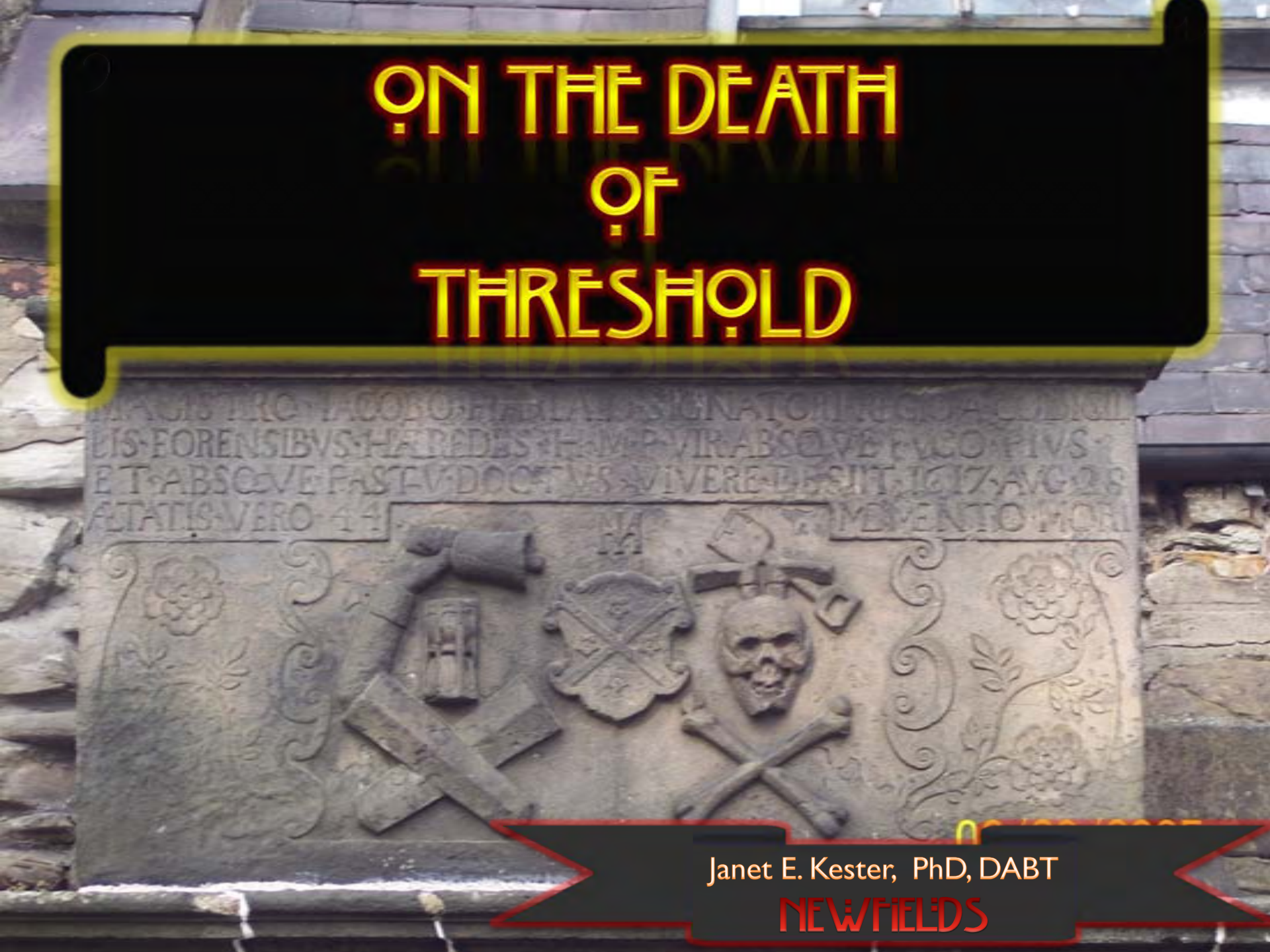
On the Death of Threshold



Janet E. Kester, PhD, DABT

NEWFIELDS

Historical Development of Health Risk Assessment

- **Risk assessment arose from the needs of policymakers to:**
  - Interpret environmental data
  - Estimate potential health risks,
  - Provide a scientific rationale for regulatory decisions
- **Risk assessment is a hybrid of science and policy**

Elements of Risk Assessment and Risk Management in the 'Red Book' (NRC 1983)

RESEARCH

Laboratory and field observations of adverse health effects and exposures to particular agents

Information on extrapolation methods for high to low dose and animal to human

Field measurements, estimated exposures, characterization of populations

RISK ASSESSMENT

HAZARD IDENTIFICATION

(does the agent cause an adverse effect?)

DOSE-RESPONSE RELATIONSHIP

(what is the relationship between dose and incidence in humans?)

EXPOSURE ASSESSMENT

(what exposures are currently experienced or anticipated under different conditions?)

RISK CHARACTERIZATION

RISK MANAGEMENT

Development of regulatory options

Evaluation of public health, economic, social, political consequences of regulatory options

Agency decisions and actions

Historical Development of Health Risk Assessment

- **In the beginning, there was Paracelsus' doctrine: "the dose makes the poison"**
- **1940s - 1960s - standards for occupational exposure and pesticide residues in food set according to threshold concept**
  - "Allowable daily intake" (ADI) for non-carcinogenic chemicals
  - Carcinogenic chemicals banned or regulated according to technical/economic feasibility

Historical Development of Health Risk Assessment

- **Beginning in the 1970s, this approach to carcinogens became less satisfactory, because**
  - Many post-WWII chemicals were found to be high-dose animal carcinogens
  - Improved analytical methods enabled detection of lower and lower quantities in environmental media, including biological tissue
  - Analogy to radiation: low-dose linear, non-threshold (LNT) model extended to chemical carcinogenesis

Of the three "pillars" of risk assessment…hazard identification, exposure assessment, and dose-response assessment – the latter is by far the most difficult.

Crump, K.C. (2003). Quantitative risk assessment since the Red Book: Where have we come and where should we be going? *Hum Ecol Risk Assess* 9:1105-1112.

Magnitude of Uncertainty

- Parameter uncertainty in exposure assessment is typically 5- to 100-fold
- Uncertainty in non-cancer toxicity criteria is typically 100- to 3,000-fold
- Much more uncertainty in cancer risk assessment if chemical is incorrectly considered to be a human carcinogen

Input Parameters For CalTOX Multimedia Model

Compound name	Name
Chemical abstract number	CAS
Molecular weight (g/mol)	MW
Octanol-water partition coefficient	Kow
Melting point (K)	Tm
Vapor pressure (Pa)	VP
Solubility (mol/m³)	S
Henry's law constant (Pa-m³/mol)	H-
Diffusion coefficient in pure air (m²/d)	Dair
Diffusion coefficient in pure water (m²/d)	Dwater
Organic carbon partition coefficient	Koc -
Distribution coefficient, ground and root soil (L/kg)	Kd_s-
Distribution coefficient in vadose-zone soil (L/kg)	Kd_v -
Distribution coefficient in ground-water zone (L/kg)	Kd_q -
Distribution coefficient in sediment particles (L/kg)	Kd_d -
Partition coefficient in plant relative to soil concentration [kg(pFM)/kg(sFM)]	Kps -
Biotransfer factor in plants relative to contaminant air concentration (m³[a]/kg[pFM])	Kpa -
Biotransfer factor in milk relative to cattle-diet contaminant intake (d/L)	Bk -
Biotransfer factor in meat relative to cattle-diet contaminant intake (d/kg)	Bt -
Biotransfer factor in eggs relative to hen-diet contaminant intake (d/kg)	Be -
Biotransfer in breast milk relative to contaminant intake by the mother (d/kg)	Bbmk -
Bioconcentration factor in fish relative to comtaminant water concentration	BCF -
Skin permeability coefficient (cm/h)	Kp_w -
Skin-water/soil partition coefficient (L/kg)	Km -
Reaction half-life in air (d)	Thalf_a
Reaction half-life in ground-surface soil (d)	Thalf_g
Reaction half-life in root-zone soil (d)	Thalf_s
Reaction half-life in the vadose-zone soil (d)	Thalf_v
Reaction half-life in groundwater zone soil (d)	Thalf_q
Reaction half-life in surface water	Thalf_w
Reaction half-life in the sediment zone (d)	Thalf_d

Table IB: Exposure Factors

Exposure factors
Body weight (kg)
Surface area (m²/kg)
Active breathing rate (m³/kg-h)
Resting breathing rate (m³/kg-h)
Fluid intake (L/kg-d)
Fruit and vegetable intake (kg/kg-d)
Grain intake (kg/kg-d)
Milk intake (kg/kg-d)
Meat intake (kg/kg-d)
Egg intake (kg/kg-d)
Fish intake (kg/kg-d)
Soil ingestion (kg/kg-d)
Breast milk ingestion by infants (kg/kg-d)
Inhalation by cattle (m³/d)
Inhalation by hens (m³/d)
Ingestion by pasture by dairy cattle (kg[FM]/d)
Ingestion of pasture by beef cattle (kg[FM]/d)
Ingestion of pasture by hens (kg[FM]/d)
Ingestion of water by dairy cattle (L/d)
Ingestion of water by beef cattle (L/d)
Ingestion of water by hens (L/d)
Ingestion of soil by cattle (kg/d)
Ingestion of soil by hens (kg/d)
Fraction of water needs provided by ground water
Fraction of water needs provided by surface water
Fraction of water contaminants transferred to soil by irrigati
Fraction of fruits and vegetables that are exposed produce
Fraction of fruits and vegetables local
Fraction of grains local
Fraction of milk local
Fraction of meat local
Fraction of eggs local
Fraction of fish local
Plant-air partition factor for particles, m³/kg[FM]
Rainsplash rate constant [(mg/kg[plnt FM])/(mg/kg[soil])]
Water use in the shower (L/min)
Water use in the house (L/h)
Room ventilation rate, bathroom (m³/min)
Room ventilation rate, house (m³/h)
Exposure time, in shower or bath (h/day)
Exposure time, active indoors (h/day)
Exposure time, outdoors at home (h/day)
Exposure time, indoors resting (h/day)
Indoor dust load (kg/m³)
Exposure frequency to soil on skin, (d/y)
Soil adherence to skin (mg/cm²)
Ratio of indoor gas conc. to soil gas conc.
Exposure time swimming (h/d)
Exposure frequency, swimming (d/y)
Water ingestion while swimming (L/kg-h)
Exposure duration (years)
Averaging time (days)
AT

Table IC: Landscape Data

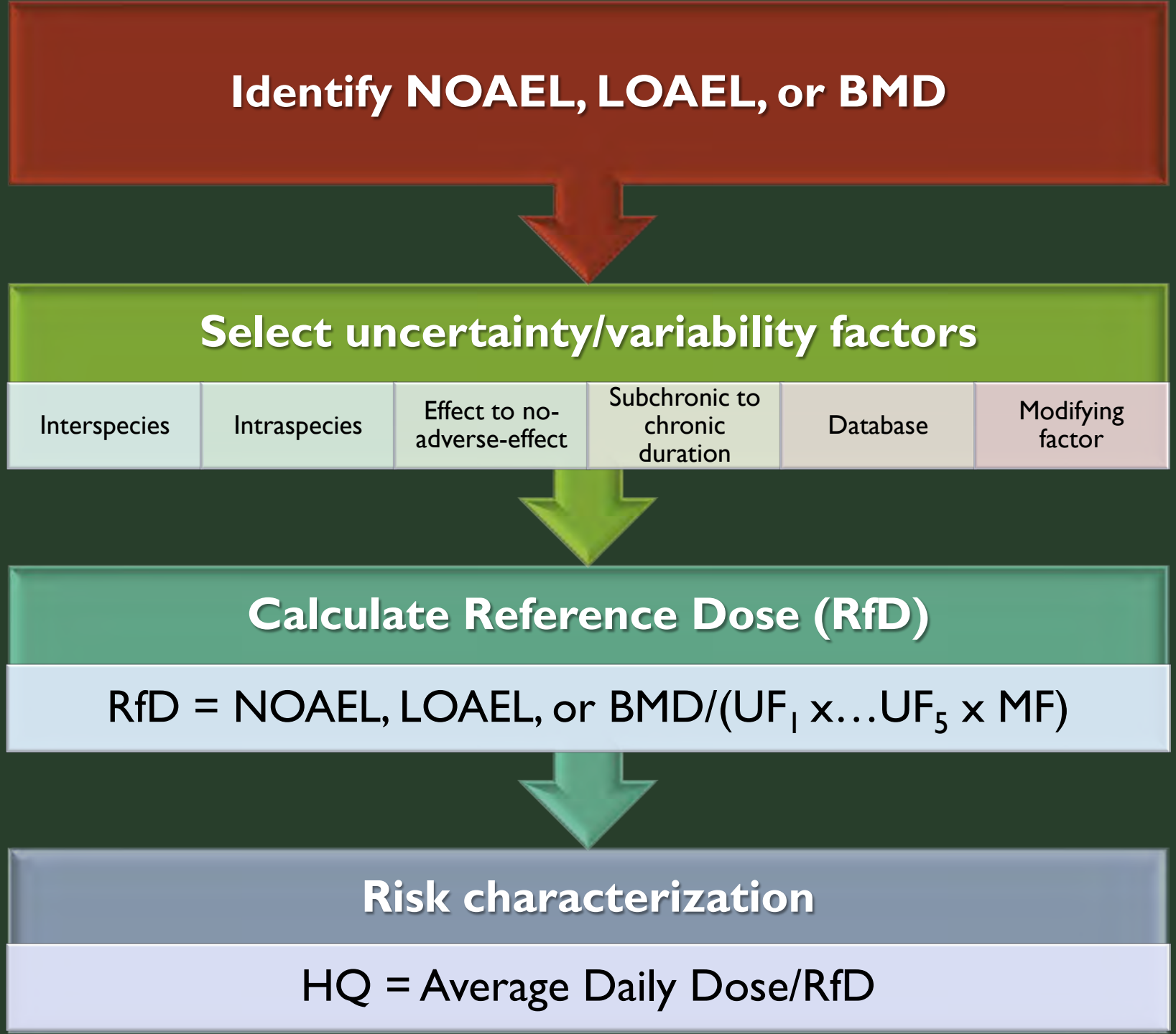
Landscape properties	
Contaminated area in m²	Area
Annual average precipitation (m/d)	rain
Flux; surface water into landscape (m/d)	inflow
Land surface runoff (m/d)	runoff
Atmospheric dust load (kg/m³)	rhob_a
Deposition velocity of air particles (m/d)	v_d
Plant dry mass inventory (kg[DM]/m²)	bio_inv
Plant dry-mass fraction	bio_dm
Plant fresh-mass density kg/m³	rho_p
Ground-water recharge (m/d)	recharge
Evaporation of water from surface water (m/d)	evaporate
Thickness of the ground soil layer (m)	d_g
Soil particle density (kg/m³)	rhos_s
Water content in surface soil (volume fraction)	beta_g
Air content in the surface soil (volume fraction)	alpha_g
Erosion of surface soil (kg/m²-d)	erosion_g
Thickness of the root-zone soil (m)	d_s
Water content of root-zone soil (volume fraction)	beta_s
Air content of root-zone soil (volume fraction)	alpha_s
Thickness of the vadose-zone soil (m)	d_v
Water content; vadose-zone soil (volume fraction)	beta_v
Air content of vadose-zone soil (volume fraction)	alpha_v
Thickness of the aquifer layer (m)	d_q
Solid material density in aquifer (kg/m³)	rhos_q
Porosity of the aquifer zone	beta_q
Fraction of land area in surface water	f_arw
Average depth of surface waters (m)	d_w
Suspended sediment in surface water (kg/m³)	rhob_w
Suspended sediment deposition (kg/m²/d)	deposit
Thickness of the sediment layer (m)	d_d
Solid material density in sediment (kg/m³)	rhos_d
Porosity of the sediment zone	beta_d
Sediment burial rate (m/d)	bury_d
Ambient environmental temperature (K)	Temp
Surface water current in m/d	current_w
Organic carbon fraction in upper soil zone	foc_s
Organic carbon fraction in vadose zone	foc_v
Organic carbon fraction in aquifer zone	foc_q
Organic carbon fraction in sediments	foc_d
Boundary layer thickness in air above soil (m)	del_ag
Yearly average wind speed (m/d)	v_w

(The only) Input Parameters for Toxicity Assessment

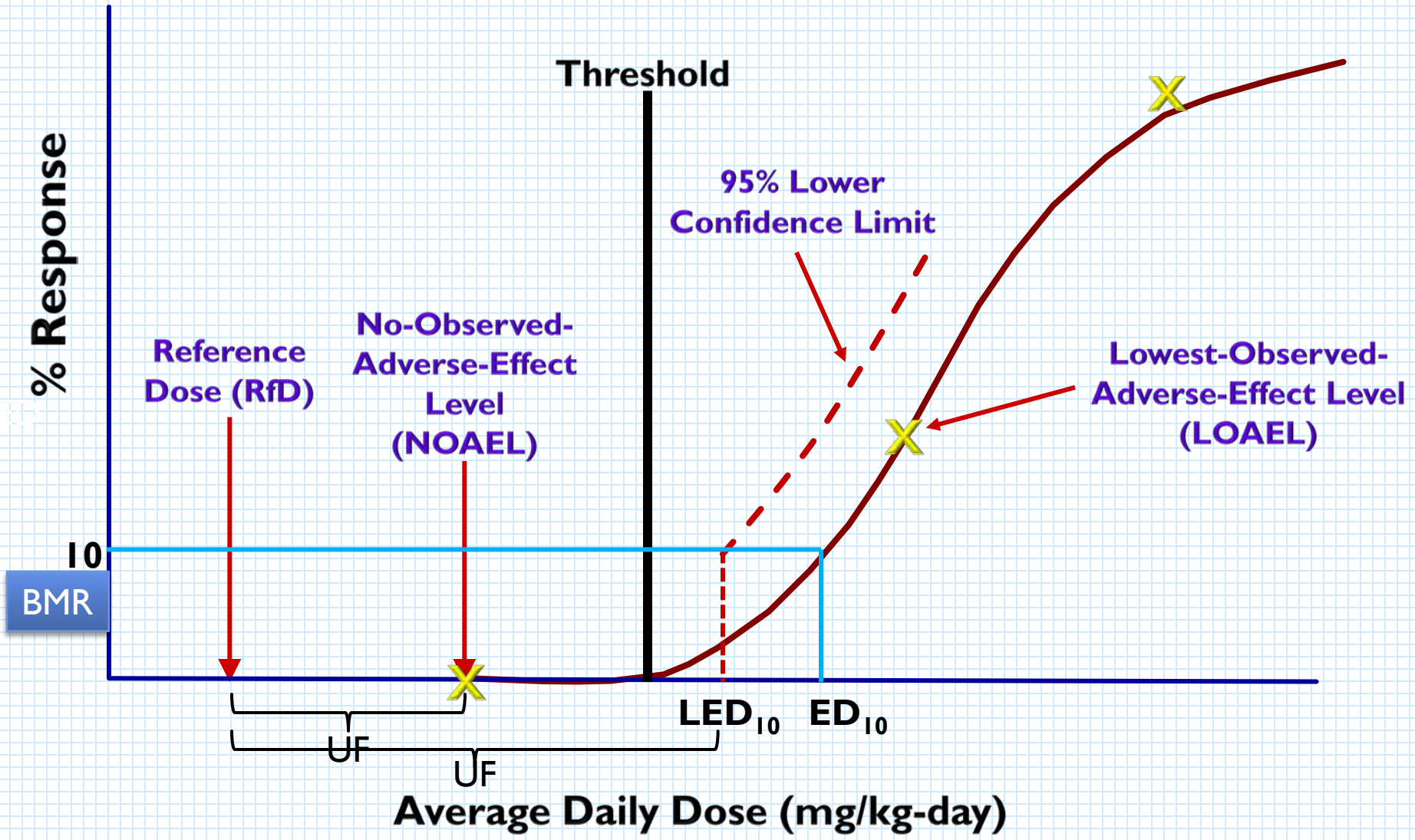
- **Non-cancer effects (threshold)**
  - Reference Dose/Tolerable Daily Intake (mg/kg-day)
  - Reference/Tolerable Concentration ($\mu g/m^3$)
- **Cancer effects**
  - Non-Threshold
    - Slope factor $(mg/kg\text{-}day)^{-1}$
    - Inhalation unit risk $(\mu g/m^3)^{-1}$
  - Threshold for non-genotoxic chemicals (not historically in U.S.)

Toxicity Assessment

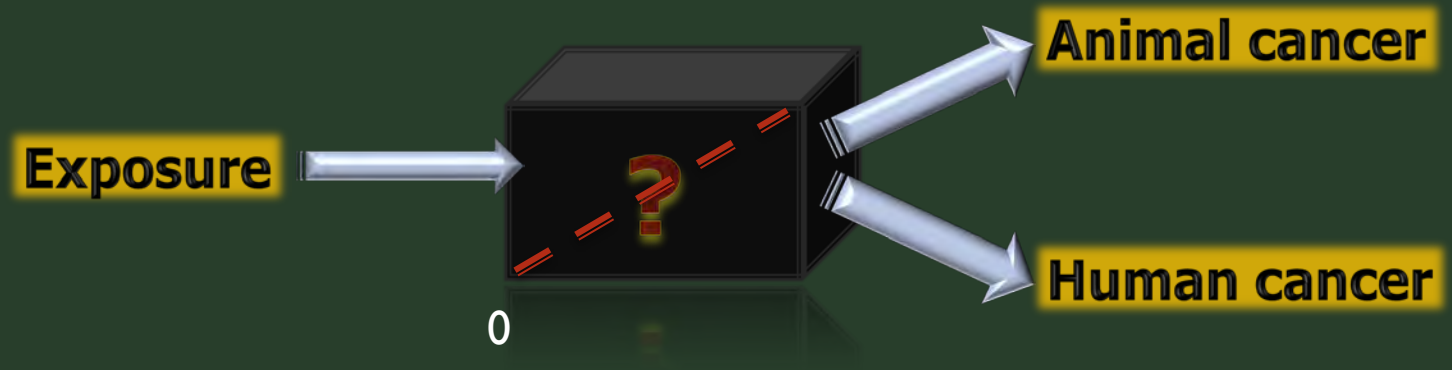
Health Endpoint	Toxicity Criterion	Definition
Non-Cancer	Reference dose (RfD) (mg/kg-day) Reference concentration (RfC) ($\mu g/m^3$)	An estimate of an exposure, designated by duration and route, to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime
Cancer	Slope factor ($[mg/kg\text{-}day]^{-1}$) Unit risk $[\mu g/m^3]^{-1}$ or $[\mu g/L]^{-1}$)	A plausible upper-bound estimate (95% upper confidence limit) of the probability of an individual developing cancer per unit intake of a potential carcinogen


Identify NOAEL, LOAEL, or BMD
Select uncertainty/variability factors
Interspecies
Intraspecies
Effect to no-adverse-effect
Subchronic to chronic duration
Database
Modifying factor
Calculate Reference Dose (RfD)
RfD = NOAEL, LOAEL, or BMD/(UF1 x…UF5 x MF)
Risk characterization
HQ = Average Daily Dose/RfD

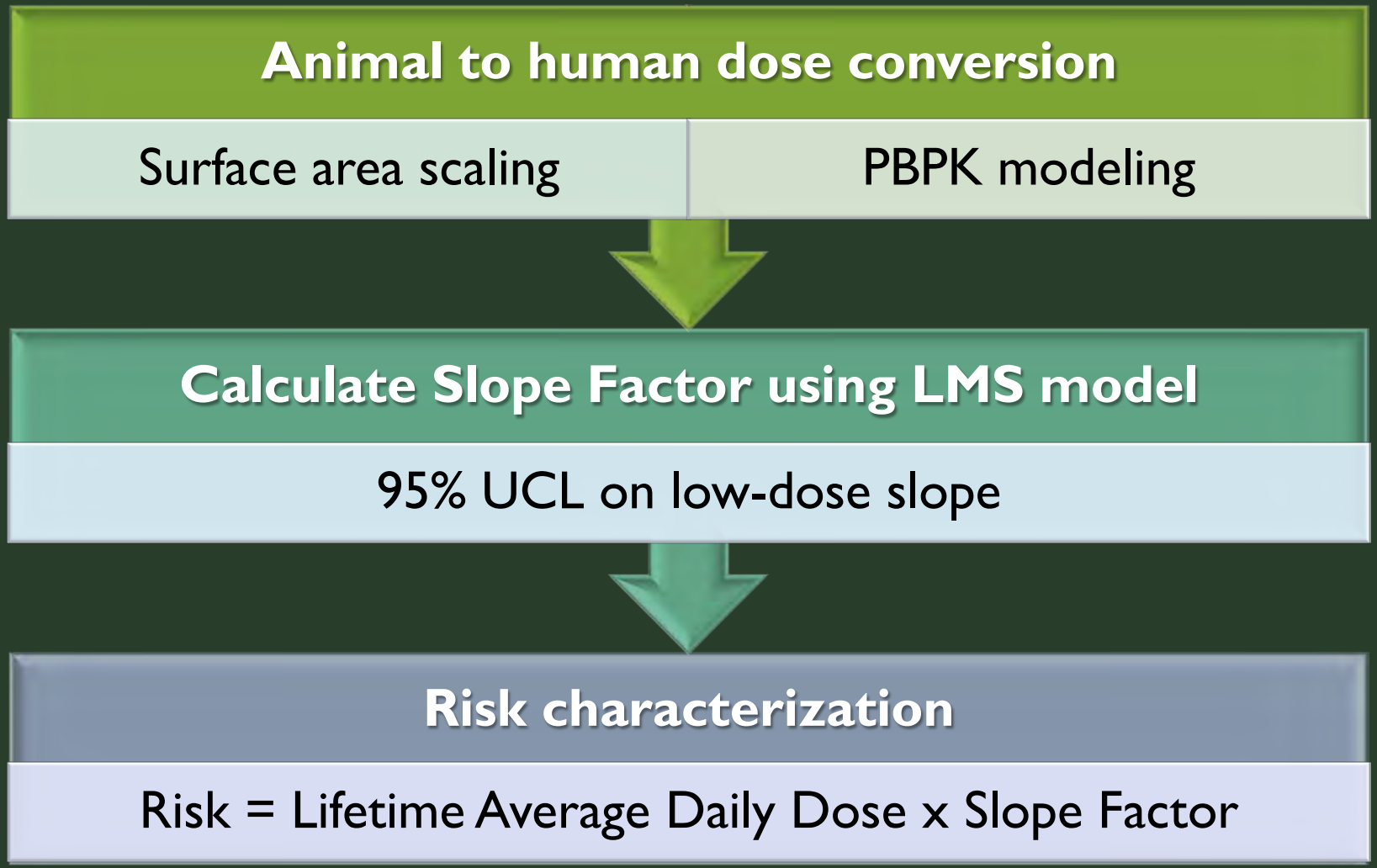
Generic Dose-Response Curve for Non-Carcinogenic Effects



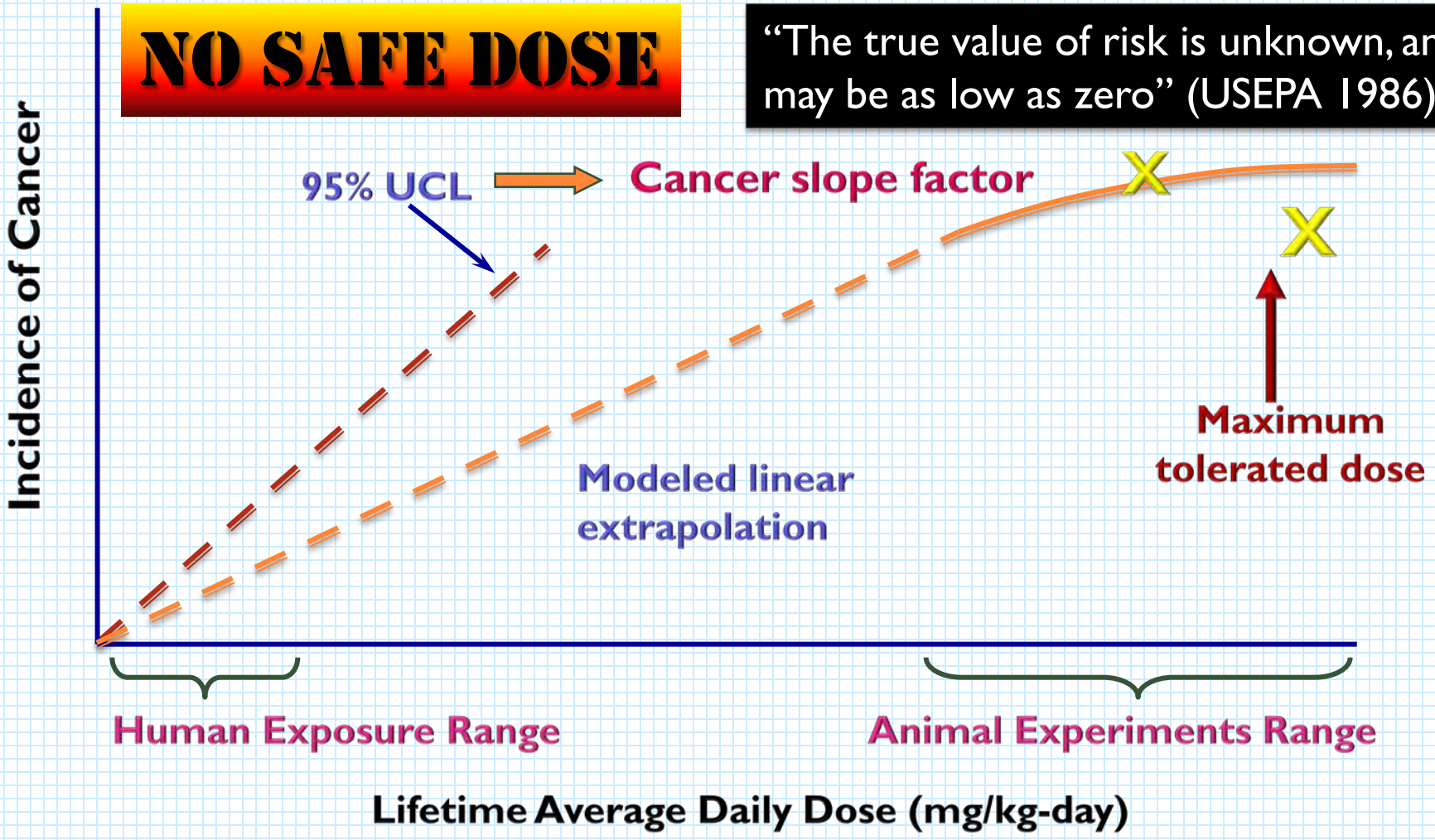
Assumptions in 1986 EPA Guidelines for Carcinogen Risk Assessment



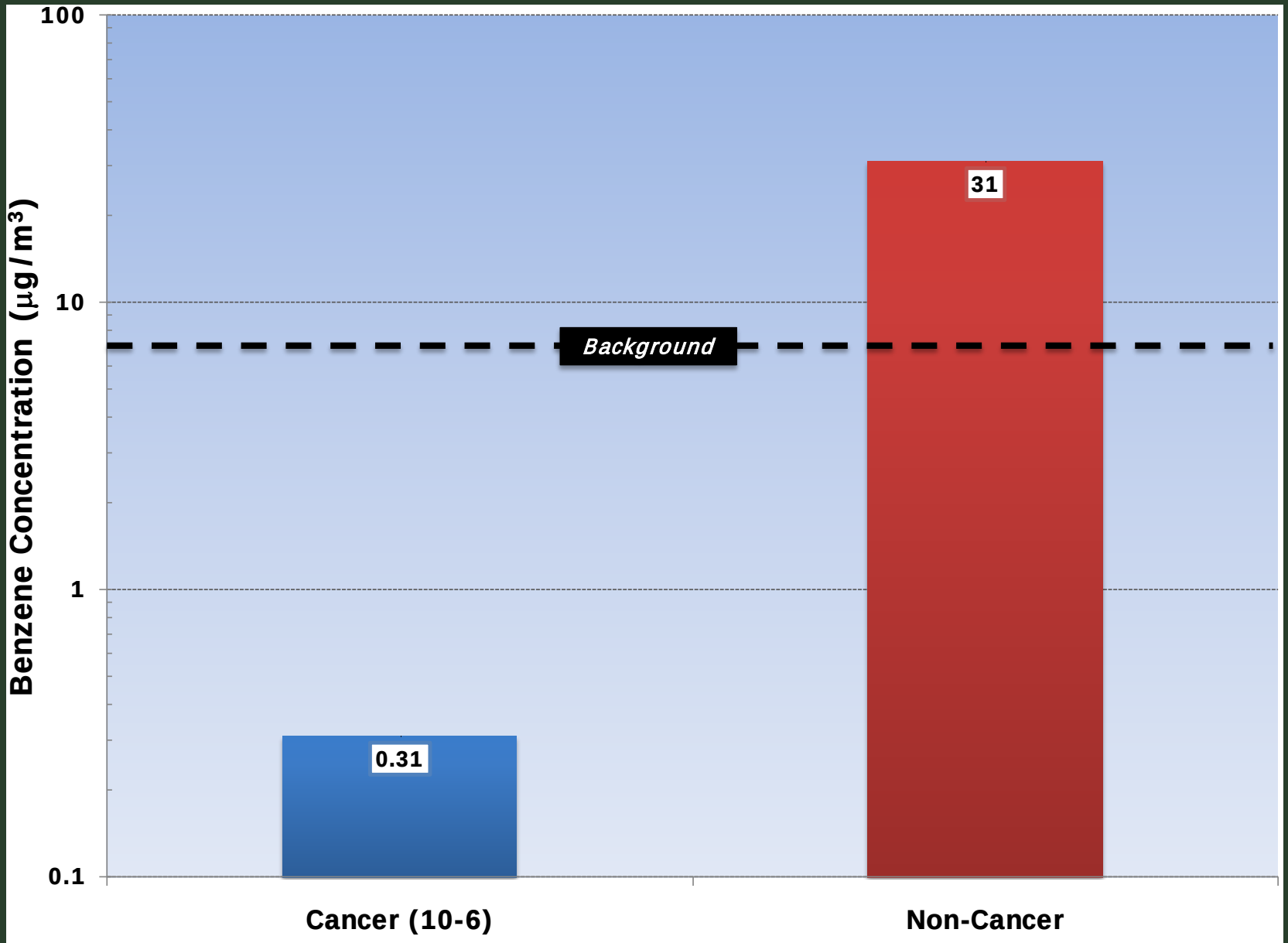
- High-dose animal carcinogens are low-dose human carcinogens
- Policy: No threshold for carcinogenic effects


Animal to human dose conversion
Surface area scaling
PBPK modeling
Calculate Slope Factor using LMS model
95% UCL on low-dose slope
Risk characterization
Risk = Lifetime Average Daily Dose x Slope Factor

Generic Cancer Dose-Response Curve



Benzene Toxicity Criteria vs. Ambient Background



Harmonization

- The practice of developing quantitative estimates of low-dose risks for cancer (despite their uncertainty) but not for non-carcinogenic toxicity…has led to an overemphasis of carcinogenic risks relative to other health risks.
- My vision of a truly harmonized approach is one in which all health effects would be treated in somewhat the same manner as non-carcinogens are presently treated.

Crump, K.C. (2003). Quantitative risk assessment since the Red Book: Where have we come and where should we be going? Hum Ecol Risk Assess 9:1105-1112.

Evolution of EPA Carcinogen Risk Assessment Guidance

1986 – *Guidelines for Carcinogen Risk Assessment*

1996 – *Proposed Guidelines for Carcinogen Risk Assessment*

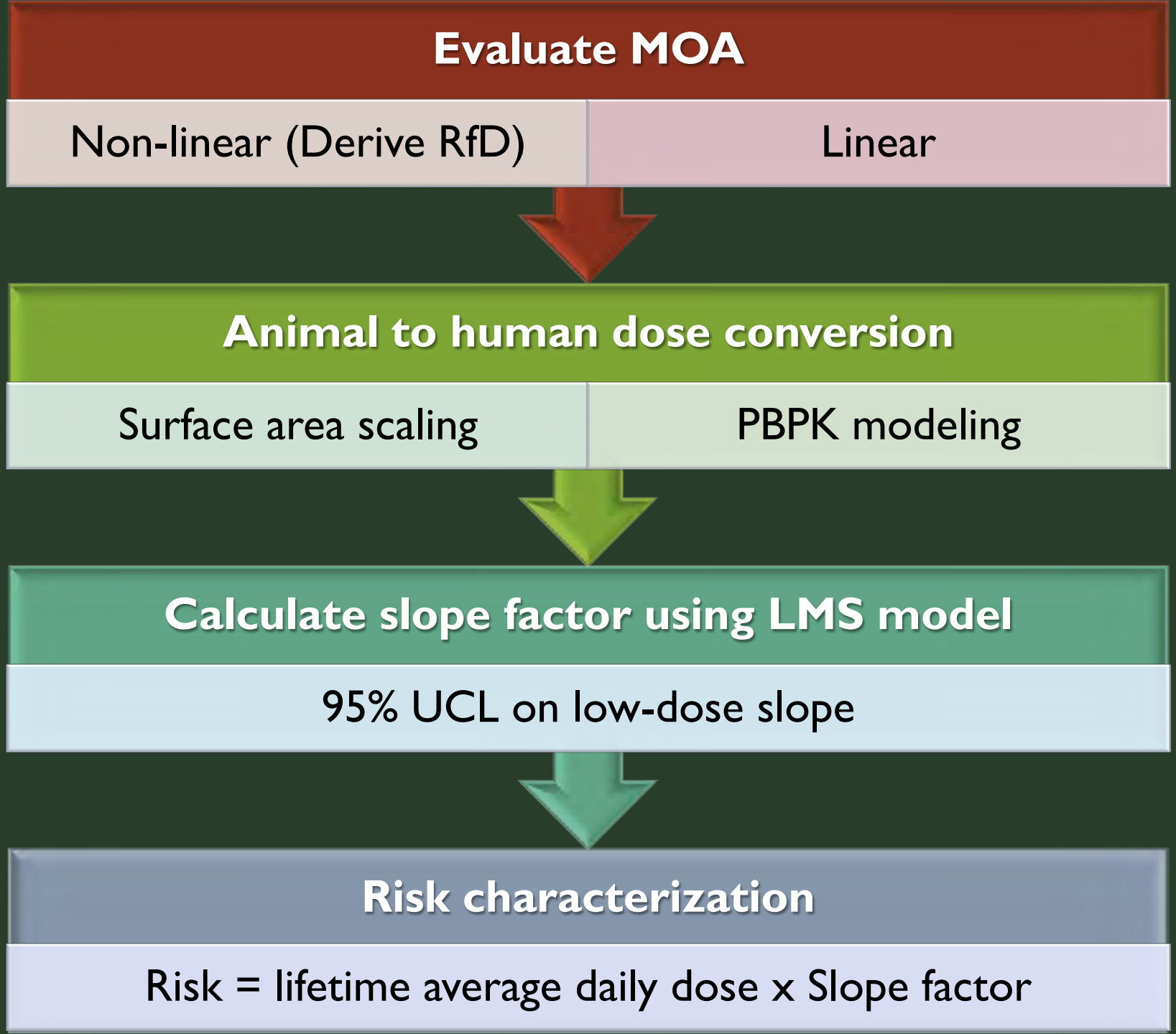
1999 – *Guidelines for Carcinogen Risk Assessment* (Review Draft)

2003 – *Guidelines for Carcinogen Risk Assessment* (Draft Final)

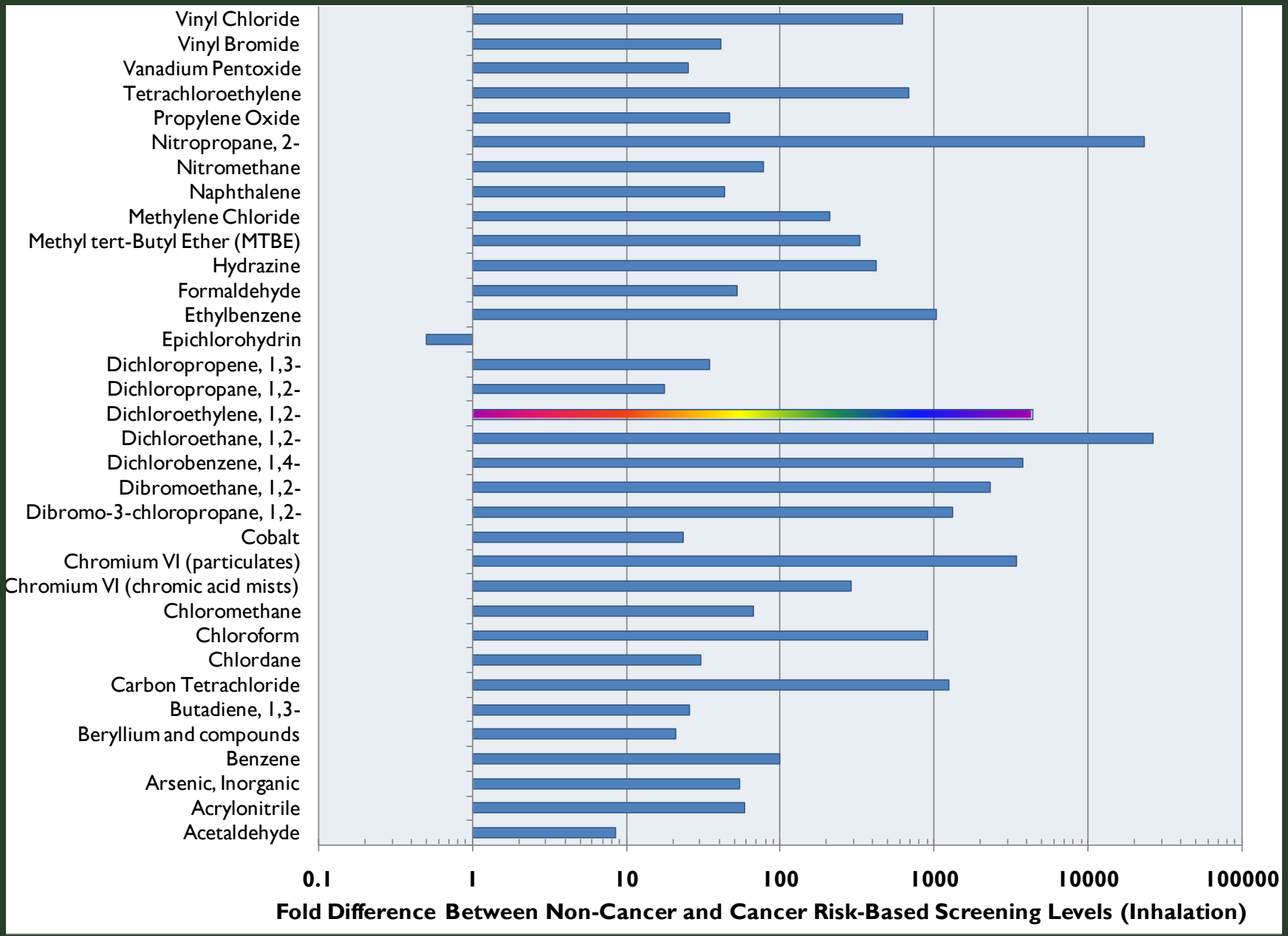
2005 – *Guidelines for Carcinogen Risk Assessment*

Major Changes in 2005 EPA *Guidelines for Carcinogen Risk Assessment*

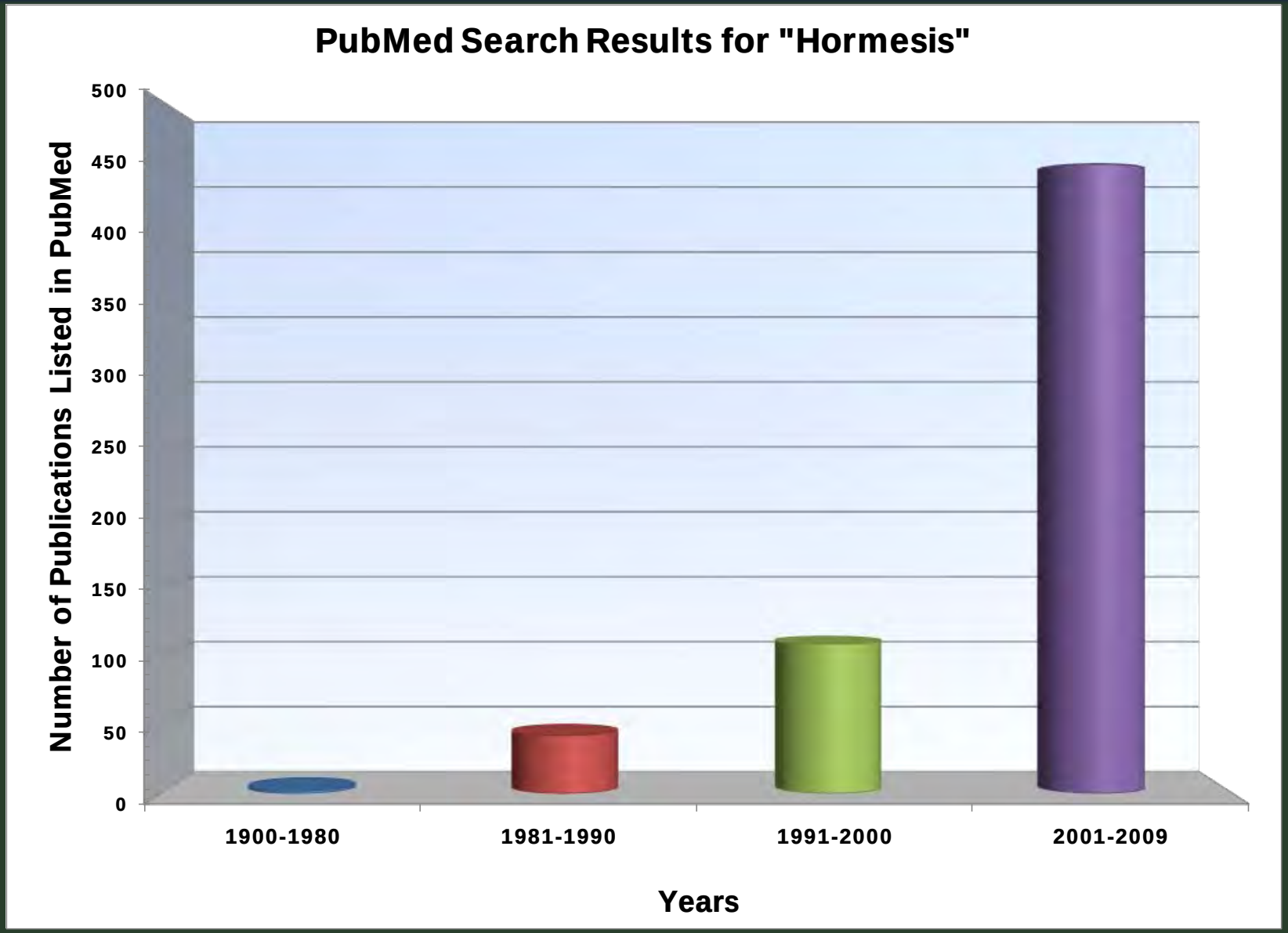
- **Policy-based defaults replaced by focus on mode of action (MOA)**
  - "…[A] sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation"
  - Human relevance of animal tumor responses
  - Human variability
  - Shape of dose-response curve
- **Multiple low-dose extrapolation methods based on MOA/human relevance instead of default linear non-threshold model**


Evaluate MOA
Non-linear (Derive RfD)
Linear
Animal to human dose conversion
Surface area scaling
PBPK modeling
Calculate slope factor using LMS model
95% UCL on low-dose slope
Risk characterization
Risk = lifetime average daily dose x Slope factor

Cancer vs. Non-Cancer Toxicity Values

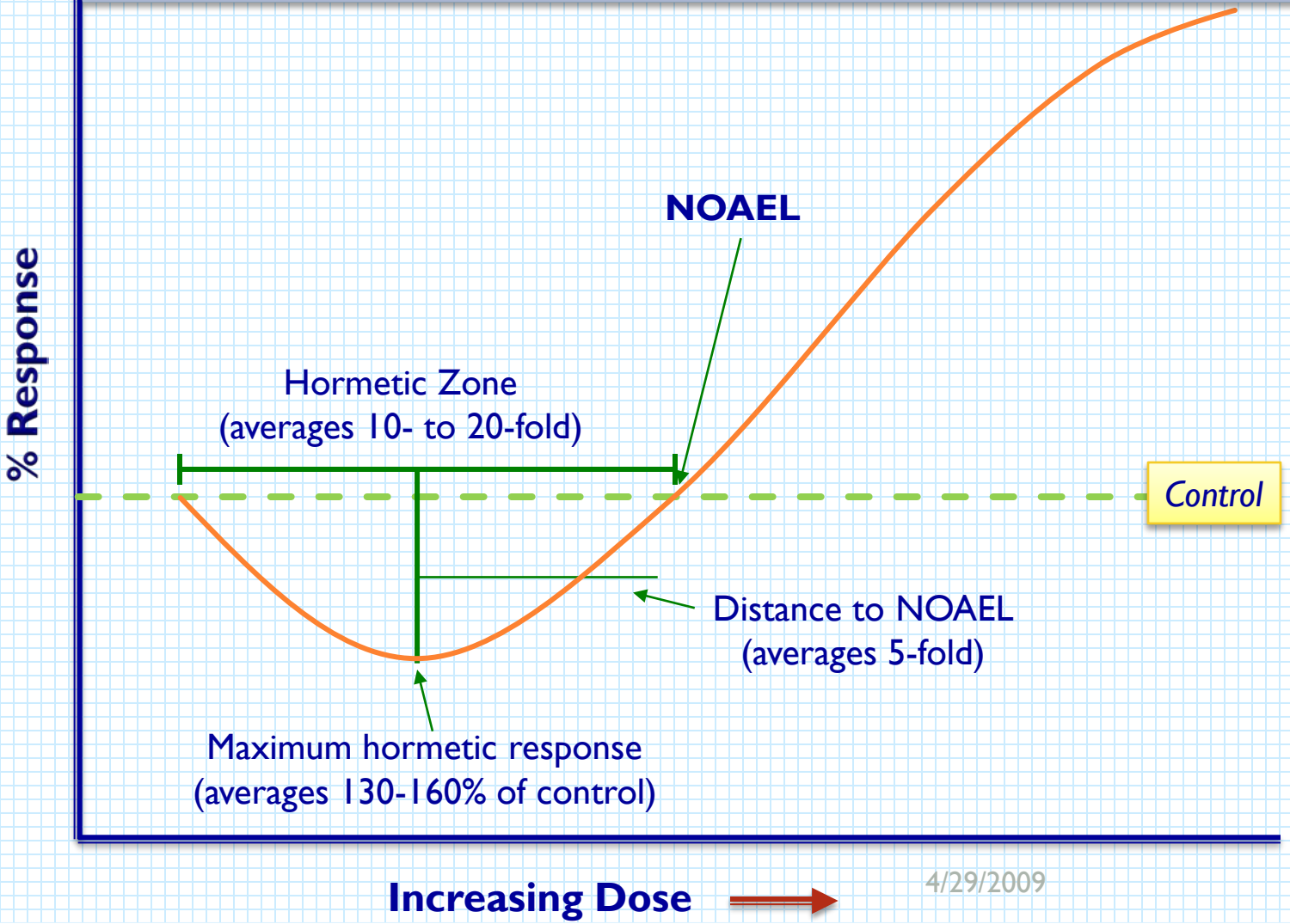


Hormesis in the Scientific Literature



Hormetic Dose-Response Curve

Adapted from Calabrese, E. (2009) Hormesis: What it Means for Toxicology, the Environment, and Public Health (PowerPoint presentation)



Recent Developments

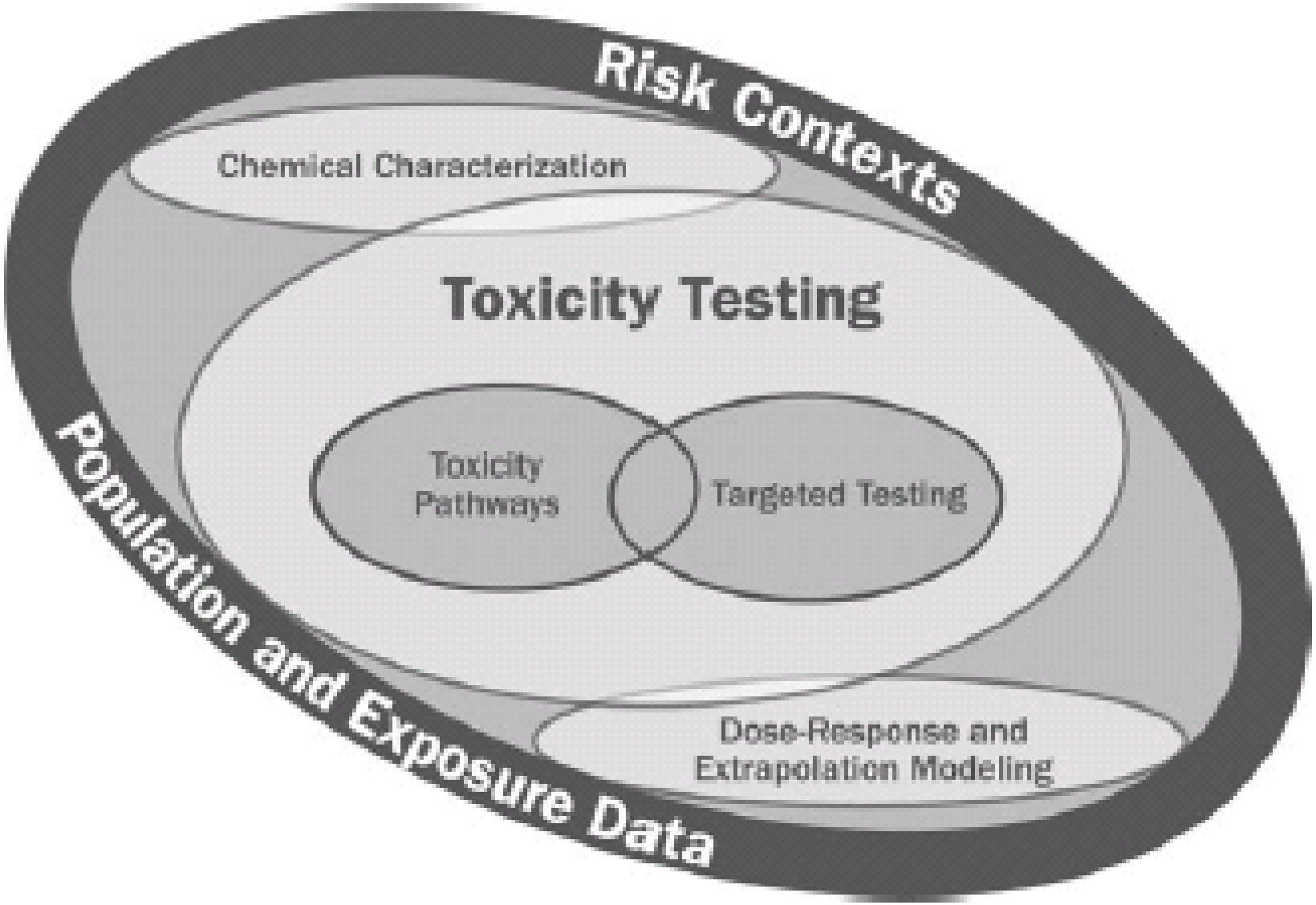
Toxicity Testing in the 21st Century: A Vision and a Strategy

2007

National Research Council
Committee on Toxicity Testing and Assessment of Environmental Agents
Board on Environmental Studies and Toxicology

"A revolution is taking place in biology. At its center is the progress being made in the elucidation of cellular-response networks…composed of complex biochemical interactions of genes, proteins, and small molecules that maintain normal cellular function, control communication between cells, and allow cells to adapt to changes in their environment."

Components of Toxicity Testing Framework



Major Elements of Toxicity Testing Framework

- *In silico* methods for physicochemical property estimation
- Responses of specific toxicity pathways in human cells or tissues quantified with robotic-assisted medium- and high-througput cellular assays
- Toxicity pathway testing complemented as necessary by targeted *in vitro* or *in vivo* studies
- Dose-response modeling based on empirical or mechanistic computational systems biology models of key toxicity pathway perturbations
- PBPK modeling to link *in vitro* with *in vivo* concentrations

Science And Decisions: Advancing Risk Assessment

2008

National Research Council
Committee on Improving Risk Analysis Approaches Used by EPA
Board on Environmental Studies and Toxicology

Chapter 5: "Toward a Unified Approach to Dose-Response Assessment"

- Separation of cancer and noncancer outcomes in dose-response analysis is artificial because **noncancer end points can occur without a threshold or low-dose nonlinearity** on the population level and in some cases on the individual level.
- . . .RfDs. . .do not provide a basis for formally quantifying the magnitude of harm at various exposure levels. Therefore, the Committee finds the 2005 *Guidelines for Carcinogen Risk Assessment* toward RfDs and away from an expression of risk posed by nonlinear carcinogens problematic.

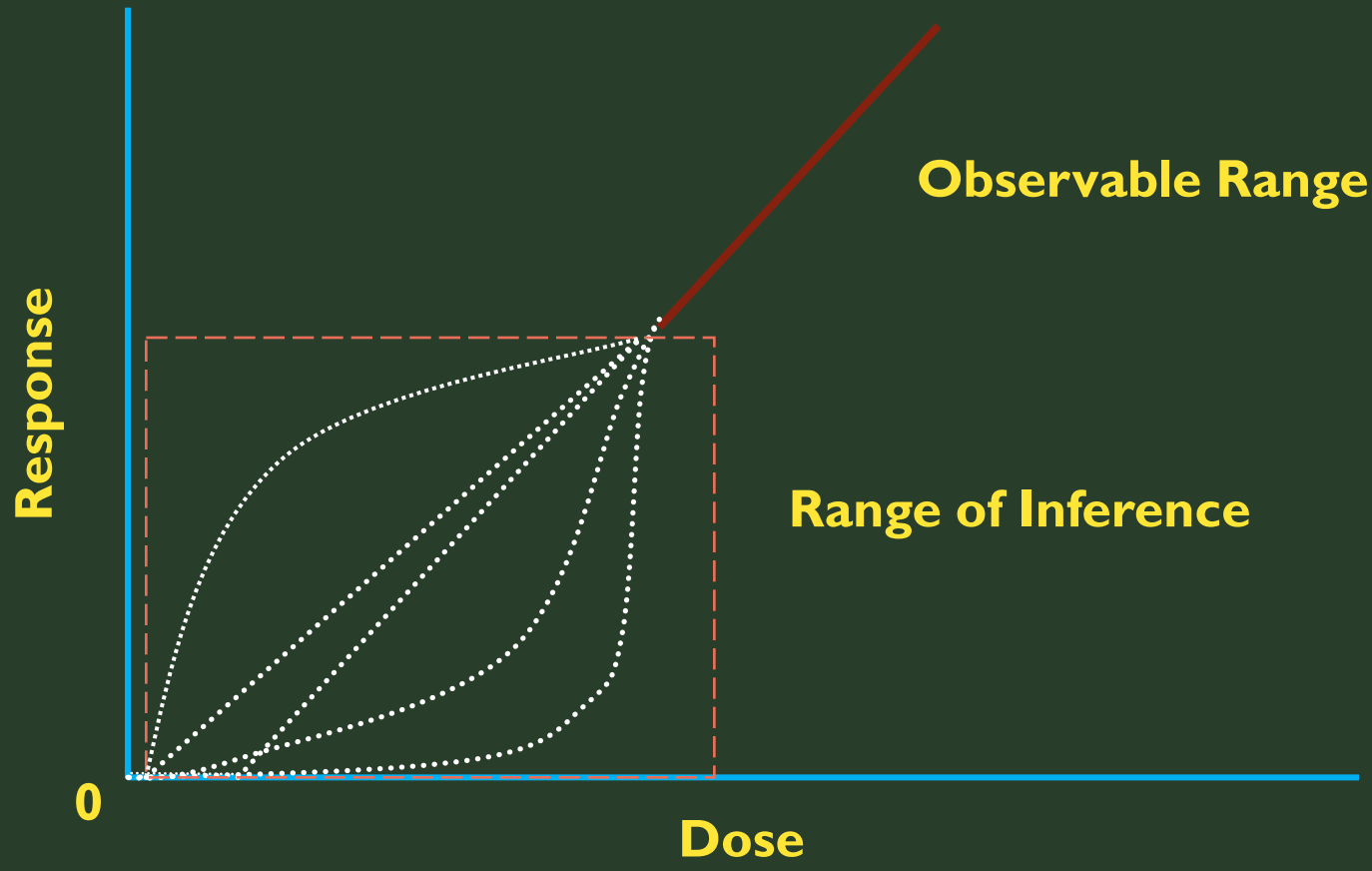
White *et al.* (2009)*

- Almost all workshop participants preferred **a linear, no-threshold approach** to low-dose extrapolation, combined with modeled estimates of the low range of the observed **data…for both cancer and noncancer outcomes**.
- A small minority of participants expressed some reservation regarding selection of a linear nonthreshold dose-response function as the default model assumption for cancer and noncancer outcomes **given information on human biologic processes such as reversibility and repair**.

*State of the Science Workshop Report: Issues and Approaches in Low Dose-Response Extrapolation for Environmental Health Risk Assessment. *Environ Health Perspect* **117**:283-287.

The Universe of Dose-Response Curves?

Slide from 1/14/09 SOT RASS telecon to discuss conclusions of "State of the Science Workshop: Low Dose-Response Extrapolation for Environmental Health Risk Assessment"



Rationale

- Risk managers require probabilistic risk estimates for cost-benefit analysis
- Chemical exposures are additive to background processes and exposures that produce disease, therefore any exposure must exceed threshold
- Individuals may have response thresholds, but human heterogeneity in susceptibility means no threshold in population

Evidence

- Observed linearity of noncancer effects on populations in ecological epidemiological studies of criteria pollutants (particulate matter, ozone)
- Lack of apparent threshold for IQ loss and neurobehavioral deficits associated with lead and methylmercury

Conceptual Models

Conceptual Model 1	Conceptual Model 2	Conceptual Model 3
• Individual: threshold • Population: linear • Background: additive	• Individual: threshold • Population: threshold • Background: independent	• Individual: linear • Population: linear • Background: irrelevant (?)

- **"The committee recommends that cancer and noncancer responses be assumed to be linear as a default."**

Impressions

- Decades of scientific advances have led to increased understanding of biological mechanisms of chemical action and their central importance in dose-response.
- Decades of international efforts to harmonize non-cancer and cancer chemical risk assessment methods have led to reduced dependence on default linear non-threshold in favor of biologically based dose-response models for both carcinogenic and non-carcinogenic effects.

Impressions

- The phenomenon of hormesis likely derives from activation of adaptive pathways involved in maintenance of homeostasis (inherent in the condition of life).
- It is therefore reasonable to suppose that any hormetic characteristics would be apparent in properly designed mechanistic studies such as those proposed in *Toxicity Testing in the 21st Century: A Vision and a Strategy*, and hence incorporated into dose-response modeling and risk assessment practice.

Impressions

- BUT…In *Advancing Risk Assessment*, an NRC committee appears to advocate linear non-threshold models as defaults not only for carcinogenesis, but also non-carcinogenic effects based on speculation that (1) background exposures and disease processes and (2) human variability in susceptibility effectively eliminate thresholds (never mind hormesis).
- The scientific merit of these recommendations (and their compatibility with other suggested improvements in dose-response assessment) must be carefully evaluated by the wider scientific community.

Linear Low-Dose Extrapolation – For Everything!
by Howlin' Harv Clewell

Well the epidemiologists are protecting me and you
By scaring us to death with dire threats of what them chemicals are gonna do.
I just read the NAS report and it shocked me to the core
In chapter 5 regarding thresholds, quoth the NAS: "Nevermore."

They think that evidence from epidemiology, and population variability,
Plus background additivity, all support low-dose linearity.
So just forget about mode of action, and dose dependent thresholds
Cause with all of the uncertainty, science has no risk assessment roles.

Linear low-dose extrapolation, can you get all the risk that you want?

Well I say keep your epidemiology, it's never done a thing for me.
And all your articles in EHP, the "National Enquirer" of toxicology.
I've had it up to here with linearity; I guess I've learned too much biology.
If that's all risk assessment has come to be,
then there'll have to be a different job for me.

Thanks!