

PROBABILISTIC APPROACHES IN HUMAN HEALTH RISK ASSESSMENT AND MEDICAL DECISION ANALYSIS

Lorenz Rhomberg . . . State-of-the-
Gradient Corp. Science

Donald M. Berry Barriers and Bridges

Greg Campbell Facilitated Discussion
Dale Hattis

OUTLINE

- Motivations
- Framework
- Casting D-R Problems for PRA
- Estimating Distributions
- Variation in Susceptibility
- (Propagating Distributions, Sensitivity Analysis, Representing Probabilistic Results)
- Using PRA in Decision-Making

MOTIVATIONS FOR PRA IN HUMAN HEALTH RISK ASSESSMENT

- Large qualitative and quantitative uncertainties acknowledged, but not described well
 - (so *de facto*, treated as certain)
- Presumably Conservative defaults may combine to be overly conservative in aggregate
- Comparing point risks hard when they differ in allowance for uncertainty

. . . and . . .

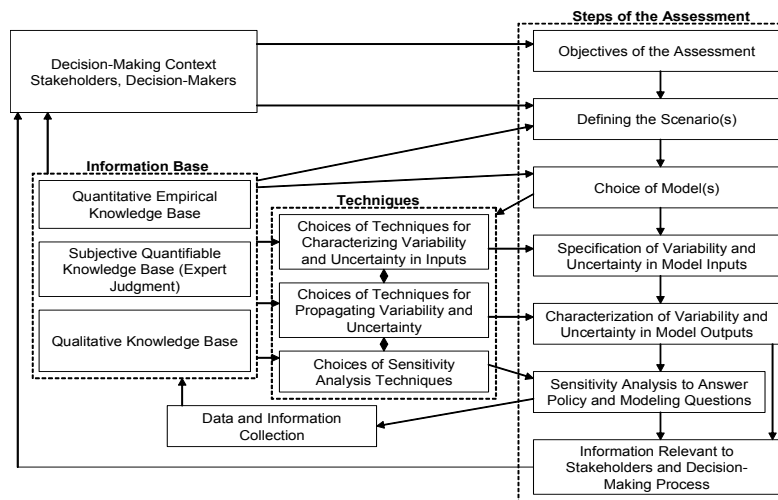
MOTIVATIONS FOR PRA IN HUMAN HEALTH RISK ASSESSMENT

- Want to address risk variation among individuals, especially “sensitive subpopulations”
- Combine probabilistic *Toxicity* with probabilistic *Exposure* assessment
- Want to use projected risks in decision analysis about actions:
 - unbiased estimates and their uncertainties (distributions)
 - descriptions of variation among individuals
 - in probability of response, severity, time of onset

CHALLENGES

- Uncertainties are Large
- Many of them about the very existence of risk and the relevance of data
- Outcomes are generally not observable
- Some relevant phenomena are rarely tested (time-varying exposure, severity, interactions)
- Laws call for scientifically based "findings" yet demand public health protection with "an adequate margin of safety"
- A public process conducted in the face of conflicting interests

Framework



Limits and Problem Scope

- Limits to what U and V can be considered
- Need to set explicit boundaries and note assumptions not being treated as uncertain
 - recognize that the answer will be contingent on these
- Challenge: be narrow enough to make the analysis possible and interpretable, but not so narrow as to make it unhelpful to the decisions to be made.

UNCERTAINTY IN HAZARD IDENTIFICATION

What toxicities is the agent capable of causing?

ISSUES

- lack of testing
- fallible screening assays (false negatives)
- high-dose studies of questionable relevance to low doses (false positives)
- incomplete information
- lack of carcinogen site concordance
- indirect information
 - animal outcomes to be extrapolated to humans,
 - high-dose outcomes to be extrapolated to low doses
 - biomarkers, precursor effects, mode-of-action studies
- contradictory information

EPA Weight-of-Evidence Factors for Carcinogens

- Human Tumor Epidemiology
- **Animal Bioassays**
- Physicochemical Properties
- Pharmacokinetics
- Mode of Action / Precursor Effects
- Similar Chemicals

BIOASSAY FACTORS

Increase Weight	Decrease Weight
Number of independent studies with consistent results	Single study
Same site across species, structural analogues	Inconsistent results
Multiple observations <ul style="list-style-type: none"> Species Sites Sexes 	Single site/species/sex
Severity and progression of lesions <ul style="list-style-type: none"> Early in life tumors/malignancy Dose response relationships Lesion progression Uncommon tumor 	Benign tumors only
Route of administration like human exposure	High background of incidence tumors
	Route of administration unlike human exposure

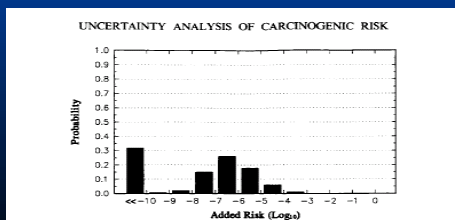
WoE is a kind of expert judgment about uncertain existence of causation

Carcinogenicity

- Carcinogenic to Humans
- Likely...
- Suggestive Evidence...
- Inadequate Information
- Not Likely

Other Toxicities

- WoE is smaller issue
- fewer formal systems



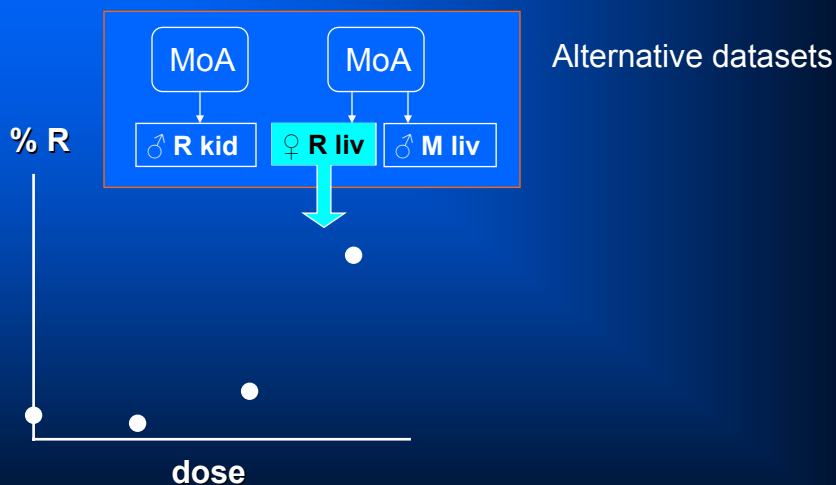
Possibilities:

- More formal expert judgment?
- Meta-analysis?
- Priors from other chemicals?

Main Components of Estimating Potency at Environmental Human Doses

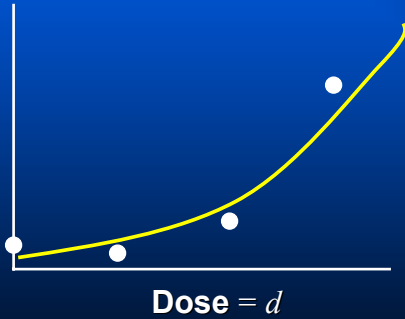
- (choice of dataset to represent human risk)
1. fitting D-R model to data on varying response with dose
 2. low-dose extrapolation of high-dose effects
 3. toxicologic equivalency of exposures across species

Choice of Dataset to Represent Human Risk

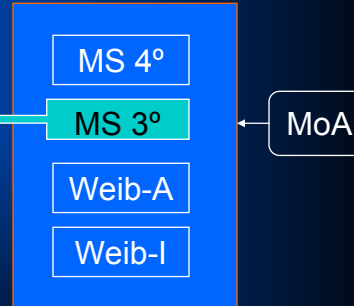


1. Fitting D-R Model to Data on Varying Response With Dose

% R = P(d)



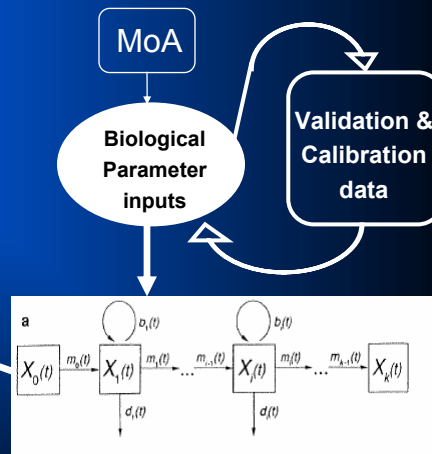
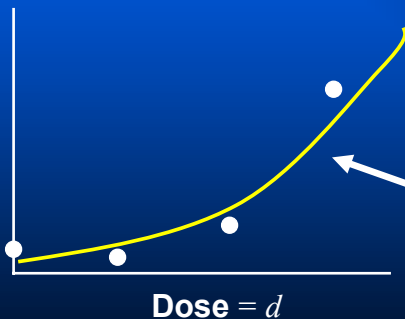
Alternative models



$$P(d) = 1 - \exp[-q_0 - q_1d - q_2d^2 - q_3d^3]$$

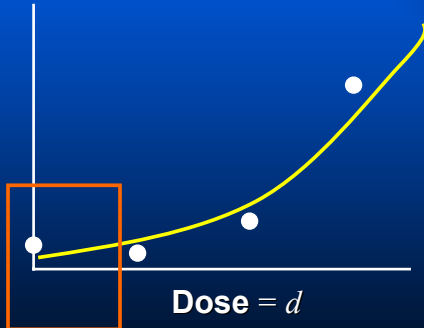
Biologically Based Dose-Response Model (BBDR)

% R = P(d)



2. Low-Dose Extrapolation of High-dose Effects

% R = $P(d)$



Consequence of model choice and fitted parameters

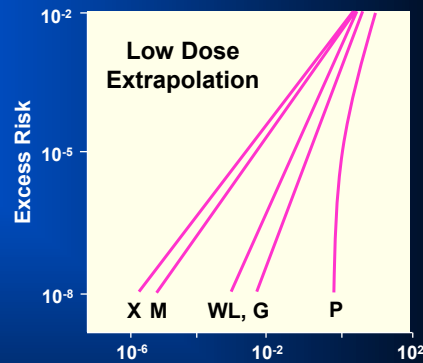
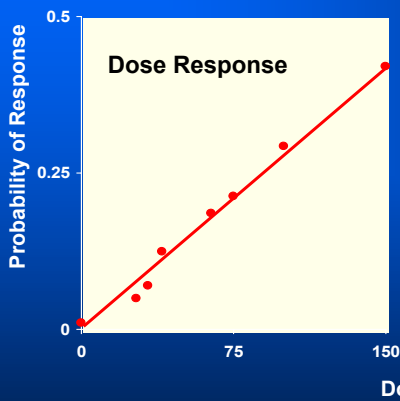
OR ...

- PoD + Linear
- Margin of Exposure

MoA

$$P(d) = 1 - \exp[-q_0 - q_1d - q_2d^2 - q_3d^3]$$

Uncertainty of Low-Dose Extrapolation

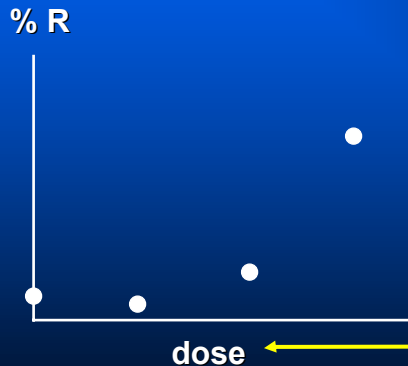


X – Linear Extrapolation
M – Multi-Stage Model
W – Weibull Model

L – Logit Model
G – Gamma Multi-Hit Model
P – Probit Model

Low-dose extrapolation for 2-acetylaminofluorene under several mathematical models.

3. Toxicologic Equivalency of Exposures (Doses) Across Species



Really 2 issues:

- Choosing a dose *scale* appropriate to endpoint, MoA, PK, and PD
- Equivalence of that scale in animals and humans

Aims

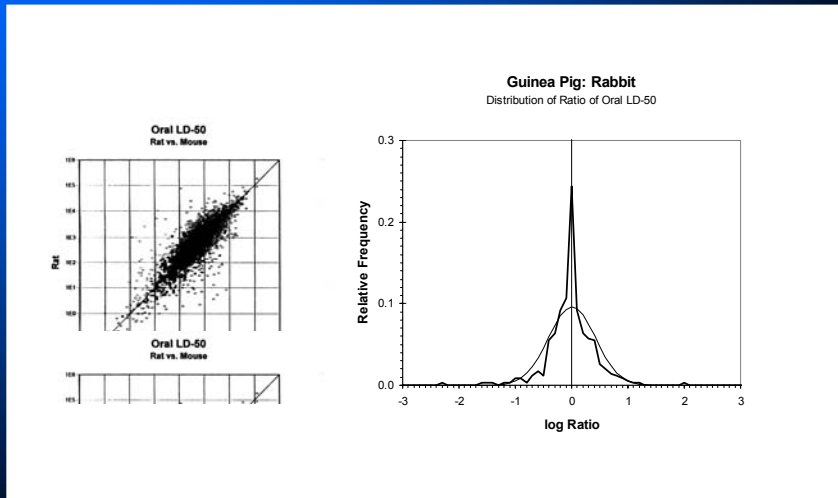
- To *generalize* the D-R observation
- Equitoxicity, not dosimetric equivalence, at issue

3. Toxicologic Equivalency of Exposures Across Species

Approaches to Characterizing Uncertainty in Dose Equivalence

- Judge relative plausibility of commonly used scales
(mg/kg/d, mg/kg^{3/4}/d, ppm-hr,...)
- Observe chemical-to-chemical variation in a population of observable relative potencies
(reduce uncertainty by stratifying)
- Investigate causative factors and their interactions
(including PBPK, BBDR – evaluate uncertainty in explanatory models)

Distribution of Cross-Species LD₅₀ Ratios



Rhomberg and Wolff. *Risk Analysis* 18(6):741-53

Observing a Population of Cases

- If the chemical of interest is a random draw from the frequency distribution, that distribution represents the *uncertainty* about its particular value
- Question: of what “population” is the chemical a member? -- stratify
- A “top-down” approach – observe the whole factor, and explain its variation by subdividing variance components
- Beware: measurement error inflates observed variation beyond the variation that matters
- But ignorance doesn’t inflate uncertainty beyond the “reality check” of observed variation among cases

Observing Human Variability in Susceptibility

Summary of Unweighted Log(CSD) Variability Observations for Different types of Parameters Including Pharmacodynamic Variability

	GI Tract	Nervous System	Respiratory System	Cardiovascular Renal System+ Receptor-Based Effects	Other (e.g. eye, skin irritation)	All Effects
Local (Contact Site) Parameter Change/External Exposure or Dose			Acute: 655 (17) ^a 369-1.16 ^b Chronic: 279 (1)			Acute: 655 (17) 369-1.16 Chronic: 279 (1)
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Response/External Dose (IV or Oral Admin.) Without Large Dose-to-Dose Uncertainty		Oral: 396 (4) IV: 359 (3) Inhal: 051 (2)		.266 (1)		.245 (10) 079-761
Response/External Dose With Large Dose-to-Dose Uncertainty (e.g. workplace epidemiology)			1.33 (1-talc lung disease)	.684 (3) 430-1.09		.307 (4) 456-1.43
Total Observations Including Pharmacodynamic Variability	(1)	(27)	(30)	(23)	(16)	(97)

^aNumbers in parentheses are the number of data groups in each category

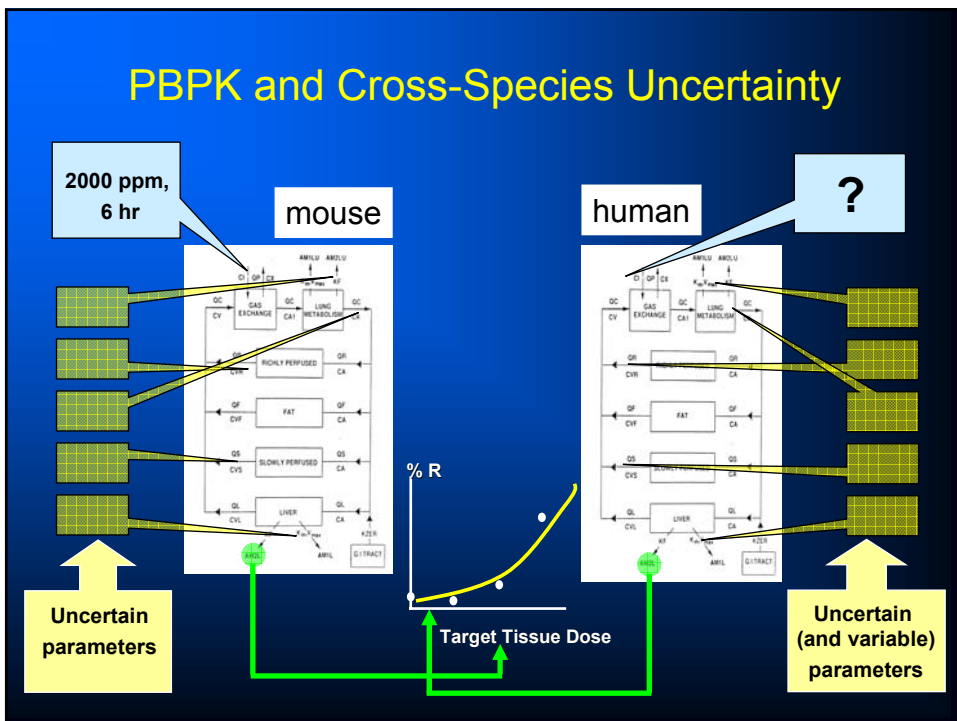
^bRanges are approximate 10th and 90th percentiles of the individual data sets in each category.

A Scale for Understanding Lognormal Variability—Fold Differences Between Particular Percentiles of Lognormal Distributions

Log ₁₀ (GSD)	Probit slope [1/Log ₁₀ (GSD)]	Geometric Standard Deviation	95th/50 th Percentile Ratio (1.645 standard deviations)	99 th /50th Percentile Ratio (2.326 standard deviations)
0.1	10	1.26	1.46 fold	1.71 fold
0.2	5	1.58	2.13 fold	2.92 fold
0.3	3.33	2.0	3.11 fold	4.99 fold
0.4	2.5	2.5	4.55 fold	8.52 fold
0.5	2	3.2	6.64 fold	14.6 fold
0.6	1.67	4.0	9.70 fold	24.9 fold
0.7	1.43	5.0	14.1 fold	42.5 fold
0.8	1.25	6.3	20.7 fold	72.6 fold
0.9	1.11	7.9	30.2 fold	124 fold
1	1.0	10.0	44.1 fold	212 fold

Hattis, D. and Lynch, M. K. In *Toxicokinetics in Risk Assessment*, J. Lipscomb, ed., Marcel Dekker, Inc. in press, 2005.

PBPK and Cross-Species Uncertainty



Characterizing a Distribution by Modeling the Causes of Variation

- Synthesize the unknown overall distribution by propagating distributions of its causal components
- A “bottom-up” approach – observe the parts and deduce the combined consequences
- Benefit: understanding of (and perhaps reduction of) uncertainty
- Danger: poorly known parts can inflate the overall uncertainty unrealistically; but left-out parts can lead to underestimates

The Part/Whole Problem

Default UF_a = 10 and has a PK and a PD component

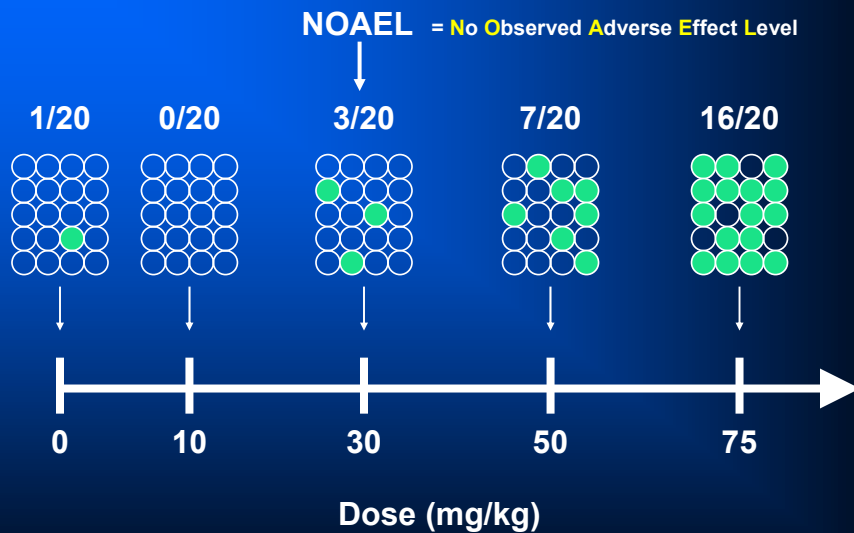
PK modeling shows kinetically equivalent doses in animals and humans (with an uncertainty of 3-fold)

How should UF_a be altered to reflect this added information?

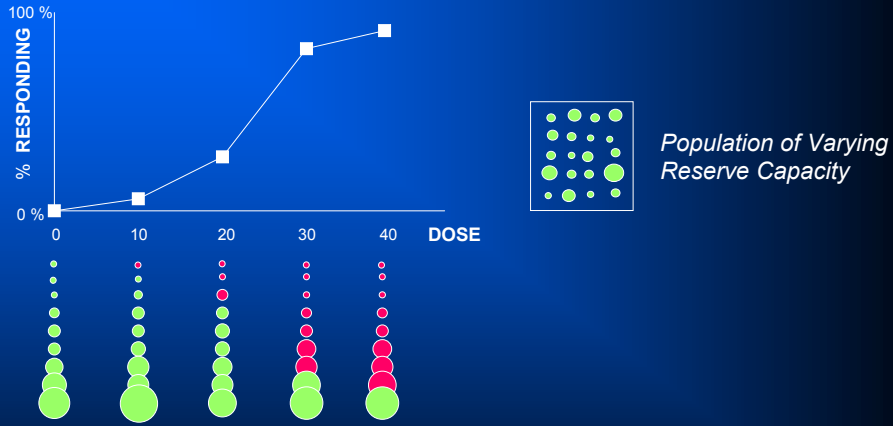
4 KINDS OF DOSE-RESPONSE

- Quantal Tolerance Distribution
- Continuous Endpoint
- Stochastic Event
- Mechanistic (BBDR)

Quantal Tolerance Distribution Models

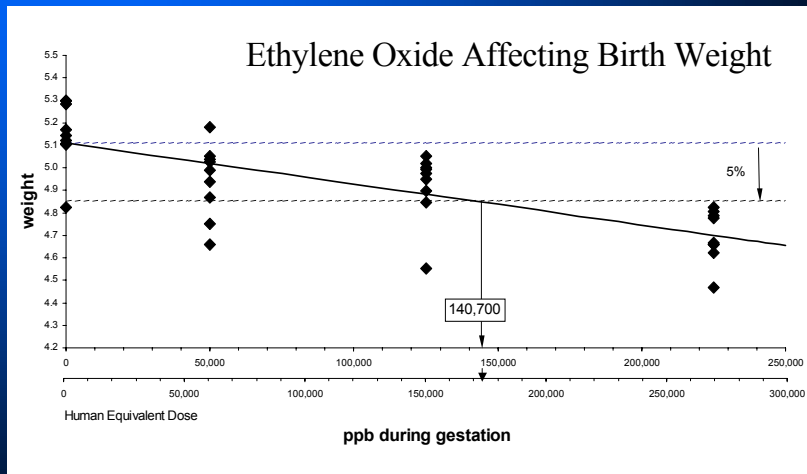


Tolerance Distribution

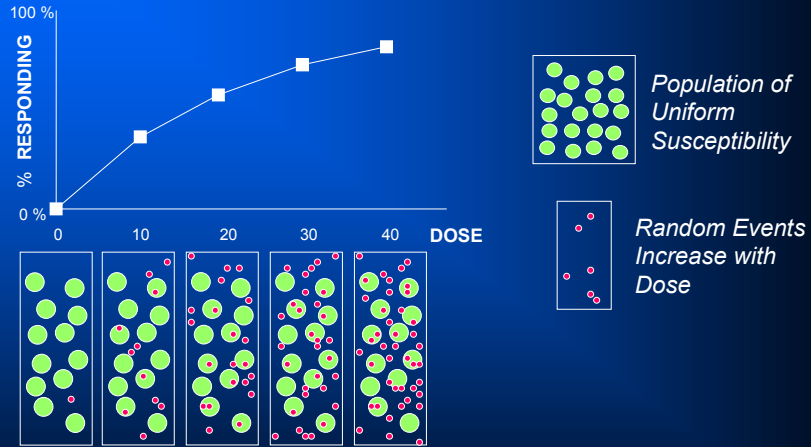


There is a dose-response because higher doses exceed the ability to tolerate the challenge in an increasing fraction of the population.

Continuous Variable

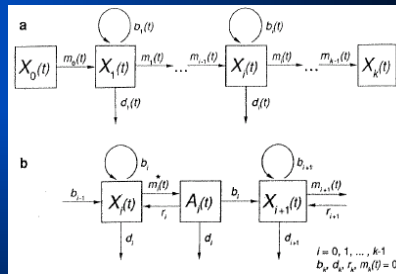
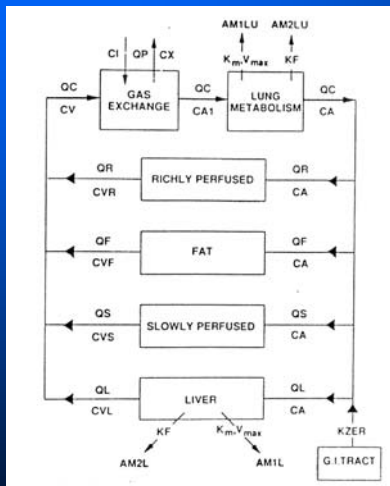


Stochastic Events



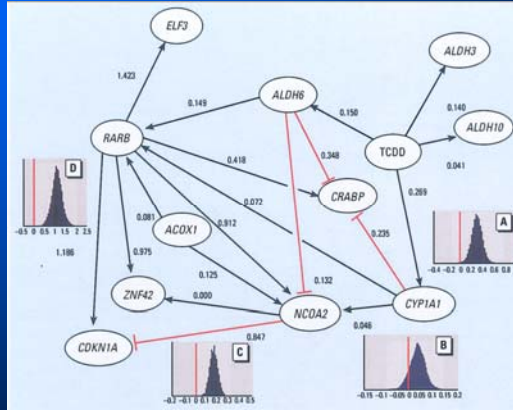
There is a dose-response because, for all individuals, higher doses cause a higher random chance of being "hit" (but only some actually are).

Mechanistic Models



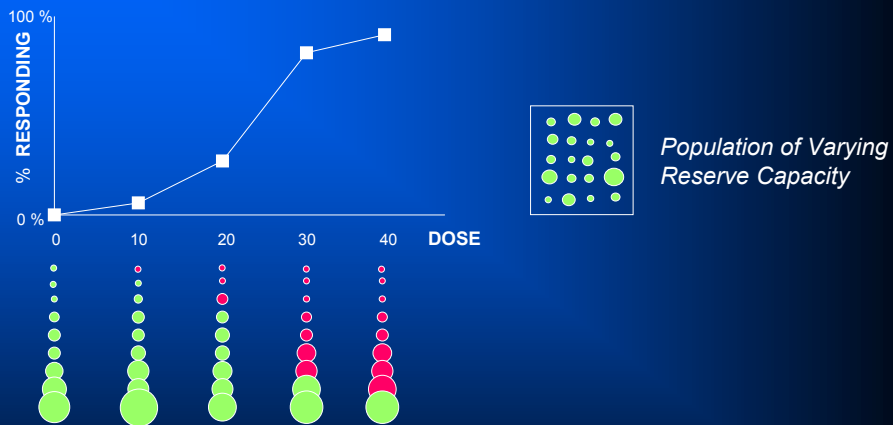
Source: Bogen KT. 1989. JNCI 81:267

Epigenetic Networks



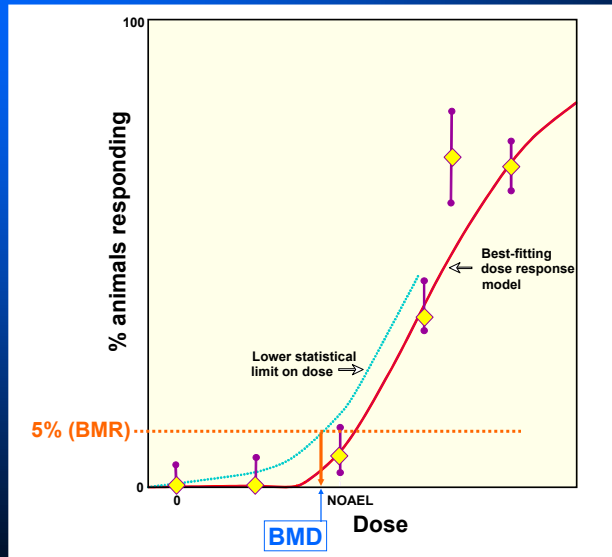
Toyoshiba, H. et al. (2004) Environ. Health Perspect. 112(12), 1217-1224.

Tolerance Distribution



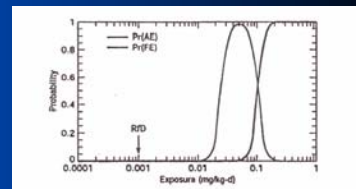
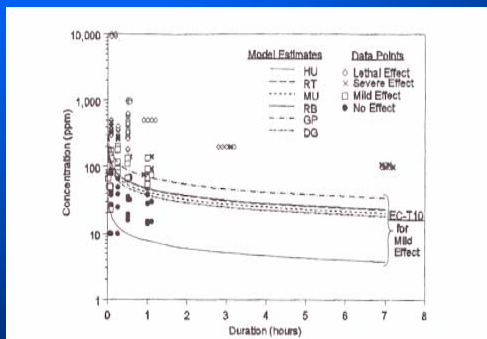
There is a dose-response because higher doses exceed the ability to tolerate the challenge in an increasing fraction of the population.

Benchmark Dose (BMD)



Source: US EPA, 1995. The use of the benchmark dose approach in health risk assessment. Risk Assessment Forum, Office of Research and Development, Washington, DC. EPA/630/R-94/007.

Categorical Regression



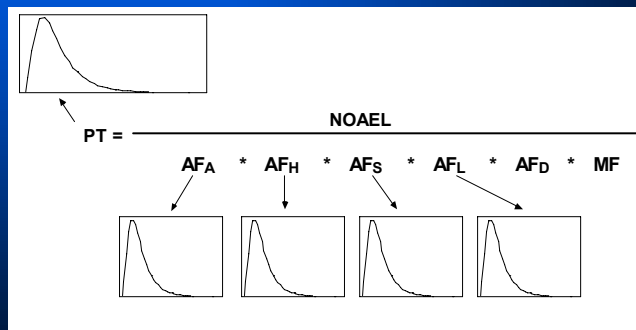
Calculating the Reference Dose (RfD)

$$\text{RfD} = \frac{\text{NOAEL}}{\text{UF}_A \cdot \text{UF}_H \cdot \text{UF}_S \cdot \text{UF}_L \cdot \text{UF}_D}$$

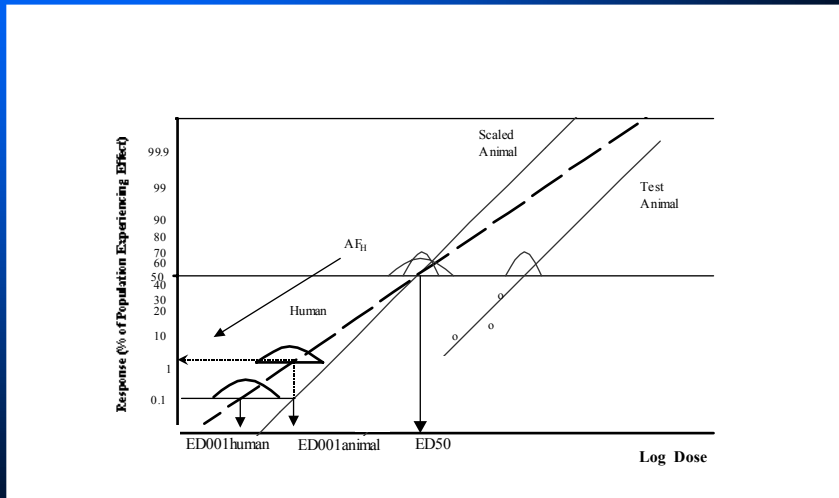
		Range	Usual Value
UF_A	- animal to human extrapolation	1-10	10
UF_H	- average human to sensitive human	1-10	10
UF_S	- subchronic to chronic exposure	1-10	10
UF_L	- LOAEL to NOAEL	1-10	10
UF_D	- database considerations	1-10	10

Distributional Uncertainty Factors

$$\text{RfD} = \frac{\text{NOAEL}}{\text{UF}_A * \text{UF}_H * \text{UF}_S * \text{UF}_L * \text{MF} * \text{D}}$$

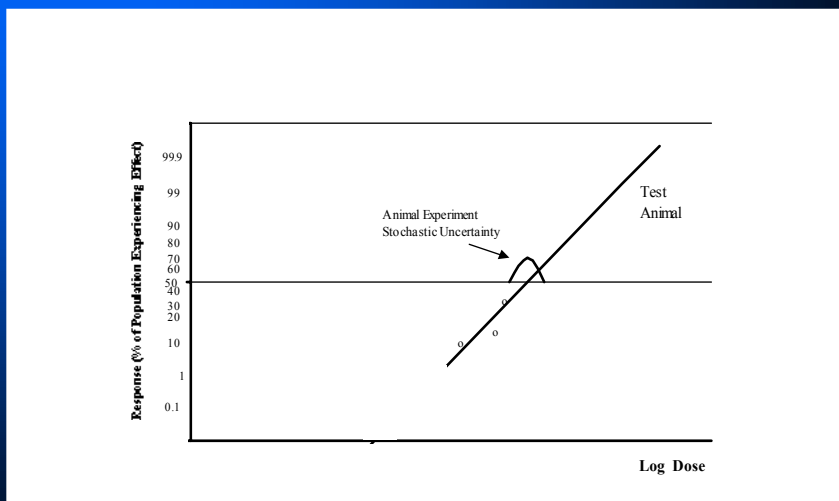


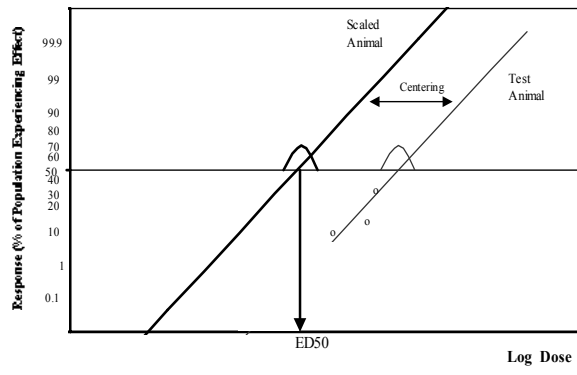
Probabilistic Projection of a Human ED₀₀₁



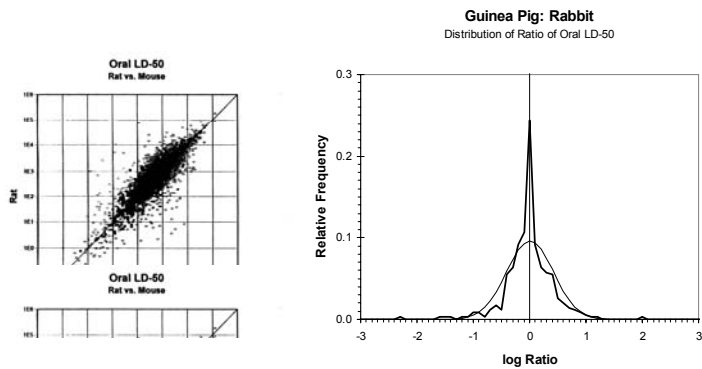
Evans et al. 2001. Risk Anal. 21:697; Baird et al. 1997 SRA

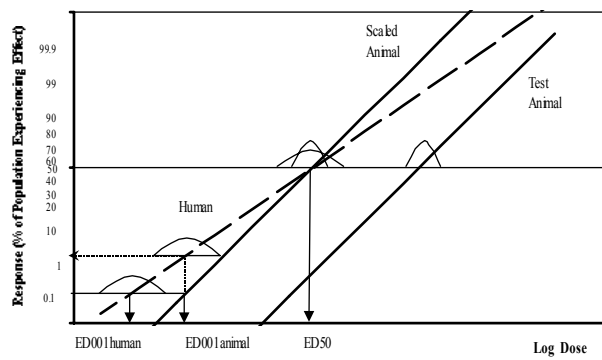
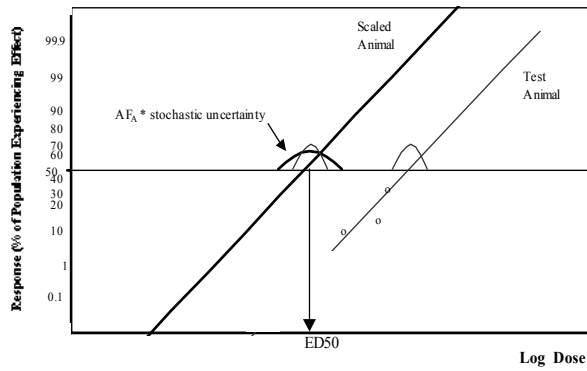
Fit Probit to Animal Data

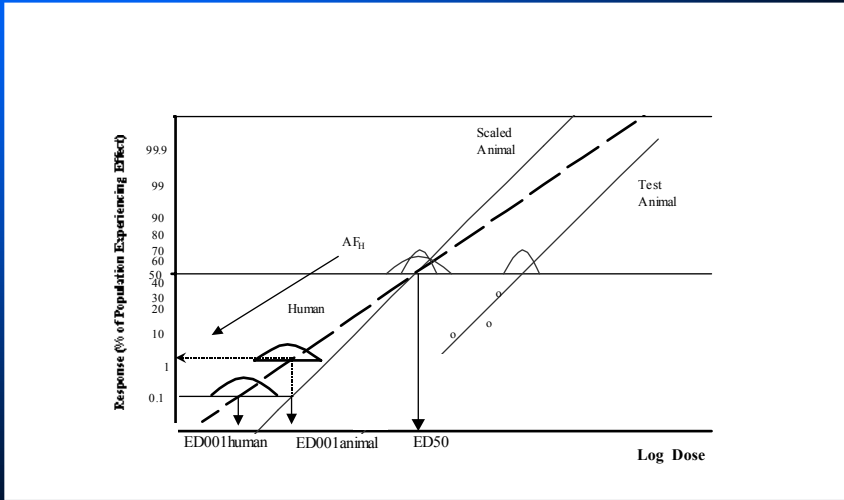




Distribution of Cross-Species LD₅₀ Ratios

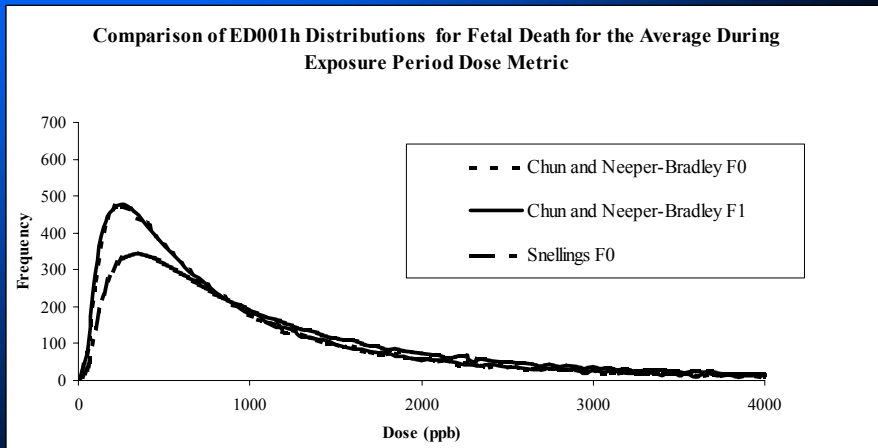






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Case Study: Ethylene Oxide



Expert Judgment Assessment of Chloroform Carcinogenic Potency

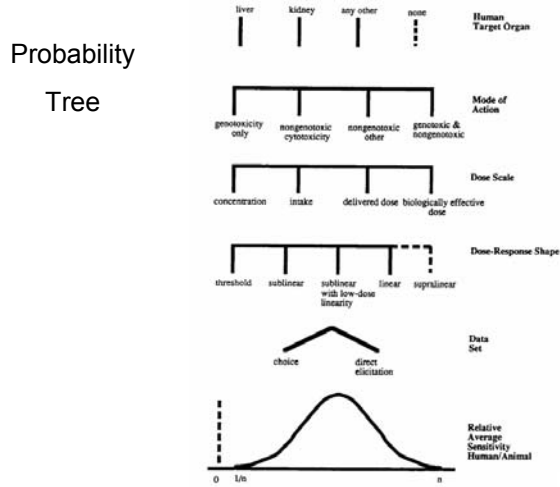
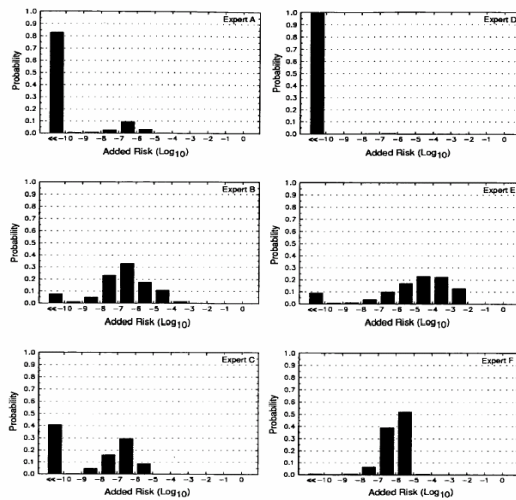


FIG. 1. Chloroform probability tree.

Evans et al. (1994)
Reg Toxicol Pharmacol 20:15-36

Individual Expert's Distributions for excess cancer risk from 100 ppb Chloroform in Drinking Water



Evans et al. (1994)
Reg Toxicol Pharmacol 20:15-36

Combined Judgment (based on peer nomination of experts on each level)

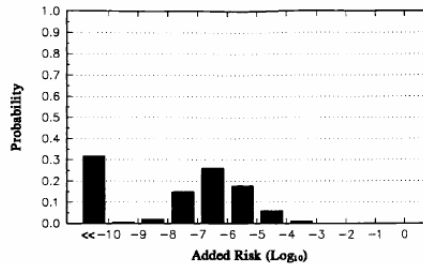


FIG. 5. Combined expert assessment based on peer nomination (any organ). Risk distribution combined across experts with the expert judged by the other experts in the group to be most knowledgeable about each level of the tree providing weights for each branch.

Evans et al. (1994)
Reg Toxicol Pharmacol 20:15-36

Characterizing Variability in Susceptibility

- Continuous Population Variation
- Sensitive Subpopulations
 - defined by their sensitivity per se or its cause (e.g., diabetics)
 - defined by demographics or other external factors, but with sensitivity concerns (e.g., children, elderly, ethnic)
- Pharmacokinetic and “Sensitivity” components
- Covariation with variability in exposure?

Pharmacokinetic Contributors

- Size, body mass, physiological parameters
- Activity of key metabolic enzymes
 - Genetic Polymorphism
 - Inducible Enzymes and Lifestyle
- Co-exposures to other agents with PK interactions

PHARMACODYNAMIC (“Sensitivity”) Contributors

- Defenses and Repair Capacities
 - Constitutive
 - Induced defenses and lifestyle
- Reserve Capacity
- Stressors (current and in the past)
- Genetic Differences

For Cancer

- Inherited mutations
- Somatic mutations
- Cell division
- Age
- Immune surveillance

Observing Human Variability in Susceptibility

Summary of Unweighted Log(CSD) Variability Observations for Different types of Parameters Including Pharmacodynamic Variability

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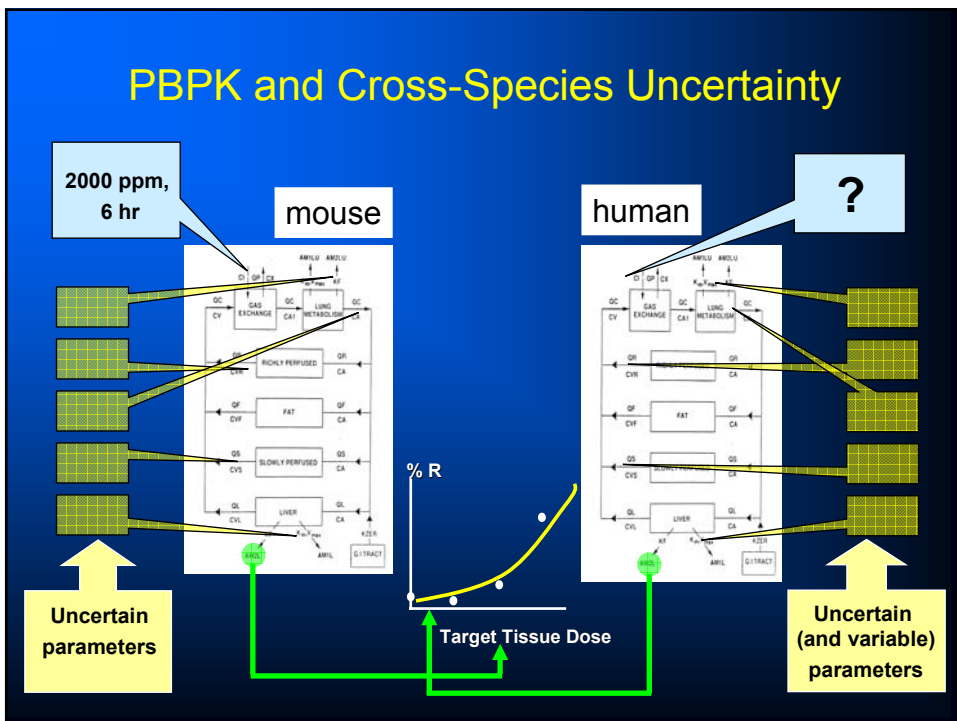
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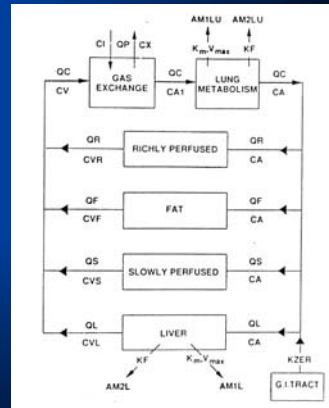
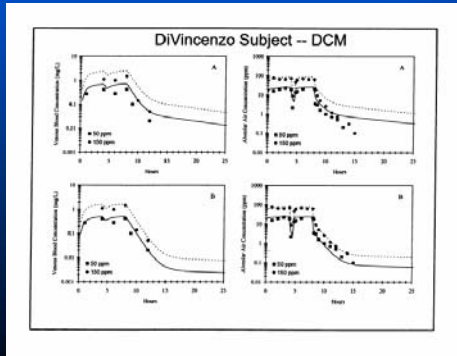
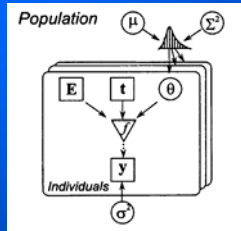
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PBPK and Cross-Species Uncertainty



Individual Variation in PK



Source: Harvey Clewell

Effect of Enzyme Polymorphism on Individual Variation in PK -- Warfarin

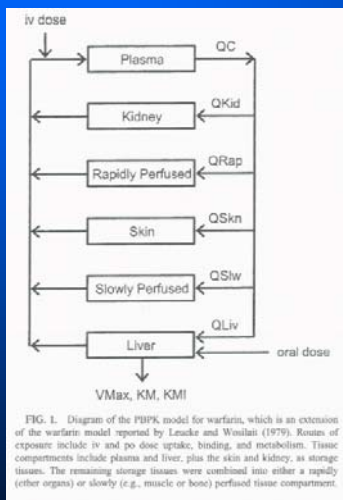


FIG. 1. Diagram of the PDPK model for warfarin, which is an extension of the warfarin model reported by Lesca and Woullat (1979). Routes of exposure include iv and po dose uptake, binding, and metabolism. Tissue compartments include plasma and liver, plus the skin and kidney, as storage tissues. The remaining storage tissues were combined into either a rapidly (other organs) or slowly (e.g., muscle or bone) perfused tissue compartment.

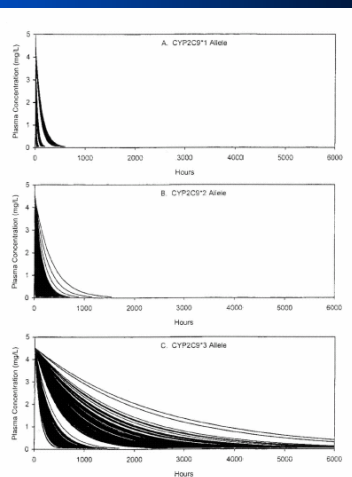


FIG. 5. Case 1 results for (S)-warfarin, in which the plasma concentration over time was simulated for each of the three homozygous genotypes: (A) CYP2C9*1, (B) CYP2C9*2, (C) CYP2C9*3. Each line in the figure represents one Monte Carlo simulation.

Effect of Enzyme Polymorphism on Individual Variation in PK -- Parathion

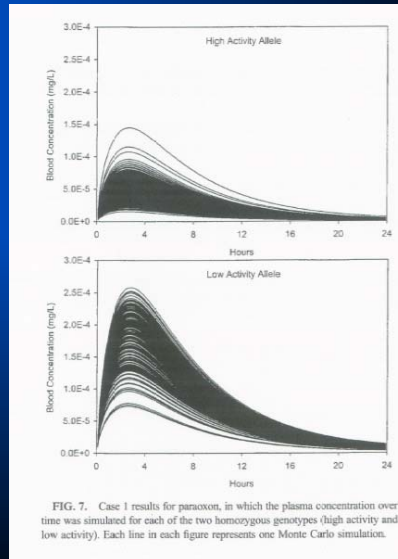
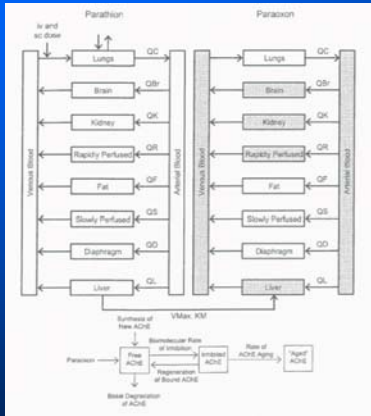


FIG. 7. Case 1 results for parathion, in which the plasma concentration over time was simulated for each of the two homozygous genotypes (high activity and low activity). Each line in each figure represents one Monte Carlo simulation.

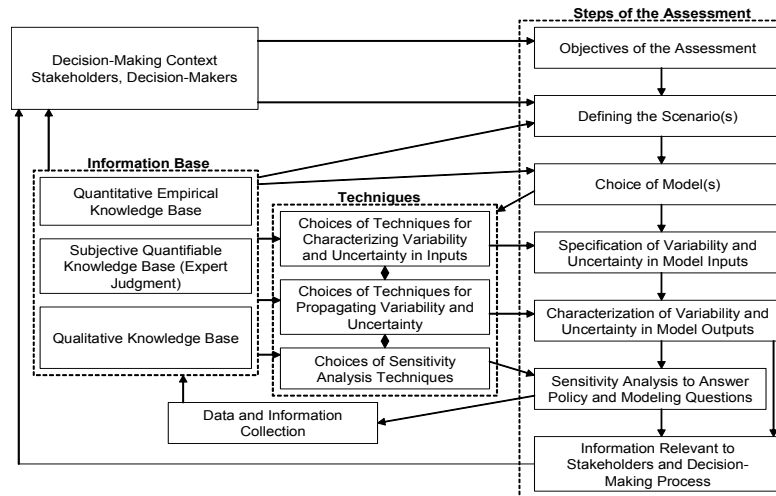
Gentry et al. 2002. Toxicol Sci 70:120.

Hattis' Caveat

- tend to overstate real variability by including measurement errors
 - and it is only the real variability that affects the spread of individual risks.

- tend to understate uncertainty by excluding unsuspected systematic errors that affect all data points in common (including unrepresentativeness of population samples).

Framework



Using PRA in Decision-Making

- Uncertainty and Variability play differently in how they affect public health policy decisions
 - Uncertainty affects population risks, and consequently trade-offs with other considerations
 - Variability affects equity
- Partial probabilistic analyses (of some contributors but not others) can aid in understanding problems, and will serve some policy questions but not others (so be clear about scope)
- Nonetheless, sound decisions require acknowledging and appropriately treating uncertainty in the supporting analyses