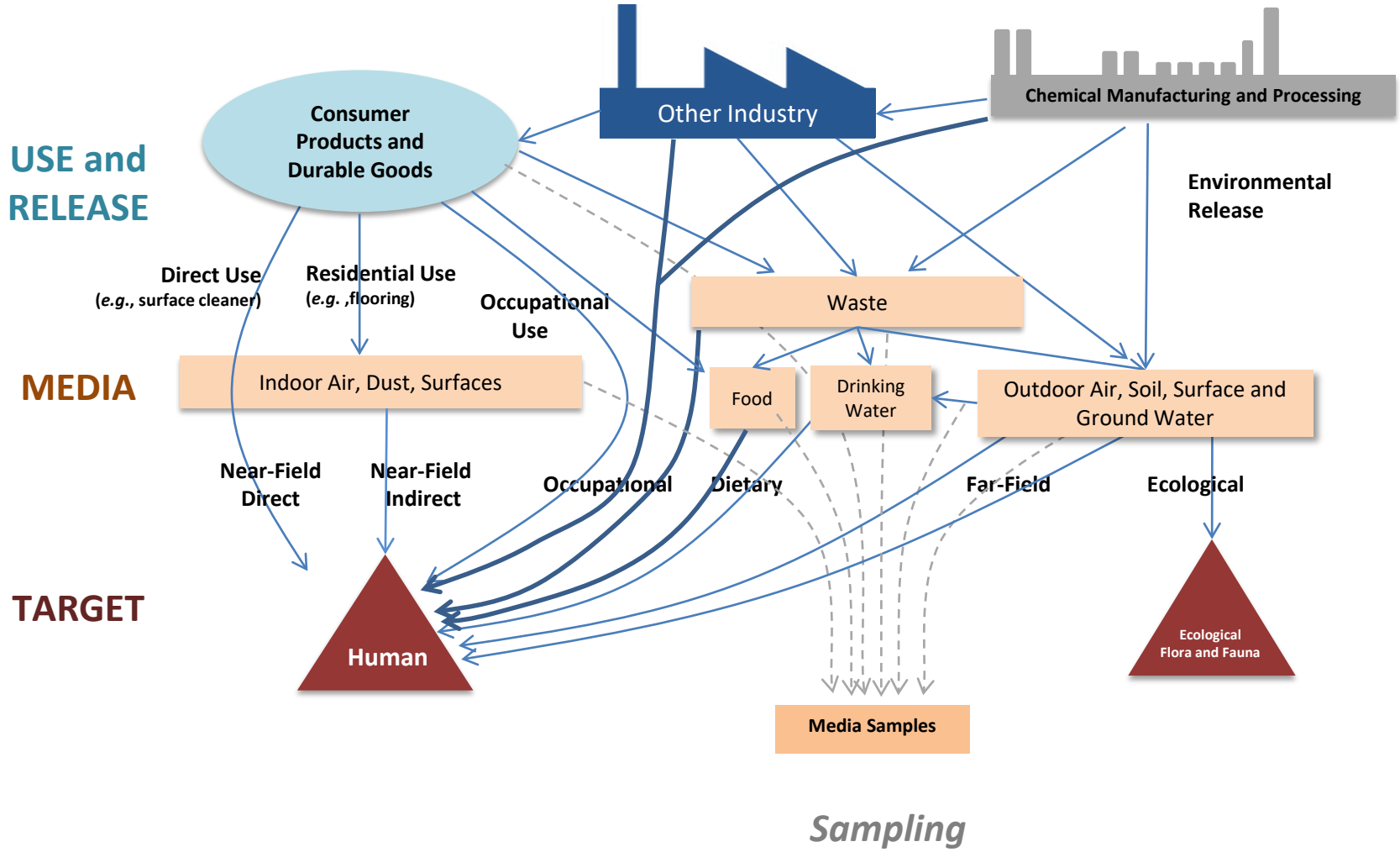


Figure from Kristin Isaacs

EPA United States Environmental Protection Agency

Source-based Exposure Pathways

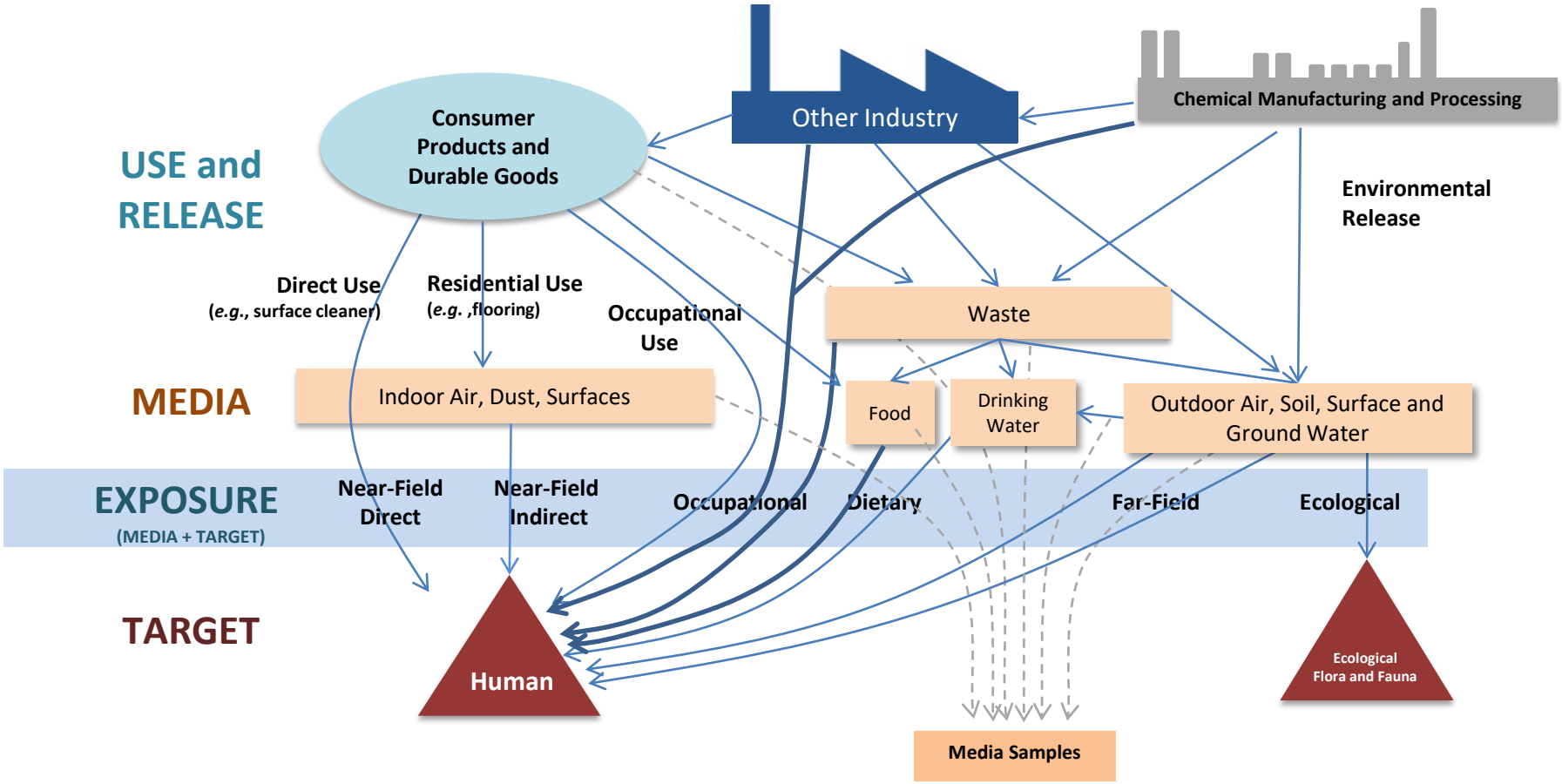


Figure from Kristin Isaacs

The Exposure Event is Often Unobservable

- The exposure pathway is the actual interaction of the receptor and media, e.g. consuming potato chips
- For humans in particular, these events are often unobserved and for many reasons (including ethics and privacy) may remain unobservable
  - *Did you eat the serving size or the whole bag of potato chips?*
- **Either predict** exposure using data and models up-stream of the exposure event
- **Or infer** exposure pathways from down-stream data, especially biomarkers of exposure

Figure modified from original by Kristin Isaacs

Models to Predict Exposure

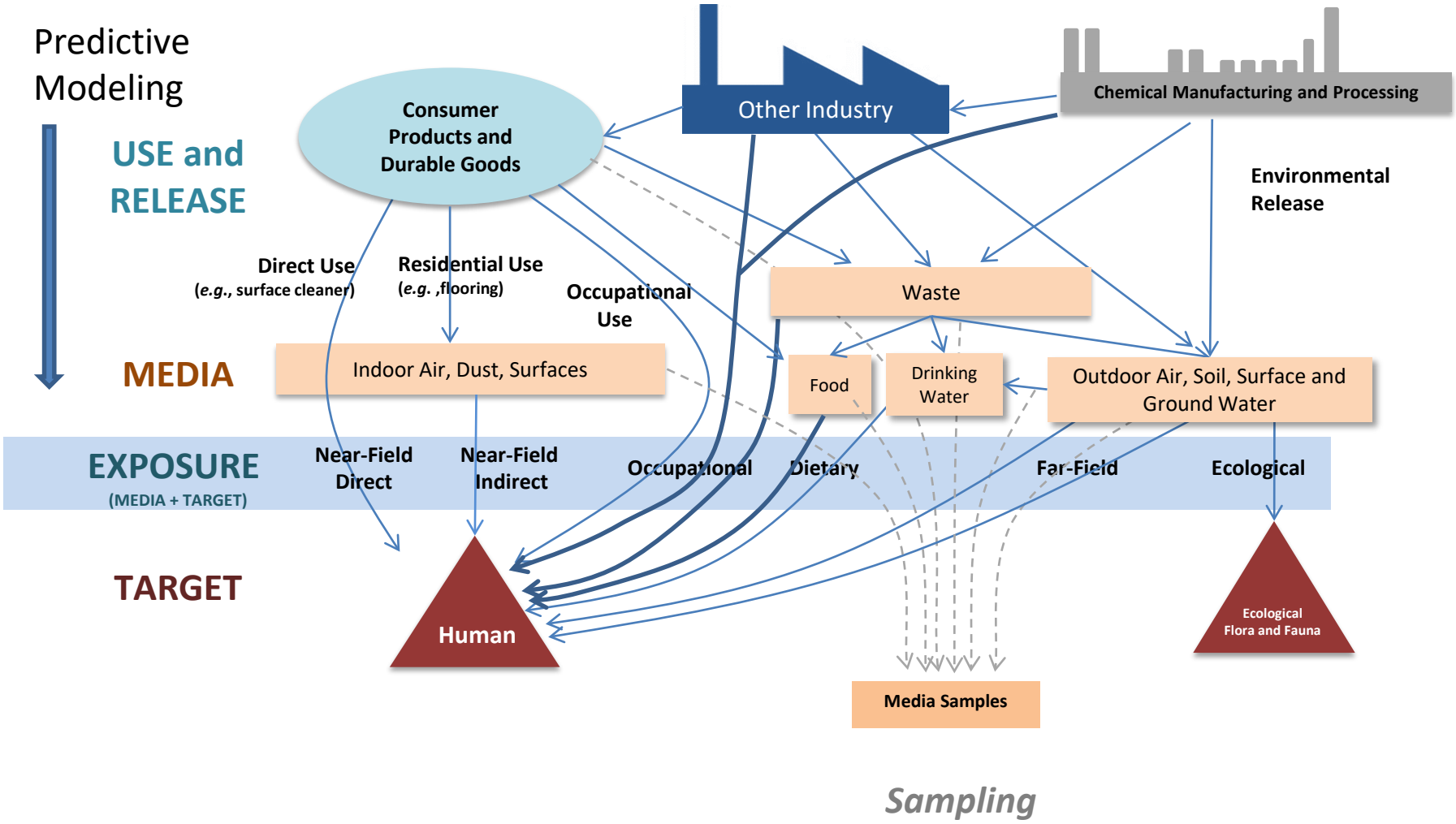


Figure from Kristin Isaacs

Monitoring Data

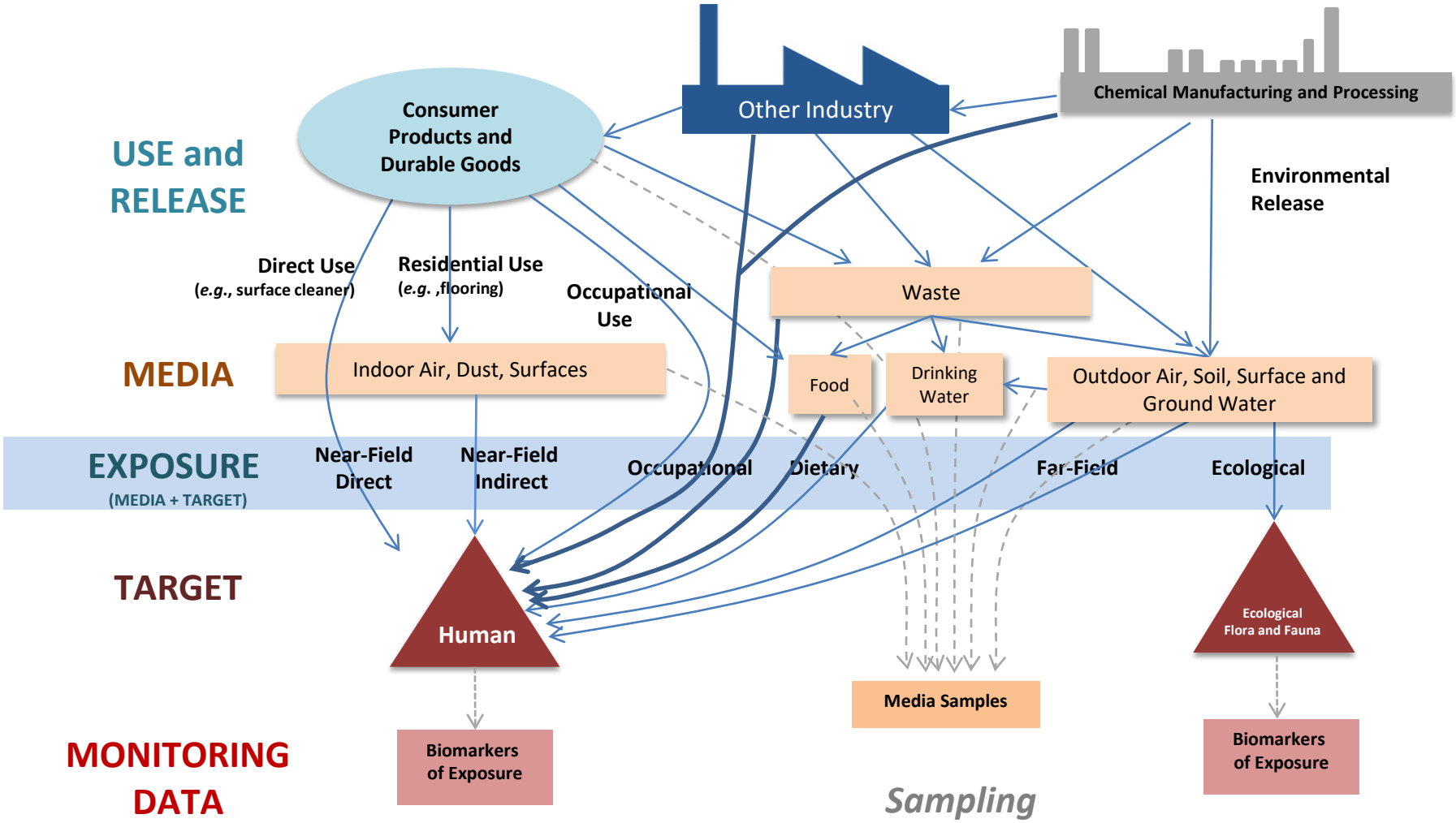


Figure from Kristin Isaacs

EPA United States Environmental Protection Agency

Monitoring Data

Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination Survey (NHANES) provides an important tool for monitoring public health

Large, ongoing CDC survey of US population: demographic, body measures, medical exam, biomonitoring (health and exposure), …

Designed to be representative of US population according to census data

Data sets publicly available (http://www.cdc.gov/nchs/nhanes.htm)

Includes measurements of:

- Body weight
- Height
- **Chemical analysis of blood and urine**

Models to Infer Exposure

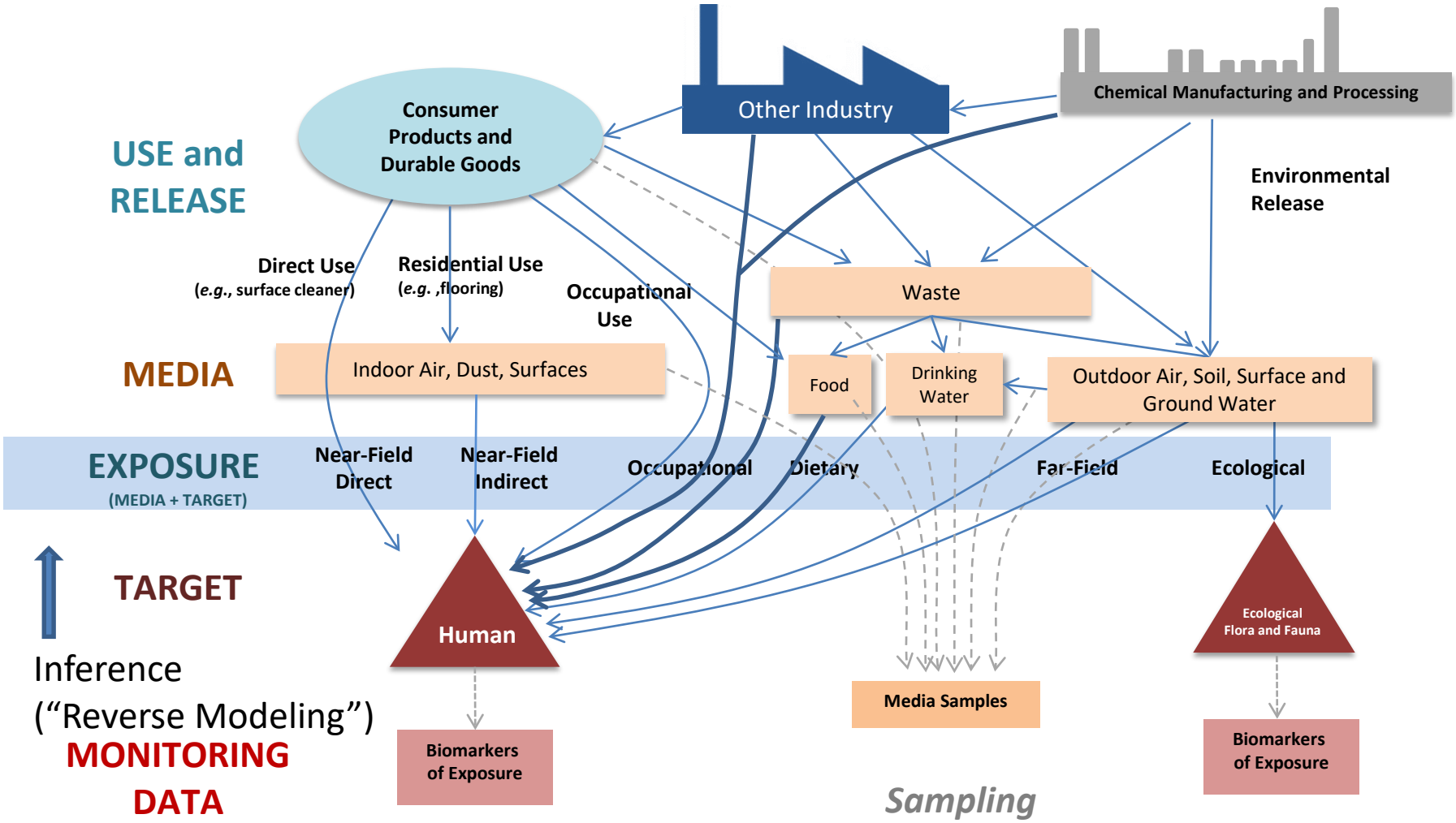
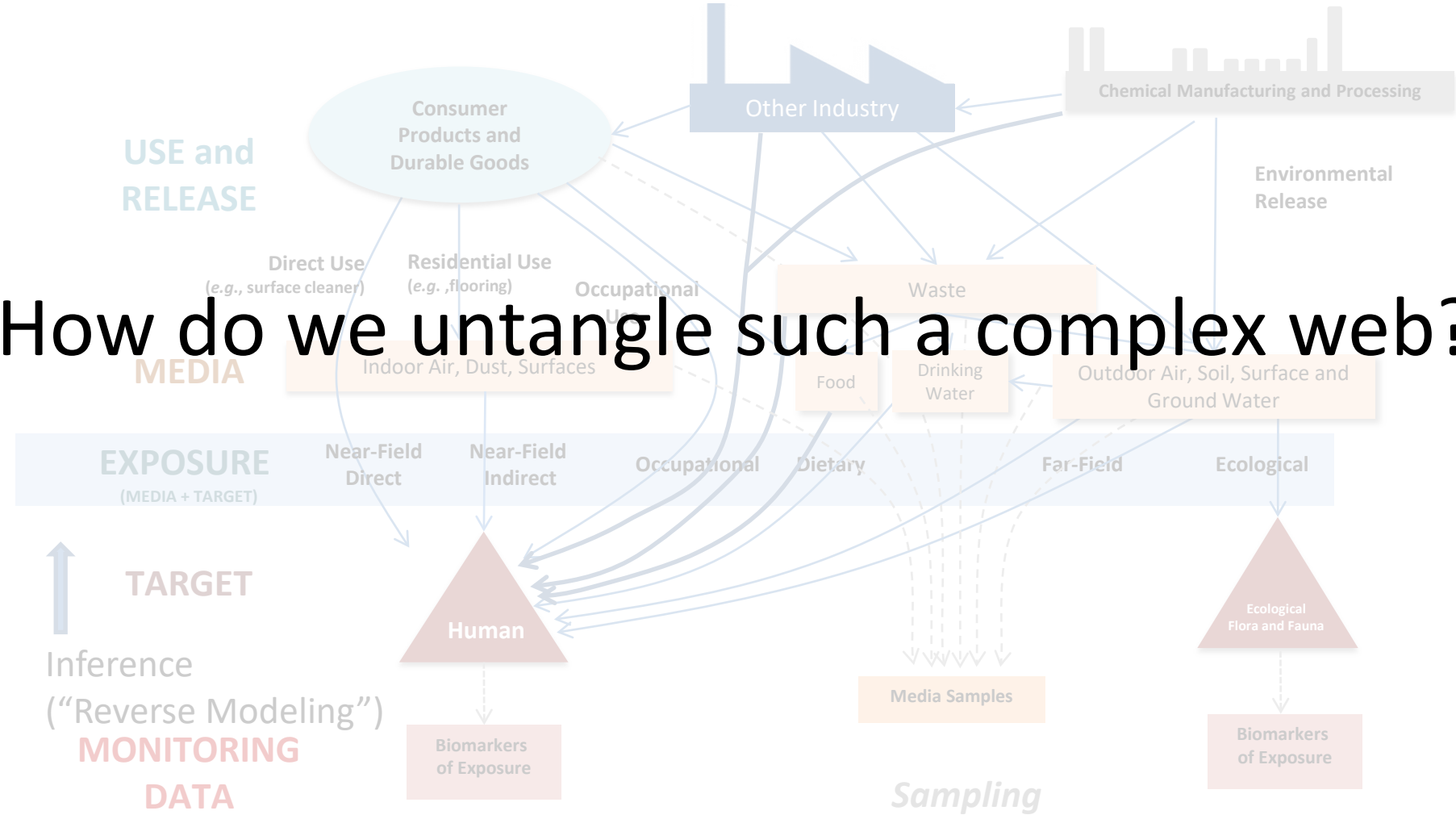


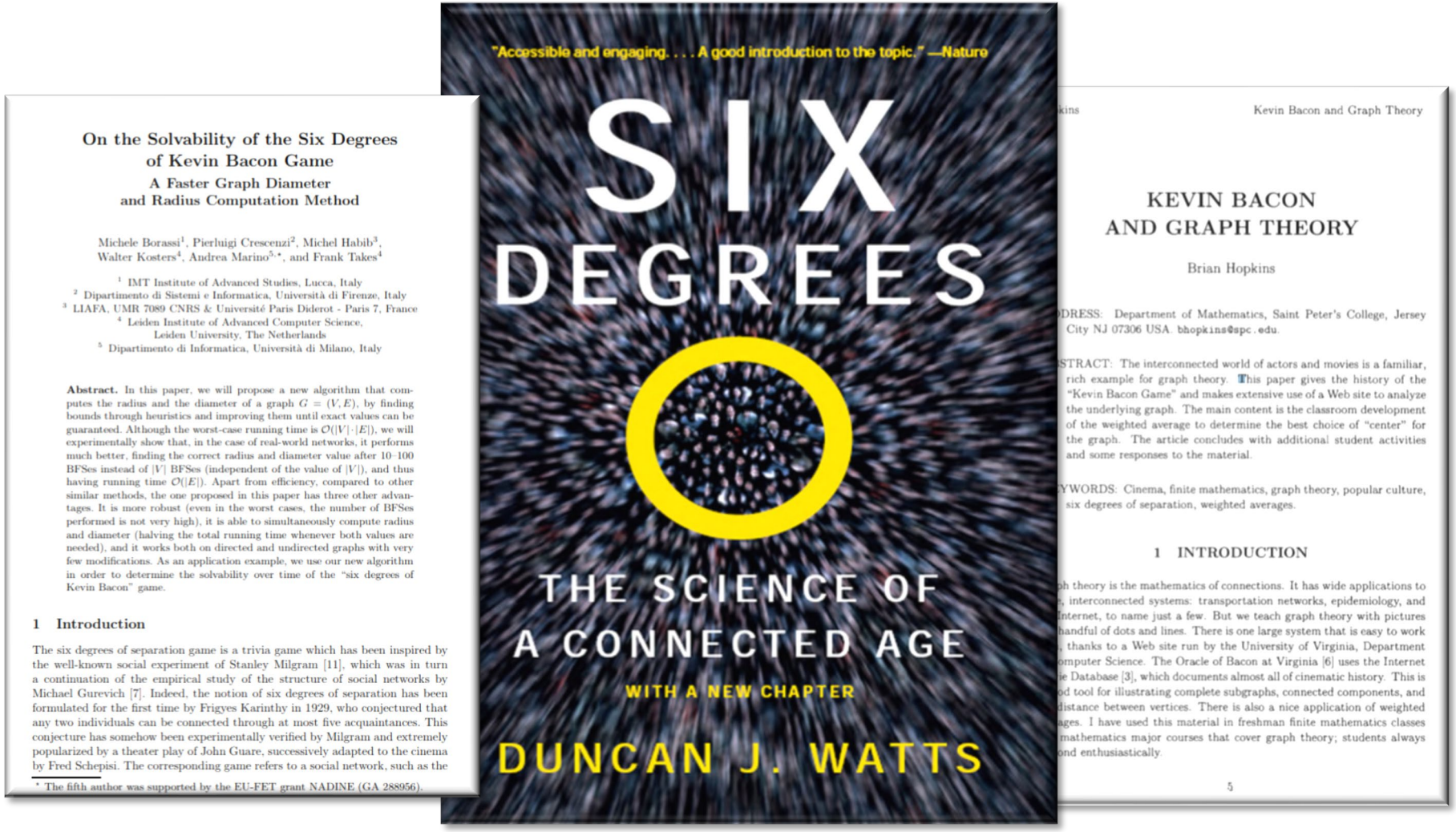
Figure from Kristin Isaacs



How do we untangle such a complex web?

Figure from Kristin Isaacs

The Six Degrees of Kevin Bacon



On the Solvability of the Six Degrees of Kevin Bacon Game

A Faster Graph Diameter and Radius Computation Method

Michele Borassi[1], Pierluigi Crescenzi[2], Michel Habib[3], Walter Kosters[4], Andrea Marino[5,*], and Frank Takes[4]

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Abstract. In this paper, we will propose a new algorithm that computes the radius and the diameter of a graph $G = (V, E)$, by finding bounds through heuristics and improving them until exact values can be guaranteed. Although the worst-case running time is $\mathcal{O}(|V| \cdot |E|)$, we will experimentally show that, in the case of real-world networks, it performs much better, finding the correct radius and diameter value after 10–100 BFSes instead of $|V|$ BFSes (independent of the value of $|V|$), and thus having running time $\mathcal{O}(|E|)$. Apart from efficiency, compared to other similar methods, the one proposed in this paper has three other advantages. It is more robust (even in the worst cases, the number of BFSes performed is not very high), it is able to simultaneously compute radius and diameter (halving the total running time whenever both values are needed), and it works both on directed and undirected graphs with very few modifications. As an application example, we use our new algorithm in order to determine the solvability over time of the "six degrees of Kevin Bacon" game.

1 Introduction

The six degrees of separation game is a trivia game which has been inspired by the well-known social experiment of Stanley Milgram [11], which was in turn a continuation of the empirical study of the structure of social networks by Michael Gurevich [7]. Indeed, the notion of six degrees of separation has been formulated for the first time by Frigyes Karinthy in 1929, who conjectured that any two individuals can be connected through at most five acquaintances. This conjecture has somehow been experimentally verified by Milgram and extremely popularized by a theater play of John Guare, successively adapted to the cinema by Fred Schepisi. The corresponding game refers to a social network, such as the

* The fifth author was supported by the EU-FET grant NADINE (GA 288956).

"Accessible and engaging. . . . A good introduction to the topic." —Nature

SIX DEGREES

THE SCIENCE OF A CONNECTED AGE

WITH A NEW CHAPTER

DUNCAN J. WATTS

KEVIN BACON AND GRAPH THEORY

Brian Hopkins

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STRACT: The interconnected world of actors and movies is a familiar, rich example for graph theory. This paper gives the history of the "Kevin Bacon Game" and makes extensive use of a Web site to analyze the underlying graph. The main content is the classroom development of the weighted average to determine the best choice of "center" for the graph. The article concludes with additional student activities and some responses to the material.

YWORDS: Cinema, finite mathematics, graph theory, popular culture, six degrees of separation, weighted averages.

1 INTRODUCTION

h theory is the mathematics of connections. It has wide applications to , interconnected systems: transportation networks, epidemiology, and Internet, to name just a few. But we teach graph theory with pictures handful of dots and lines. There is one large system that is easy to work , thanks to a Web site run by the University of Virginia, Department omputer Science. The Oracle of Bacon at Virginia [6] uses the Internet ie Database [3], which documents almost all of cinematic history. This is od tool for illustrating complete subgraphs, connected components, and distance between vertices. There is also a nice application of weighted ages. I have used this material in freshman finite mathematics classes mathematics major courses that cover graph theory; students always ond enthusiastically.

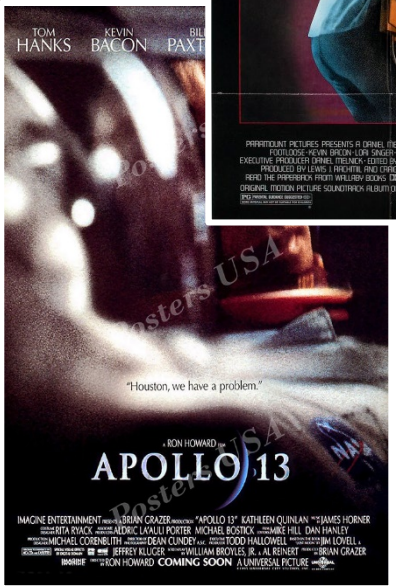
Kevin Bacon

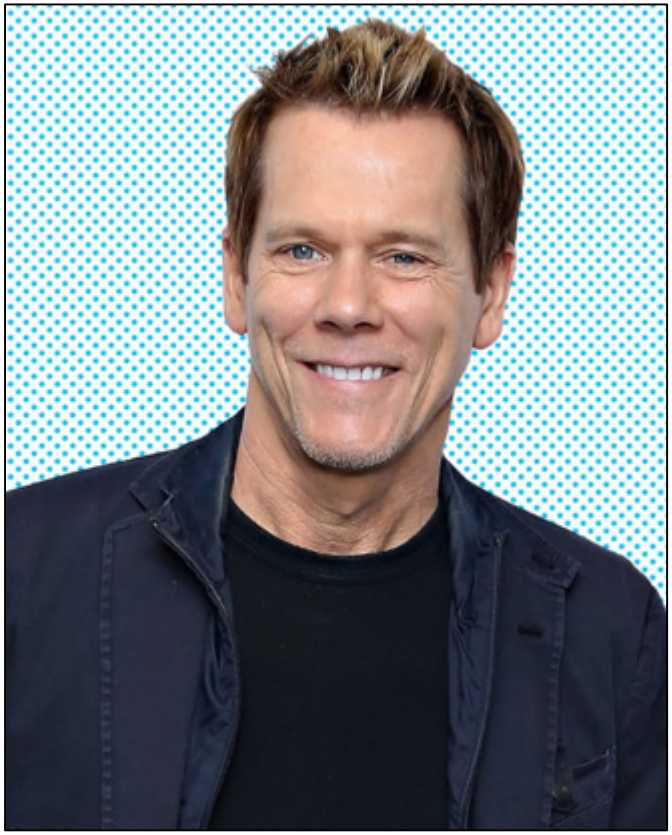
1978

1984

1992

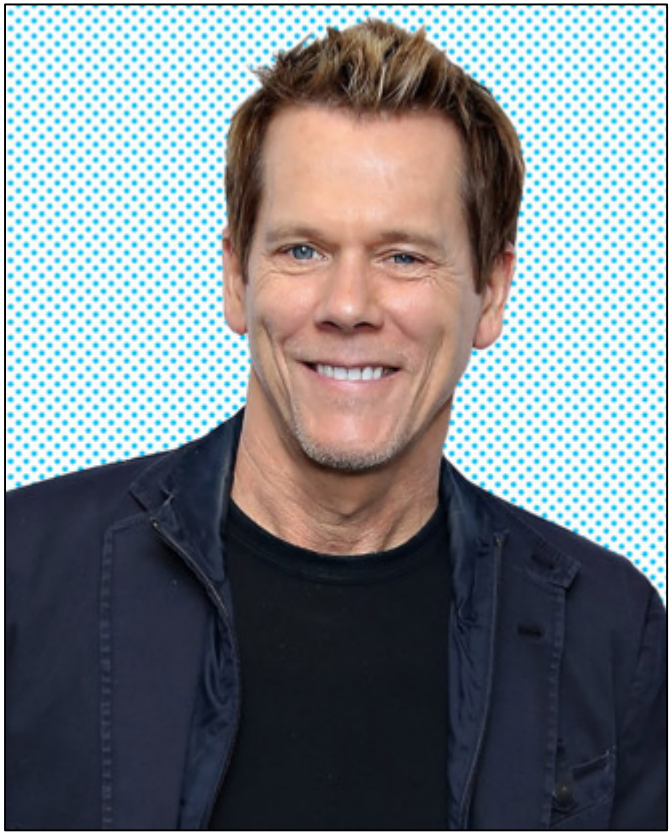
1995





Kevin Bacon

1990



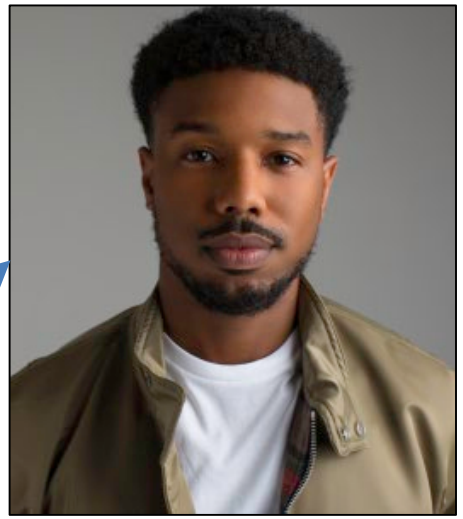
Michael B. Jordan

Connectedness to Michael B. Jordan

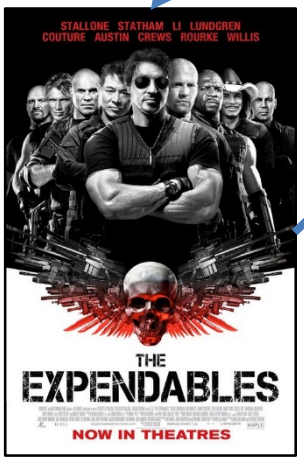
Frances McDormand
Best Actress Winner 2018

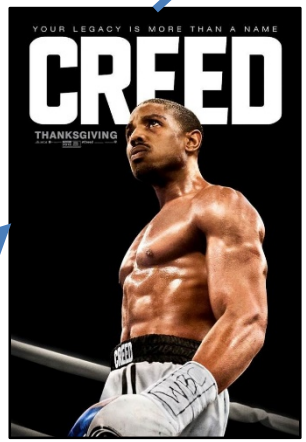
Hail Caesar
McDormand &
Channing Tatum

GI Joe: Retaliation
Tatum & Bruce Willis



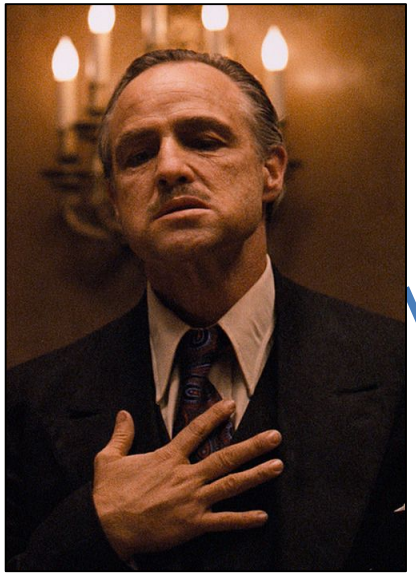
Expendables
Willis &
Sylvester Stallone





Creed
Stallone & Jordan

Connectedness to Michael B. Jordan



Marlon Brando
Best Actor 1954 and 1972
Died 2004

Avengers: Infinity War
Paltrow & Chadwick Boseman

Black Panther
Boseman & Jordan

Superman
with Gene Hackman

The Royal Tenenbaums
Hackman & Gwyneth Paltrow

EPA United States Environmental Protection Agency

Small World Networks

Travers and Milgram (1977):

296 arbitrary individuals in Nebraska and Boston were asked to give a letter to an acquaintance most likely to help it reach a target person in Massachusetts. 64 reached the target person, average number of intermediaries was 5.2

Watts and Strogatz (1998)

letters to nature

typically slower than ~1 km s^{-1}) might differ significantly from what is assumed by current modelling efforts[27]. The expected equation-of-state differences among small bodies (ice versus rock, for instance) presents another dimension of study; having recently adapted our code for massively parallel architectures (K. M. Olson and E.A, manuscript in preparation), we are now ready to perform a more comprehensive analysis.

The exploratory simulations presented here suggest that when a young, non-porous asteroid (if such exist) suffers extensive impact damage, the resulting fracture pattern largely defines the asteroid's response to future impacts. The stochastic nature of collisions implies that small asteroid interiors may be as diverse as their shapes and spin states. Detailed numerical simulations of impacts, using accurate shape models and rheologies, could shed light on how asteroid collisional response depends on internal configuration and shape, and hence on how planetesimals evolve. Detailed simulations are also required before one can predict the quantitative effects of nuclear explosions on Earth-crossing comets and asteroids, either for hazard mitigation[28] through disruption and deflection, or for resource exploitation[29]. Such predictions would require detailed reconnaissance concerning the composition and internal structure of the targeted object. □

Received 4 February; accepted 18 March 1998.

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Acknowledgements. This work was supported by NASA's Planetary Geology and Geophysics Program.

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Collective dynamics of 'small-world' networks

Duncan J. Watts* & Steven H. Strogatz

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Networks of coupled dynamical systems have been used to model biological oscillators[1–4], Josephson junction arrays[5,6], excitable media[7], neural networks[8–10], spatial games[11], genetic control networks[12] and many other self-organizing systems. Ordinarily, the connection topology is assumed to be either completely regular or completely random. But many biological, technological and social networks lie somewhere between these two extremes. Here we explore simple models of networks that can be tuned through this middle ground: regular networks 'rewired' to introduce increasing amounts of disorder. We find that these systems can be highly clustered, like regular lattices, yet have small characteristic path lengths, like random graphs. We call them 'small-world' networks, by analogy with the small-world phenomenon[13,14] (popularly known as six degrees of separation[15]). The neural network of the worm *Caenorhabditis elegans*, the power grid of the western United States, and the collaboration graph of film actors are shown to be small-world networks. Models of dynamical systems with small-world coupling display enhanced signal-propagation speed, computational power, and synchronizability. In particular, infectious diseases spread more easily in small-world networks than in regular lattices.

To interpolate between regular and random networks, we consider the following random rewiring procedure (Fig. 1). Starting from a ring lattice with n vertices and k edges per vertex, we rewire each edge at random with probability p. This construction allows us to 'tune' the graph between regularity ($p = 0$) and disorder ($p = 1$), and thereby to probe the intermediate region $0 < p < 1$, about which little is known.

We quantify the structural properties of these graphs by their characteristic path length $L(p)$ and clustering coefficient $C(p)$, as defined in Fig. 2 legend. Here $L(p)$ measures the typical separation between two vertices in the graph (a global property), whereas $C(p)$ measures the cliquishness of a typical neighbourhood (a local property). The networks of interest to us have many vertices with sparse connections, but not so sparse that the graph is in danger of becoming disconnected. Specifically, we require $n \gg k \gg \ln(n) \gg 1$, where $k \gg \ln(n)$ guarantees that a random graph will be connected[16]. In this regime, we find that $L \sim n/2k \gg 1$ and $C \sim 3/4$ as $p \to 0$, while $L \approx L_{\text{random}} \sim \ln(n)/\ln(k)$ and $C \approx C_{\text{random}} \sim k/n \ll 1$ as $p \to 1$. Thus the regular lattice at $p = 0$ is a highly clustered, large world where L grows linearly with n, whereas the random network at $p = 1$ is a poorly clustered, small world where L grows only logarithmically with n. These limiting cases might lead one to suspect that large C is always associated with large L, and small C with small L.

On the contrary, Fig. 2 reveals that there is a broad interval of p over which $L(p)$ is almost as small as L_{random} yet $C(p) \gg C_{\text{random}}$. These small-world networks result from the immediate drop in $L(p)$ caused by the introduction of a few long-range edges. Such 'short cuts' connect vertices that would otherwise be much farther apart than L_{random}. For small p, each short cut has a highly nonlinear effect on L, contracting the distance not just between the pair of vertices that it connects but between their immediate neighbourhoods, neighbourhoods of neighbourhoods and so on. By contrast, an edge

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Collins and Chow (1998)

news and views

It's a small world

James J. Collins and Carson C. Chow

The concept of Six Degrees of Separation has been formalized in so-called 'small-world networks'. The principles involved could be of use in settings as diverse as improving networks of cellular phones and understanding the spread of infections.

A few years ago, on American campuses, it was popular to play Six Degrees of Kevin Bacon. In this game, participants attempt to link the actor Kevin Bacon to any other actor through as few common films and co-stars as possible. Links are formed directly between Bacon and another actor if they appeared in the same film or indirectly through a chain of co-stars in different films (Fig. 1).

In the world of mathematics, a similar amusement involves assessing one's Erdös number, which measures the number of links needed to connect one to the prolific mathematician Paul Erdös through jointly authored papers. For example, individuals have an Erdös number of 1 if they co-authored a paper with Erdös. If one of their co-authors wrote a paper with Erdös, then they have an Erdös number of 2, and so forth. It has been pointed out[1] that Dan Kleitman has a combined Erdös/Bacon number of 3 because he wrote a paper with Erdös and appeared in *Good Will Hunting* with Minnie Driver, who appeared with Bacon in *Sleepers*.

These games are related to the popular concept of Six Degrees of Separation[2], which is based on the notion that everyone in the world is connected to everyone else through a chain of at most six mutual acquaintances. If two people have one mutual acquaintance, then they have one degree of separation. The estimate of six degrees of separation, which is related to the small-world phenomenon[3,4], arises from pioneering empirical work by Milgram[2] and can be understood heuristically from a somewhat unrealistic assumption of random connectivity. That is, if each person knows about one hundred individuals, and given that there are about a billion people on the Earth, then seven connections or six degrees of separation are enough to link everyone together.

On page 440 of this issue[5], Watts and Strogatz formalize this idea in what they call small-world networks. They demonstrate through numerical simulations that a network need not be very random to get this small-world effect. They consider a connected network with nodes and links. In the friendship analogy, each node represents a person and each link represents a single connection to an acquaintance. They then define two measures. The first is a characteristic path length. This is the smallest number of links it takes to connect one node to another, averaged over all pairs of nodes in the network. The second measure is the clustering coefficient. This measures the amount of cliquishness of the network, that is, the fraction of neighbouring nodes that are also connected to one another. For example, in an all-to-all connected network, the clustering coefficient is one.

An example of a large-world network is one that is regularly and locally connected like a crystalline lattice. Such a network is highly clustered and the characteristic path length is large, scaling with the typical linear dimension of the network. On the other hand, a completely random network is poorly clustered and the characteristic path length is short, scaling logarithmically with the size of the network.

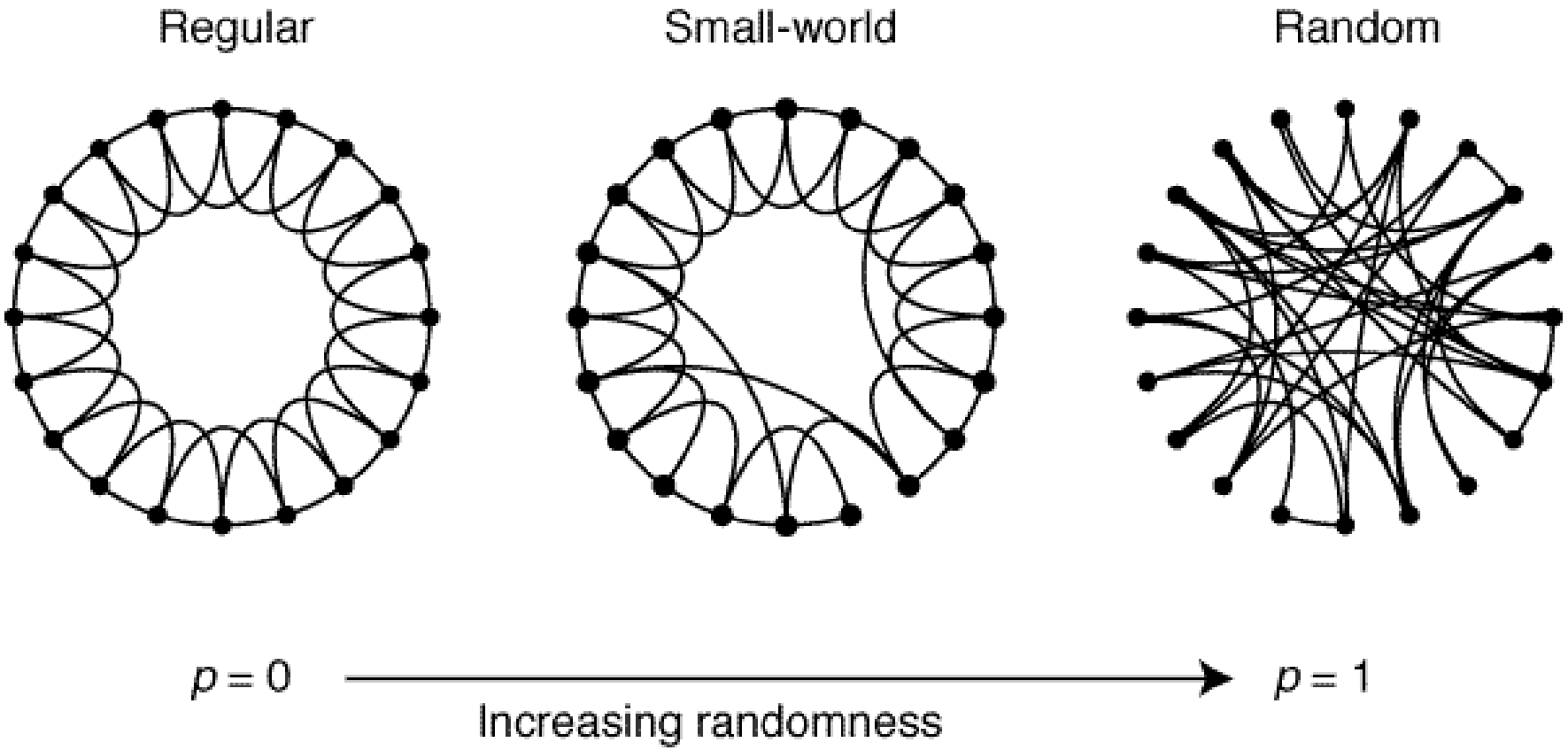
What Watts and Strogatz[5] do is to shift gradually from a regular network to a random network by increasing the probability of making random connections from 0 to 1 (see Fig. 1, page 441). They then measure the characteristic path length and the amount of clustering of the network as a function of the amount of randomness. They find that path length and clustering depend differently on the amount of randomness in the network. The characteristic path length drops quickly, whereas the amount of clustering drops rather slowly. This leads to a small-world network in which the amount of clustering is high and the characteristic path length is short. So a small world can exist even when the cliquishness is imperceptibly different from that of a large world.

The explanation for this effect is that it only takes a few short cuts between cliques to turn a large world into a small world. In the friendship analogy, it only takes a small number of well-connected people to make a world small. The interesting and surprising thing is that it is impossible to determine whether or not you live in a small world or a large world from local information alone. The average person (node) is not directly associated with the key people (the clique-linkers).

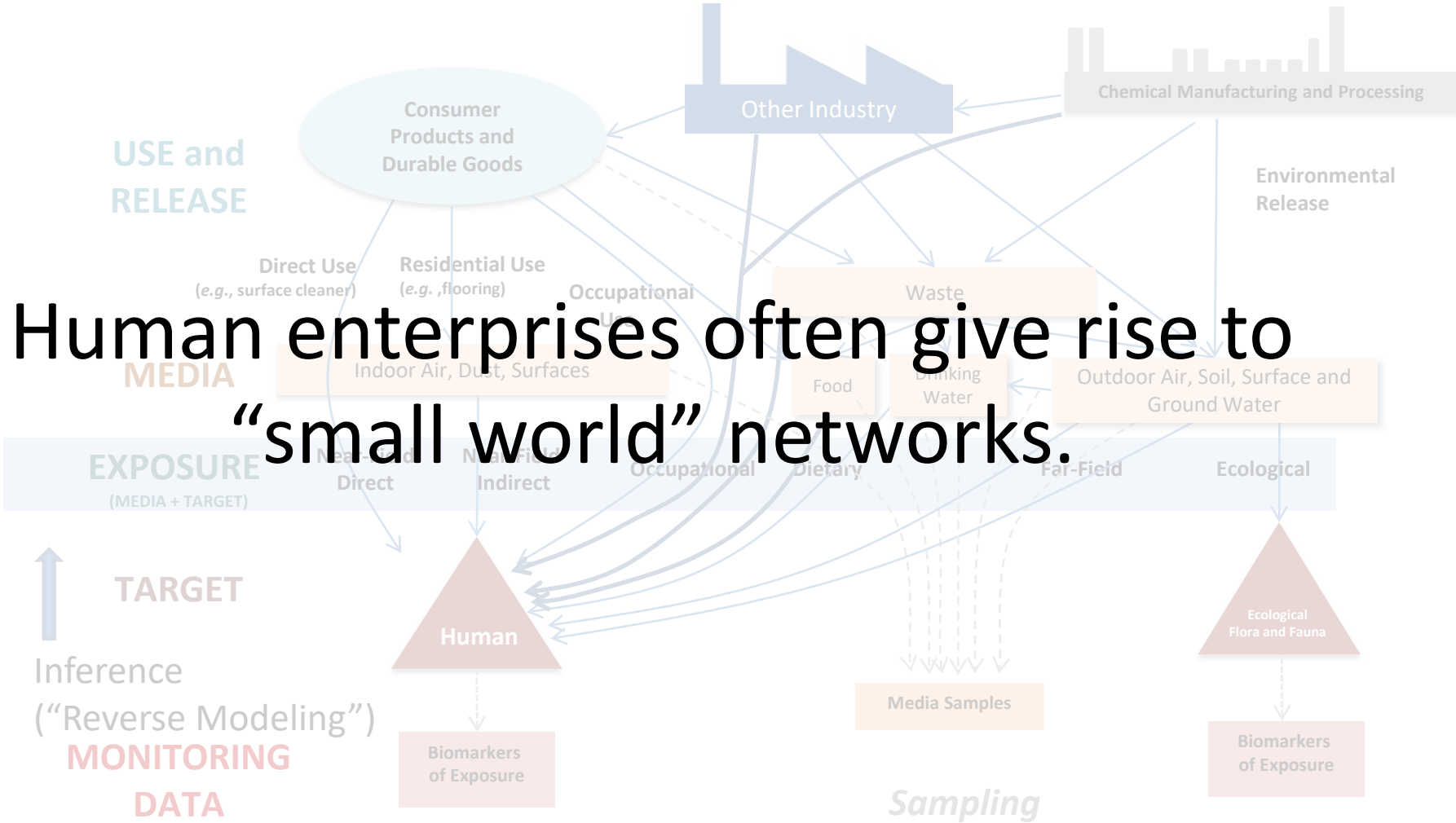
Small-world connectivity has consequences that could be good or bad,

Figure 1 **Three degrees. Because Kevin Bacon has appeared in many films, most actors have low Bacon numbers and the game Six Degrees of Kevin Bacon has declined in popularity. It is possible to centre the game around a newer star such as Leonardo DiCaprio. These film stills, running clockwise, show that in this case there are at most three degrees of separation between DiCaprio and Helena Bonham-Carter, through Kate Winslet (*Titanic*, Columbia TriStar; *Sense and Sensibility*, Columbia TriStar), Emma Thompson (*Sense and Sensibility*; *Much Ado About Nothing*, Entertainment Films) and Kenneth Branagh (*Much Ado About Nothing*; *Frankenstein*; Columbia TriStar). Short cuts between cliques could be created in this game through some of DiCaprio's well-connected co-stars such as Sharon Stone (*The Quick and the Dead*; TriStar; not shown).**

Complex is Not the Same as Random



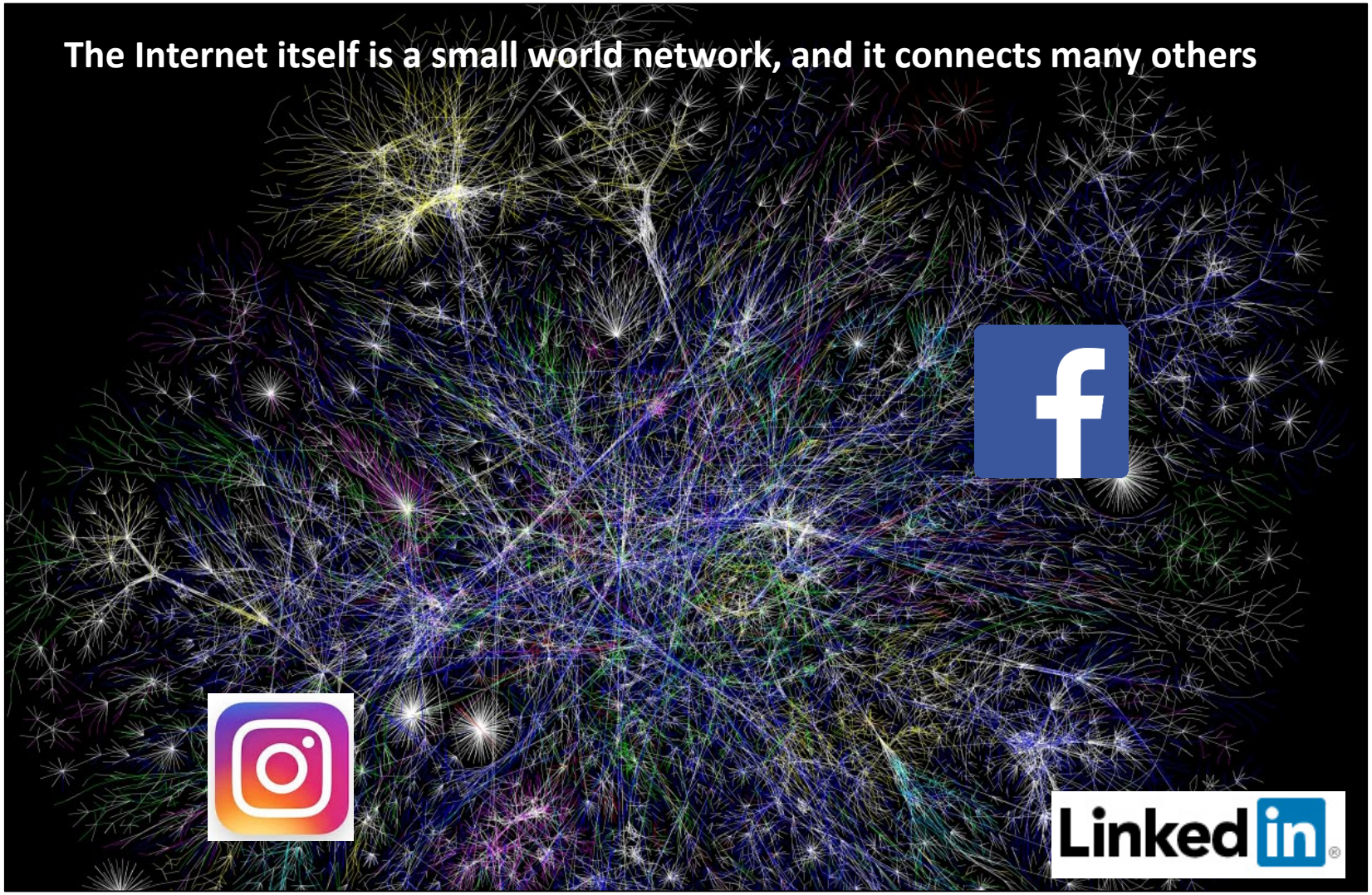
Watts and Strogatz (1998)



Human enterprises often give rise to "small world" networks.

Figure from Kristin Isaacs

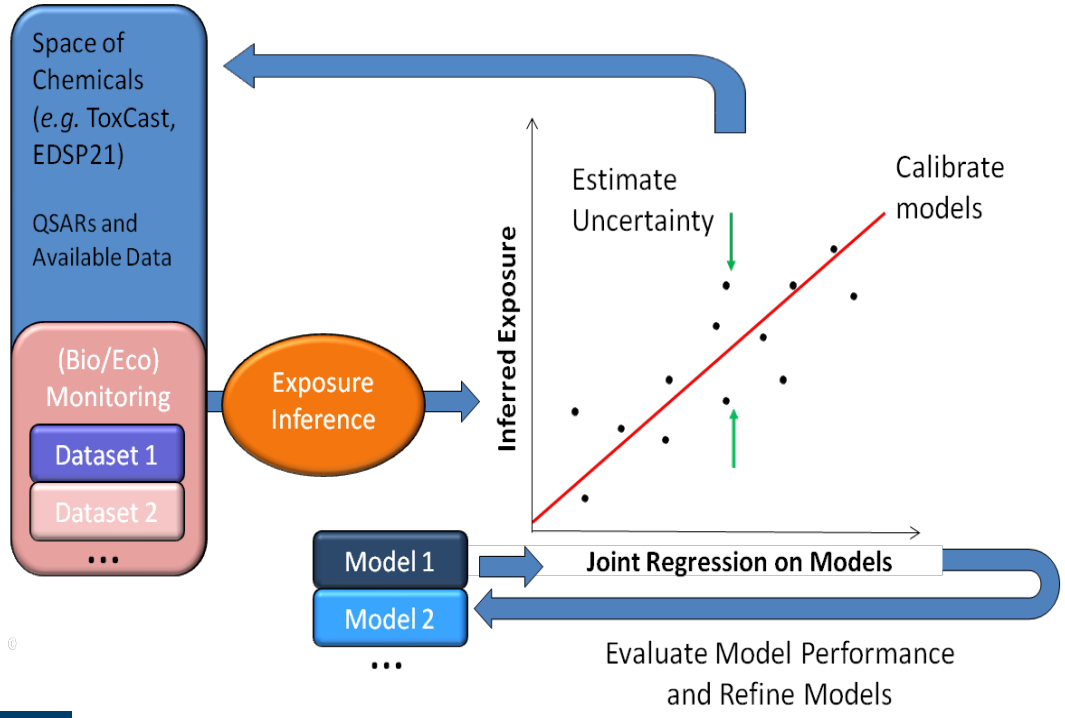
The Internet (Circa 2005)

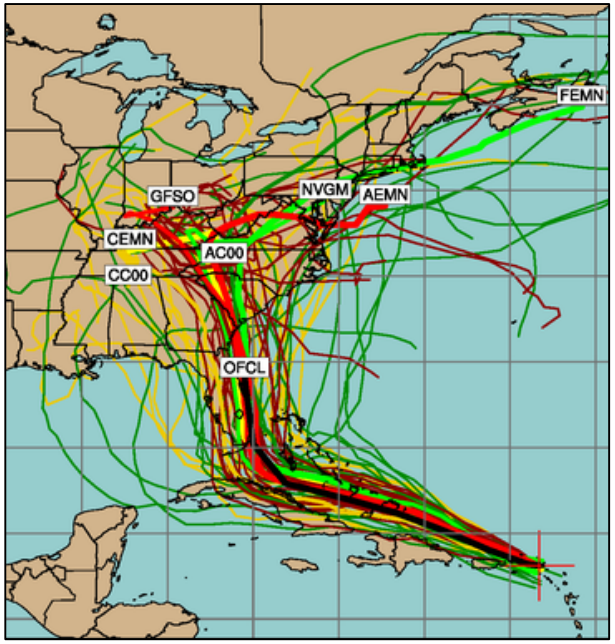


https://upload.wikimedia.org/wikipedia/commons/d/d2/Internet_map_1024.jpg

Consensus Exposure Predictions with the SEEM Framework

- We incorporate multiple models into consensus predictions for 1000s of chemicals within the **Systematic Empirical Evaluation of Models (SEEM)** (Wambaugh et al., 2013, 2014)
- *Each chemical with measured intake rate provides an additional evaluation of exposure model predictions*
- Evaluation is similar to a sensitivity analysis: What models are working? What data are most needed?

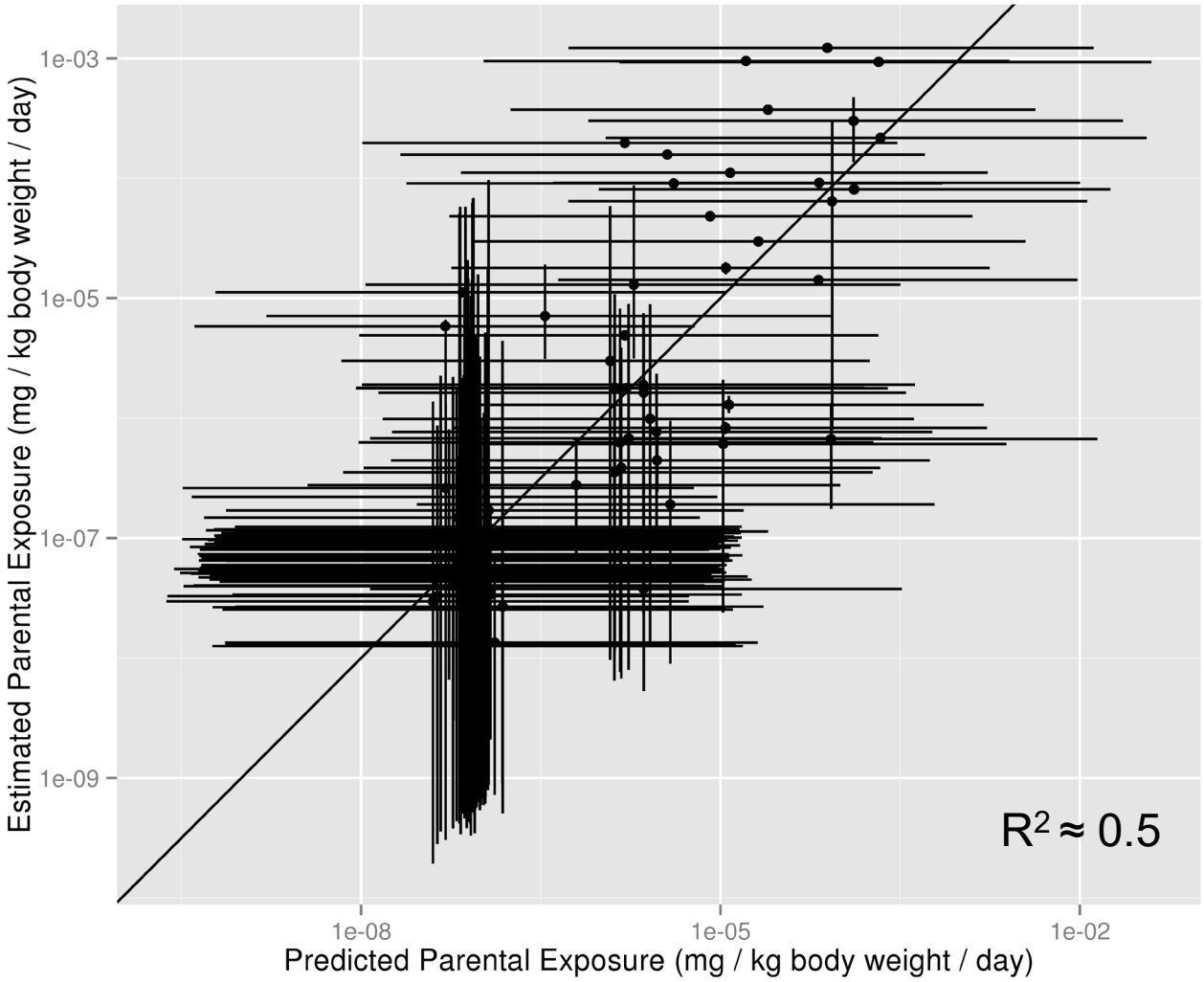




Integrating Multiple Models

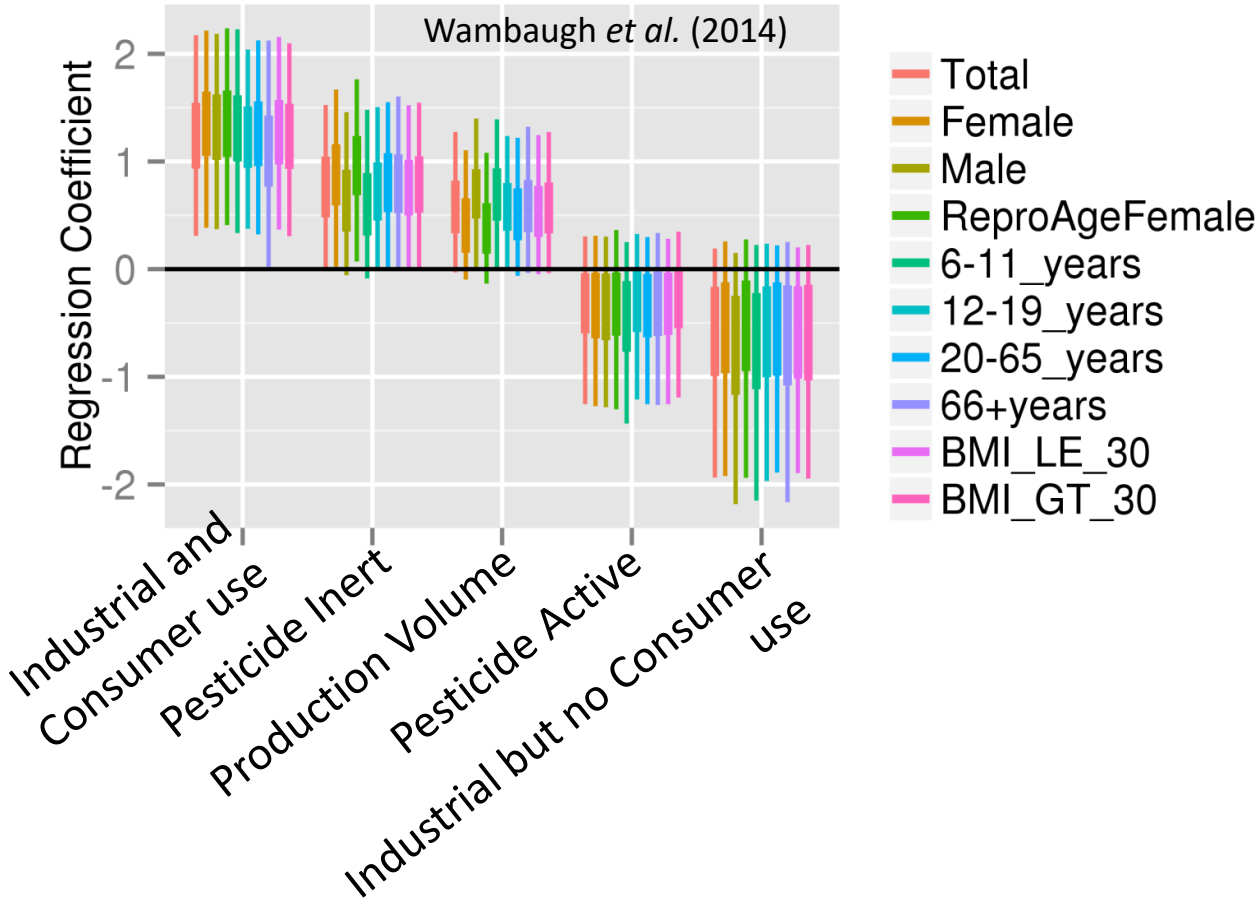
SEEM Analysis (circa 2014)

Each point is a different chemical



Wambaugh et al, 2014

Heuristics of Exposure



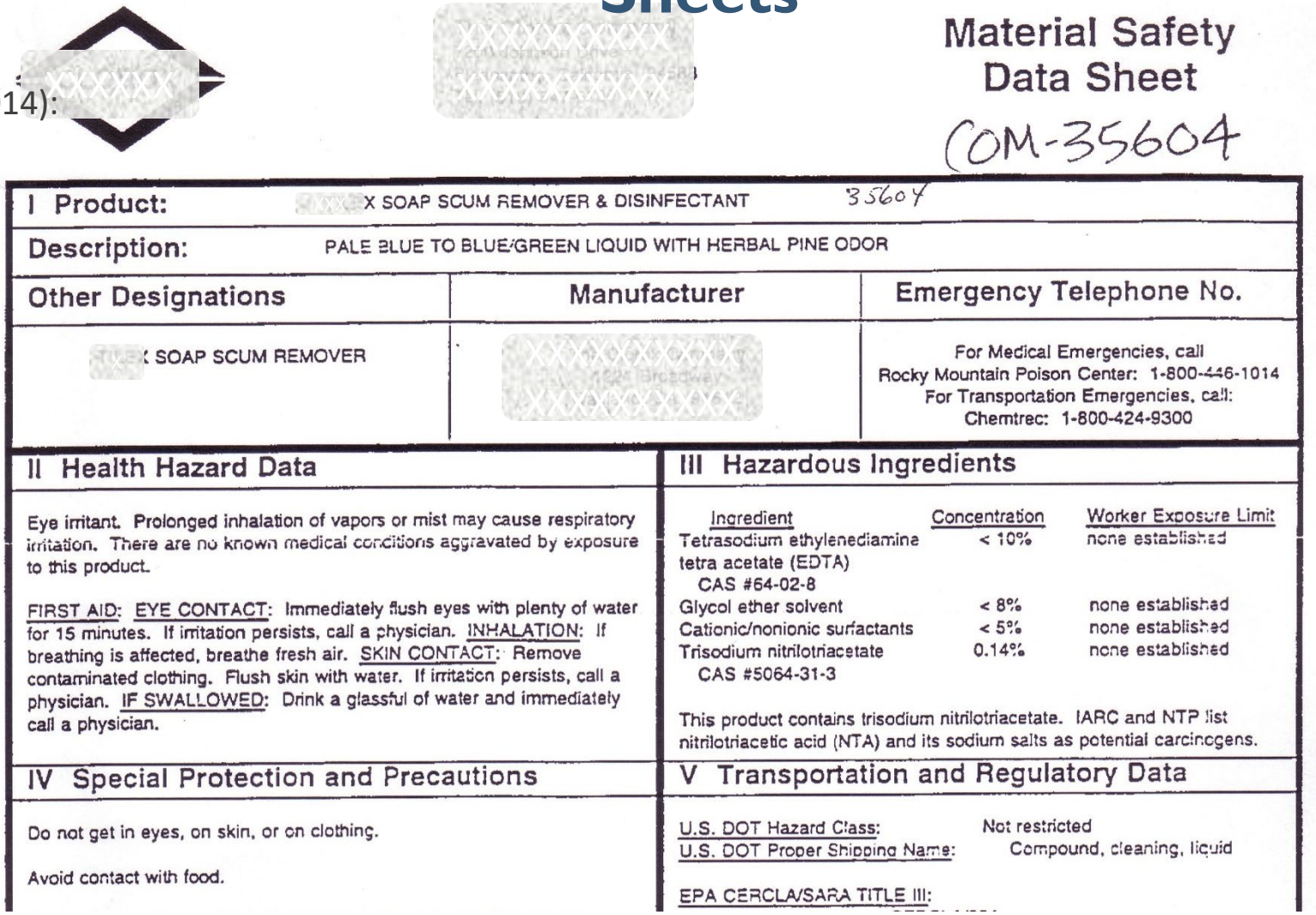
- Five descriptors explain roughly 50% of the chemical-to-chemical variability in median NHANES exposure rates
- Same five predictors work for all NHANES demographic groups analyzed – stratified by age, sex, and body-mass index
- Chemical use identifies relevant pathways
- Some pathways have much higher average exposures (Wallace et al., 1987)

CPCPdb: Material Safety Data Sheets

Goldsmith et al. (2014):

- ~20,000 product-specific Material Safety Data Sheets (MSDS) curated
- ~2,400 chemicals

Product-specific uses determined using web spider to click through categories (e.g., home goods, bath soaps, baby) to find each product



Material Safety Data Sheet

COM-35604

I Product:	X SOAP SCUM REMOVER & DISINFECTANT 35604	
Description:	PALE BLUE TO BLUE/GREEN LIQUID WITH HERBAL PINE ODOR	
Other Designations	Manufacturer	Emergency Telephone No.
X SOAP SCUM REMOVER	[redacted]	For Medical Emergencies, call Rocky Mountain Poison Center: 1-800-446-1014 For Transportation Emergencies, call: Chemtrec: 1-800-424-9300

II Health Hazard Data

Eye irritant. Prolonged inhalation of vapors or mist may cause respiratory irritation. There are no known medical conditions aggravated by exposure to this product.

FIRST AID: EYE CONTACT: Immediately flush eyes with plenty of water for 15 minutes. If irritation persists, call a physician. INHALATION: If breathing is affected, breathe fresh air. SKIN CONTACT: Remove contaminated clothing. Flush skin with water. If irritation persists, call a physician. IF SWALLOWED: Drink a glassful of water and immediately call a physician.

III Hazardous Ingredients

Ingredient	Concentration	Worker Exposure Limit
Tetrasodium ethylenediamine tetra acetate (EDTA) CAS #64-02-8	< 10%	none established
Glycol ether solvent	< 8%	none established
Cationic/nonionic surfactants	< 5%	none established
Trisodium nitrilotriacetate CAS #5064-31-3	0.14%	none established

This product contains trisodium nitrilotriacetate. IARC and NTP list nitrilotriacetic acid (NTA) and its sodium salts as potential carcinogens.

IV Special Protection and Precautions

Do not get in eyes, on skin, or on clothing.

Avoid contact with food.

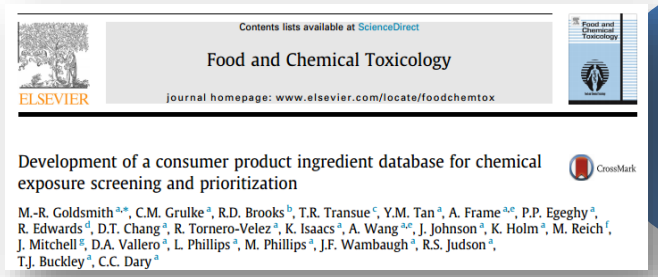
V Transportation and Regulatory Data

U.S. DOT Hazard Class: Not restricted

U.S. DOT Proper Shipping Name: Compound, cleaning, liquid

EPA CERCLA/SARA TITLE III:

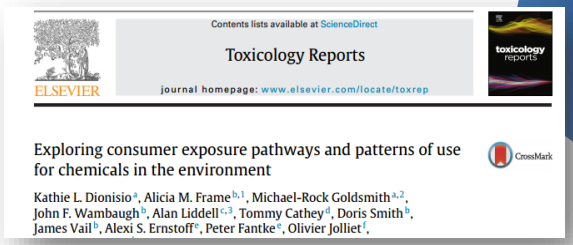
What Do We Know About Chemical Use? Chemicals and Products Database



MSDS Data

Occurrence and quantitative chemical composition

Broad "index" of chemical uses



CPCat

CPDat

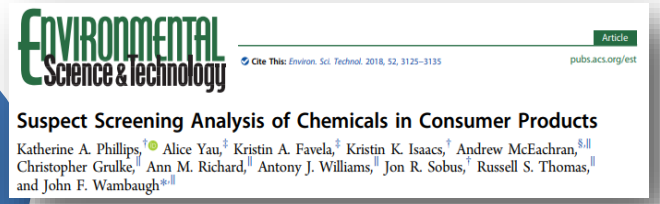
EPA United States Environmental Protection Agency
Chemistry Dashboard

Functional Use Data

The roles that chemicals serve in products

Ingredient Lists

Occurrence data



Measured Data

Measurement of chemicals in consumer products

https://comptox.epa.gov/dashboard

Slide from Kristin Isaacs

EPA United States Environmental Protection Agency

Ring et al. (2019)

Predicting Pathways

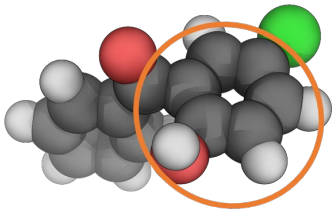
We use the method of Random Forests to relate chemical structure and properties to exposure pathway

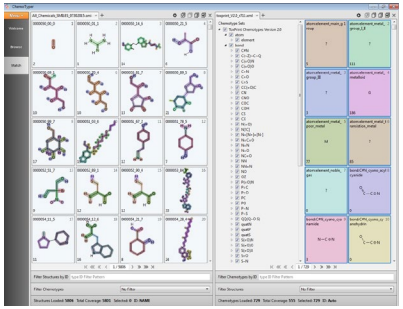
	NHANES Chemicals	Positives	Negatives	OOB Error Rate	Positives Error Rate	Balanced Accuracy	Sources of Positives	Sources of Negatives
Dietary	24	2523	8865	27	32	73	FDA CEDI, ExpoCast, CPDat (Food, Food Additive, Food Contact), NHANES Curation	Pharmapendium, CPDat (non-food), NHANES Curation
Near-Field	49	1622	567	27	25	73	CPDat (consumer_use, building_material), ExpoCast, NHANES Curation	CPDat (Agricultural, Industrial), FDA CEDI, NHANES Curation
Far-Field Pesticide	94	1480	6522	20	36	80	REDs, Swiss Pesticides, Stockholm Convention, CPDat (Pesticide), NHANES Curation	Pharmapendium, Industrial Positives, NHANES Curation
Far Field Industrial	42	5089	2913	19	17	81	CDR HPV, USGS Water Occurrence, NORNAN PFAS, Stockholm Convention, CPDat (Industrial, Industrial_Fluid), NHANES Curation	Pharmapendium, Pesticide Positives, NHANES Curation

Pathway Prediction is Similar to Methods for Predicting Chemical Function From Structure

Machine Learning Based Classification Models
(Random Forest, Breiman, 2001)

Chemical Structure and Property Descriptors





Use Database (FUSE)

Prediction of Of Potential Alternatives from Chemical Libraries

Phillips et al. (2017)

Collaboration on High Throughput Exposure Predictions

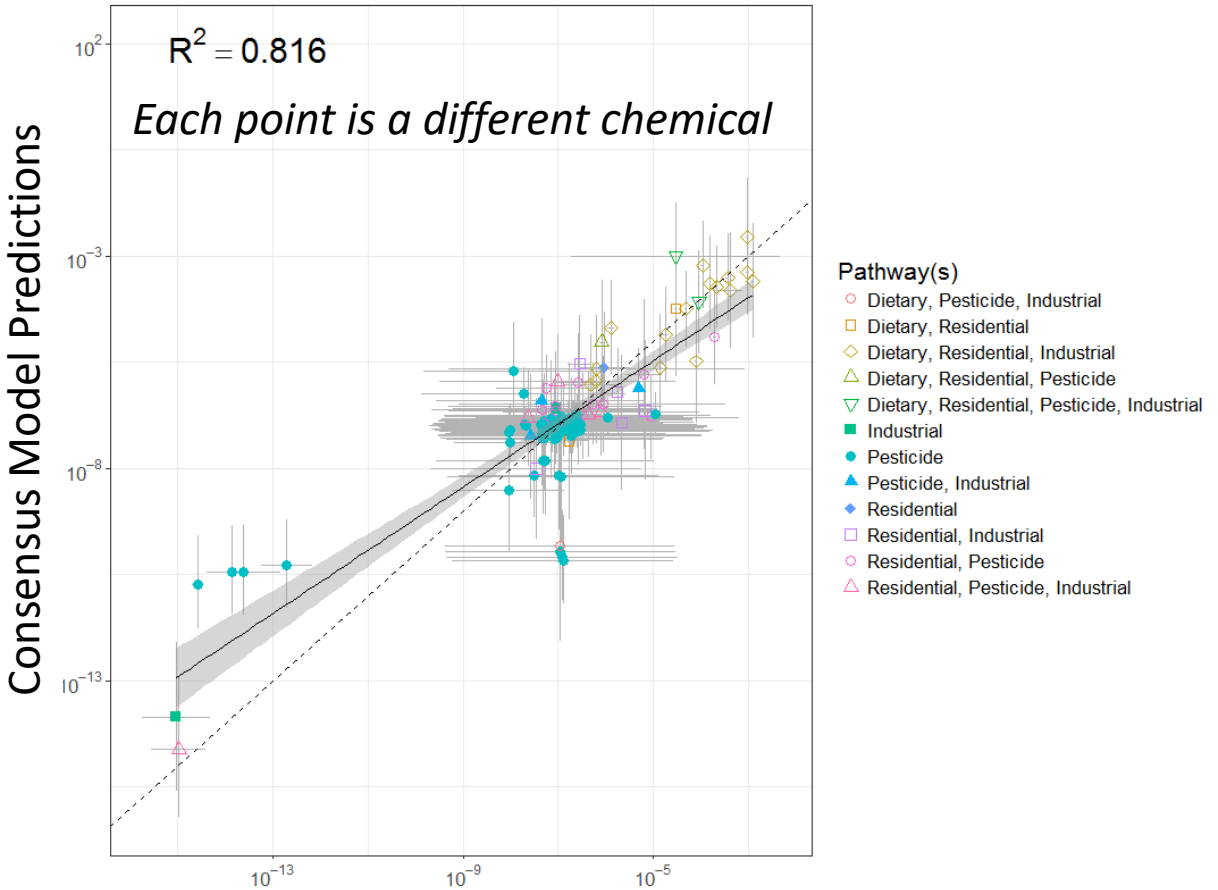
Jon Arnot, Deborah H. Bennett, Peter P. Egeghy, Peter Fantke, Lei Huang, Kristin K. Isaacs, Olivier Jolliet, Hyeong-Moo Shin, Katherine A. Phillips, Paul S. Price, Caroline Ring, R. Woodrow Setzer, John F. Wambaugh, Johnny Westgate

Ring et al., 2019

Predictor	Reference	Chemicals Predicted	Pathways
EPA Inventory Update Reporting and Chemical Data Reporting (CDR) (2015)	US EPA (2018)	7856	All
Stockholm Convention of Banned Persistent Organic Pollutants (2017)	Lallas (2001)	248	Far-Field Industrial and Pesticide
EPA Pesticide Reregistration Eligibility Documents (REDs) Exposure Assessments (Through 2015)	Wetmore et al. (2012, 2015)	239	Far-Field Pesticide
Food Contact Substance Migration Model (2017)	Biryol et al. (2017)	940	Dietary
United Nations Environment Program and Society for Environmental Toxicology and Chemistry toxicity model (USEtox) Industrial Scenario (2.0)	Rosenbaum et al. (2008)	8167	Far-Field Industrial
USEtox Pesticide Scenario (2.0)[48]USEtox Pesticide Scenario (2.0)	Fantke et al. (2011, 2012, 2016)	8167	Far-Field Pesticide
Risk Assessment IDentification And Ranking (RAIDAR) Far-Field (2.95)	Arnot et al. (2008)	7511	Far-Field Industrial and Pesticide
EPA Stochastic Human Exposure Dose Simulator High-Throughput (SHEDS-HT) Near-Field Direct (2017)	Isaacs (2017)	1119	Consumer (Near-Field)
SHEDS-HT Near-field Indirect (2017)	Isaacs (2017)	645	Consumer
Fugacity-based INdoor Exposure (FINE) (2017)	Bennett et al. (2004), Shin et al. (2012)	1221	Consumer
RAIDAR-ICE Near-Field (0.804)	Arnot et al., (2014), Zhang et al. (2014)	615	Consumer
USEtox Consumer Scenario (2.0)	Jolliet et al. (2015), Huang et al. (2016,2017)	8167	Consumer
USEtox Dietary Scenario (2.0)	Jolliet et al. (2015), Huang et al. (2016), Ernstoff et al. (2017)	8167	Dietary

Pathway-Based Consensus Modeling of NHANES

- Exposure predictors (data and models) have been grouped into four pathways (residential, dietary, pesticidal, and industrial)
- New machine learning tools match chemicals to exposure pathways and calibrated exposure models
- Multivariate regression using human intake rates inferred for 114 chemicals provides calibration and evaluation



Ring et al., 2019

Consensus Modeling of Median Chemical Intake

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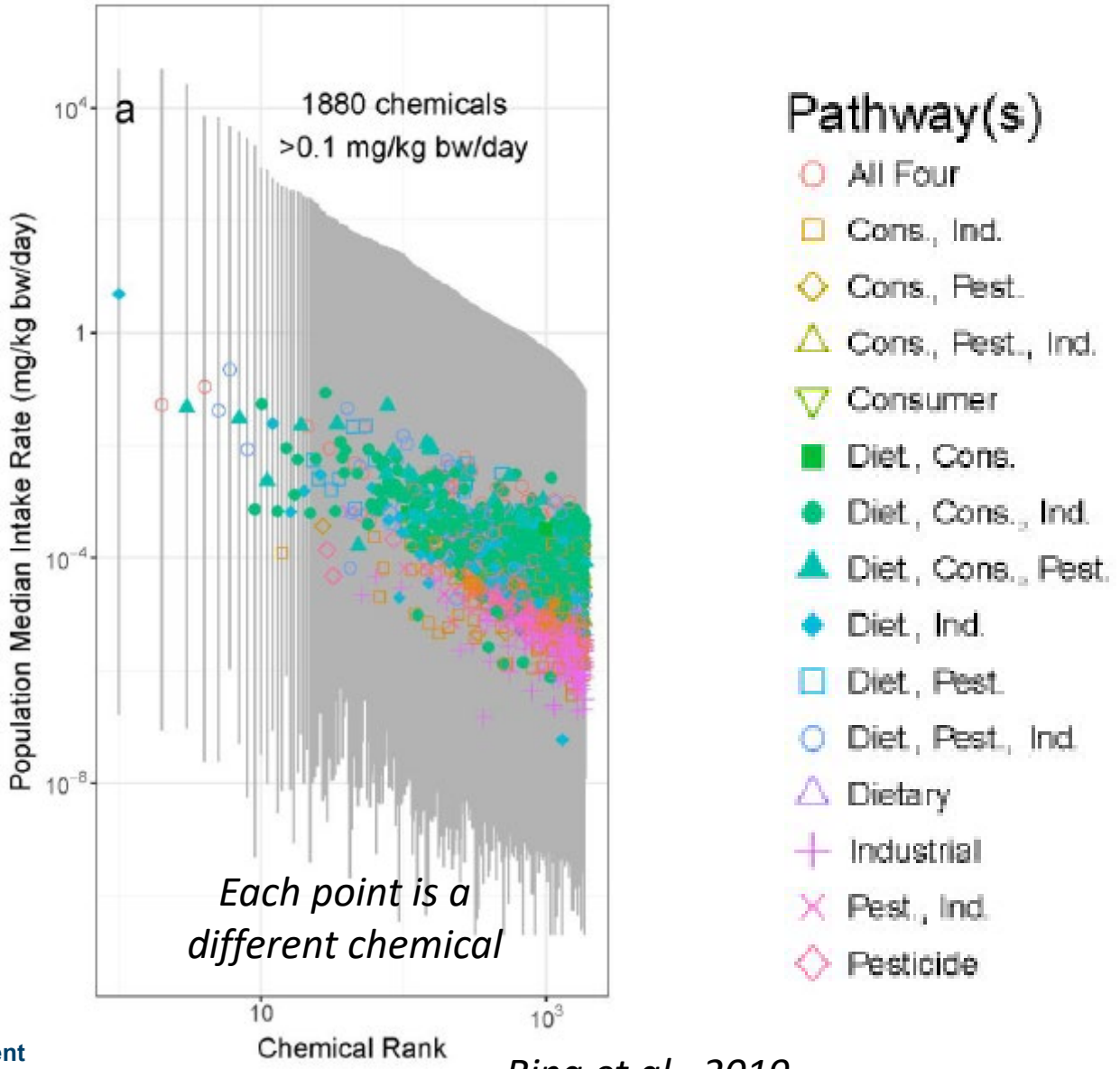

Ring et al., 2019

Office of Research and Development

Consensus Modeling of Median Chemical Intake

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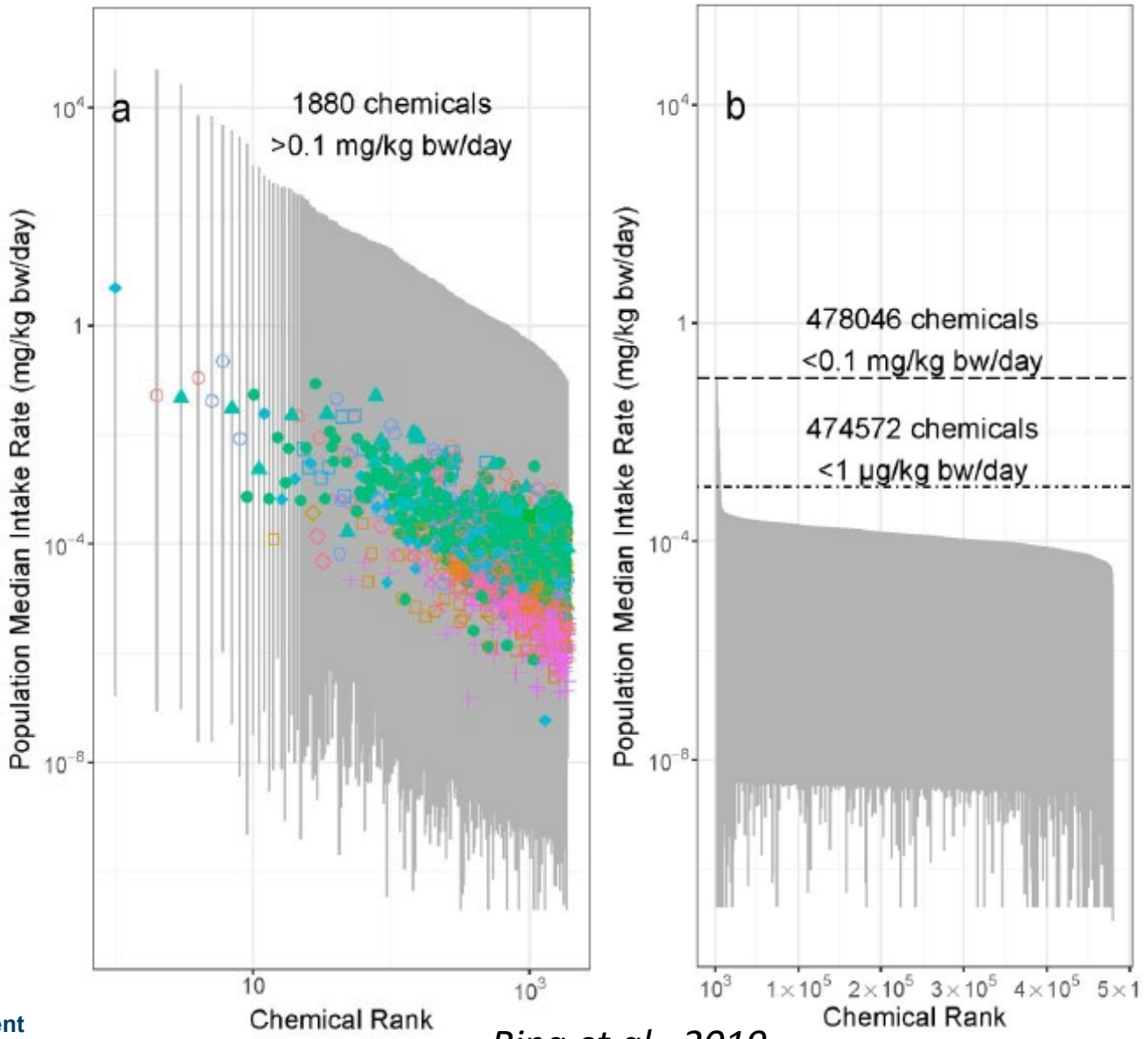
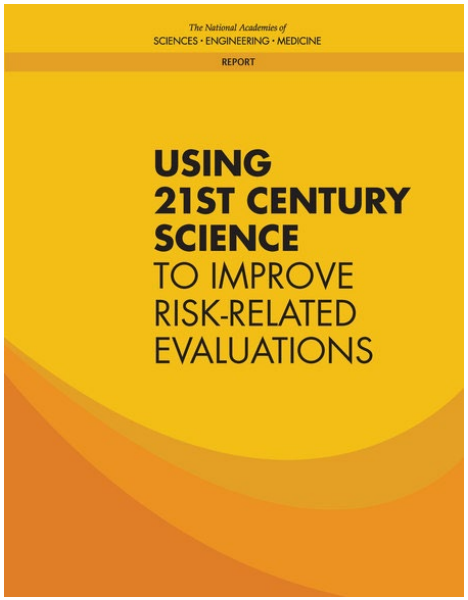
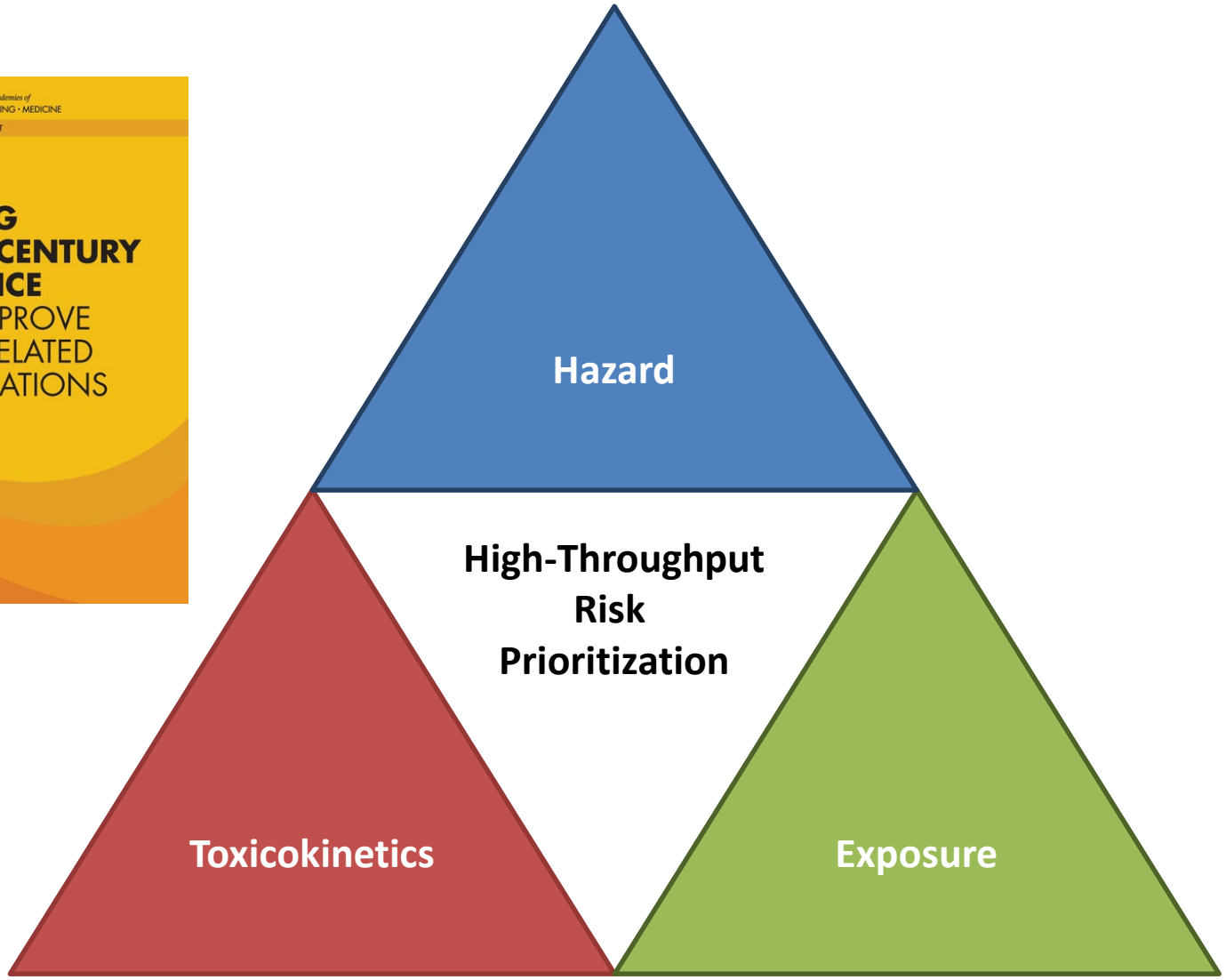


Ring et al., 2019

Office of Research and Development

Exposure-Based Priority Setting





EPA United States Environmental Protection Agency

Conclusions

- We would like to know more about the risk posed by thousands of chemicals in the environment – which ones should we start with?
  - High throughput screening (HTS) provides one path forward for identifying potential hazard, but the real world is complicated by toxicokinetics, mixtures, variability (and more)

- Using *in vitro* methods developed for pharmaceuticals, we can make useful predictions of TK for large numbers of chemicals

- Exposure predictions and data are key to risk-based prioritization
  - Although exposure is a complex system, certain patterns emerge – in particular, near field (in the home) sources of exposure are important
  - Consensus modeling provides one path forward, but only as good as available data (at best)

- Exposure-based priority setting allows the identification of the chemicals most likely to be relevant to the public health

ExpoCast Project (Exposure Forecasting)

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