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Careers in Toxicology: US EPA Research Physical Scientist

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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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US EPA Office of Research and Development

- The Office of Research and Development (ORD) is the scientific research arm of EPA
  - 543 peer-reviewed journal articles in 2019
- Research is conducted by ORD's four national centers, and three offices organized to address:
  - Public health and env. assessment; comp. tox. and exposure; env. measurement and modeling; and env. solutions and emergency response.
- 13 facilities across the United States
- 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

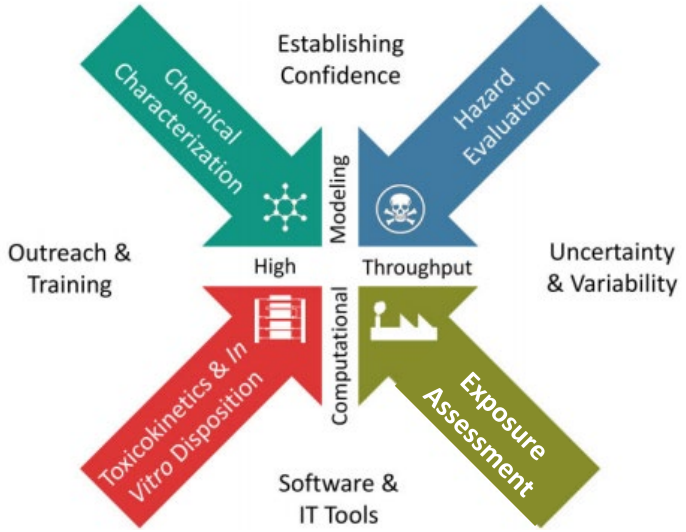
ORD Facility in
Research Triangle Park, NC

US EPA's ExpoCast Project:
New Approach Methodologies for Exposure Forecasting

*"**Investment in 21st century exposure science is now required** to fully realize the potential of the NRC vision for toxicity testing."*
Cohen Hubal (2009)

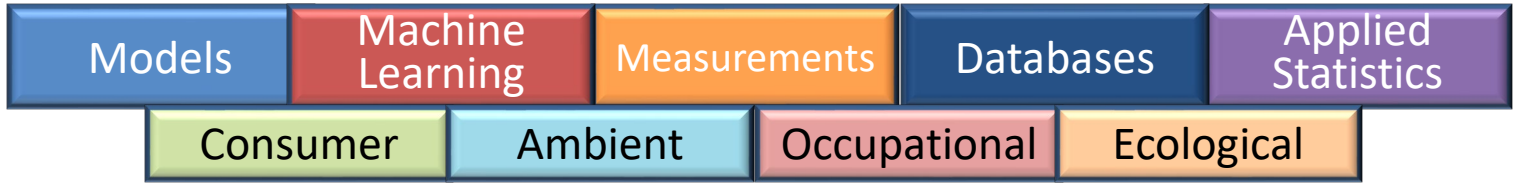
"Obama's FY10 Budget Includes Increased Toxicology" (Lovell and Hegstad, 2009) noted that:

- Funding allows for complementary exposure predictions from ExpoCast, which is slated to be **launched in FY10**
- Aim to predict the impact of chemicals on the human body using data from ToxCast



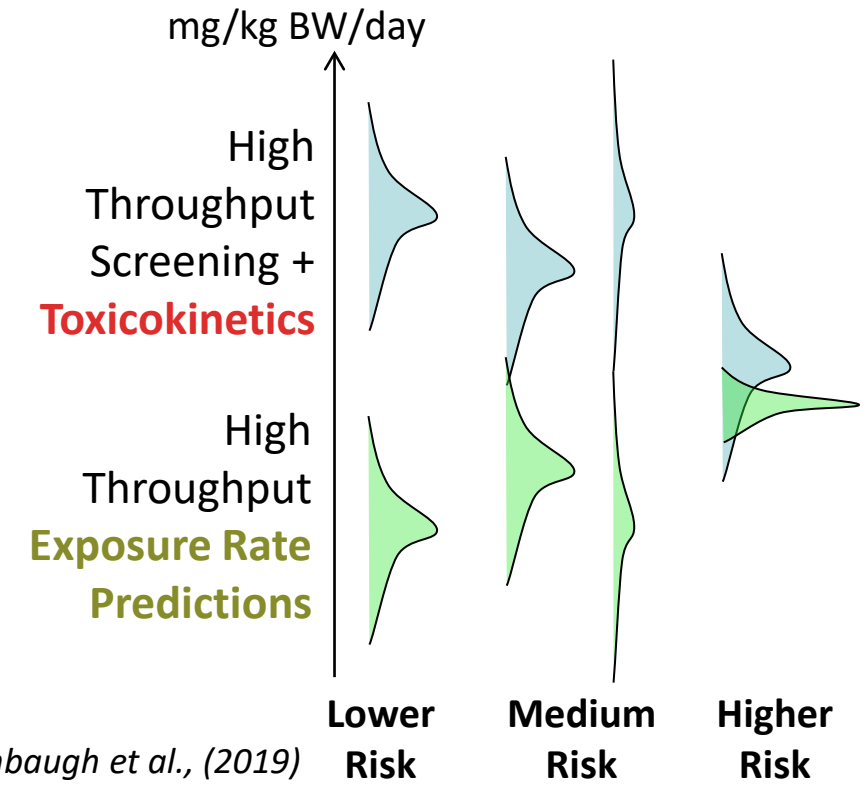
Thomas et al. (2019)

ExpoCast is



Since 2010:

- 45 peer-reviewed publications
- 5 STAR grants awarded
- 3 Federal research contracts (SWRI and Battelle)



Wambaugh et al., (2019)

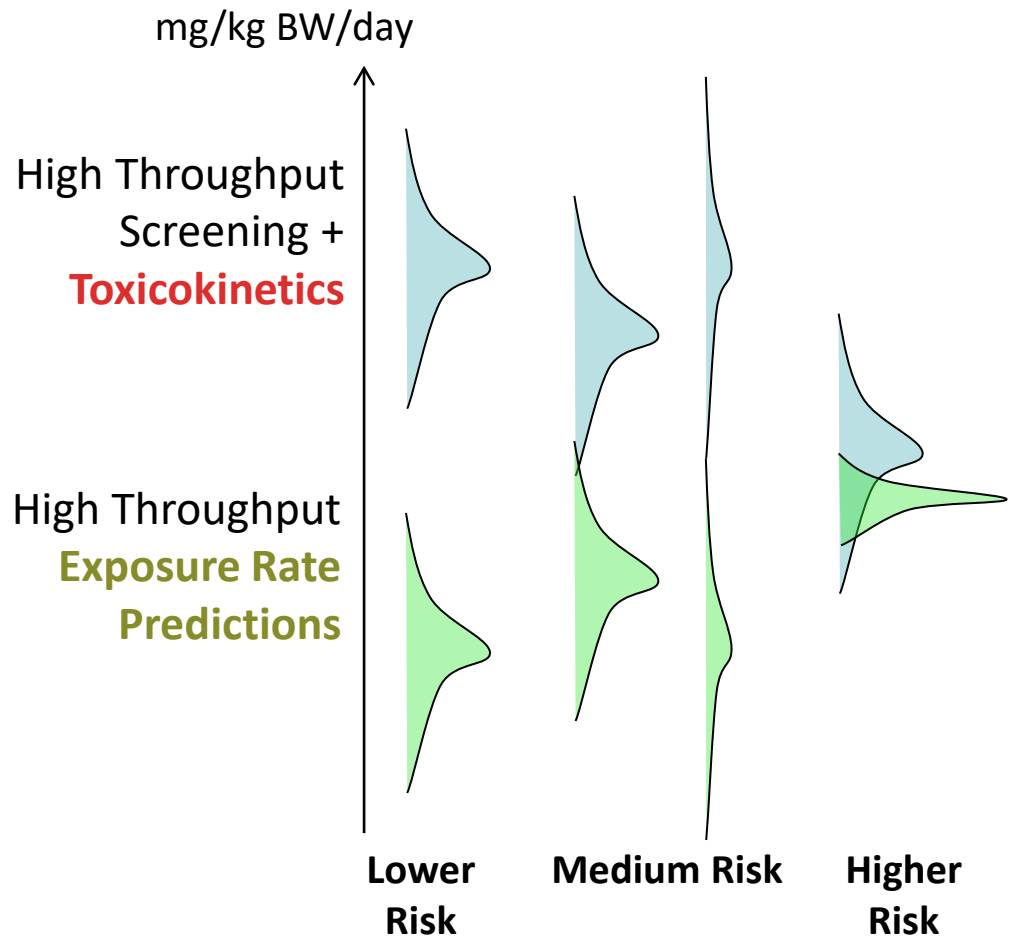
Chemical Regulation in the United States

- 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)
- Most other chemicals, ranging from industrial waste to dyes to packing materials, are covered by the Toxic Substances Control Act (TSCA)
  - Thousands of new chemical use submissions are made to the EPA every year
  - TSCA was updated in June 2016 to allow evaluation of these and other chemicals

November 29, 2014

Chemical Risk = Hazard x Toxicokinetics x Exposure

- National Research Council (1983) identified chemical risk as a function of both inherent hazard and exposure
  - Most TSCA-relevant chemicals lack the data needed to assess risk
- To address thousands of chemicals, we need to use "high throughput methods" to prioritize chemicals for additional study
- **High throughput risk prioritization** needs:
  - High throughput **hazard** characterization (Dix et al., 2007, Collins et al., 2008)
  - High throughput **exposure** forecasts (Wambaugh et al., 2013, 2014)
  - High throughput **toxicokinetics** linking hazard response to exposure dose (Wetmore et al., 2012, 2015)
- All these methods are uncertain, but if that uncertainty can be quantified, we can make informed decisions



Regulatory Science

- All projects begin with **1)** an objective, **2)** resources, **3)** a time-line
  - All three project elements can be intertwined:
    - Someone needs the best available information given the time and resources

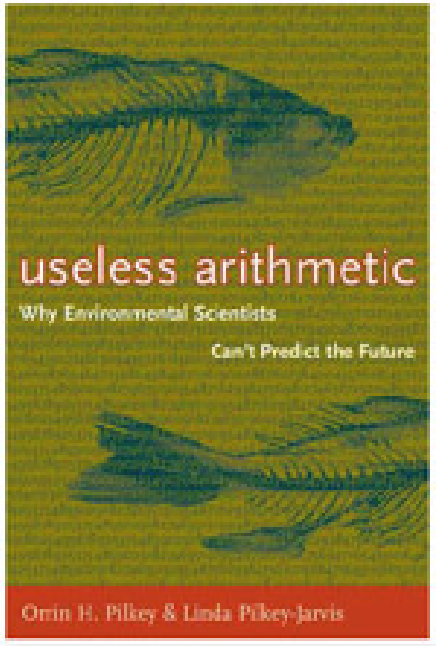
- Regulatory science balances timeliness with a new for “best available” methodology

- What is the best answer I can provide today, in a week, in a year?
  - How can I be explicit about what I did and did not consider?
  - Expect to revisit your work a decade later.

- I recommend leading with your finding (as in an executive summary)
  - Regulators need to make a decision
  - Scientists are trained to note exceptions, qualifiers, and possible confounders
    - Always include them, but don’t lead with them

How to Make Good Forecasts

Adapted from Nate Silver



Orrin Pilkey &
Linda Pilkey-Jarvis (2007)

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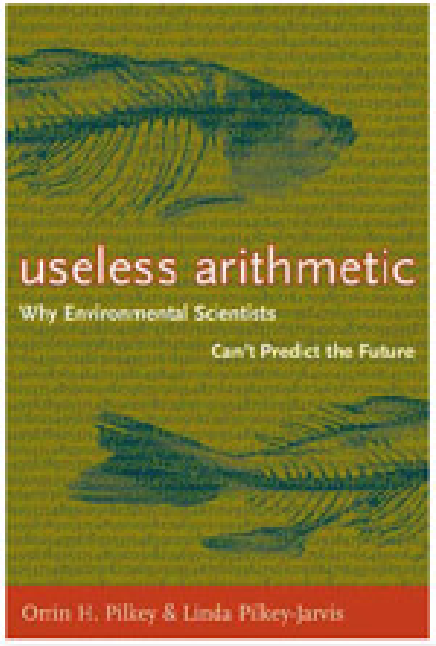
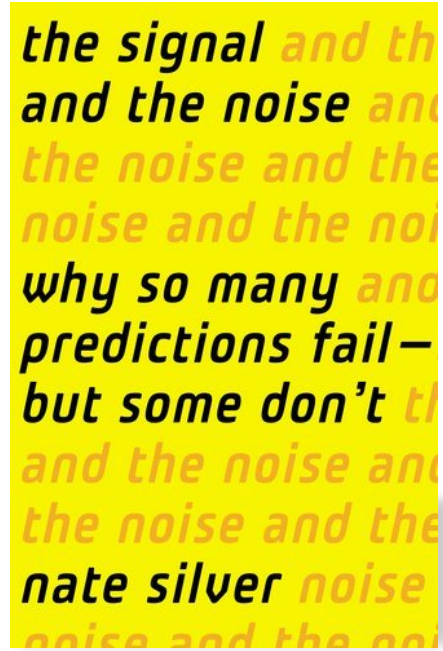


Orrin Pilkey &
Linda Pilkey-Jarvis (2007)

1) Think probabilistically (especially, Bayesian): We use an approach that evaluates model performance systematically across as many chemicals (and chemistries) as possible

2) Forecasts change: Today's forecast reflects the best available data today but we must accept that new data and new models will cause predictions to be revised

3) Look for consensus: We evaluate as many models and predictors/ predictions as possible



Nate Silver (2012)

In Nate Silver's terminology:
a ***prediction*** is a specific statement
a ***forecast*** is a probabilistic statement

Everyone Uses Models

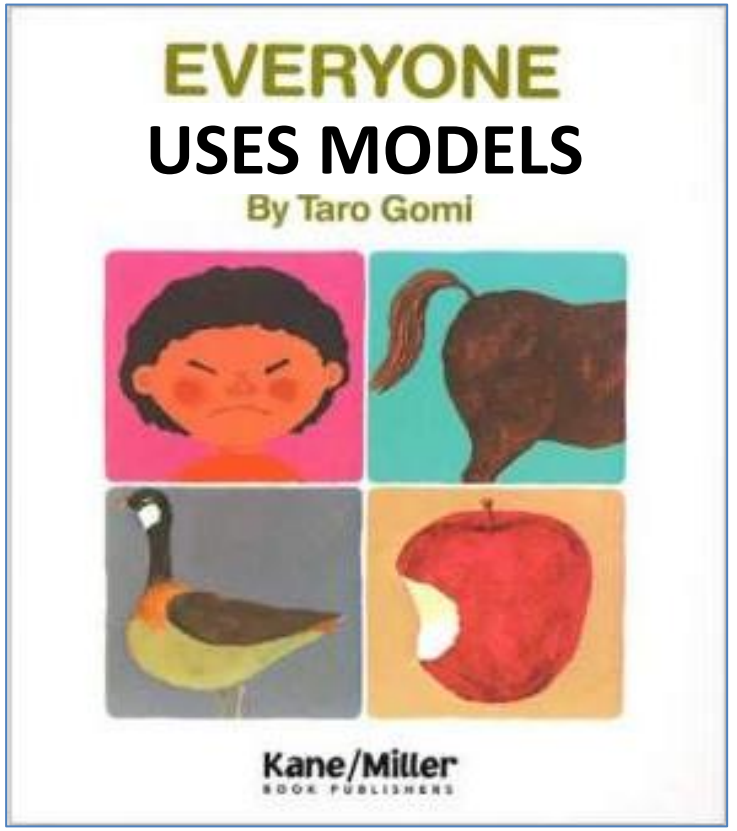
- Toxicology has long relied upon model animal species

- People rely on mental models every day
  - For example, repetitive activities like driving home from work

- Mathematical models offer some significant advantages:
  - Reproducible
  - Can (and should) be transparent

- …with some disadvantages:
  - Sometimes reality is complex
  - Sometimes the model doesn't always work well
  - How do we know we can extrapolate?

- …that can be turned into advantages:
  - If we have evaluated confidence/uncertainty and know the "domain of applicability" we can make better use of mathematical models



Fit for Purpose Models

- A “fit for purpose” model is an abstraction of a complicated problem that allows us to reach a decision.

  “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

- A fit for purpose model is defined as much by what is omitted as what is included in the model.

- We must accept that there will always be areas in need of better data and models – our knowledge will always be incomplete, and thus we wish to extrapolate.

  - How do I drive to a place I’ve never been before?

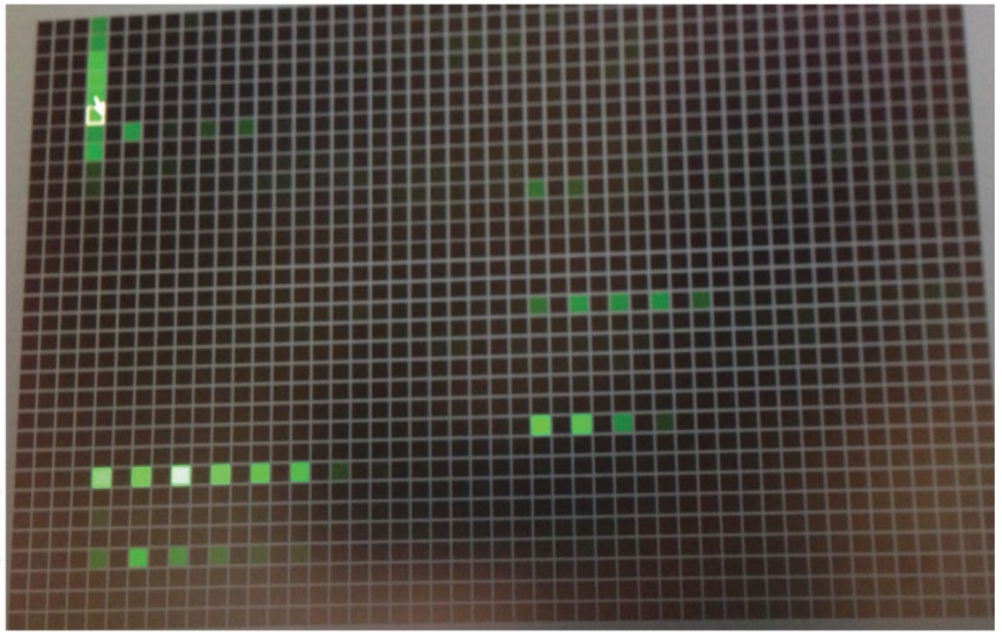
What is "High Throughput"?

- Tox21: Testing one assay across 10,000 chemicals takes 1-2 days, but only 50 assays have been developed so far that can run that fast

- ToxCast: ~1100 off-the-shelf (pharma) assay-endpoints tested for up to 4,000 chemicals over the past decade, now developing new assays as well

HTS tox assays often use single readout, such as fluorescence, across many chemicals, measuring concentration for toxicokinetics or exposure requires chemical-specific methods…

Kaewkhaw et al. (2016)



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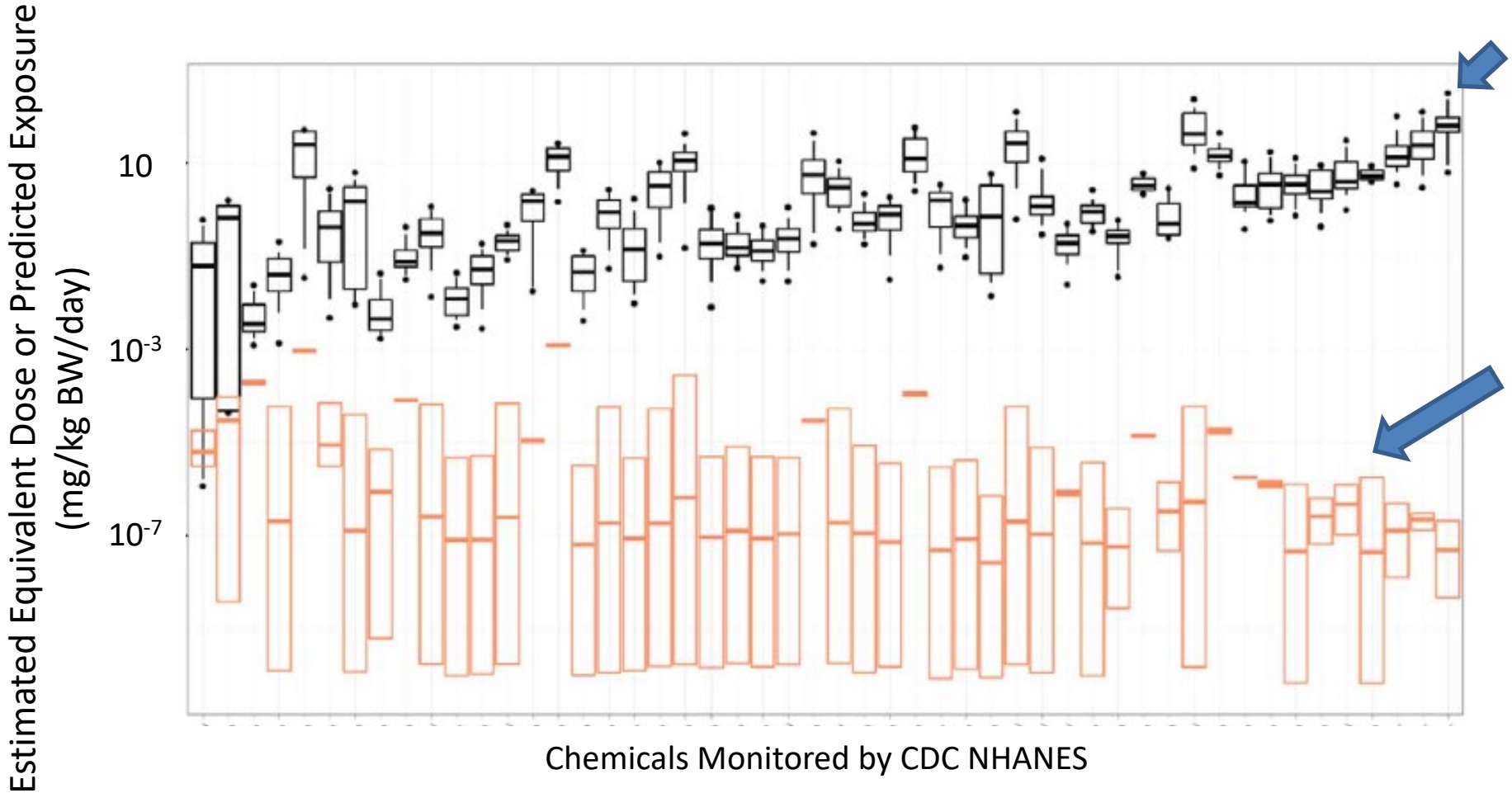
- ExpoCast: Ring et al. made *in silico* predictions for ~480,000 chemicals from structure, but based on NHANES monitoring for ~120 chemicals
  - Quantitative non-targeted analysis (NTA) may eventually provide greater evaluation data to reduce uncertainty

- HTTK: *In vitro* data on 944 chemicals collected for humans, starting with Rotroff et al. (2010)
  - Work continues to develop *in silico* tools, for example Sipes et al. (2016)

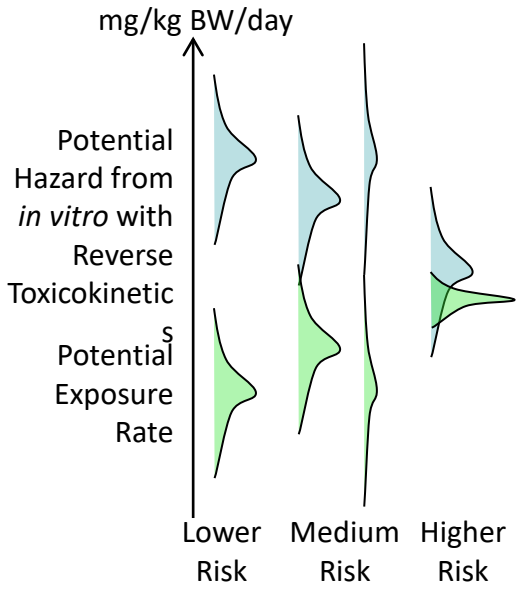
Our work is not done…

Chemical Prioritization NAMs



High throughput *in vitro* screening can estimate doses needed to cause bioactivity (for example, Wetmore et al., 2015)

Exposure intake rates can be inferred from biomarkers (for example, Ring et al., 2018)



Ring *et al*. (2017)

My Background

There are generalist and specialists. We absolutely need both.
I work as a generalist.

1997: My first conference paper was on a software interface for neural network analysis of **architectural** energy efficiency
1999: B.S. in physics and part of my thesis was my first journal paper on computer simulation of **high temperature superconductors**
2001: M.S. in physics, changed schools from Georgia Tech to Duke, spent summer in Los Alamos working on computer simulation of "stochastic ratchets"
2005: M.S. in **computer science**, published thesis on graph theoretic analysis of **granular matter**
2006: Ph.D. in **physics**, dissertation on experimental studies of granular matter
2006: started post-doc with Woody Setzer and Hugh Barton of EPA on **statistical analysis** of **toxicokinetic models**
2008: I was hired full time by EPA to help build virtual tissue simulations (**Virtual Liver**) – and I was quickly roped into the Toxicity Forecaster (**ToxCast**) project
2009: I started working with Rusty Thomas and Barbara Wetmore on **high throughput toxicokinetics**
2007 – 2011**:** I took two half-day continuing education courses on toxicology at each Society of Toxicology (SOT) meeting (ten total)
2011: I started working on high throughput exposure models and data (the **ExpoCast** project) to provide a context for ToxCast data
2014: EPA/NCCT awarded the ExpoCast data contracts, which included support for novel non-targeted analytical chemistry techniques
2015: First public release of R package "httk" on CRAN (https://CRAN.R-project.org/package=httk)
2017: I became an associate editor at the journal Environmental Health Perspectives
2019: I co-founded the **SOT Exposure Specialty Section** and became its first president
2019: I became adjunct faculty in Department of Environmental Sciences and Engineering at UNC Chapel Hill
2020: I joined the scientific programming committee of SOT
2021: I still co-lead the ExpoCast project and head development of the R package "httk"

What I Do: Research

- Mentorship
  - I work and have worked with post-docs and post-bacc trainees, helping them develop research projects and publish papers on their way to permanent positions in industry and government
- I develop mathematical models – I like to work with ordinary differential equations (ODEs) and Bayesian statistics
- I provide statistical support to other researchers, mostly at the EPA, often using frequentist methods
- I design new experiments, mostly *in vitro*
- I supervise work of contractors who do research to support the EPA
- I contribute to government reports describing the state of the science for chemicals

What I Do: Communicate Research

- I publish papers in peer-reviewed academic journals
- I advise EPA policy makers on what the current science tells us
- I participate in various consortiums of international governments developing and evaluating tools for assessing if chemicals pose any risk to the public health
- I attend scientific conferences and give various webinars
  - When there are no pandemics I do a fair amount of travel
  - I have gotten to attend scientific meetings in various European and Japan
- I give guest lectures at universities and sometimes hold half-day or day-long workshops at conferences or universities
- Occasionally I am involved in presenting to scientific advisory panels who review the suitability of EPA research for decision making

What I Do: Review Papers

- I participate as a scientific manuscript peer reviewer for both internal EPA research and scientific journals
- I work as an Associate Editor for the journal Environmental Health Perspectives, where I find reviewers for manuscripts and help make decisions on suitability for the journal and any necessary revisions
- Occasionally I help write “review articles” where we summarize many different research papers

Conclusions

- I have worked in a variety of fields:
  - Be open to where life takes you – everything is experience if you learn something from it
- Regulatory science balances timeliness with a need for best available methods
  - What is the best answer I can provide today, in a week, in a year?
  - How can I be explicit about what I did and did not consider?
  - Expect to revisit your work a decade later.
  - Take project management and leadership classes
- Success is a combination of skill and luck, and networking increases your luck:
  - Get an Open Researcher and Contributor ID (**ORCID**), https://orcid.org/
  - Join sites like **LinkedIn**, https://www.linkedin.com/
  - Join sites like **ResearchGate**, https://www.researchgate.net/
  - Network at conferences: Attend SoT Specialty Section Meetings

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ExpoCast Project (Exposure Forecasting)

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