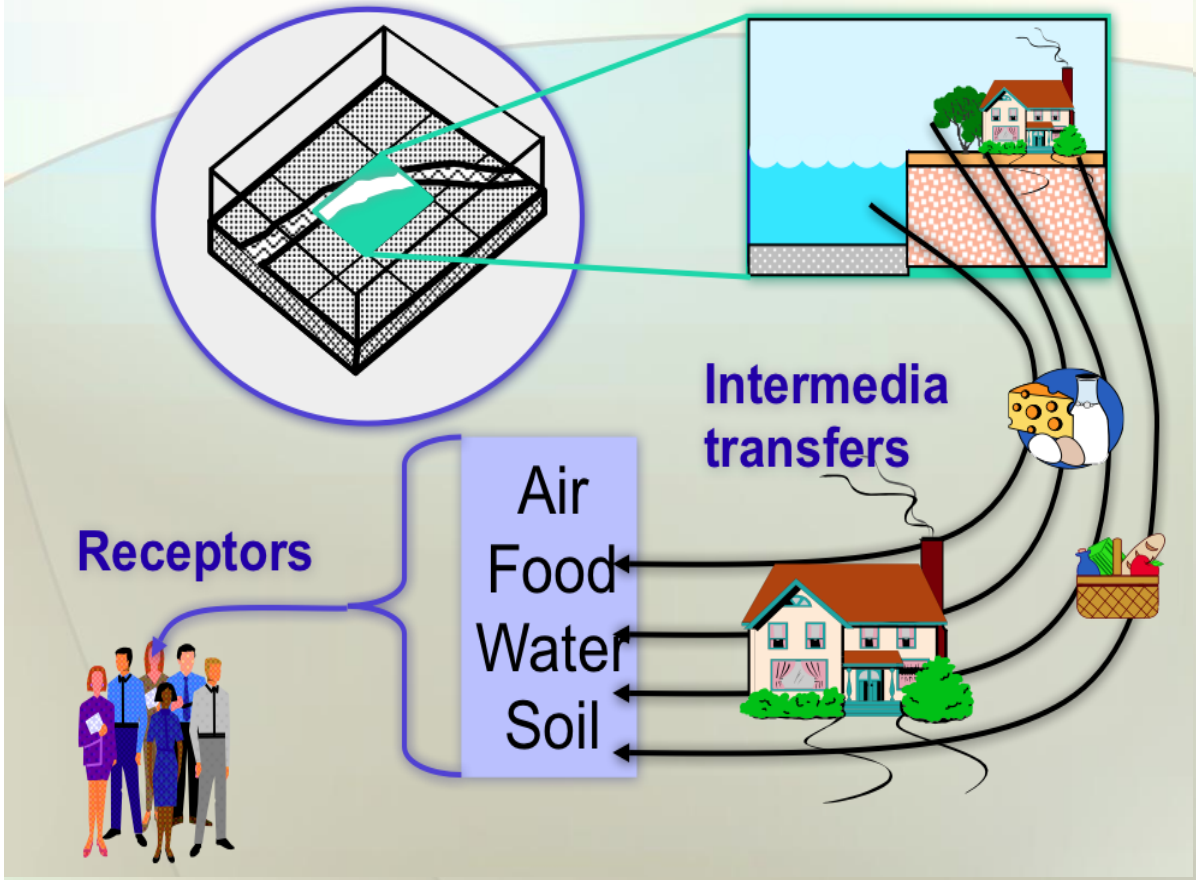
Comptox Community of Practice Seminar September 21, 2010

A Science-Based Exposure Narrative for Disease Outcome Assessment



Thomas E. McKone

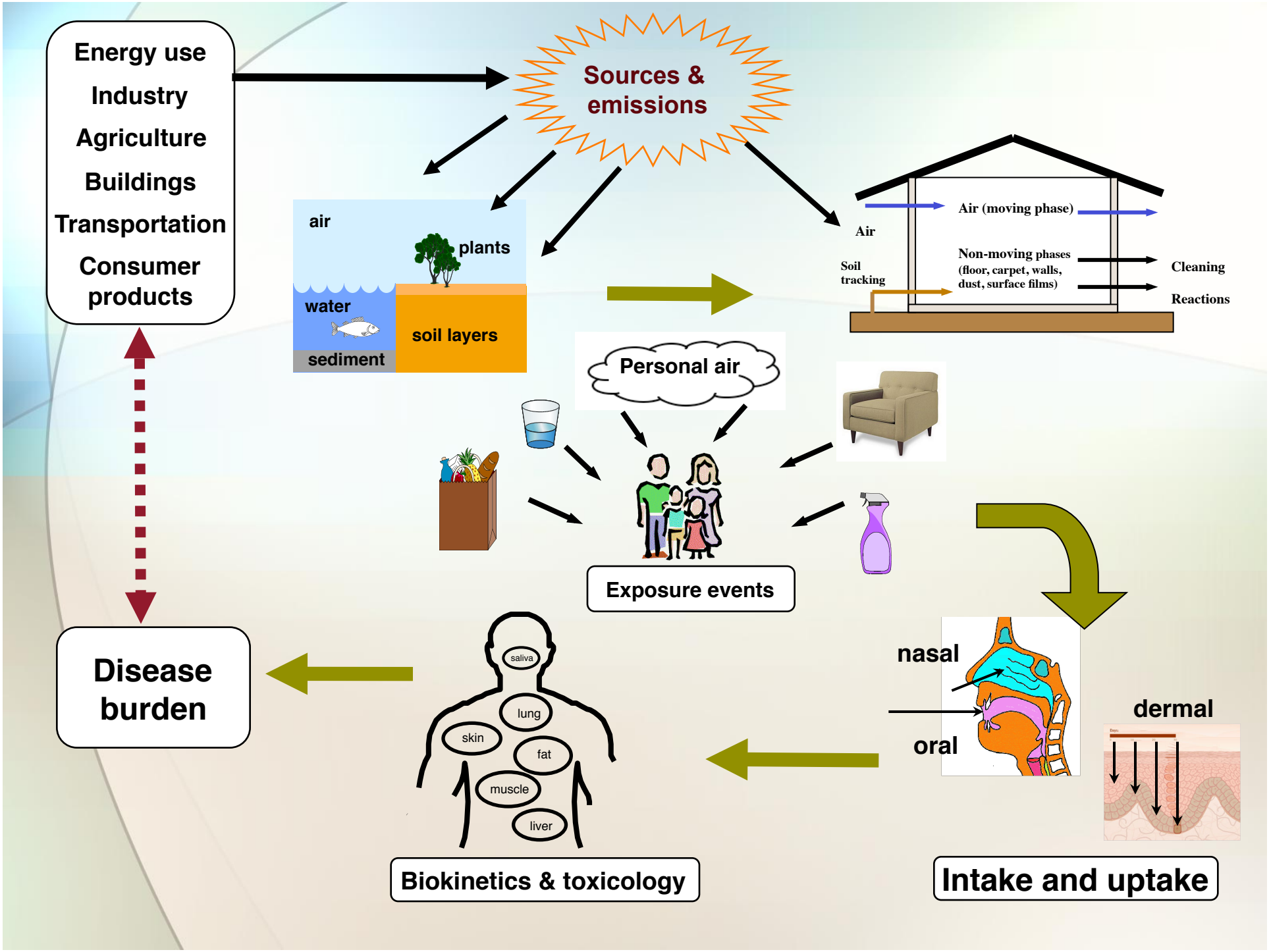
University of California, Berkeley and Lawrence Berkeley National Laboratory

Where from Where to

- The past: exposure assessment—predominantly descriptive
- The future of exposure science—hypothesis-based research
  - Ontology
  - Exposome—exposure narrative
  - Exposure Science in the 21st Century

Overview

- **Three themes**
  - Exposure as a narrative
  - Levels of organization
  - Prediction and uncertainty
- **Three elements of Exposure Science**
  - Stressors
  - Targets
  - Space and time
- **The long-term challenge: linking exposure to disease burden?**


Energy use
Industry
Agriculture
Buildings
Transportation
Consumer products
Sources & emissions
air
plants
water
soil layers
sediment
Air (moving phase)
Air
Non-moving phases (floor, carpet, walls, dust, surface films)
Soil tracking
Cleaning
Reactions
Personal air
Exposure events
Disease burden
saliva
lung
skin
fat
muscle
liver
Biokinetics & toxicology
nasal
oral
dermal
Intake and uptake

Exposome

A lifetime narrative of human exposures to a full portfolio of stressors

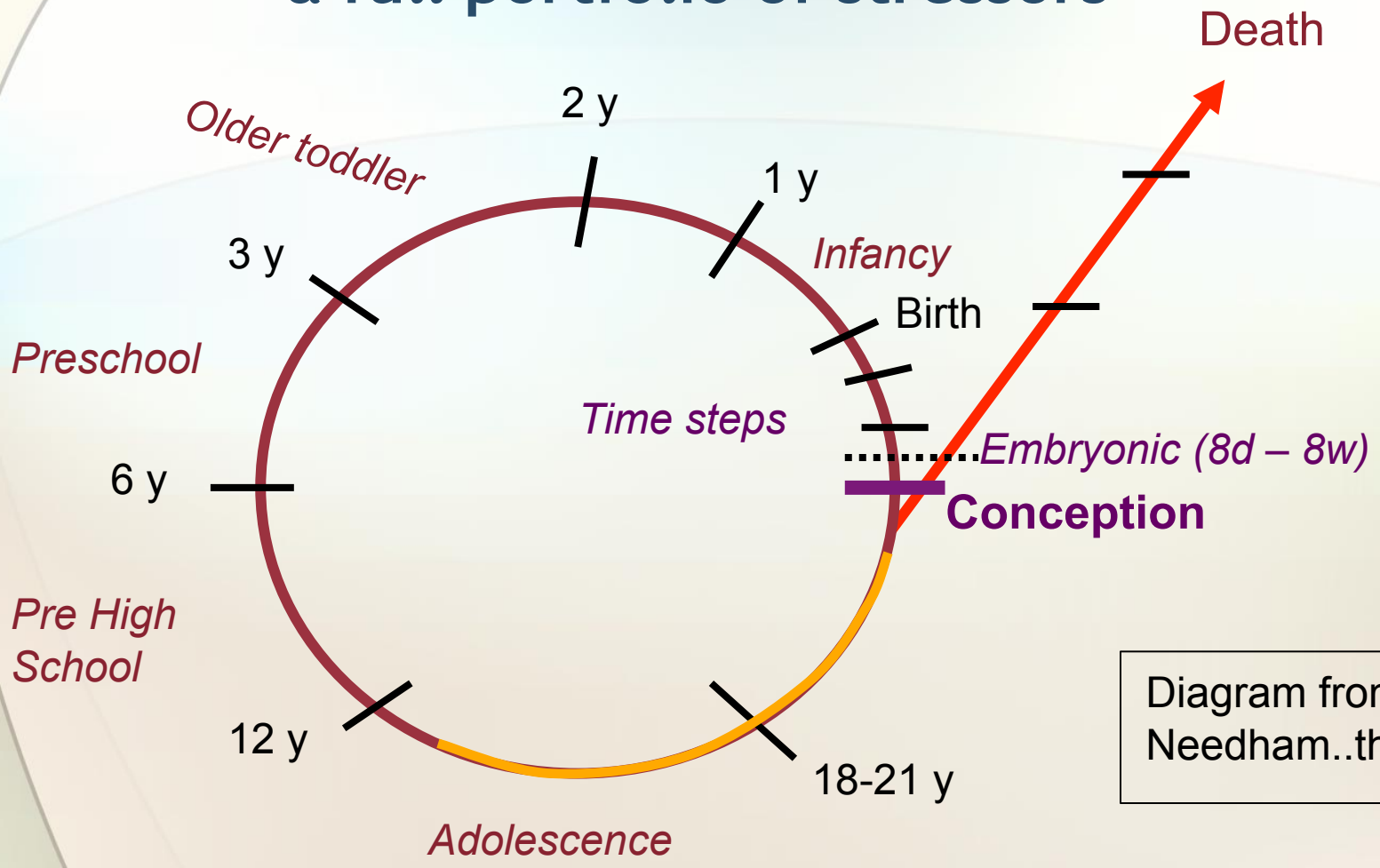
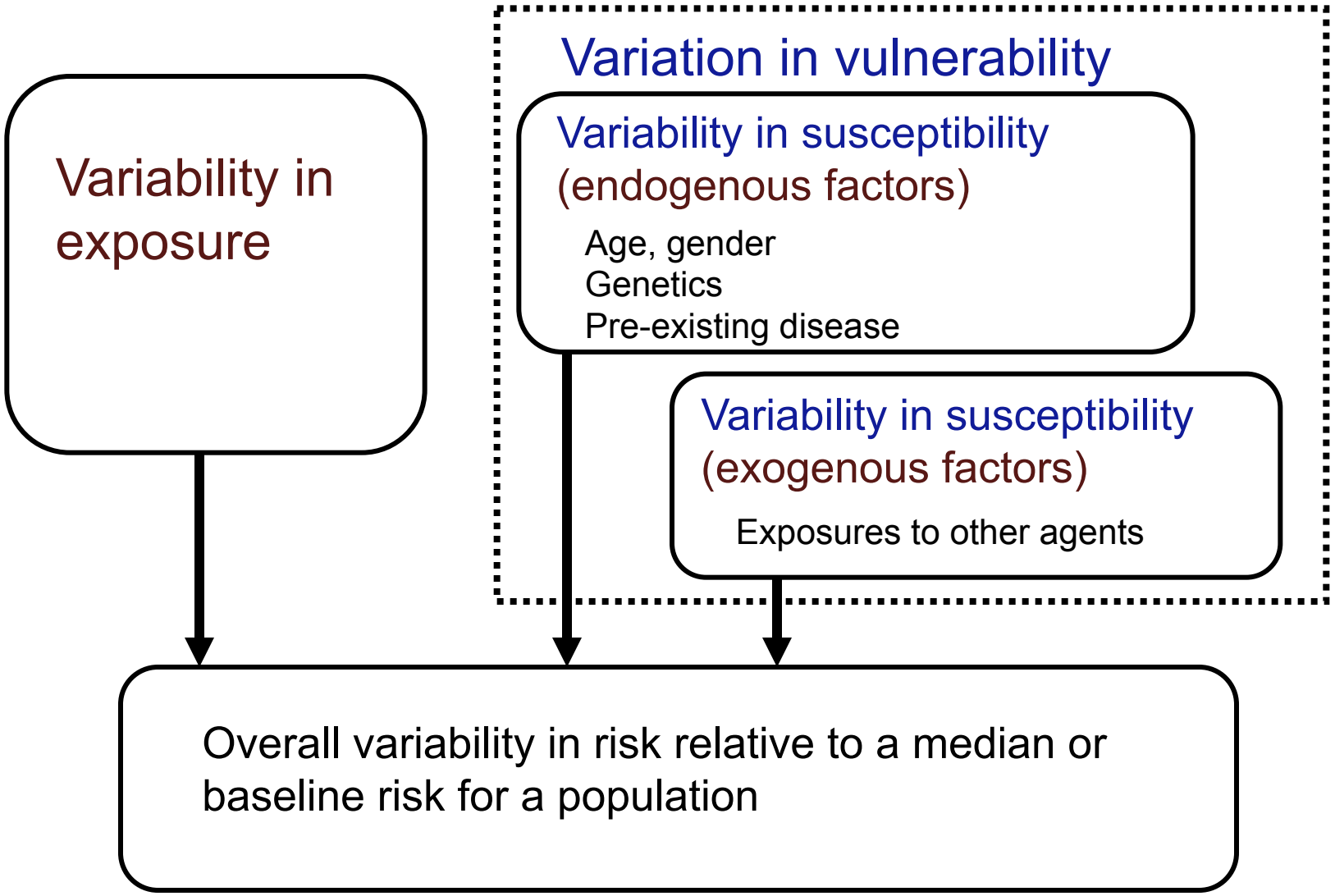


Diagram from Larry Needham..thanks

Variability, Susceptibility, Vulnerability

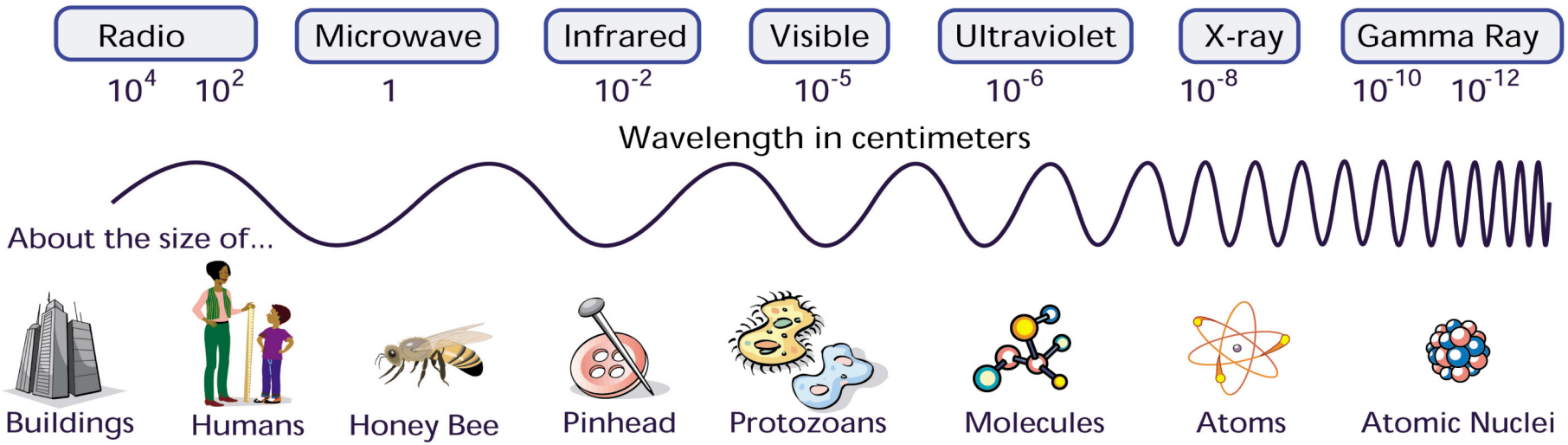


Multiple Stressors

- **Cumulative impacts from multiple substances with the same mode of action**
  The issue of cumulative exposure, aggregate risk
- **Staged sequence of harm caused by stressors with different modes of action**
  Synergy can be negative/positive/additive/unknown
- **Stressors with two modes of action—one good one bad**
  Alcohol, breast milk (PCBs), etc

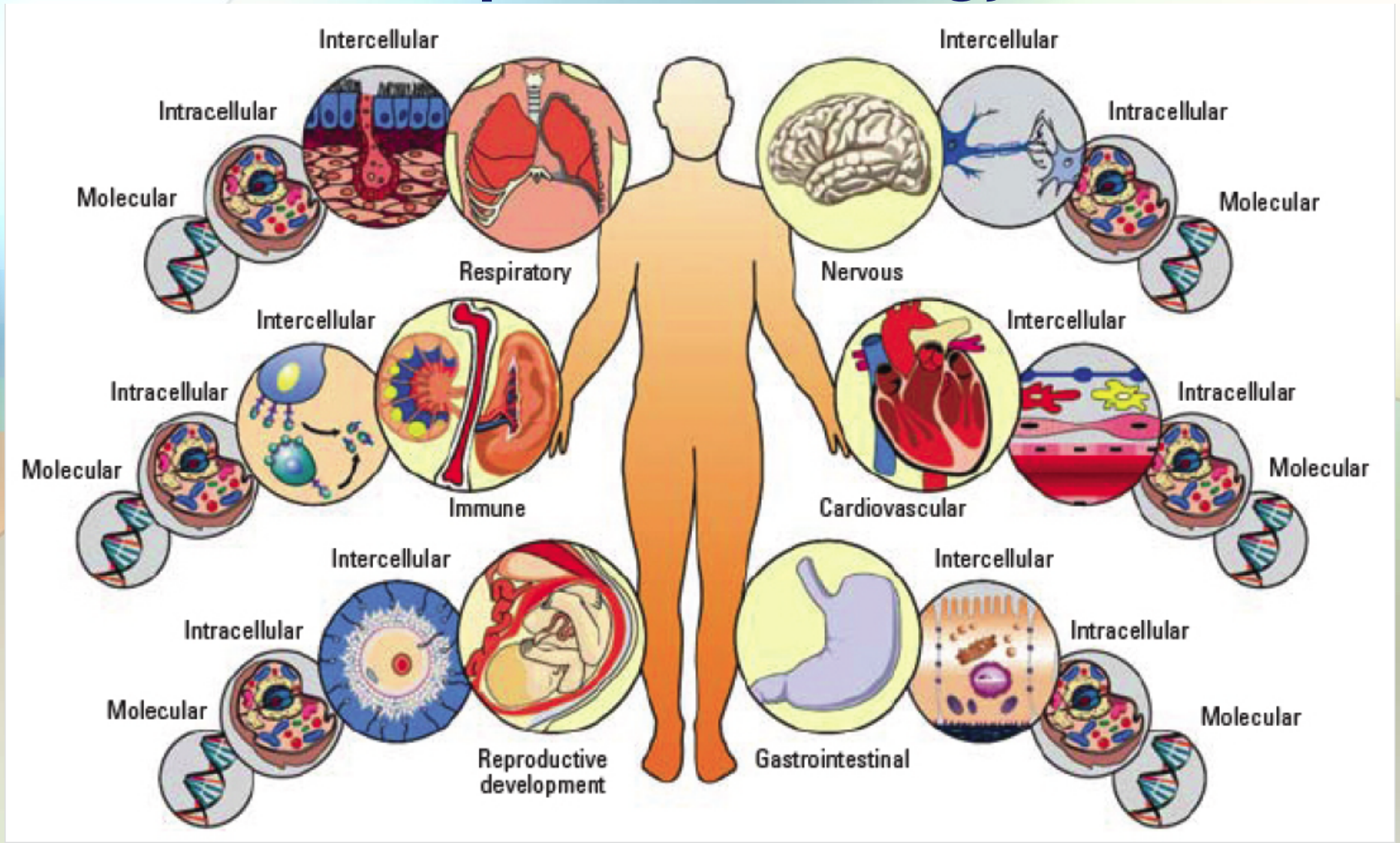
Levels of Organization

The Electromagnetic Spectrum



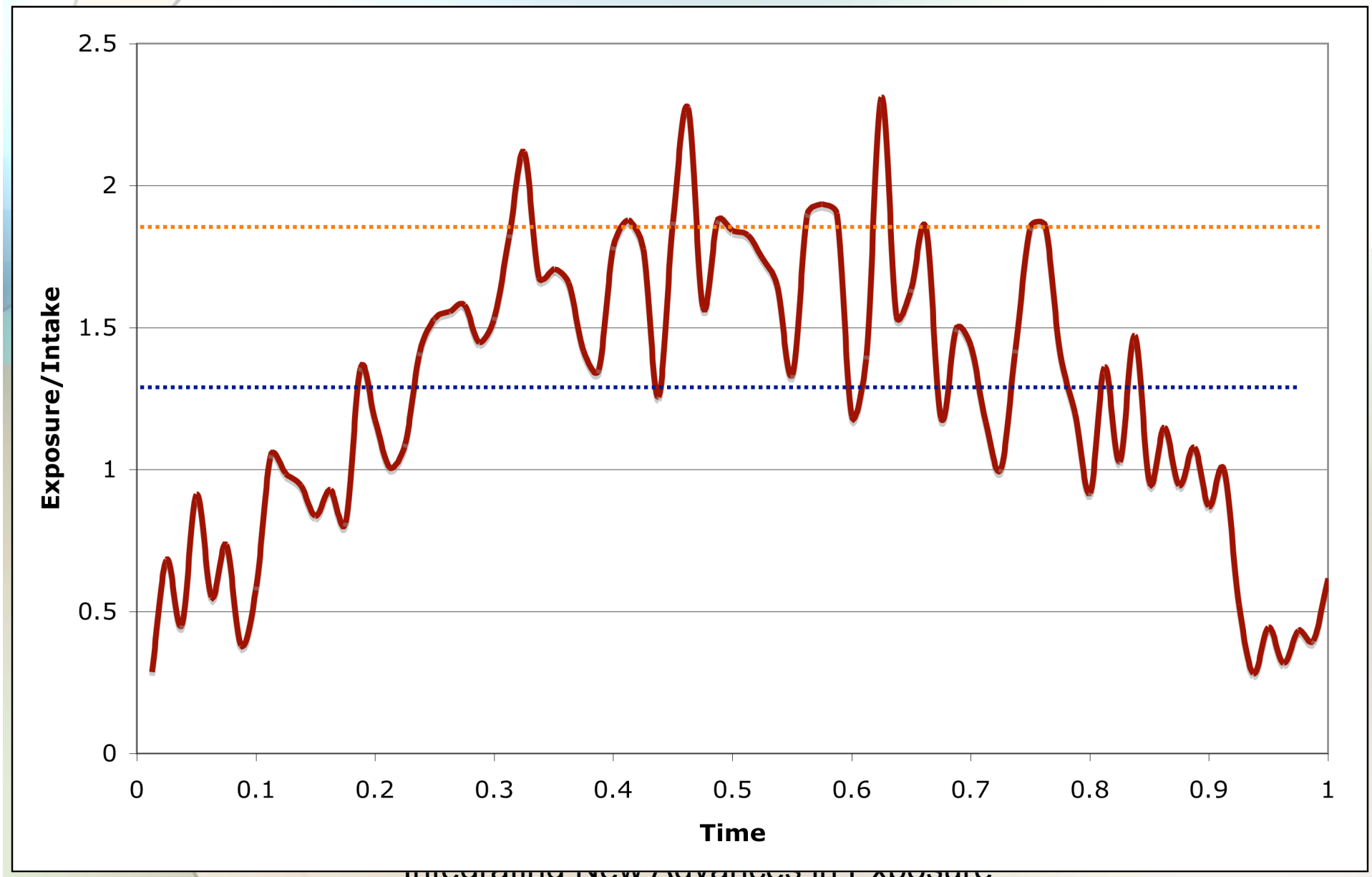
Level of damage depends on scale of the wave

Exposure Biology



The goal of systems biology is to integrate the data so that eventually a model of the whole system can be developed
RISK ANALYSIS ISSUES & REVIEWS The Newsletter of the Standing Committee on Risk Analysis Issues and Reviews Issue 4 December 2009

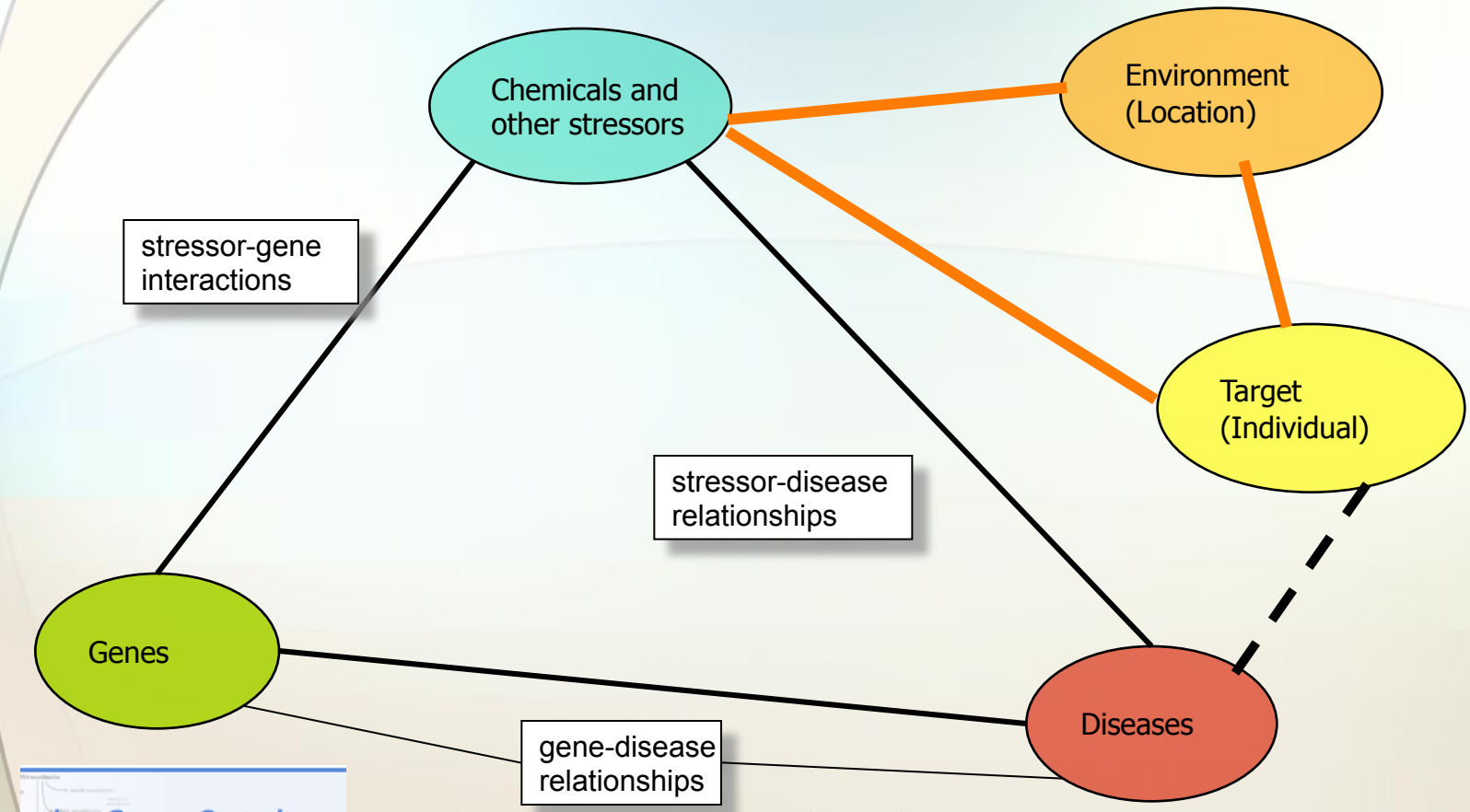
Exposure can vary in time (space)



Elements of Exposure Science

- Stressors
  - What are they and how do they relate to disease?
  - Chemical, physical, biological agents
  - Social, economic, psychological
- Targets
  - defining and characterizing the receptor
  - Humans (individuals, populations, communities, etc), ecosystems, species, forests, organs, tissues, cells?
- Space and Time

Exposure Ontology



the Gene Ontology

functional annotations

pathway data

Hypothesis-Based Research in Exposure Science

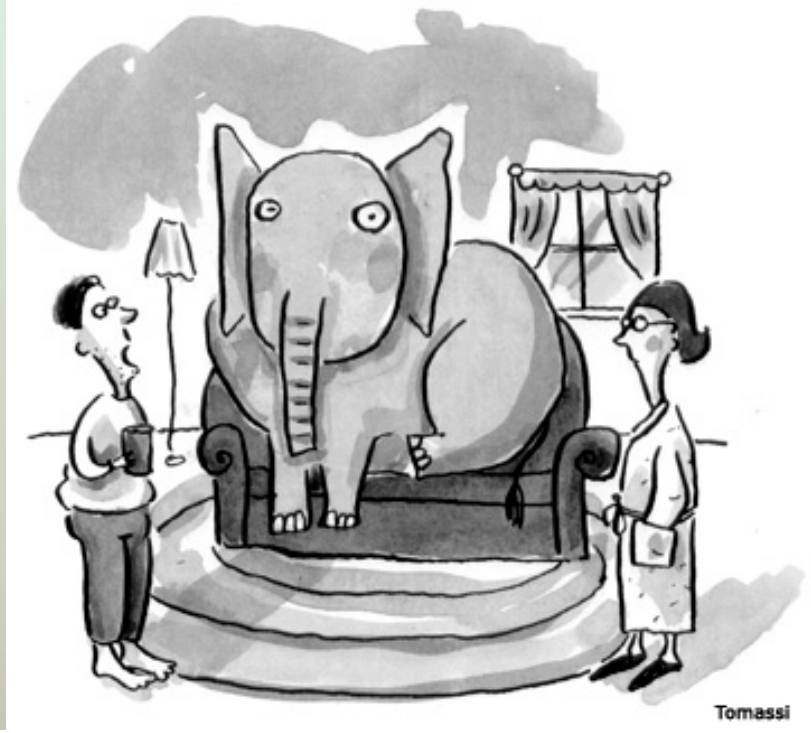
Must be built on refutable hypotheses--Avoid theories/ models that are "immune to refutation" [Oreskes]

Human exposure is an open system, one where all parameters are not and often cannot be identified and known in adequate detail

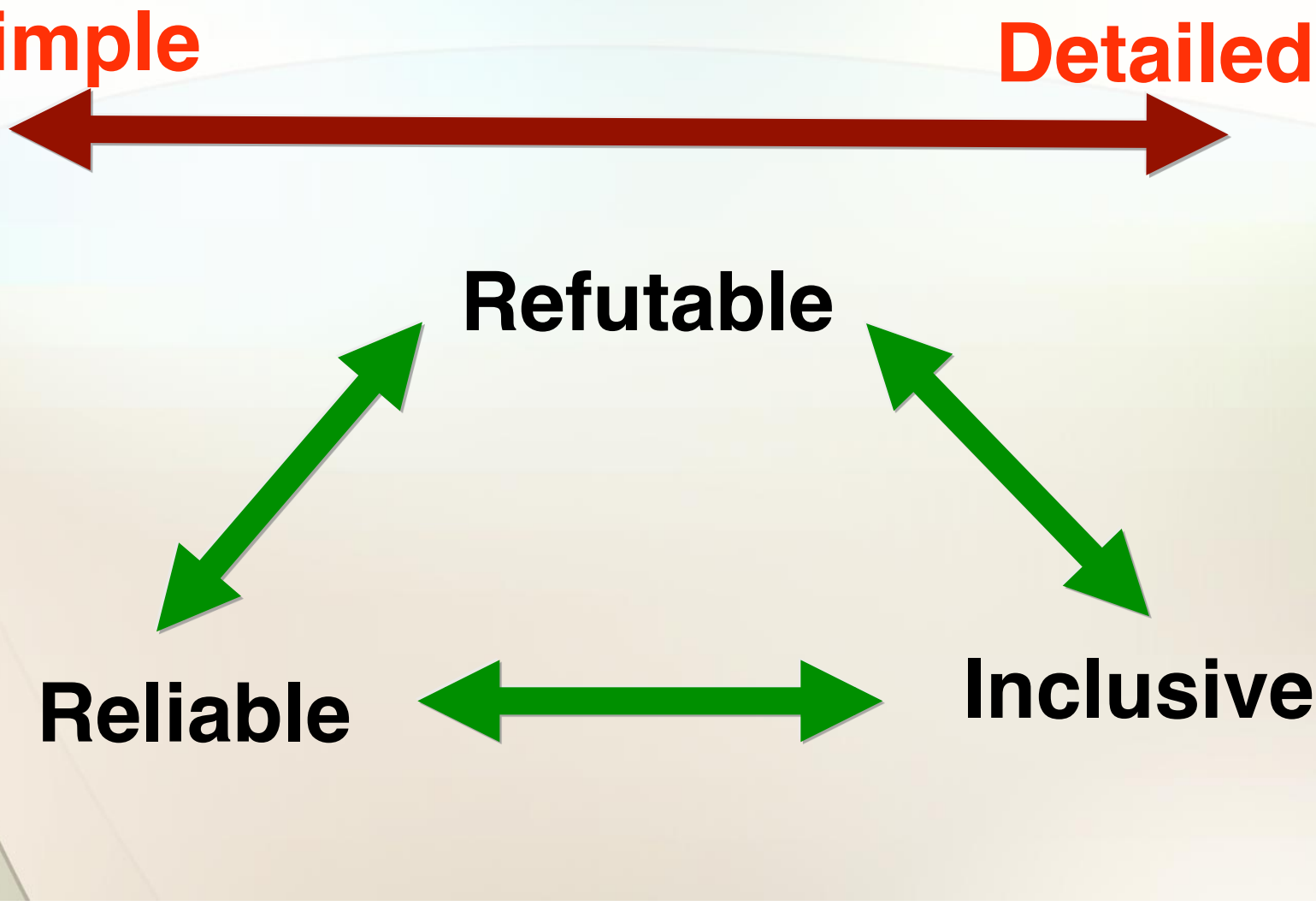
At best, we can confirm (not prove) hypotheses--that is, predicted exposures are consistent with those observed

Uncertainty

- Quantity, quality and relevance of input data
- Reliability and relevance of models used to fill data gaps or replicate known results
- Assumptions, scenarios, and decision options used in applying the assessment



Building Hypotheses
A Balancing Act



Models, Measurements, & Confidence

- Models as hypotheses rather than predictors
- The value and limitations of data for hypotheses
- Merging models and data in hypothesis-based research

Future Directions

- Weave together the elements of exposure science and make use of
  - exposure biology
  - environmental monitoring
  - disease surveillance
  - models
  - statistical tools
- Build a comprehensive and reliable exposure narrative--the type of narrative that would be encoded in the "exposome" if such an entity existed as an analog to the genome

Future Directions

- Pursue the research needed to understand how any joint occurrence of stressor, target, space and time determine a level of organization and detail that must be captured to understand disease burden and other impacts
- Case studies reveal the value of melding models, environmental data, and biomarker data

Perspective from an Artist

"Nothing is less real than realism ... It is only by selection, by elimination, by emphasis that we get at the real meaning of things."
-- Georgia O'Keeffe

(from a talk by Pasky Pascual of EPA)