Risk Assessment Roadmaps & Methods for Using 21st Century Data

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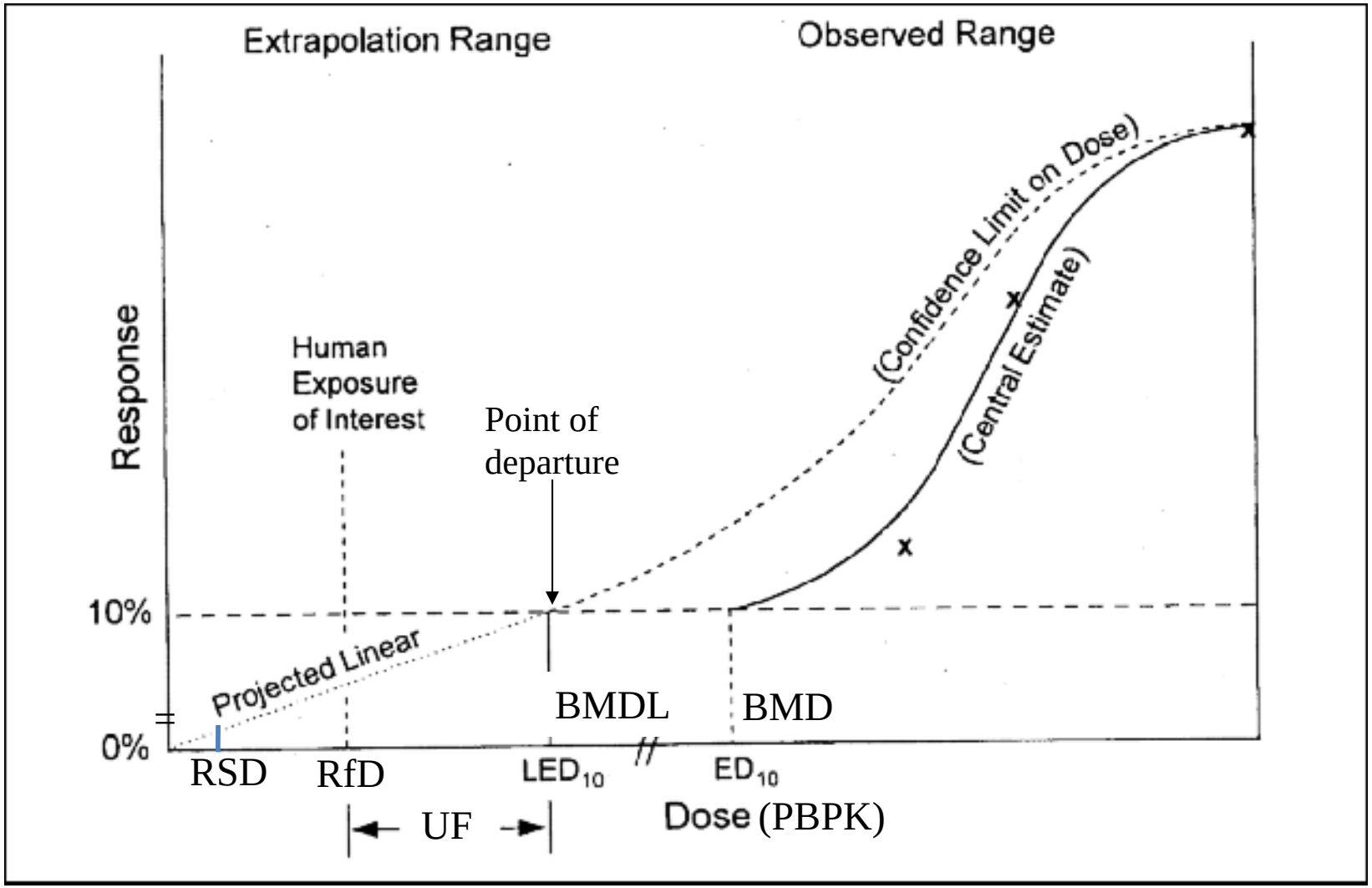
Seminar Overview

- Know traditional & contemporary risk methods
- Risk methods on the horizon via Tox 21
- Create the future by collaborative research

Do You Know the Traditional Methods?

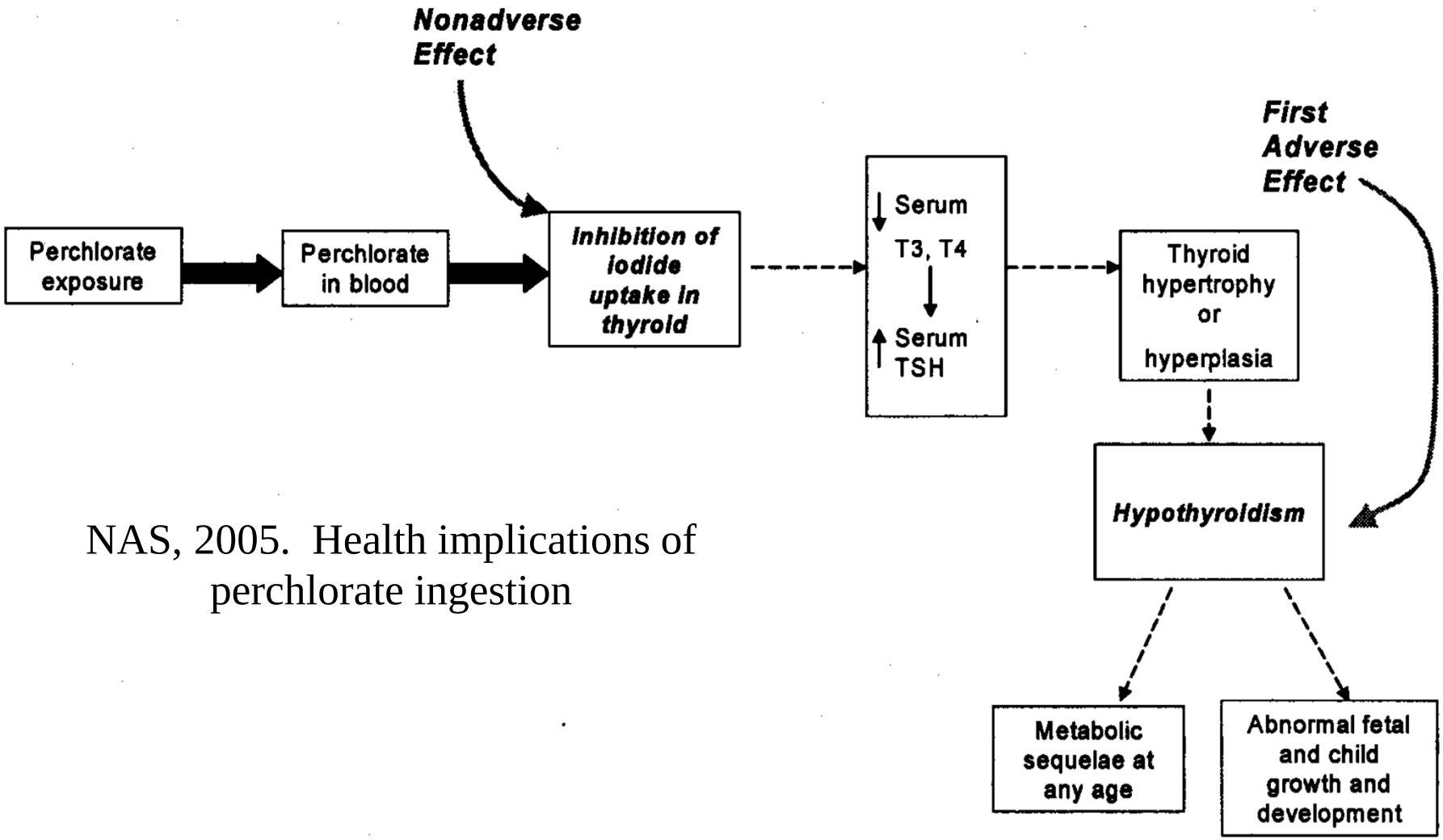


Adapted from EPA, 1999

Traditional: Critical Effect

- Risk assessment is… preventive medicine. Thus, toxicologists, epidemiologists, *and clinicians* are needed in judgment of critical effect
  - conduct hazard identifications collaboratively
  - Focus on effects of medical significance

- Critical effect is… the first adverse effect, or its known precurso**r**, that occurs as dose rate increases (EPA, 2013).



NAS, 2005. Health implications of perchlorate ingestion

FIGURE 5-2 Committee's suggested mode-of-action model for perchlorate toxicity in humans indicating first adverse effect in the continuum.

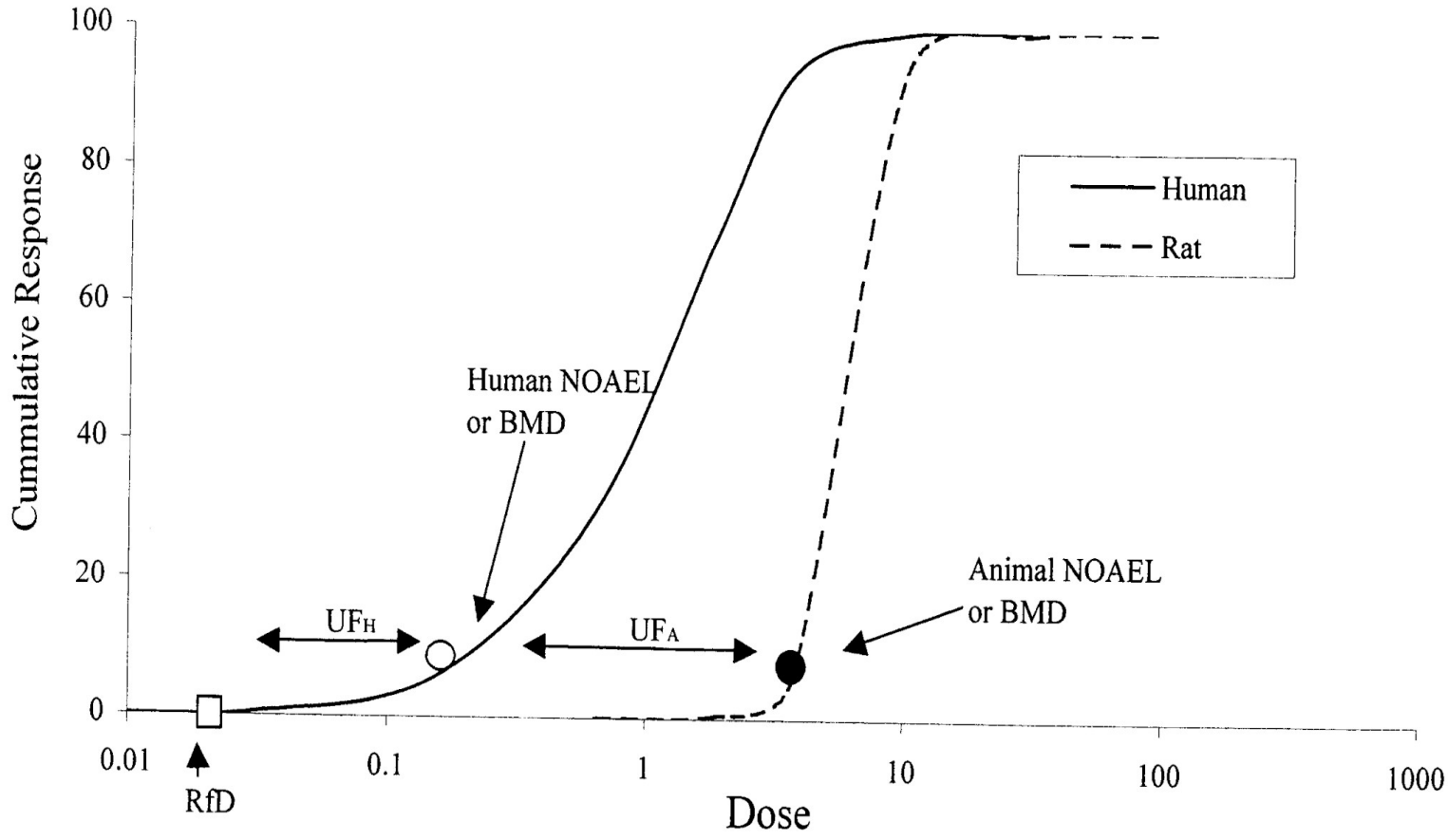
Traditional: Uncertainty Factors

- Uncertainty factors for within human variability, experimental animal to human extrapolation, LOAEL to NOAEL, subchronic to chronic, and lack of certain data.

- Misconceptions:
  - Studies with small “n” are not useful.
  - The variability of the human population is large; an uncertainty factor of 10-fold with human data is often not enough.

Factor of 10 Enough?

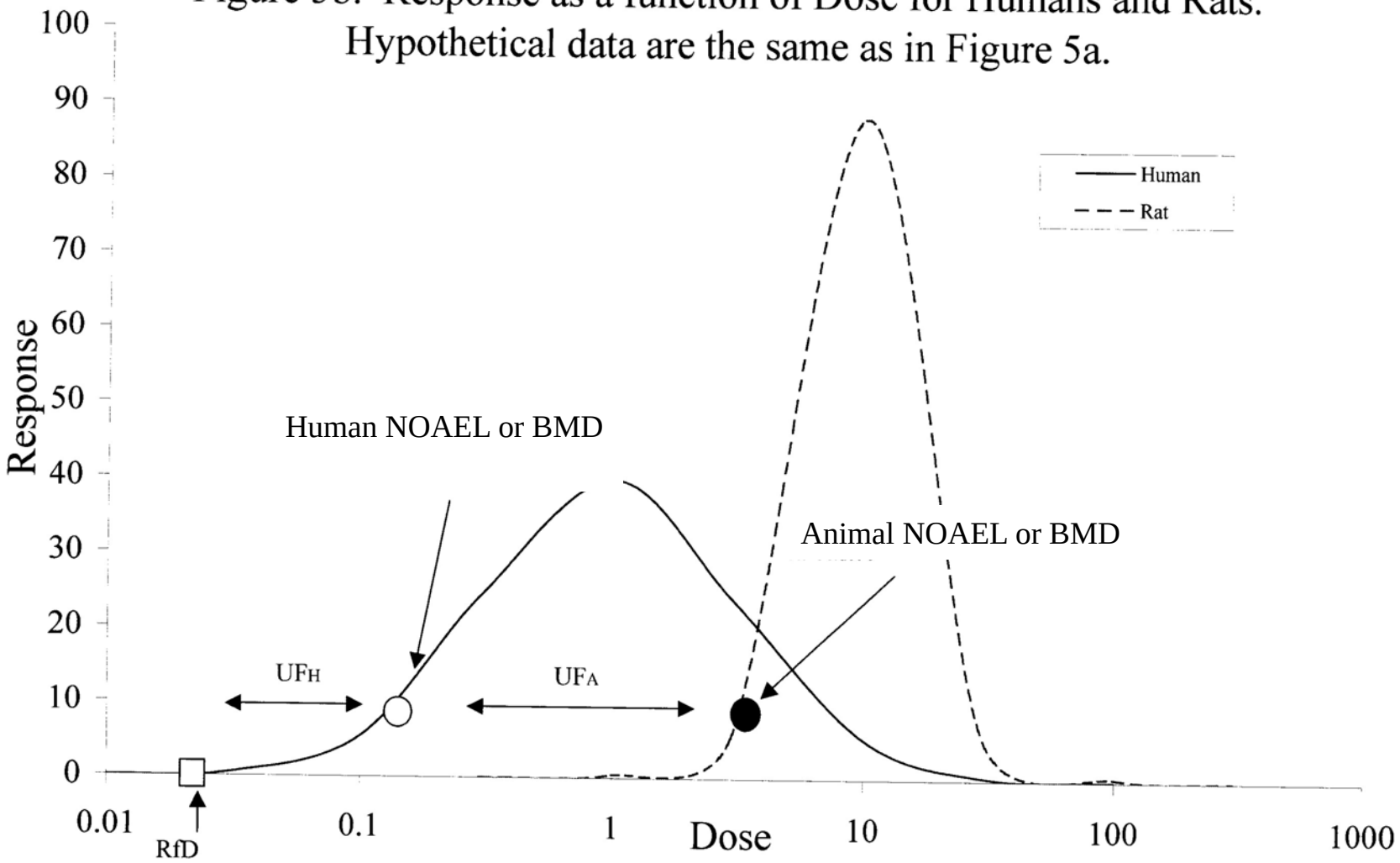
Figure 5a. Cumulative Response as a function of Dose for Humans and Rats. Data are hypothetical, but approximate real situations.



Dourson, M.L., G. Charnley and R. Scheuplein, 2002

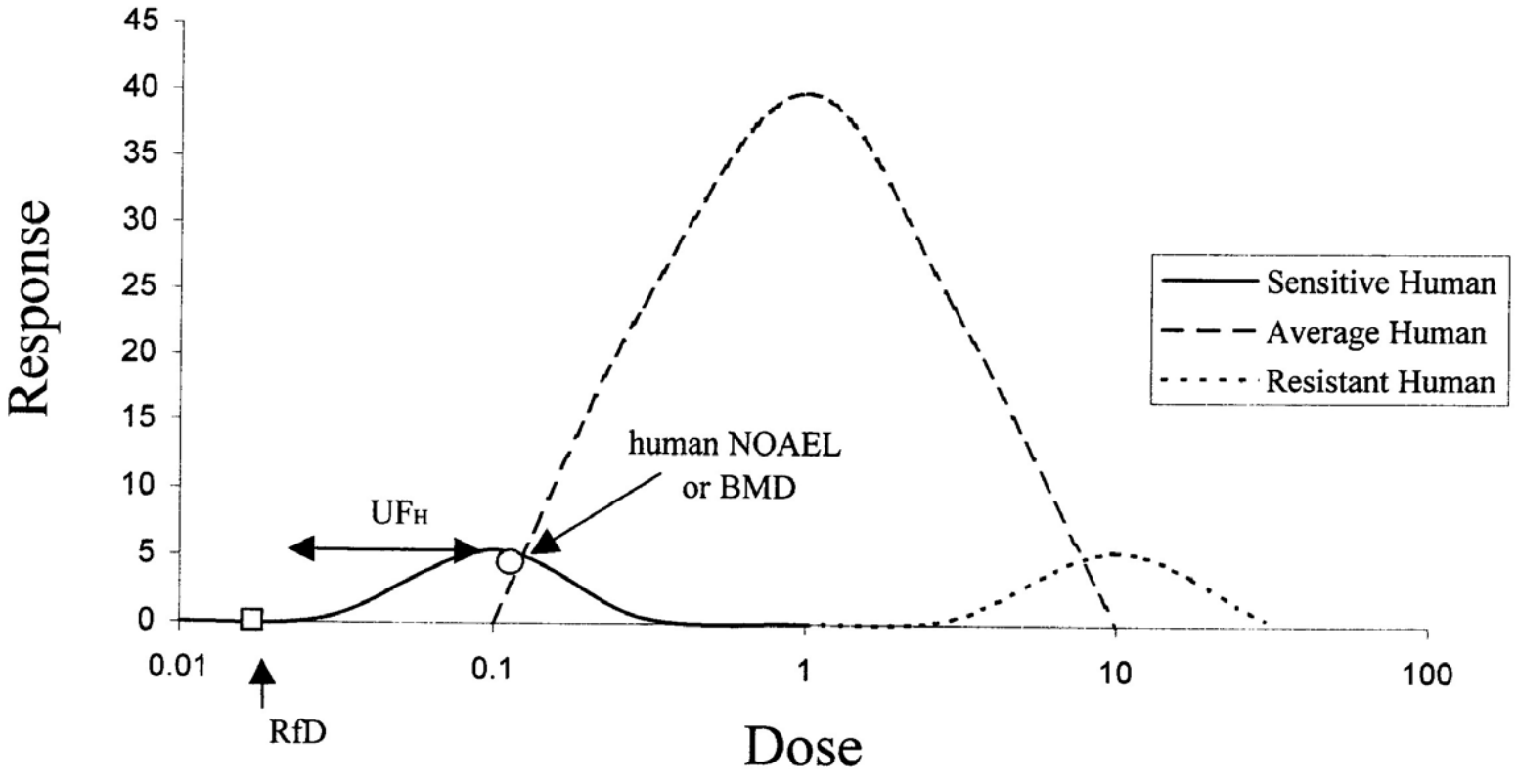
Factor of 10 Enough?

Figure 5b. Response as a function of Dose for Humans and Rats.
Hypothetical data are the same as in Figure 5a.



Factor of 10 Enough?

Figure 6a. Response as a function of dose for humans of different sensitivities. Hypothetical data for humans are the same as in Figure 5b.



Contemporary: BMD

- Clear advantages and disadvantages exist in the use of a benchmark dose (BMD)
  - Uses responses near the range of observation.
  - Includes a measure of variability in the response.
  - Determines a consistent measure of response.
  - Applies to fewer, more robust, toxicity data sets.
  - Accounts for more dose response of critical effect

Casarett and Doull (Sixth Edition) page 94

Contemporary: Categorical Regression

RfD Definition	Regression model
"without appreciable risk"	$r < 10^{-2}$
"is likely to be"	$P(*) > 0.95$
"deleterious effect"	severity = moderate or frank

New RfD Definition

$P (r < 10^{-2}$ at dose<RfD $) > 0.95$
where $r = P$ (severity >1)

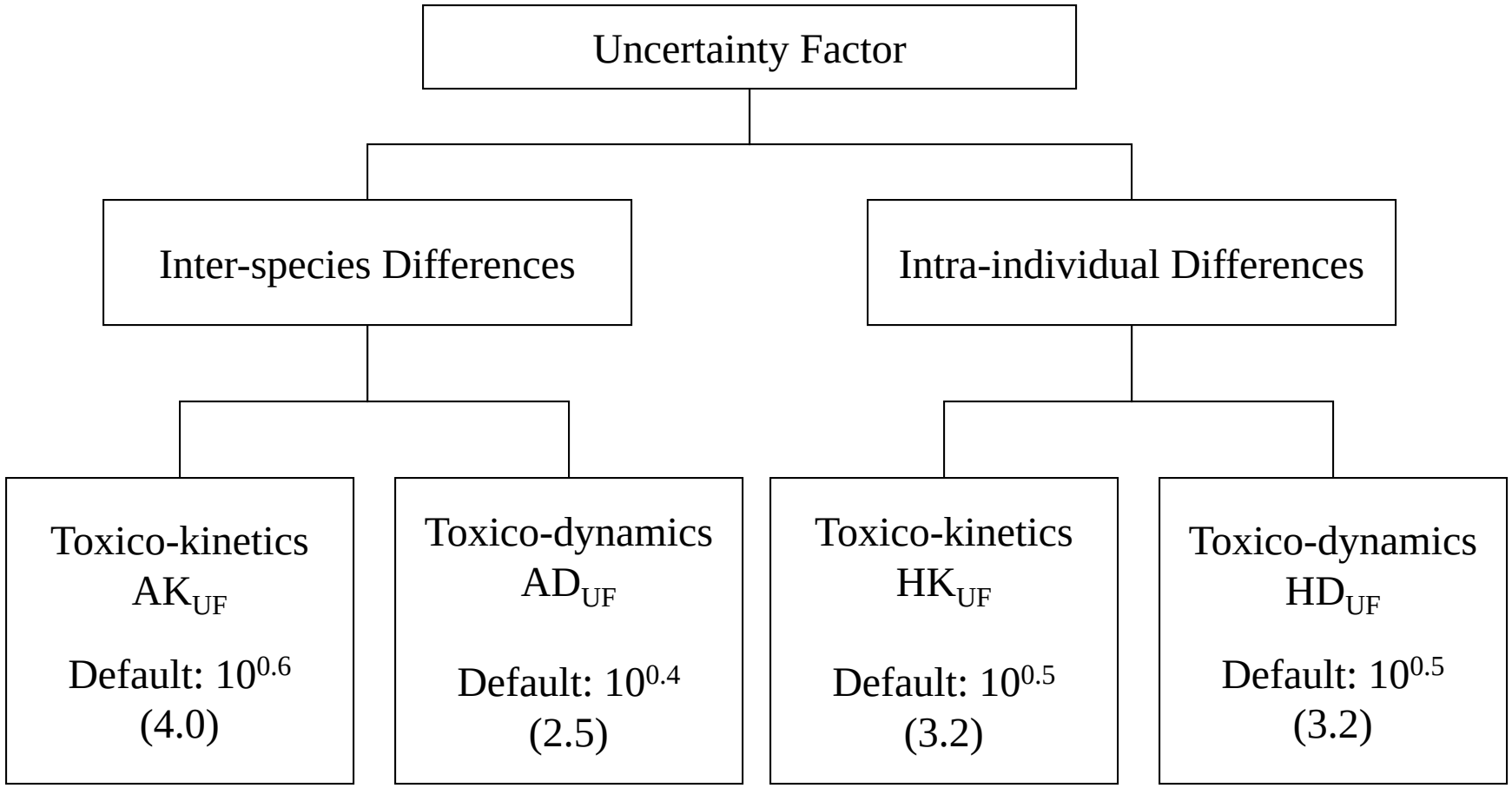
Hertzberg R.C. and M.L. Dourson, 1993

Contemporary: Categorical Regression

- Advantages:
  - provides a consistent basis for calculating risk above the RfD
  - all useful data can be categorized
  - accounts for severity of toxic effect
- Limitations:
  - animal to human extrapolation is still needed
  - data are transformed into categories which loses information

Patty's Toxicology, Volume 1 (Fifth Edition) pages 209-213

Contemporary: Chemical Specific Adjustment Factor (CSAF)



International Programme on Chemical Safety (IPCS). 2005.

Contemporary: PBPK

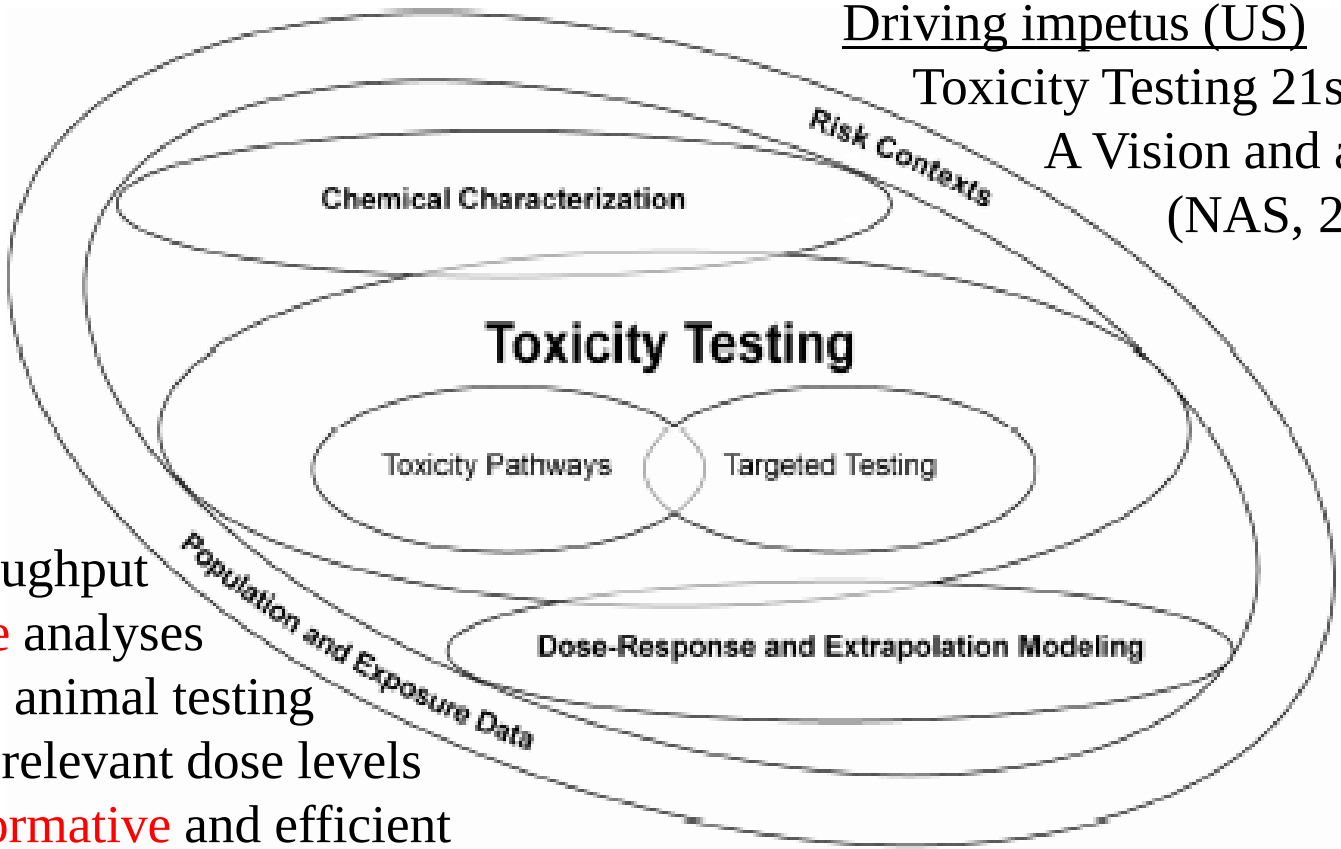
- It is now routine to ask folks whether or not a PBPK model is available for the chemical of interest.
- Numerous PBPK papers; some have been given top awards (RASS of SOT papers of the year):
  - Sweeney, L. et al. (2001). Proposed occupational exposure limits for select glycol ethers using PBPK models and Monte Carlo simulation. Toxicol. Sci. 62(1):124-139.
  - Kirman, C.R., et al. (2004). Addressing nonlinearity in the exposure-response relationship for a genotoxic carcinogen: cancer potency estimates for ethylene oxide. Risk Anal. 24:1165-1183.

The Horizon: Systems Biology-based Toxicology Testing?

- >84,000 chemicals on the Toxic Substances Control Act inventory
- >100,000 chemicals registered in REACH
- ~1000 new industrial chemicals and pesticides introduced to the market annually
- Only a fraction of new chemicals are evaluated more than superficially for human risk…

…because current testing paradigm is slow, expensive, requires large numbers of animals, and involves considerable scientific understanding to develop credible extrapolations.

Systems Biology-Based Toxicity Testing



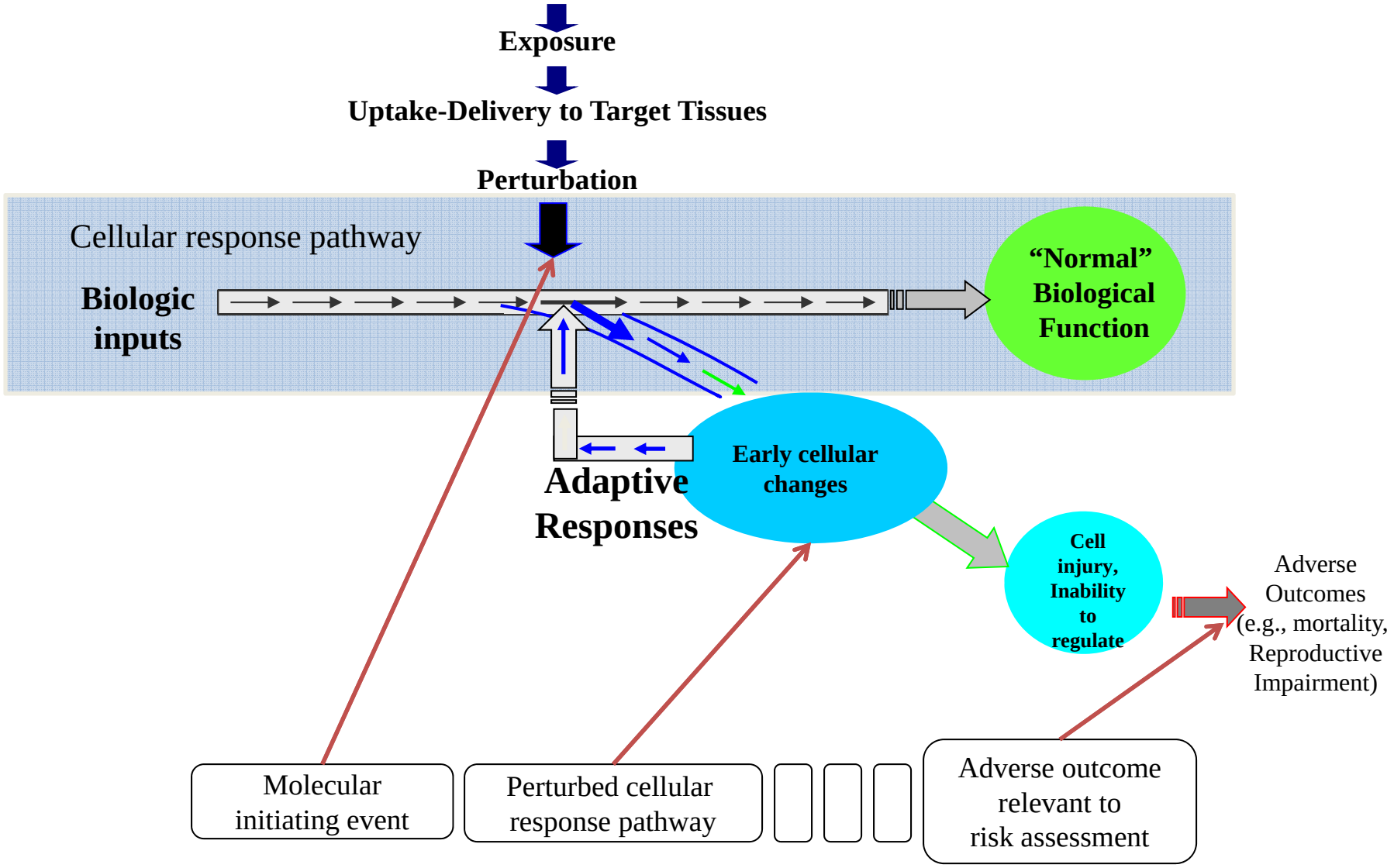
Driving impetus (US)

Toxicity Testing 21st Century: A Vision and a Strategy (NAS, 2007)

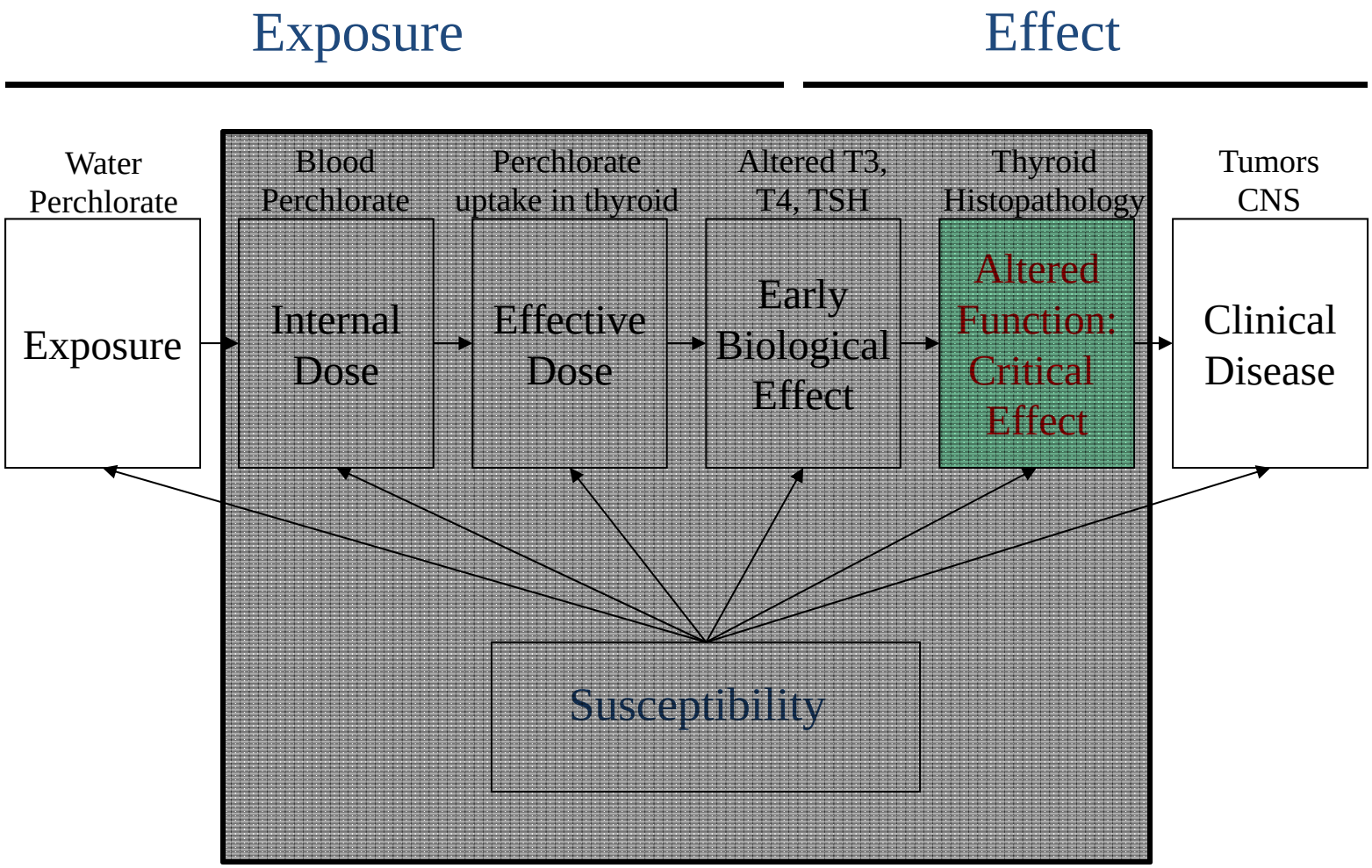
The Vision

- Cheaper
- High throughput
- Predictive analyses
- Minimize animal testing
- Focus on relevant dose levels
- More informative and efficient
- Characterize human variability
- Improve scientific basis of risk assessment
- Human cells – minimal interspecies extrapolation

The Horizon: Outcome Pathways of NAS



The Horizon: The Black Box Revealed



Adapted from Schulte (1989); Farland et al. 2000

Some Risk Assessment Uses of Systems Biology

- Hazard characterization:
  - Hypothesis generation for AOPs/MOAs (maturing)
  - Hypothesis testing of AOPs/MOAs (developing)
  - Endpoint identification (immature/developing)

- Dose-response assessment:
  - Characterize dose-response on biomarker data (developing)
  - Decreased need for low dose extrapolation (developing)
  - Reduced extrapolation across species (developing/immature)

- Exposure assessment
  - Use biomarkers of effect to combine exposures (immature)
  - High-throughput exposure assessments (EPA's ExpoCast program); RAIDAR and USETOX models – immature

Biomarkers of Effect

Bowyer et al., 2008. Subchronic acrylamide exposure in Fischer 344 rats.

Region	Gene Expressed	Expression Levels		
		% Relative to Control[a]	Relative to GADPH	P value[d]
Thyroid	Glyceraldehydephosphate dehydrogenase (GAPDH)	83±12%	NA	NA
Thyroid	Thyroglobulin	102±18%	54.6-fold	0.97
Thyroid	Thyroid peroxidase	102±18%	0.278-fold	0.77
Thyroid	Sodium iodide symporter	142±22%	0.0218-fold	0.12
Thyroid	Type I 5′-deiodinase	142±38%	0.295-fold	0.48
Thyroid	Type II 5′-deiodinase	189±33%	0.0181-fold	0.034
Thyroid	Type III 5′-deiodinase	113±18%	0.00139-fold[b]	0.53
Thyroid	Mki67	109±14%	0.0619-fold	0.71
Pituitary	Thyroid stimulating hormone β	108%	12.31	0.30
Pituitary	Thyroid hormone receptor α	103%	8.53	0.57
Pituitary	Thyroid hormone receptor β	109%	8.74	0.73

Statistically significant

The authors think this argues against a hormone MOA, but does it?

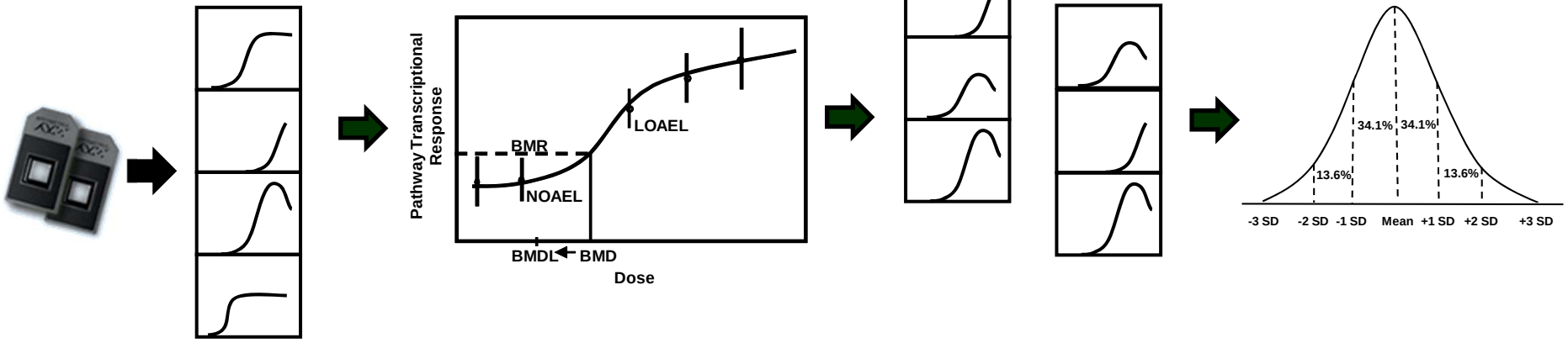
Stepwise Process for Estimating Genomic BMD Values

Fit Each Gene with Statistical Model

Calculate Dose at which response significantly deviates from control (i.e., BMD)

Group Genes by Cellular Function

Estimate Dose at Which Cellular Function is Perturbed



Thomas et al. *Tox. Sci.* 98:240, 2007

Yang et al. *BMC Genomics* 8:387, 2007

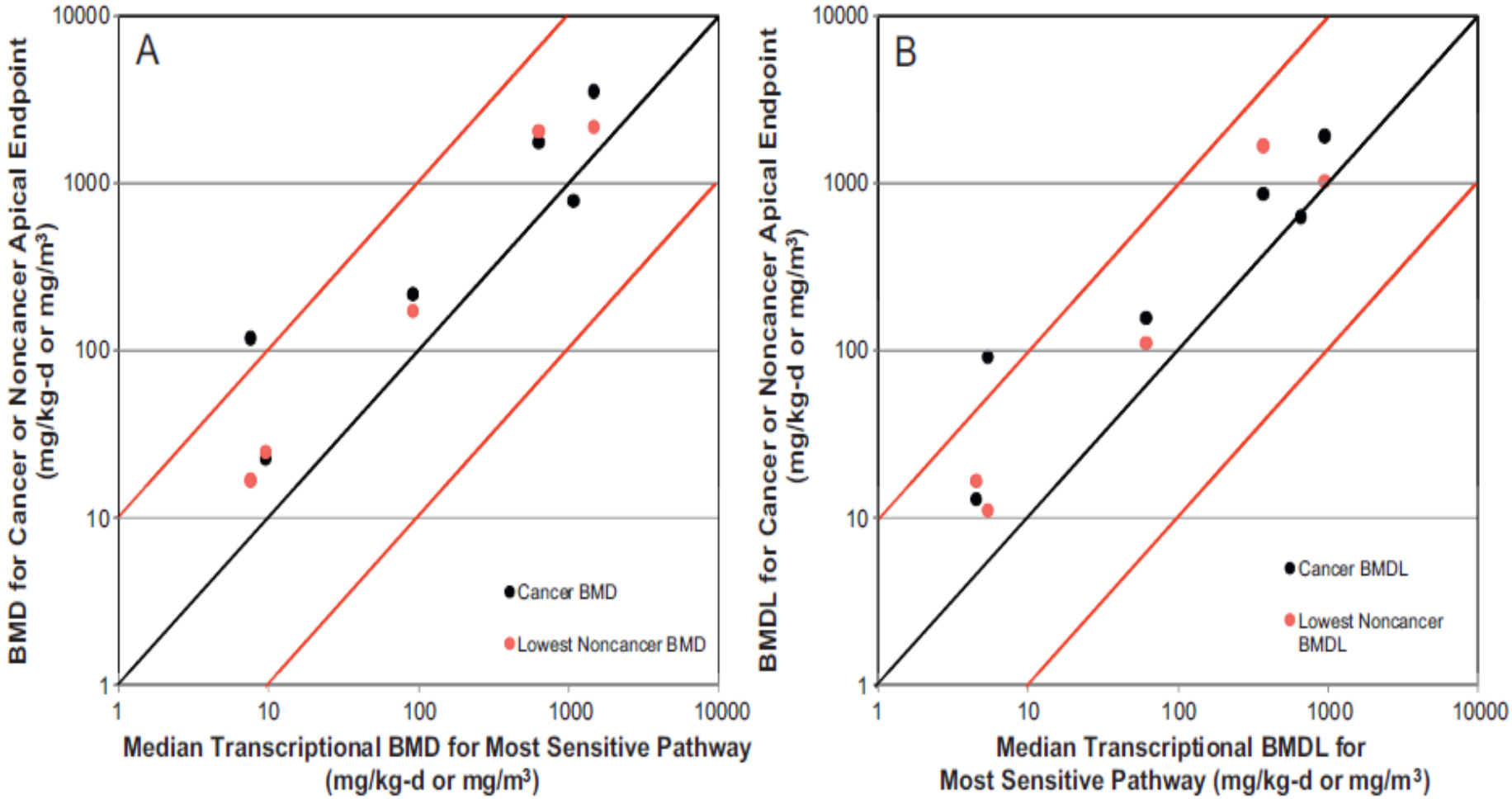


Fig. 5. Scatter plot of the relationship between (A) BMD and (B) BMDL values for the cancer and non-cancer apical endpoints and the transcriptional BMD and BMDL values for the most sensitive pathway. For each chemical and tissue, the BMD and BMDL values for tumor incidence and the lowest non-cancer BMD and BMDL values were plotted. For MECL in the lung, no non-cancer BMD or BMDL values were plotted due to the absence of histological changes. The red lines signify a 10-fold difference between the apical and transcriptional responses.

Thomas et al. (2012 - Mutation Research 746:135– 143) found a strong correlation between transcriptional BMDs for specific pathways and traditional BMDs

Risk Assessment Needs

- Phenotypic anchoring for clinical, critical, or adverse effects
- Markers for common critical effects, such as decreased body weight & models for specific "icities" – e.g., neurotoxicity
- Address communication among tissues; endocrine effects, *in vitro* to *in vivo* extrapolation
- Incorporate metabolism, differences in individuals and durations
- Test volatile chemicals

Create the Future: Collaborative Research

- Alliance for Risk Assessment (*ARA*)
  - Risk Information Exchange (RiskIE)
  - International Toxicity Estimates for Risk (*ITER*)
- Beyond Science and Decisions: From Problem Formulation to Dose Response
- Mixtures and Combined Exposures
- Guide Through Committee Recommendations
- Peer Review

Alliance for Risk Assessment (*ARA*) (www.allianceforrisk.org)

Stakeholder Process

States, Fed. Agencies, Public Interests, Industry

Initiation of Risk Issue

Document Draft

Peer Reviews

Release to Public

Risk Information Exchange (RiskIE)

ARA Process

Steering Committee

Non-profit Collaborators

Risk Document Development

Training and Certification

Risk Communication

Risk Research And Tools

Peer Review & Consult

RiskIE

Risk Information Exchange

www.allianceforrisk.org/RiskIE.htm

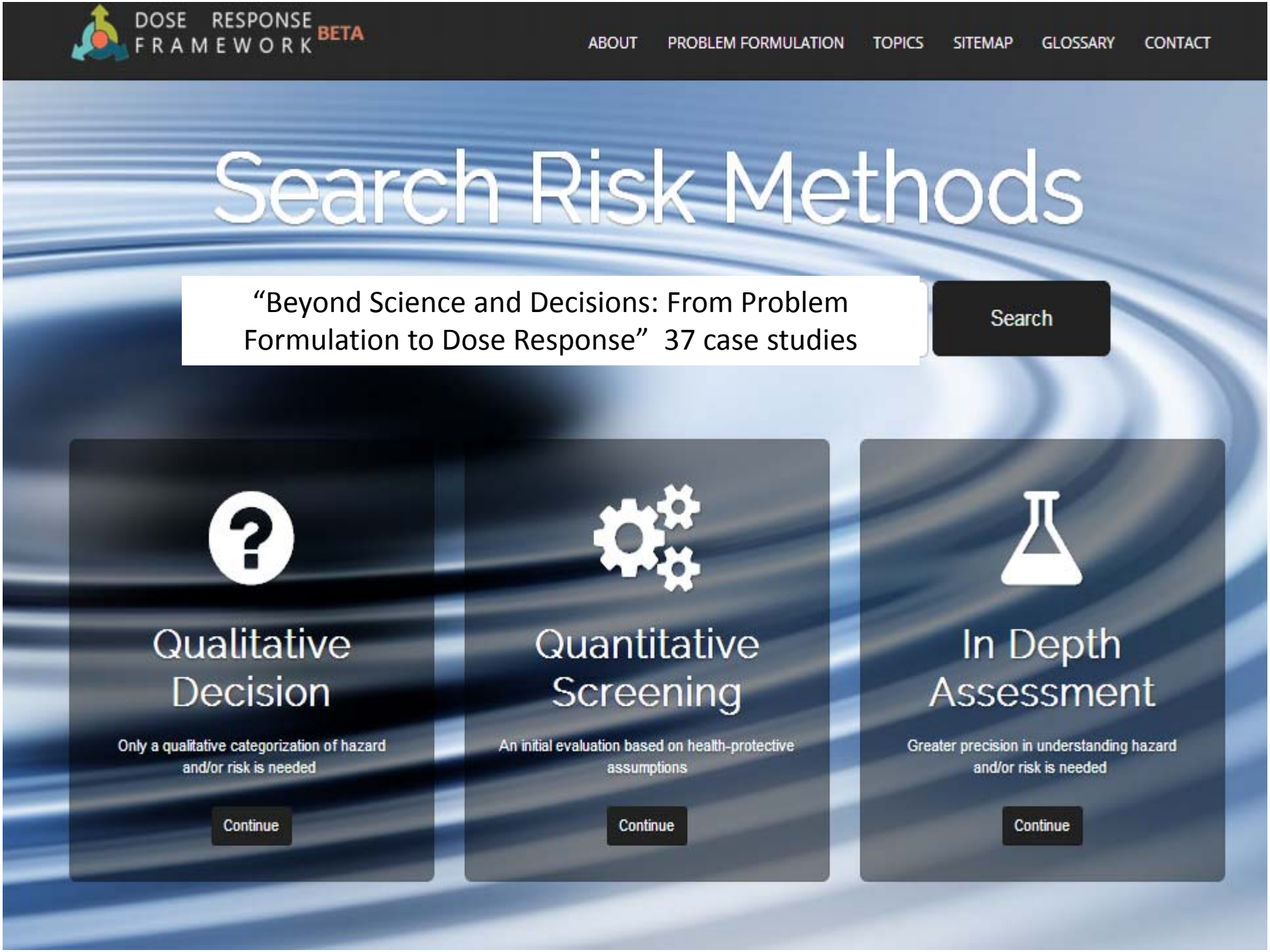
- An interactive Database to Communicate In-Progress Risk & Toxicity Assessments
- Includes over 7800 projects being conducted by more than 30 organizations representing 15 countries
- Available at the Alliance for Risk Assessment (*ARA*) website

ITER

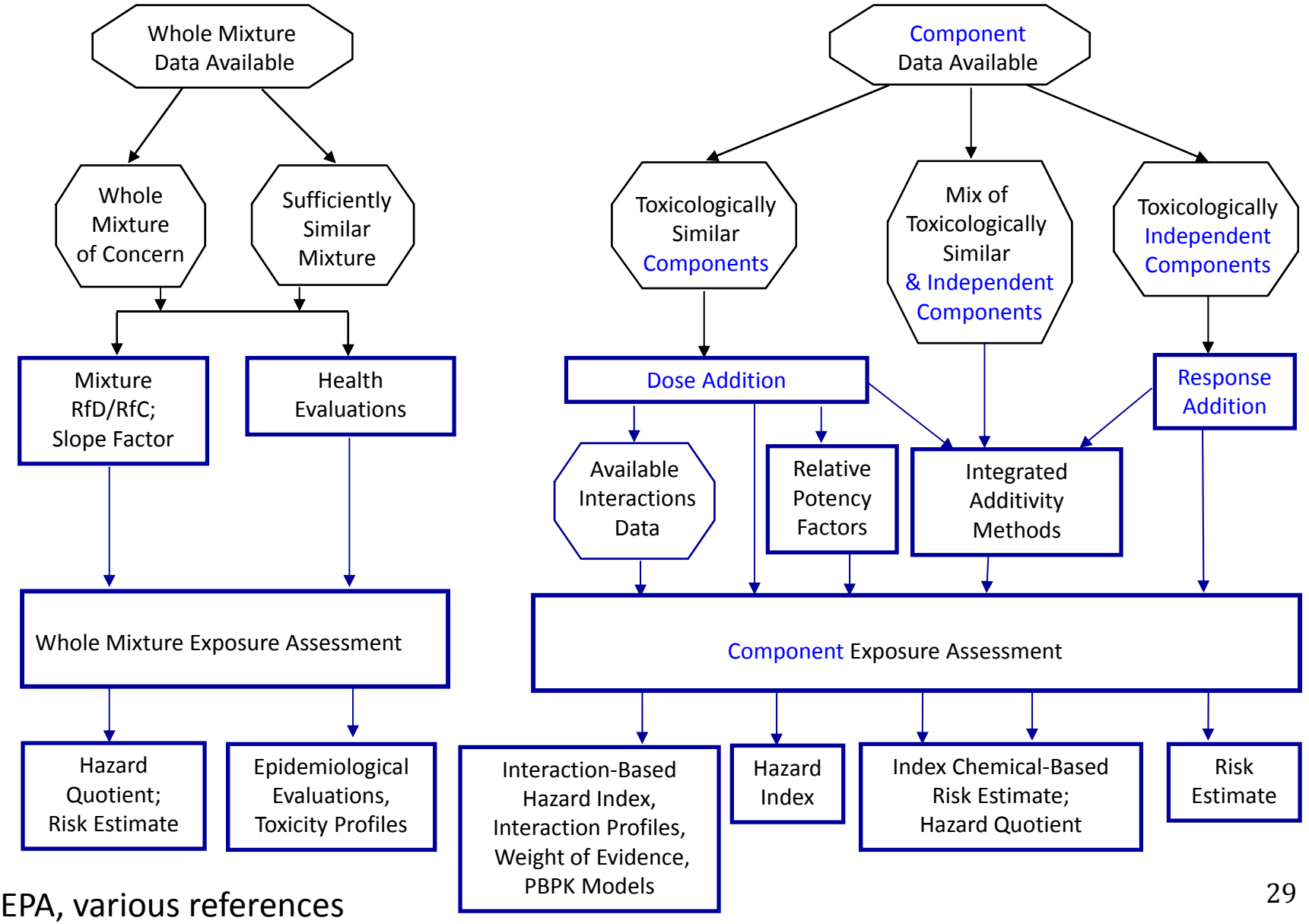
International Toxicity Estimates for Risk

www.tera.org/ITER
http://toxnet.nlm.nih.gov

- Provides chronic human health risk values and cancer classifications from organizations around the world for over 650 chemicals, including values from journal publications after quality assurance
- Includes synopsis on the underlying basis and rationale for each risk value and differences in risk values
- Links to each organization's website or source document
- A forum through which independent parties can share their peer reviewed risk values


DOSE RESPONSE FRAMEWORK BETA
ABOUT
PROBLEM FORMULATION
TOPICS
SITEMAP
GLOSSARY
CONTACT
Search Risk Methods
"Beyond Science and Decisions: From Problem Formulation to Dose Response" 37 case studies
Search
Qualitative Decision
Only a qualitative categorization of hazard and/or risk is needed
Continue
Quantitative Screening
An initial evaluation based on health-protective assumptions
Continue
In Depth Assessment
Greater precision in understanding hazard and/or risk is needed
Continue

Flow Charts for Evaluating Chemical Mixtures



EPA, various references

Advancing Risk Assessment:
Integrating Advisory Committee Recommendations

- Problem formulation should be linked to risk management; doing so does not "pollute" the risk assessment science
- The "safe" dose concept has evolved; CSAFs should be used
- Mode Of Action (MOA) is the assessment's organizing principle, but integrate key events in dose-effect continuum
- Key dose-dependent transitions are the norm; understanding MOA is essential for dose response
- Cumulative risk and mixtures assessment is iterative and should focus on the lowest tier needed to understand risk
- Biomonitoring is now interpretable; communication essential

Dourson, Becker, Haber, Pottenger, Bredfeldt, and Fenner-Crisp (Crit Rev Toxicol, 2013; 43(6): 467–492)

Risk Assessment Peer Review

- Cornerstone principles
  - Scientific robustness
  - Selection of appropriate panel expertise & chair
  - Transparency
  - Independence
- Distinguish conflict-of-interest from bias
  - Avoid COI
  - Balance biases
- Rule of thirds; ~1/3 of the panel should be
  - Experience risk assessors
  - Chemical or related-chemical experts
  - Effect experts
- Balanced affiliations

Summary

- Know traditional & contemporary risk methods
- 21st century toxicology methods will substantially aid in mixtures assessment, increase data and decrease costs, *but…*
- 21st century data need to improve the biological basis of assessments and lead to more credible extrapolations, *or they will not be used.*
- Create future by collaborative research

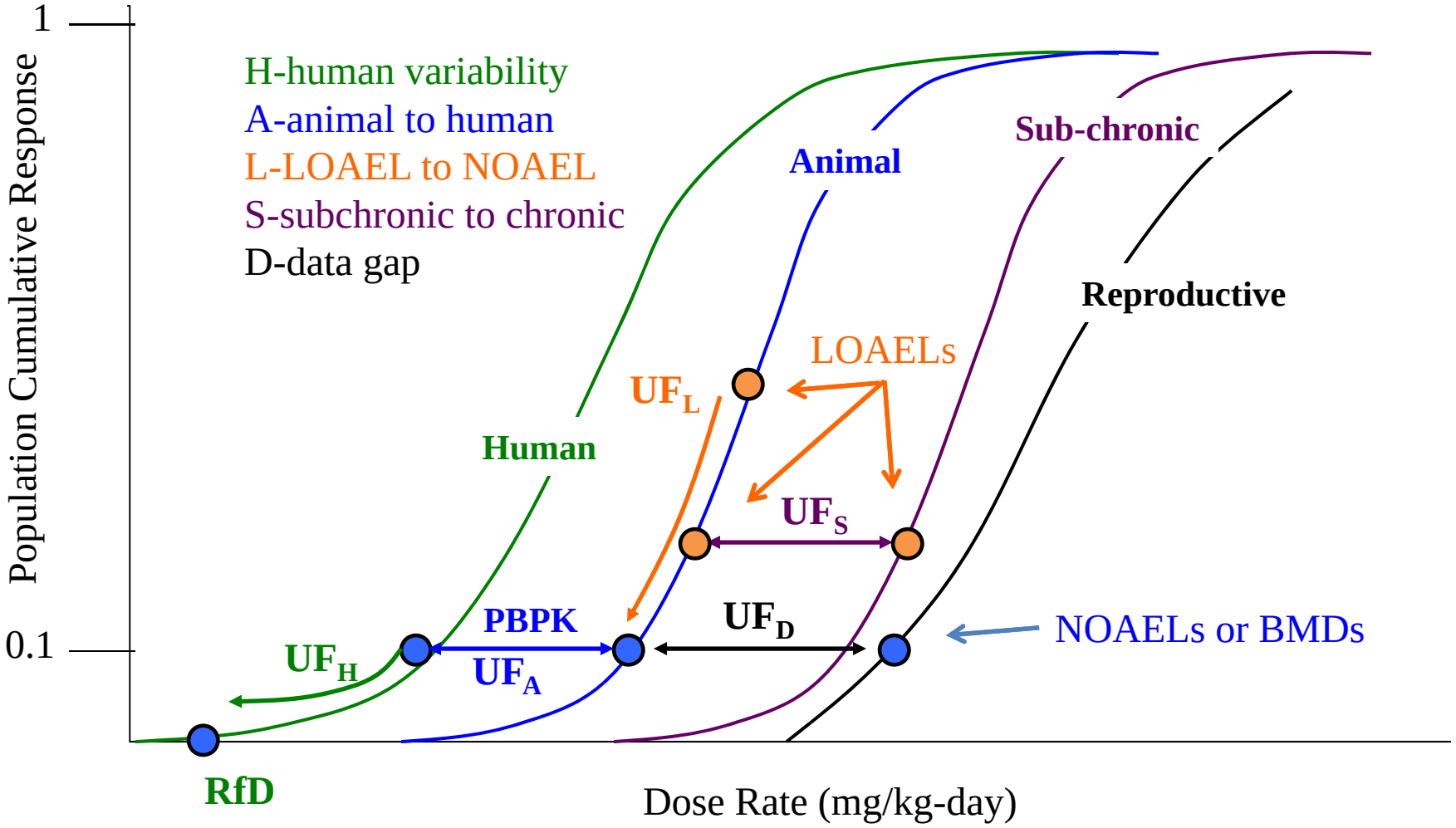
Extra Slides

Traditional Methods Quiz?

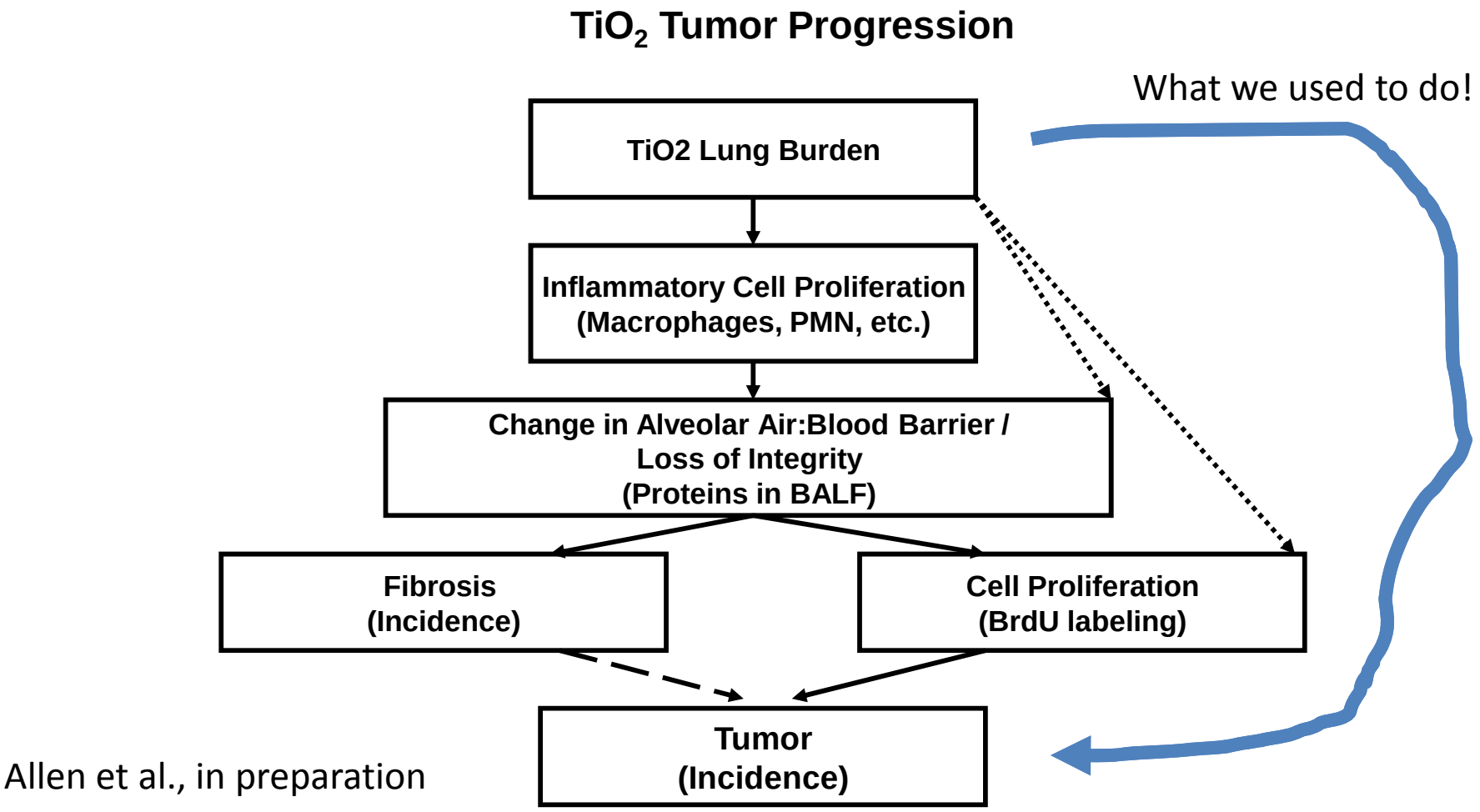
- If we had only 8 fingers, what would be the uncertainty factor covering experimental animal to human and within-human variation?

- If we had a array of effects that were all linked into one syndrome of toxicity, what would be the point of departure for a dose response assessment?

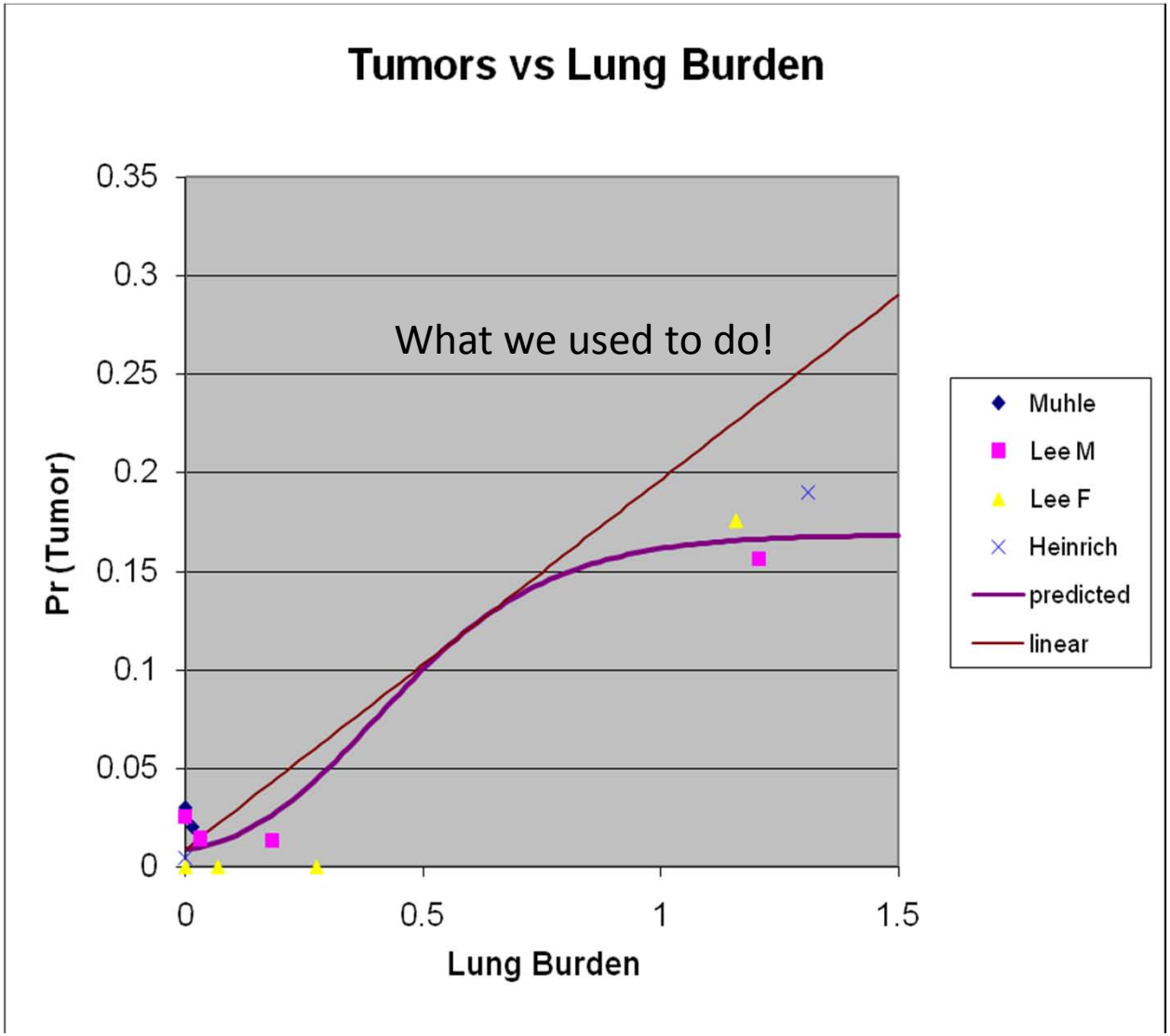
Uncertainties to Consider in Noncancer Dose Response Assessment

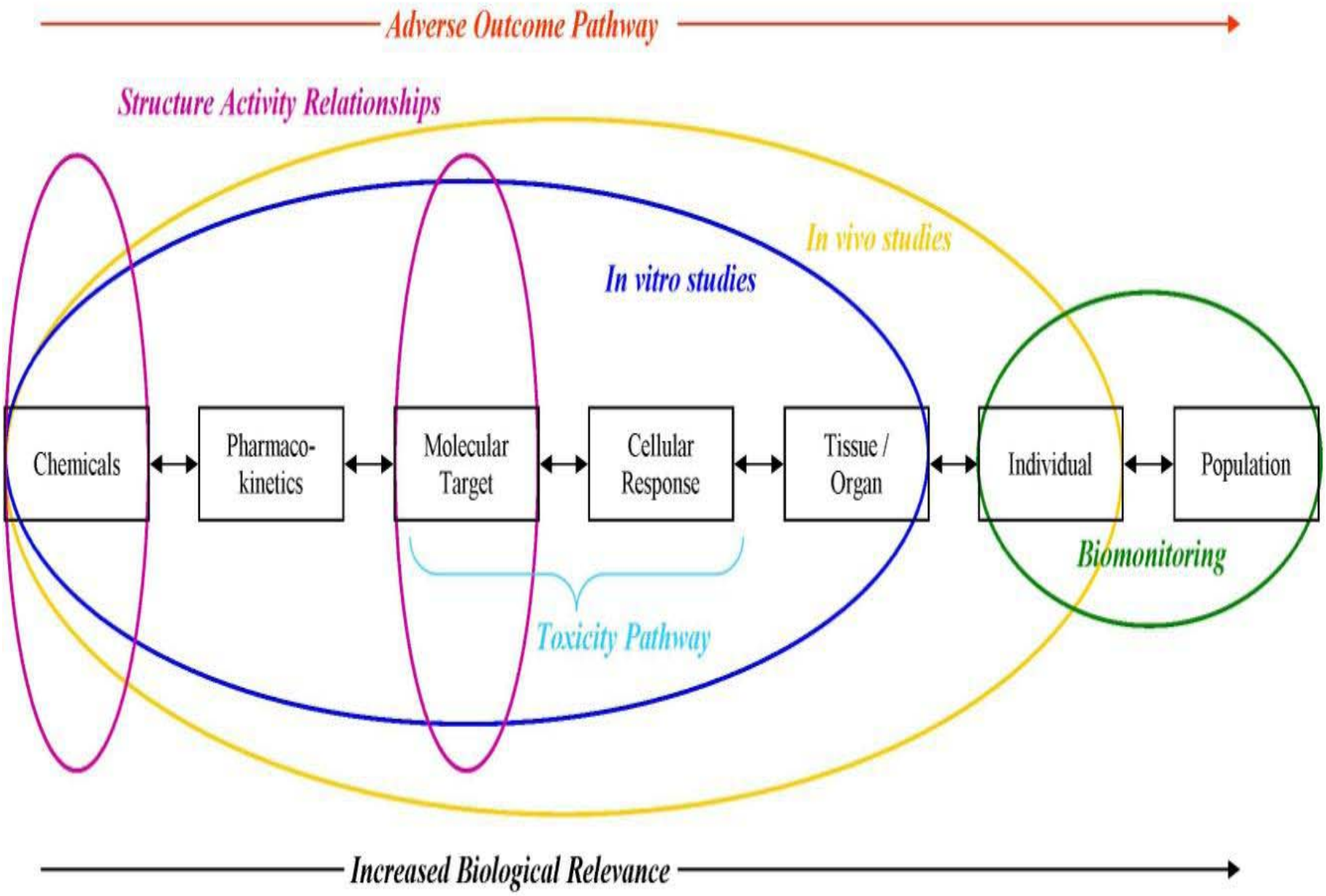


Biologically-Informed Dose-Response Modeling



Allen et al., in preparation


Tumors vs Lung Burden
What we used to do!
Pr (Tumor)
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
0
0.5
1
1.5
Lung Burden
Muhle
Lee M
Lee F
Heinrich
predicted
linear



EPA 2011; Ankley et al. 2010.

Biomarker Applications

- Biomarkers of exposure
  - Quantify/verify exposure
  - Medical monitoring (intervention)
  - Cross-species extrapolation (kinetics)
- Biomarkers of effect
  - Medical monitoring (recovery and long-term effects)
  - Cross-species extrapolation of toxicodynamics
  - Evaluate mode of action hypotheses/help characterize AOP
  - Immediate precursors for dose-response
  - Low-dose response characterization
  - Mechanistic modeling
- Biomarkers of Susceptibility
  - Identify susceptible subpopulations
  - Characterize human variability

Science and Decisions: Advancing Risk Assessment

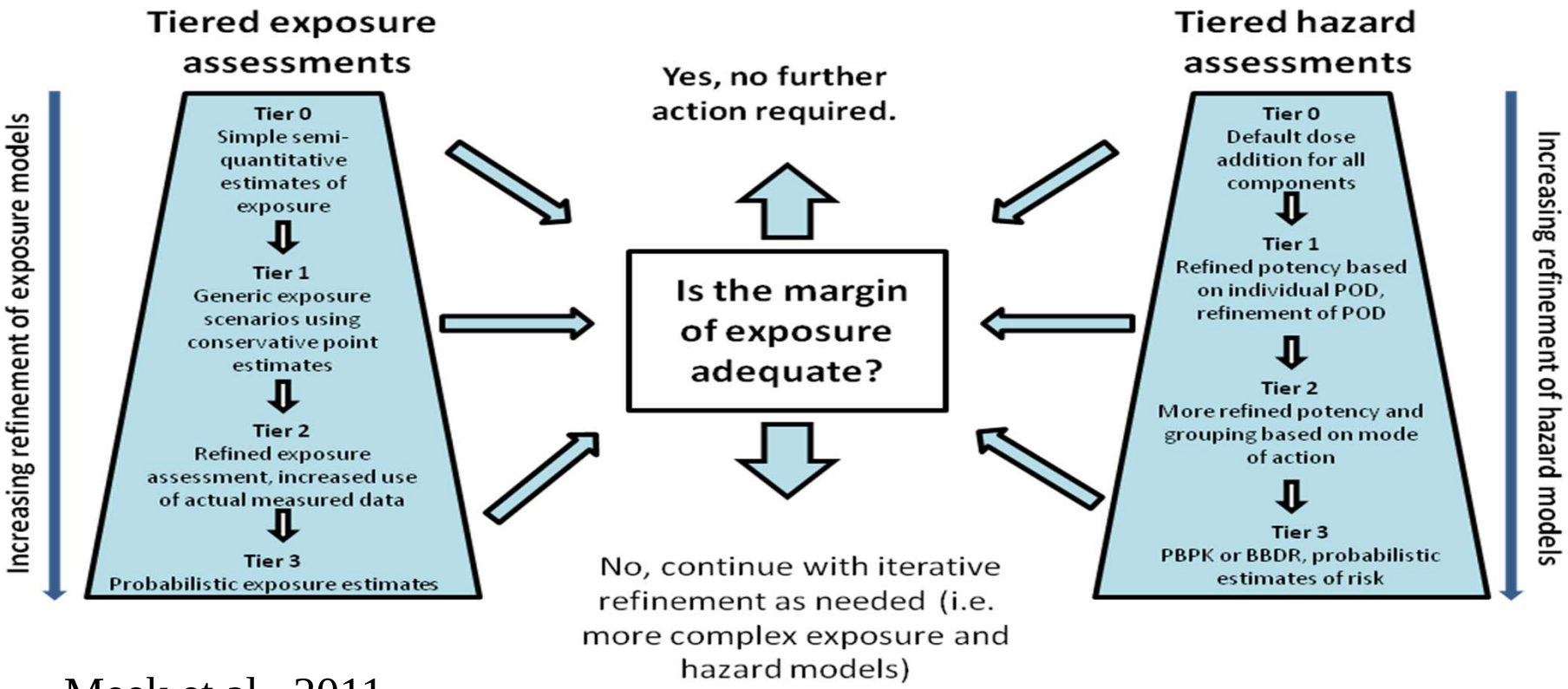
- Stressed problem formulation as upfront work prior to risk assessment
- Gave suggestions on hiring, training and planning
- Suggests incorporation of background exposures, stressors, and/or diseases in modeling efforts
- Suggests common dose response approach for all endpoints; default is a no threshold model

NAS, 2009

Problem Formulation for Combined Exposure Assessment

- *What is the nature of the exposure?*
- *Is exposure likely, taking into account the context?*
- *Is there a likelihood of co-exposure within a relevant timeframe?*
- *What is the rationale for considering compounds in an assessment group?*

Example Tiered Exposure and Hazard Considerations:
Mixture or Component Based



Meek et al., 2011