

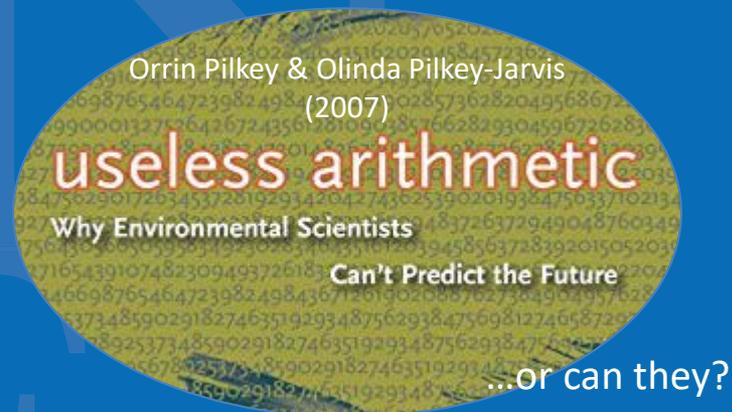
# Introduction: Occam's Razor

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*“Fit for Purpose:  
Using Computational Models for Risk”  
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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

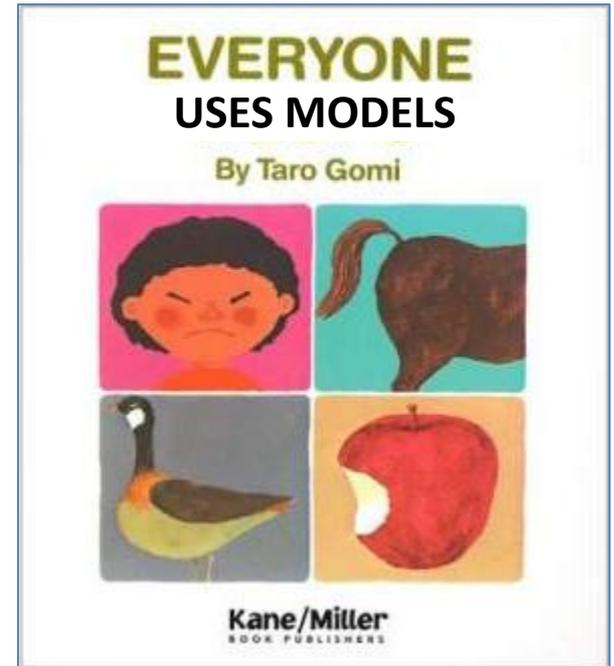
# Conflict of Interest Statement

I have no conflicts of interest to disclose

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# 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

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

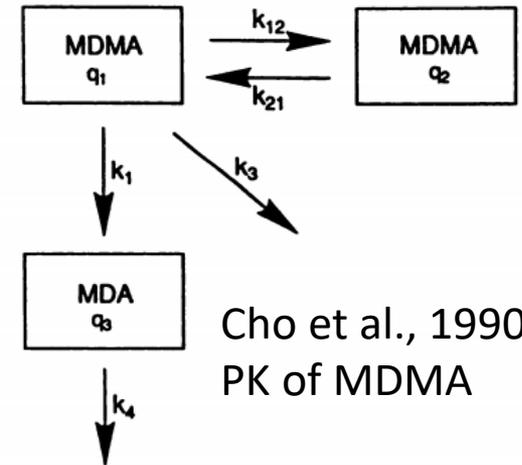
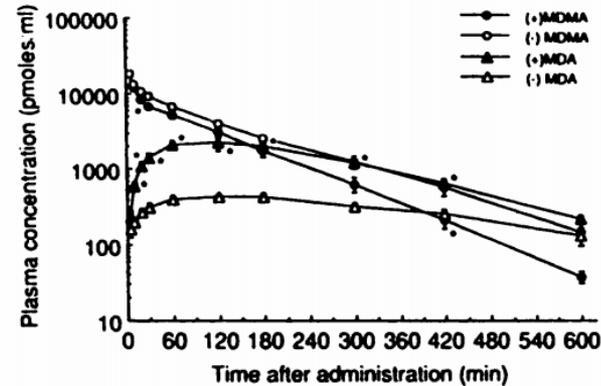
A fit for purpose model is defined as much by what is omitted as what is included in the model.

We have to 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?

# Complexity should fit the data...

“Since all models are wrong the scientist cannot obtain a ‘correct’ one by excessive elaboration. On the contrary, following William of Occam, they should seek an economical description of natural phenomena.”  
George Box



Cho et al., 1990  
PK of MDMA

Jones et al., 2012  
PK of Statins

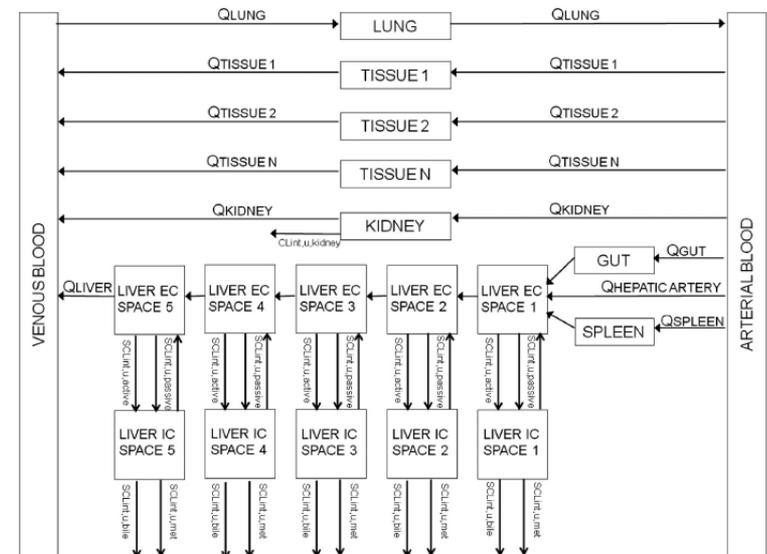


FIG. 2. Schematic diagram of the in vivo PBPK model. EC, extracellular; IC, intracellular.

# Lex Parsimoniae “Law of Parsimony”

“Among competing hypotheses,  
the one with the fewest  
assumptions should be selected.”

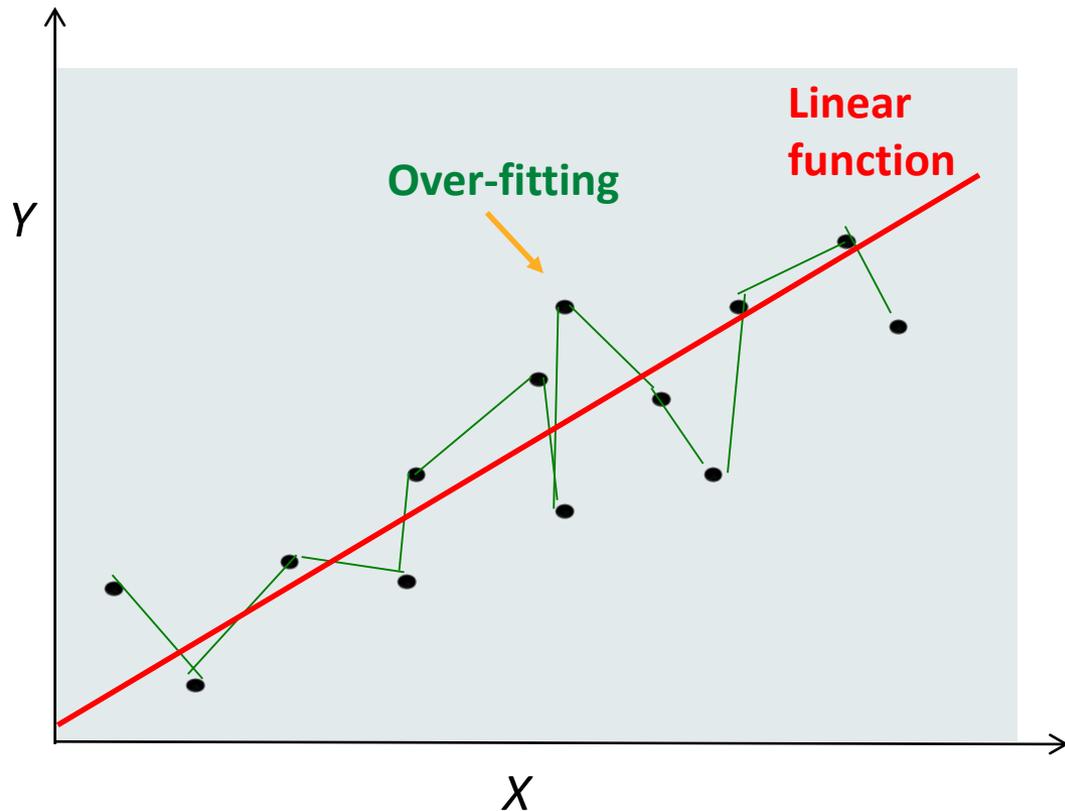
William of Occam

“While Occam's razor is a useful  
tool in the physical sciences, it can  
be a very dangerous implement in  
biology. It is thus very rash to use  
simplicity and elegance as a guide  
in biological research. “

Francis Crick

“With four parameters I can fit an  
elephant, and with five I can make  
him wiggle his trunk.”

John von Neumann



# Model Evaluation Allows Extrapolation and Confidence

Today's speakers will consider:

- How are models currently being used in risk assessment?
- What is the approach you have taken, and how is it better than alternative model approaches?
- How do you quantify and communicate uncertainty?
- What is acceptable uncertainty for you?
- As models continually improve, how can we address the risk assessors' need for 'static' numbers and reproducibility?

Scientists have been known to say things like:

*"Models can offer a means of avoiding the conclusions derived from actual experiments."*

Kristin Shrader-Frechette

Problems with a particular model or application, not the idea of modeling:

*the signal and the noise and the noise and the noise and the noise why so many and predictions fail – but some don't t and the noise and the noise and the nate silver noise noise and the no*

# Parsimony and “Domain of Applicability”

- Do not build beyond the ability to evaluate predictions
- Collect data to allow larger, systematic studies
- Carefully determine whether, when, and why model errors are conservative and **correlated**

“Nate Silver’s” Analysis on November 4:

## FiveThirtyEight

Politics Sports Science & Health Economics Culture

NOV. 4, 2016 AT 11:09 AM

### Trump Is Just A Normal Polling Error Behind Clinton

By [Harry Enten](#)

Filed under [2016 Election](#)



How this was viewed at the time (November 5):

POLITICS 11/05/2016 03:59 pm ET | Updated Nov 07, 2016

### Nate Silver Is Unskewing Polls — All Of Them — In Trump’s Direction

The vaunted 538 election forecaster is putting his thumb on the scales.

 By Ryan Grim

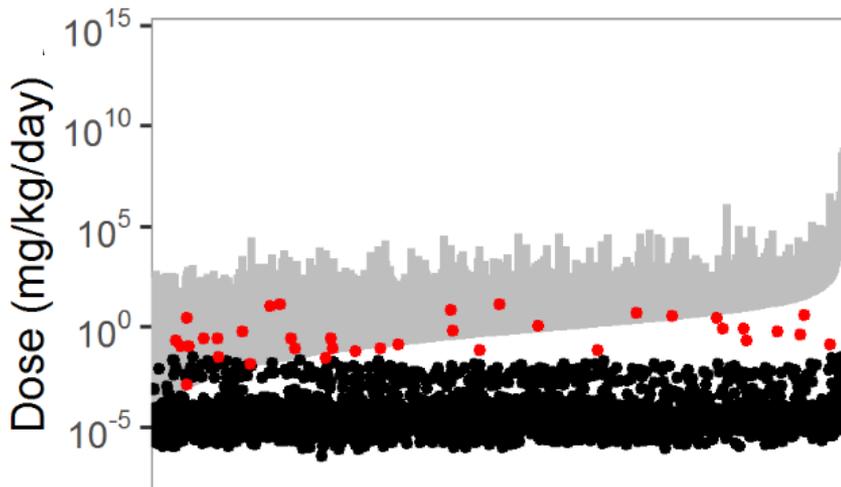
# Using 21<sup>st</sup> Century Science to Improve Risk-Related Evaluations

- **January, 2017 National Academies of Science report:**  
“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”
- **Tox21/ToxCast:** Examining thousands of chemicals using in vitro assays that test parent chemical in concentration response
- **ExpoCast:** Tentative exposure predictions for daily human exposure rates (mg/kg/day)
- What is acceptable uncertainty?

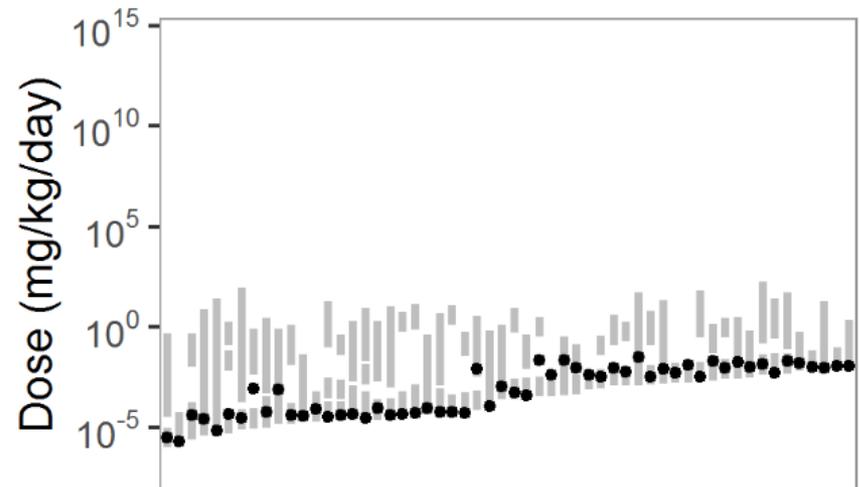
# High Throughput Risk Prioritization



Screening for toxicity has blind spots and exposure forecasts are highly uncertain, yet:



Doses ranges for all 3925 Tox21 compounds eliciting a 'possible'-to-'likely' human *in vivo* interaction alongside estimated daily exposure



56 compounds with potential *in vivo* biological interaction at or above estimated environmental exposures

# “Fit for Purpose: Using Computational Models for Risk” Society of Toxicology Annual Meeting

- Today we will address a broad range of computational models
  - From physico-chemical properties to human population risk assessment
- We will also address a broad range of chemical
  - Including pharmaceuticals and environmental exposures
- Speakers will address:
  - Objectives
  - Approaches
  - Technologies
  - Knowledge gaps and suggestions for future research
  - Emphasis on lessons learned