Biomonitoring Equivalents as Screening Tools for Interpretation of Human Biomonitoring Data

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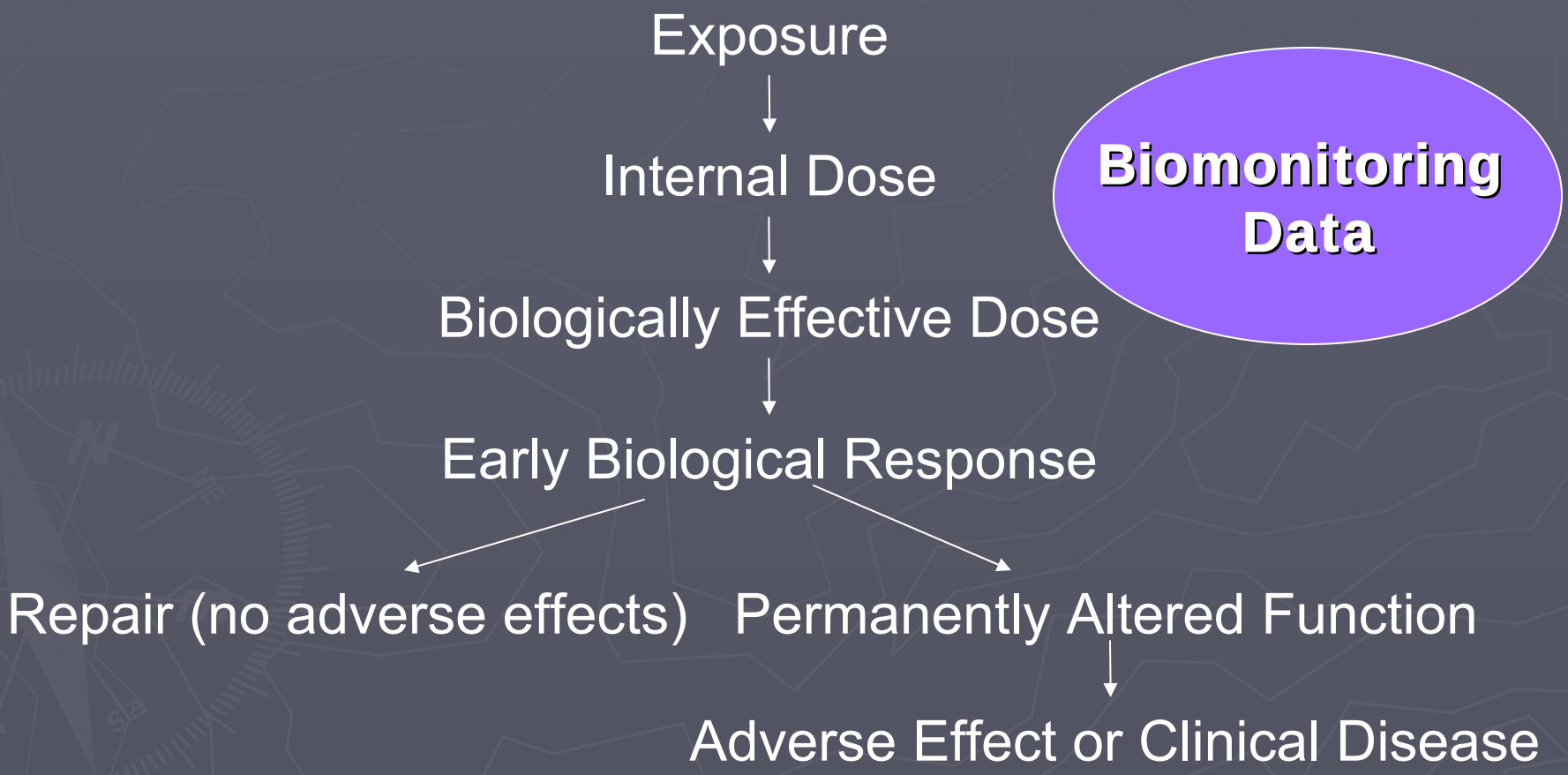
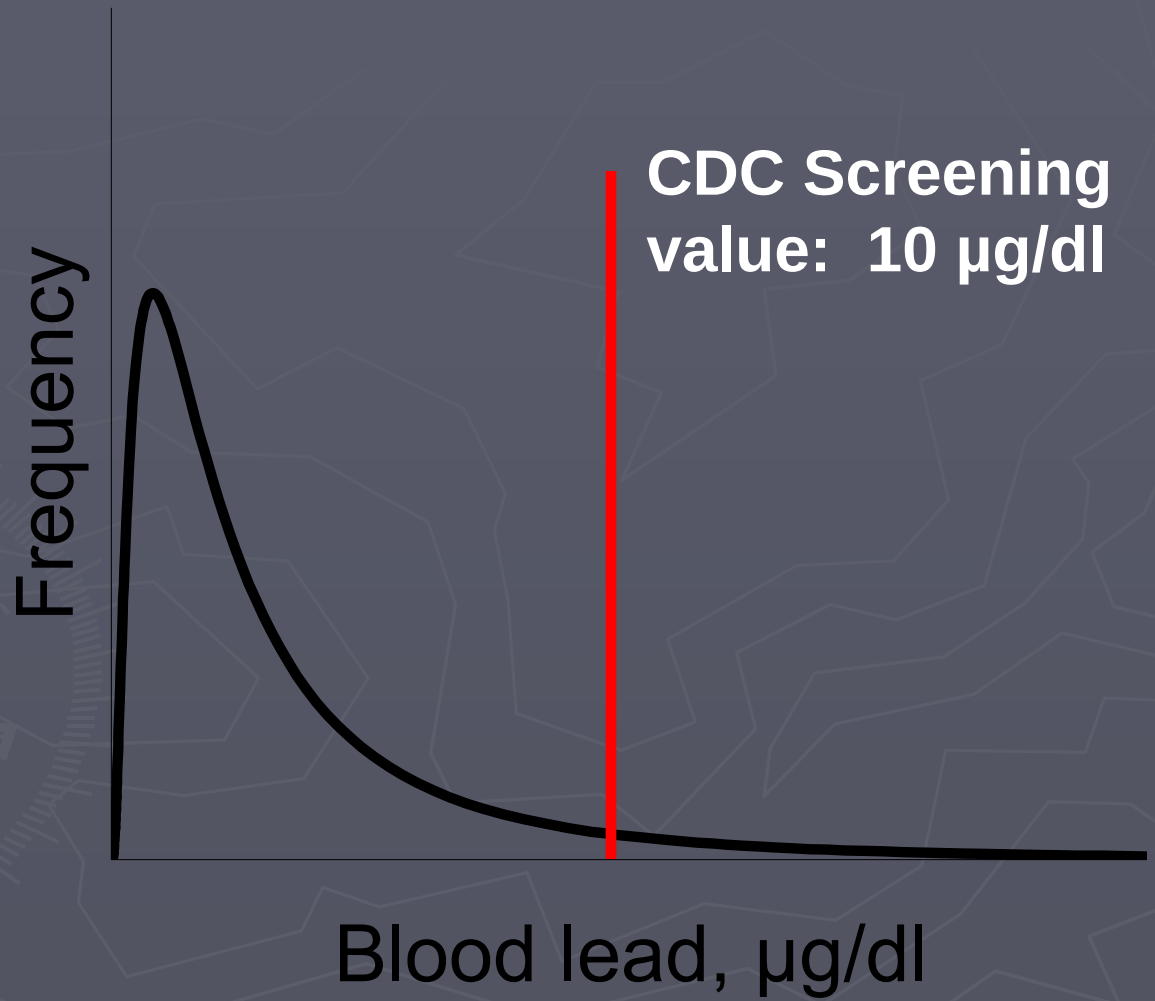
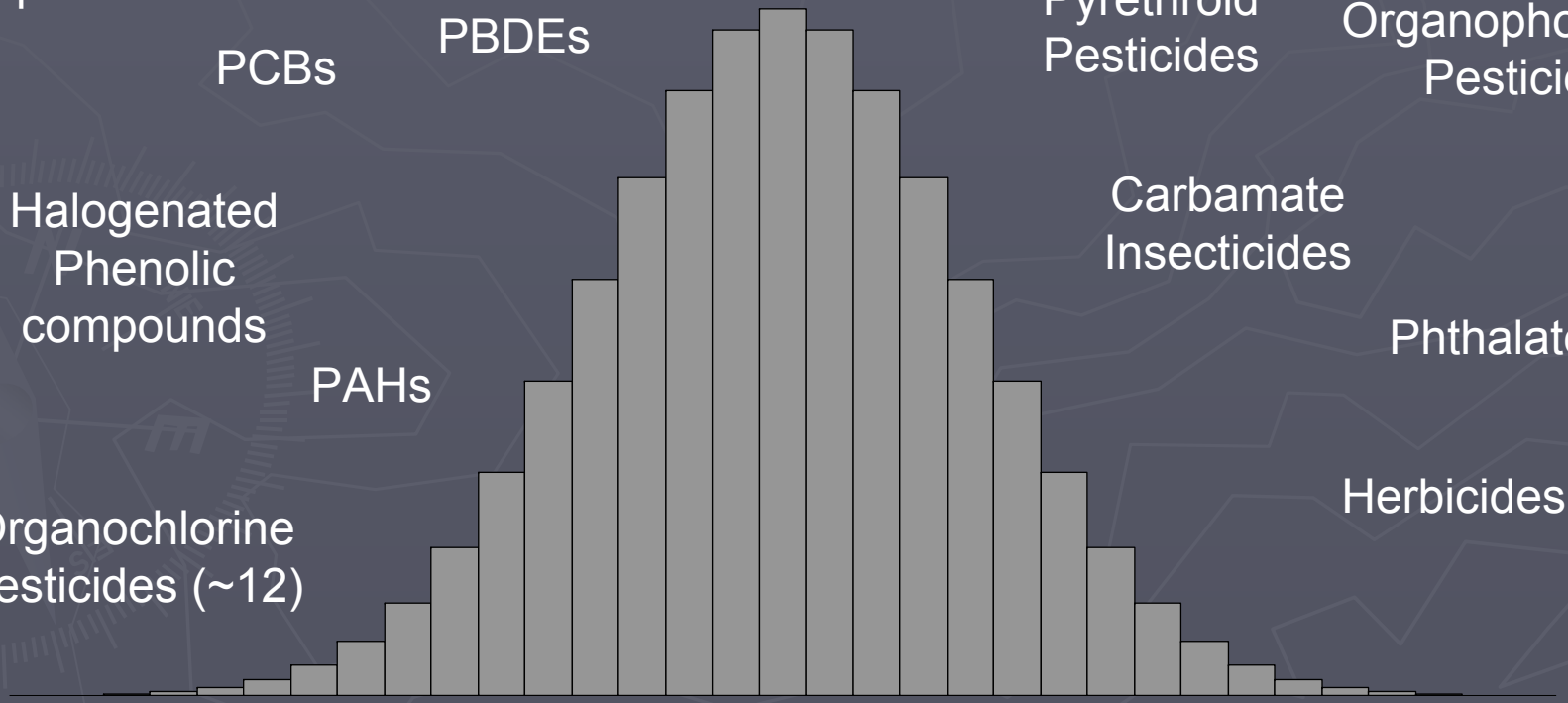
Exposure-Response



Valuable Biomonitoring Data: Lead



Valuable Biomonitoring Data



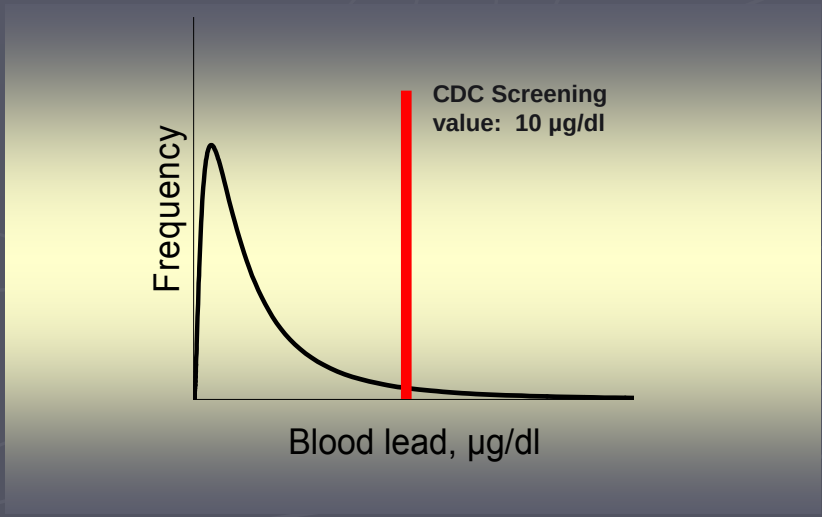
Reasons for Conducting Population Based Biomonitoring Studies

- Determine which chemicals get into members of the general population and at what concentrations
- Determine if exposure levels are higher in some groups than in others
- Track temporal trends in levels of exposure
- Assess the effectiveness of public health efforts to reduce exposure
- Establish reference ranges
- Determine the prevalence of people with levels above known toxicity levels
- Set priorities for research on human health effects

Source: (CDC, 2005)

Interpretation in a Health Risk Context

- Reference ranges (general population) do not provide health risk context
- Biomonitoring-based health risk benchmarks are available for VERY FEW chemicals
  - Lead
  - Mercury
  - ??



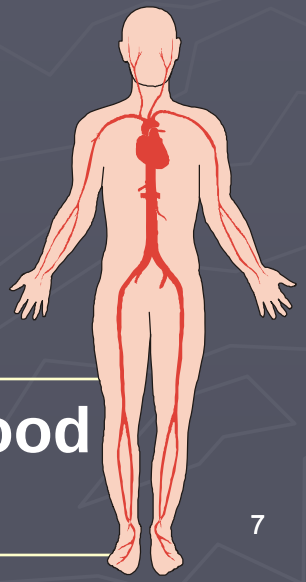
External Dose vs. Biomarker Concentrations

Rat Dose NOAEL/LOAEL

Safety Factors

“Safe” Human Dose – RfD, TDI

Human Blood Level



“Biomonitoring Equivalent”

Lay definition: What concentration of a chemical (or metabolite) is expected in blood or urine when the average human is exposed to the RfC, RfD, etc.?

Or

Technical definition: What concentration of biomarker is consistent with existing exposure guidance or reference values such as RfCs, RfDs, TDIs, etc.?

Deriving a Biomonitoring Equivalent: Utilizing Human PK Data/Model

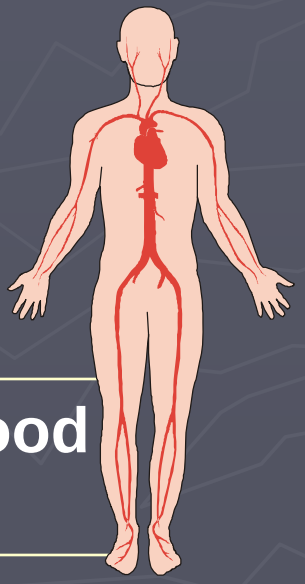
Rat Dose NOAEL/LOAEL

Safety Factors

"Safe" Human Dose – RfD, MRL

Human pharmaco-kinetic data

Human Blood Level



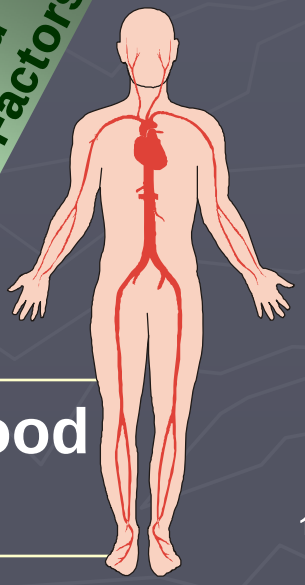
Deriving a Biomonitoring Equivalent: Utilizing Animal PK Data/Model

Rat Dose NOAEL/LOAEL

Animal pharmaco-kinetic data

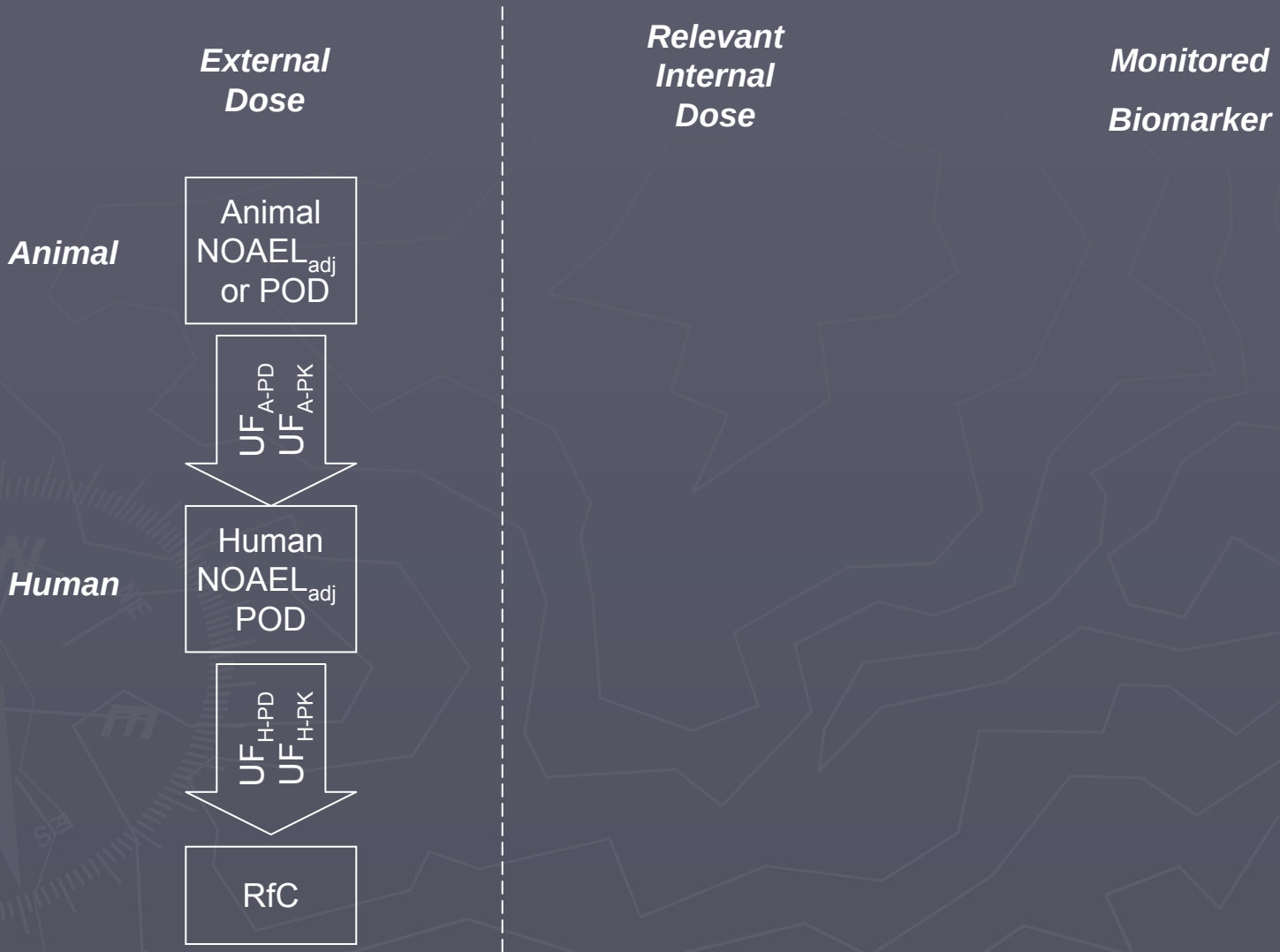
Rat Blood Level

Modified Safety Factors

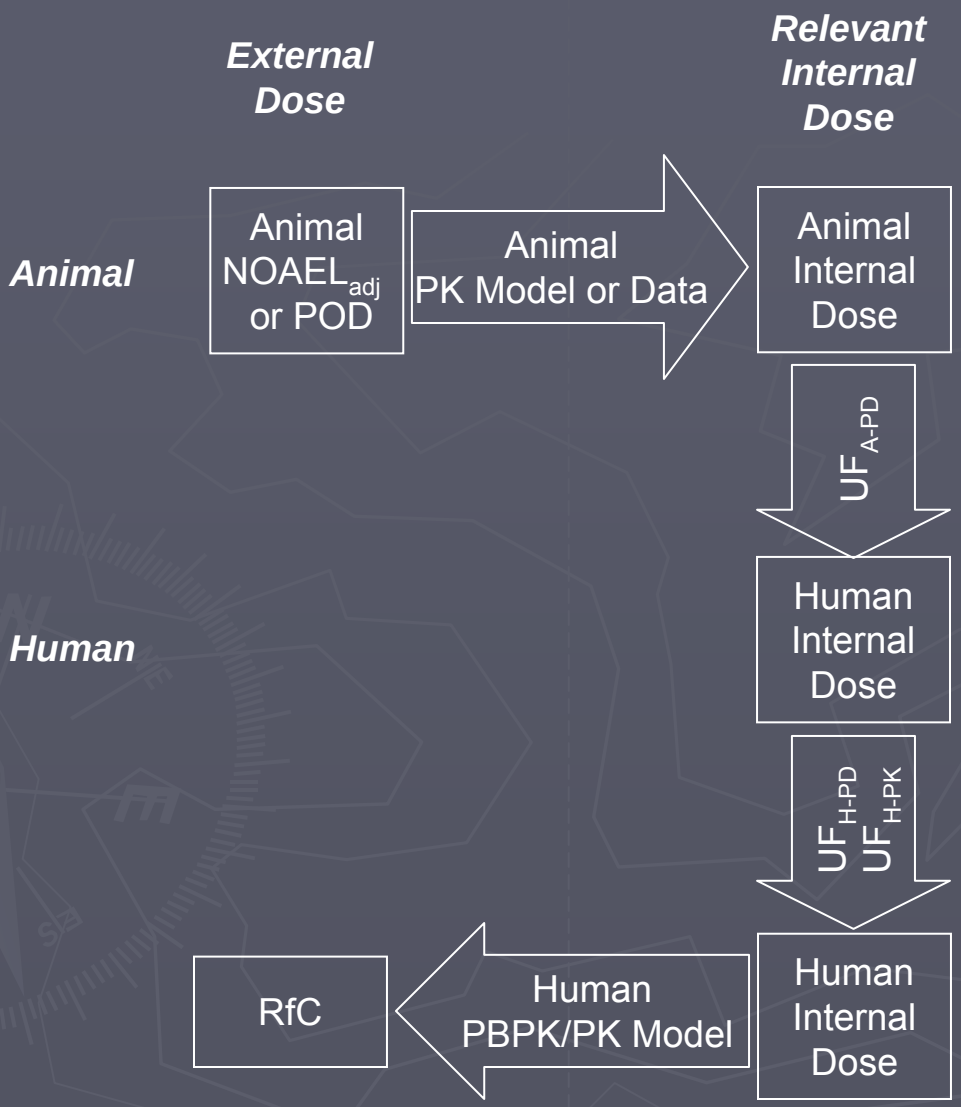


Human Blood Level

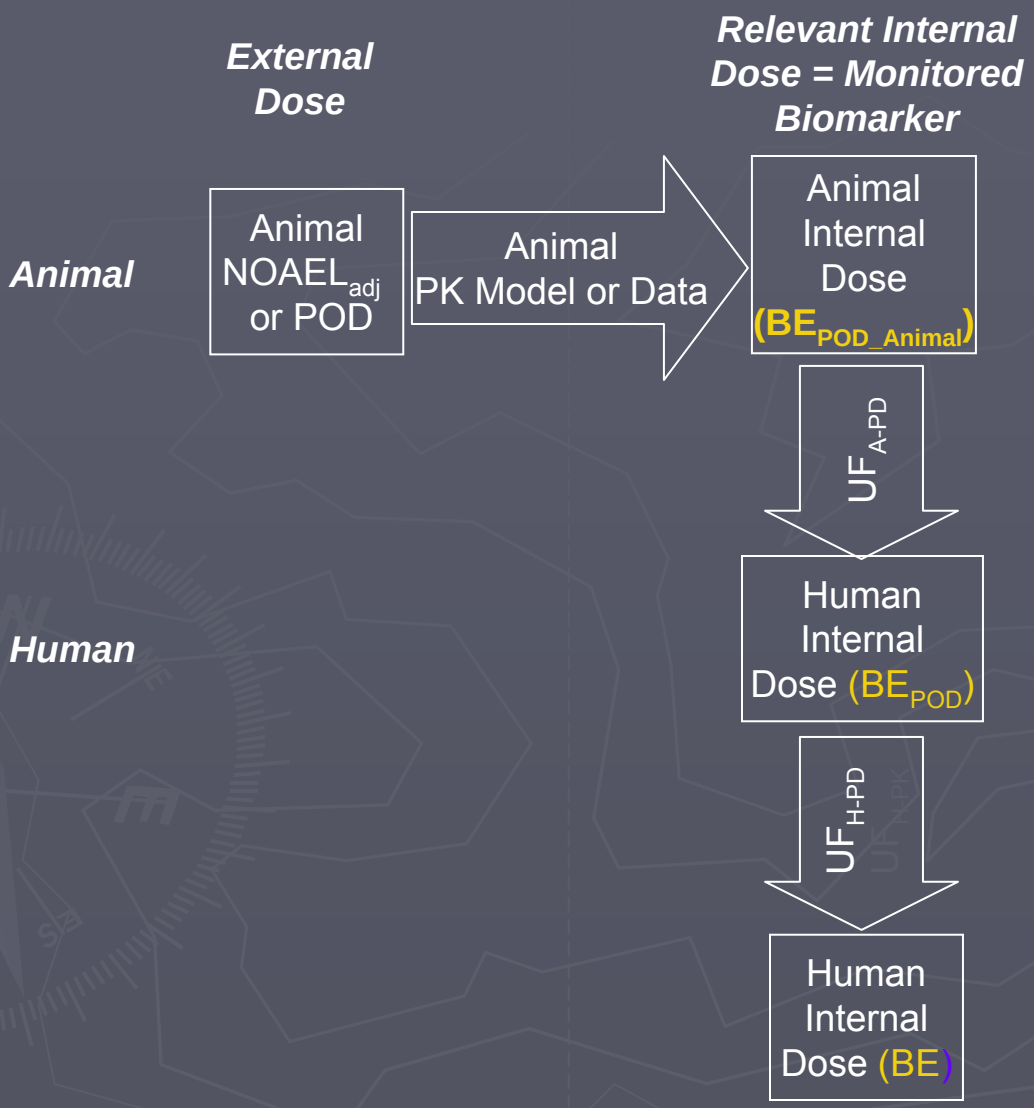
External Dose Risk Assessment



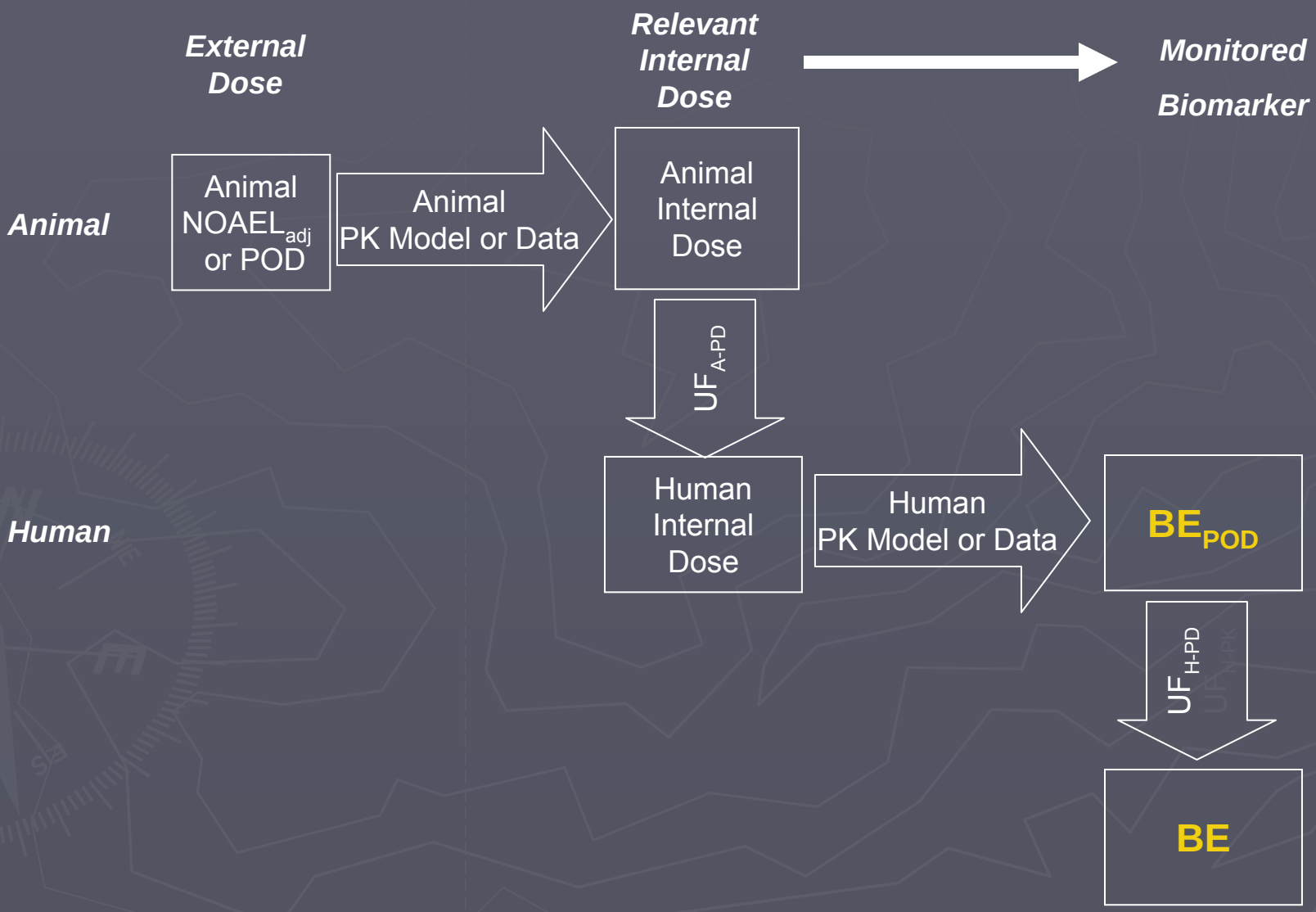
Internal Dose-Based Risk Assessment



Biomonitoring Equivalent



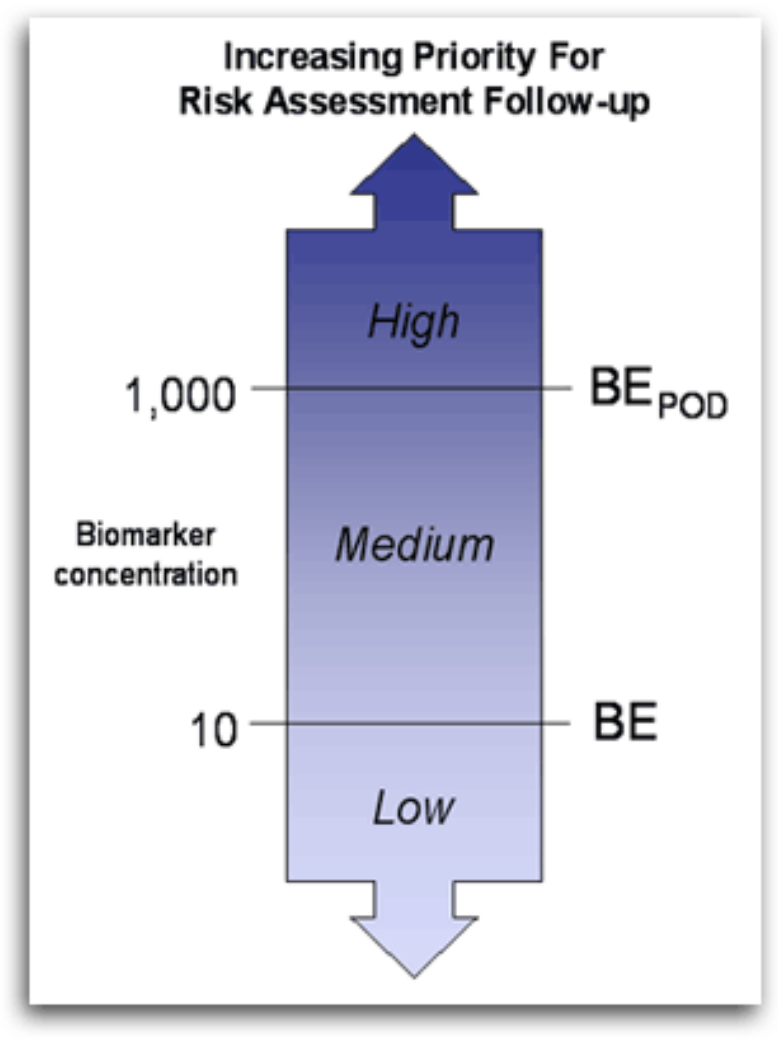
Biomonitoring Equivalent



Communicating Meaning of Biomonitoring Equivalent

- BE Definition is consistent with definition of underlying exposure guidance values
  - Level likely to be
    - Without adverse effects
    - In the general population including sensitive subpopulations
    - Over a lifetime of exposure
- Risk assessment tools, ***not*** diagnostic criteria or bright lines between “safe” and “unsafe”

Communication Model – Intended for Public Health Professionals



- BEs are not bright lines between safe and unsafe levels
- NOT diagnostic criteria for interpreting biomonitoring data from individuals
- Interpretation focuses on low to high priority for "risk assessment follow-up"
- Risk assessment follow-up may include
  - Exposure pathway evaluations, risk assessment re-evaluations, product stewardship, risk management

Workshop Publications

- Results from pilot project available in *Regul. Toxicol. Pharmacol.*, 51:S1-S77.
  - Guidelines for Derivation
  - Guidelines for Communication
  - Case Studies:
    - Toluene
    - Cadmium
    - Acrylamide
    - 2,4-Dichlorophenoxyacetic acid
    - Trihalomethane compounds

Characteristics of the BE Approach and Reverse Dosimetry

Characteristic	BE Approach	Reverse Dosimetry
Goal	Estimate steady-state biomarker concentrations consistent with exposure guidance value	Estimate distribution of plausible exposure concentrations consistent with distribution of biomarkers, assuming defined exposure patterns
Model Requirements	Can utilize animal and/or human PK/PBPK model and data	Requires human PK/PBPK model
Mathematical Solutions	Steady-state, deterministic	Non-steady state, nondeterministic
Biomonitoring study dependent?	No unique solution as a function of biomonitoring dataset	Unique solutions required for each biomonitoring dataset

Existing BEs

- Acrylamide
- 2,4-D
- Cadmium
- Toluene
- Trihalomethanes
  - Chlororom, bromoform, bromodichloromethane, chlorodibromomethane
- Dioxins and furans

BEs in Development

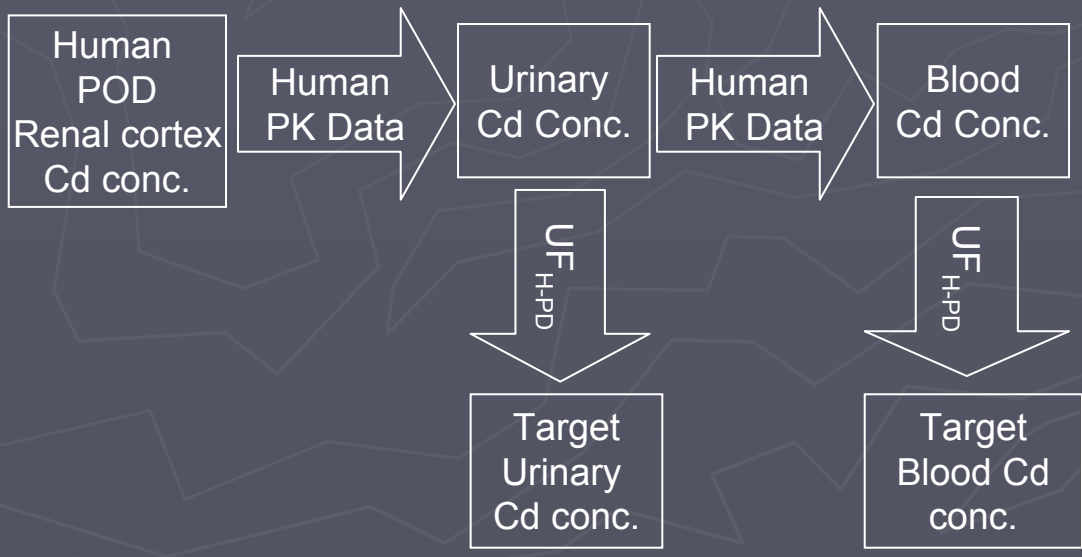
- Cyfluthrin
- Phthalates
  - DEHP
  - DEP
  - DBP
  - BzBP

Approaches to BE Derivation

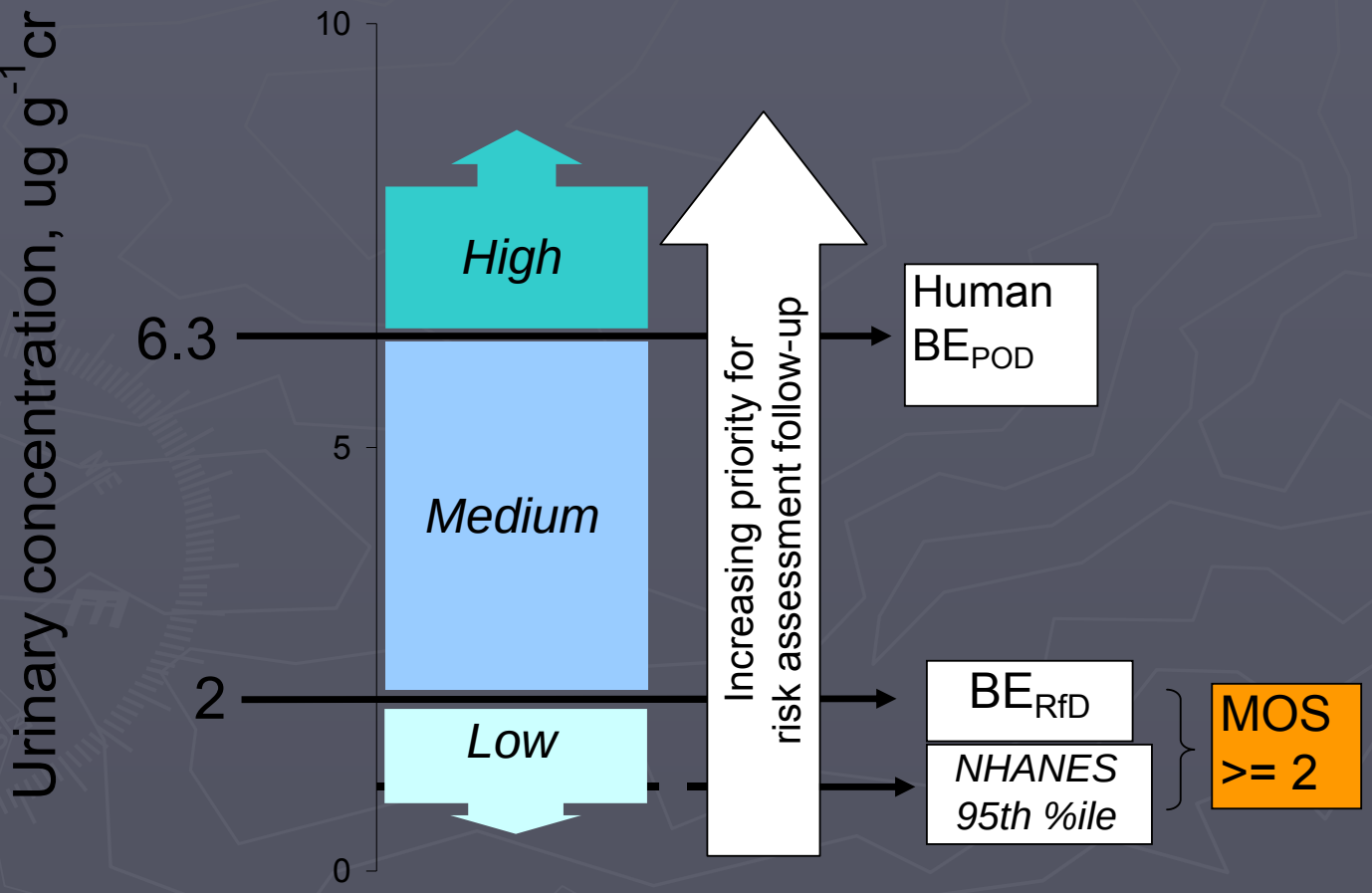
Approach / Data	Case Study Chemicals
PBPK modeling	Toluene Trihalomethanes
Urinary mass balance	2,4-D Acrylamide
Measured internal doses or biomarkers	Acrylamide 2,4-D Cadmium Dioxins/furans

Calculating the Cadmium BE

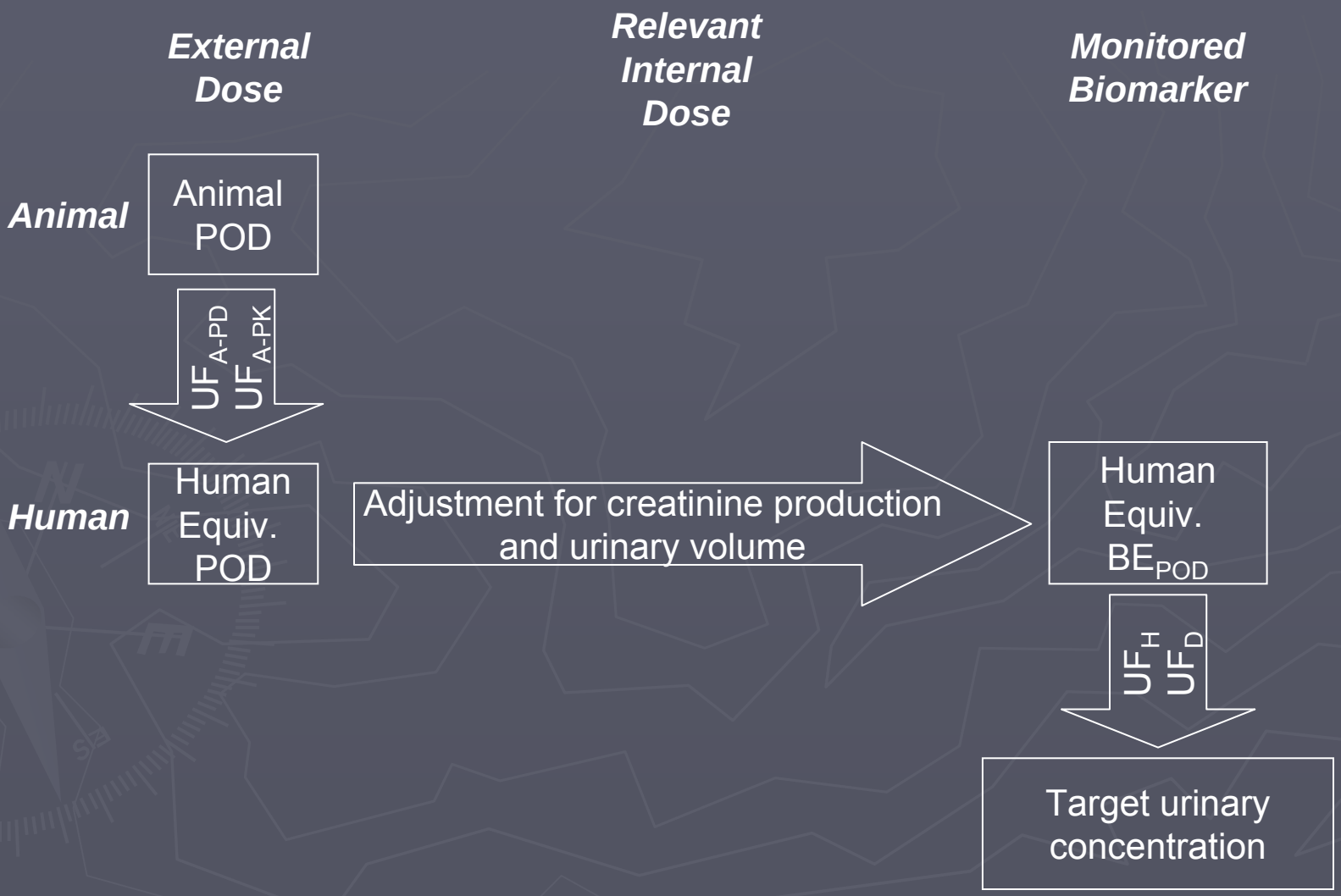
External Dose	*Relevant Internal Dose*	*Monitored Biomarker*
Animal		
Human		



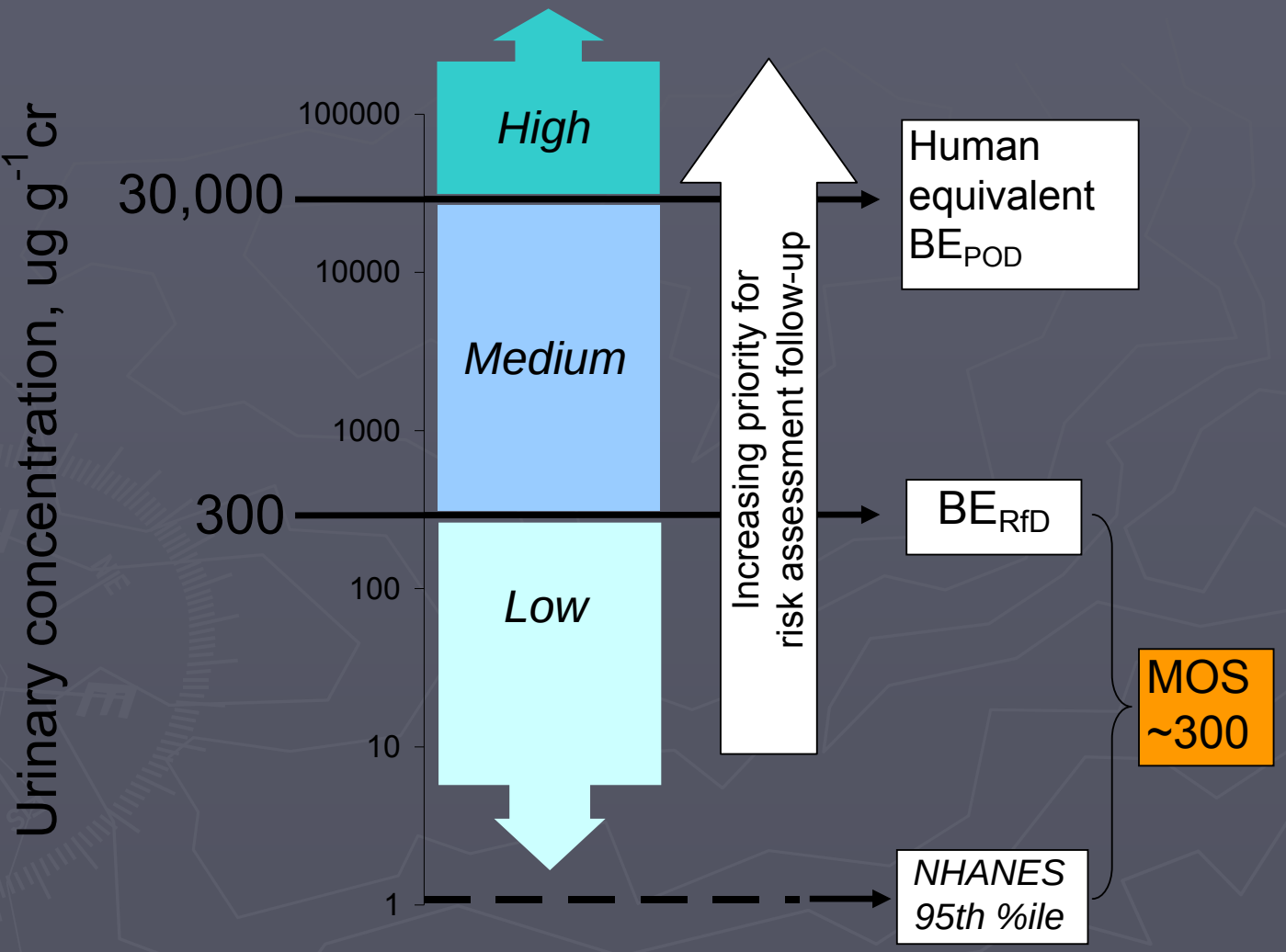
Interpretation Using Cadmium BE



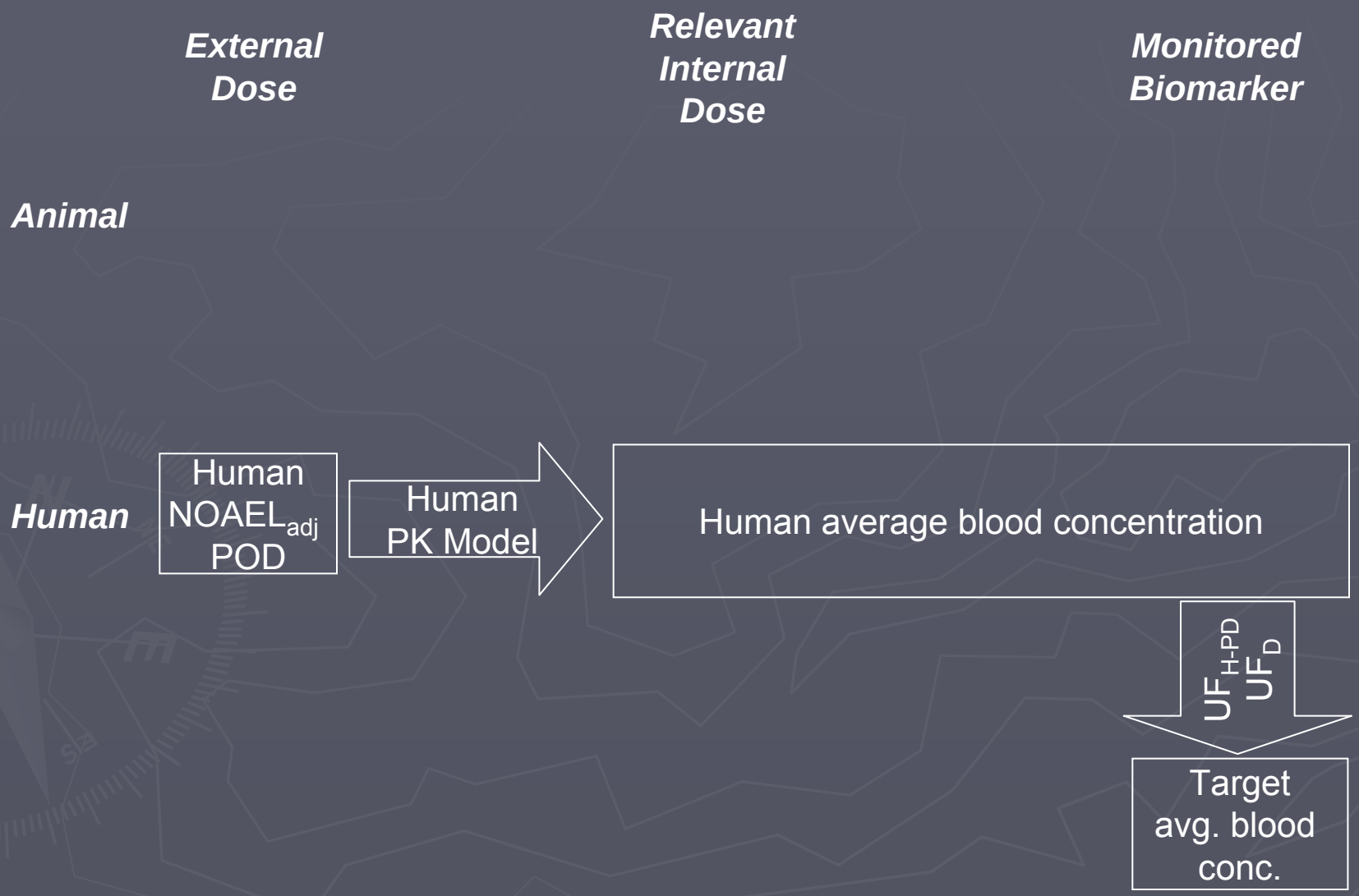
Calculating the 2,4-D BE



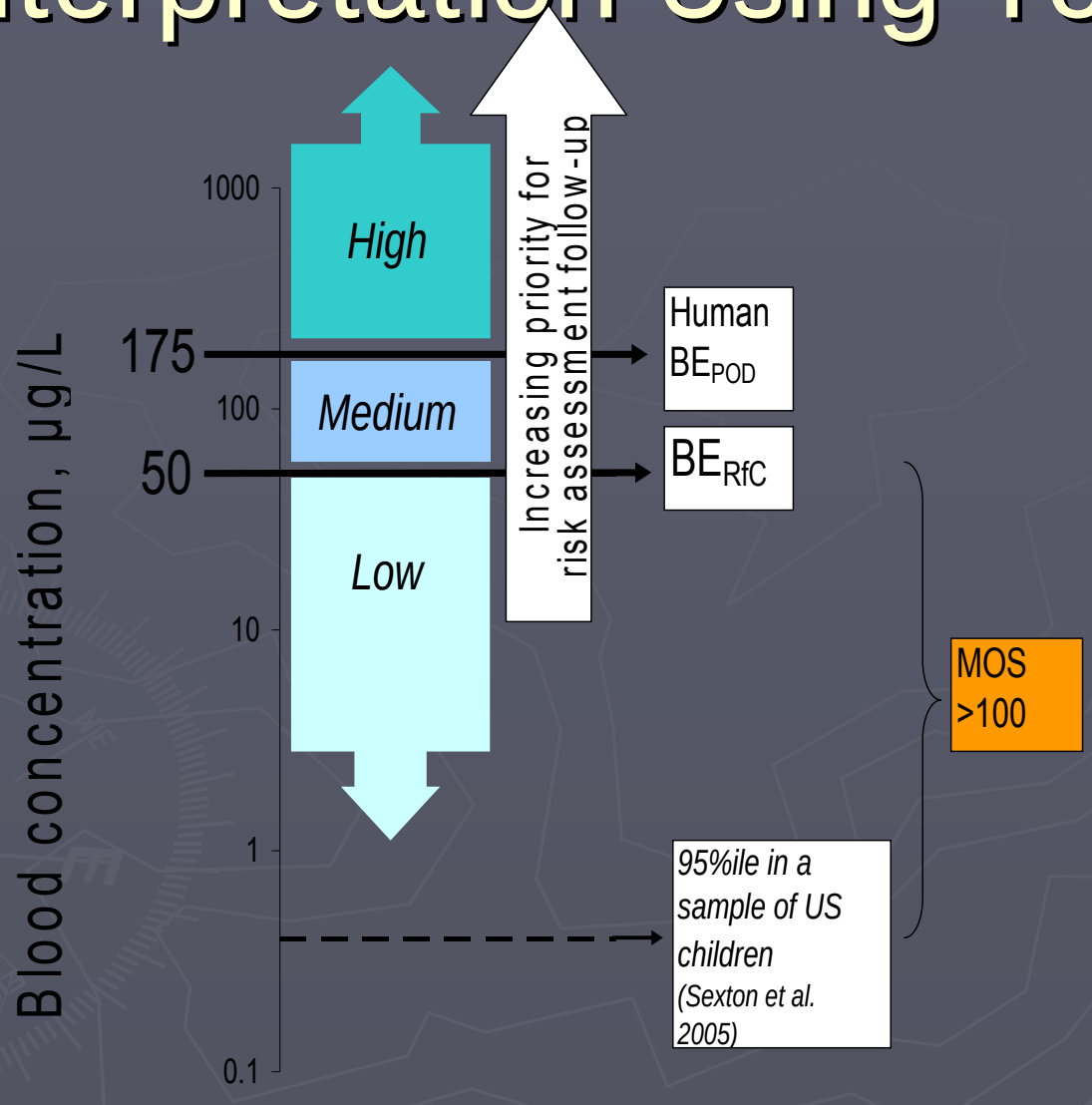
Interpretation Using 2,4-D BE



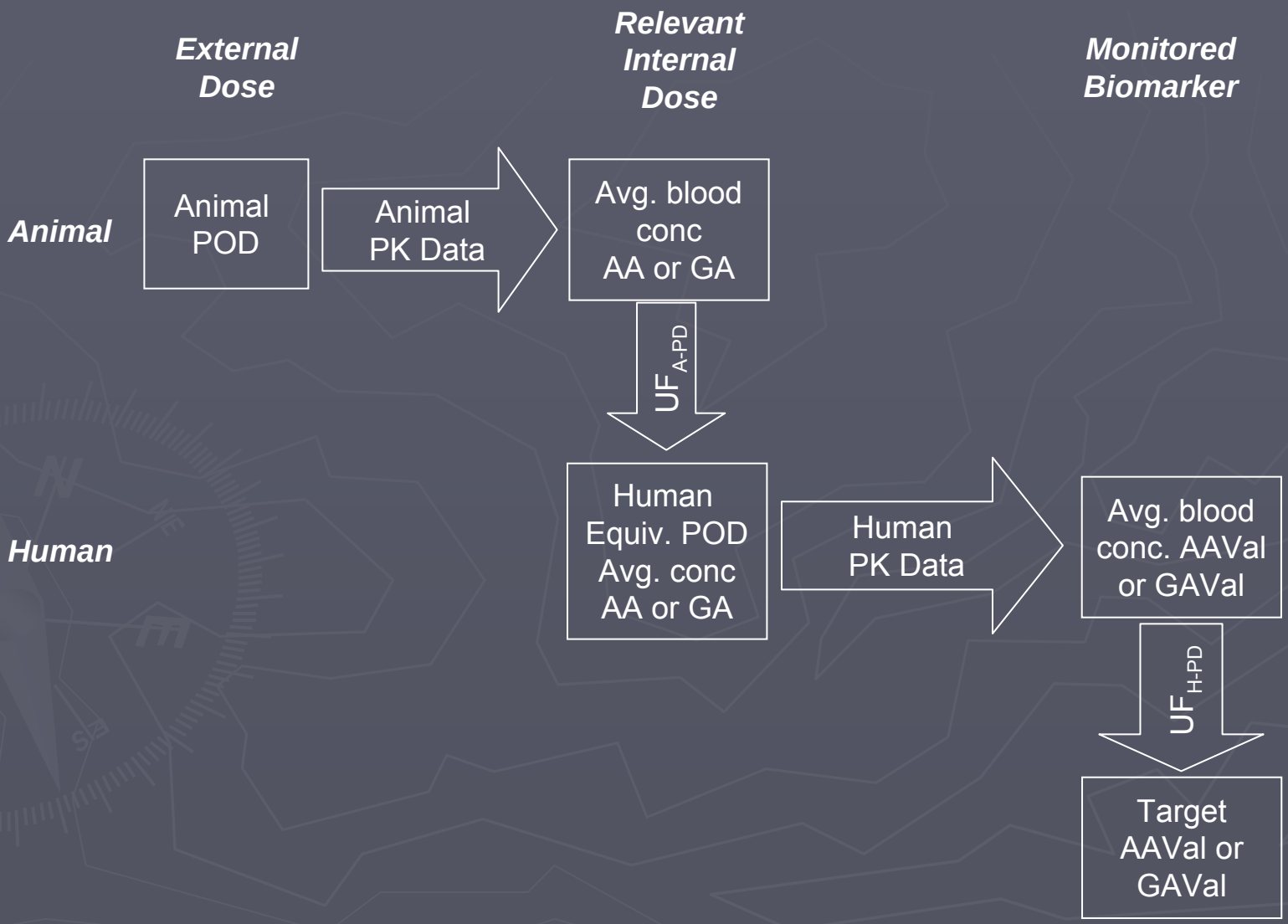
Calculating Toluene BE



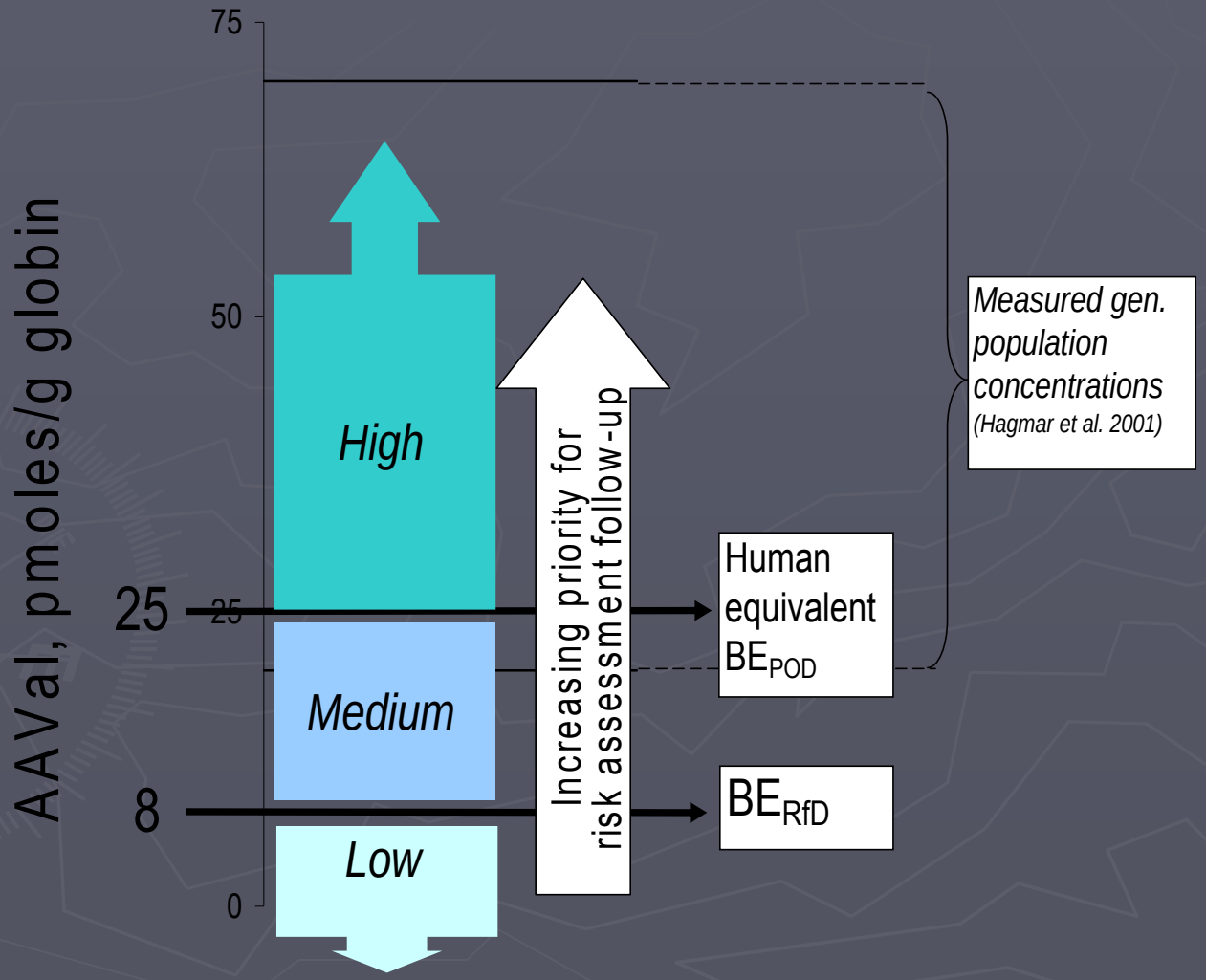
Interpretation Using Toluene BE



Calculating Acrylamide BE



Interpretation Using Acrylamide BE



Application of the BE Approach

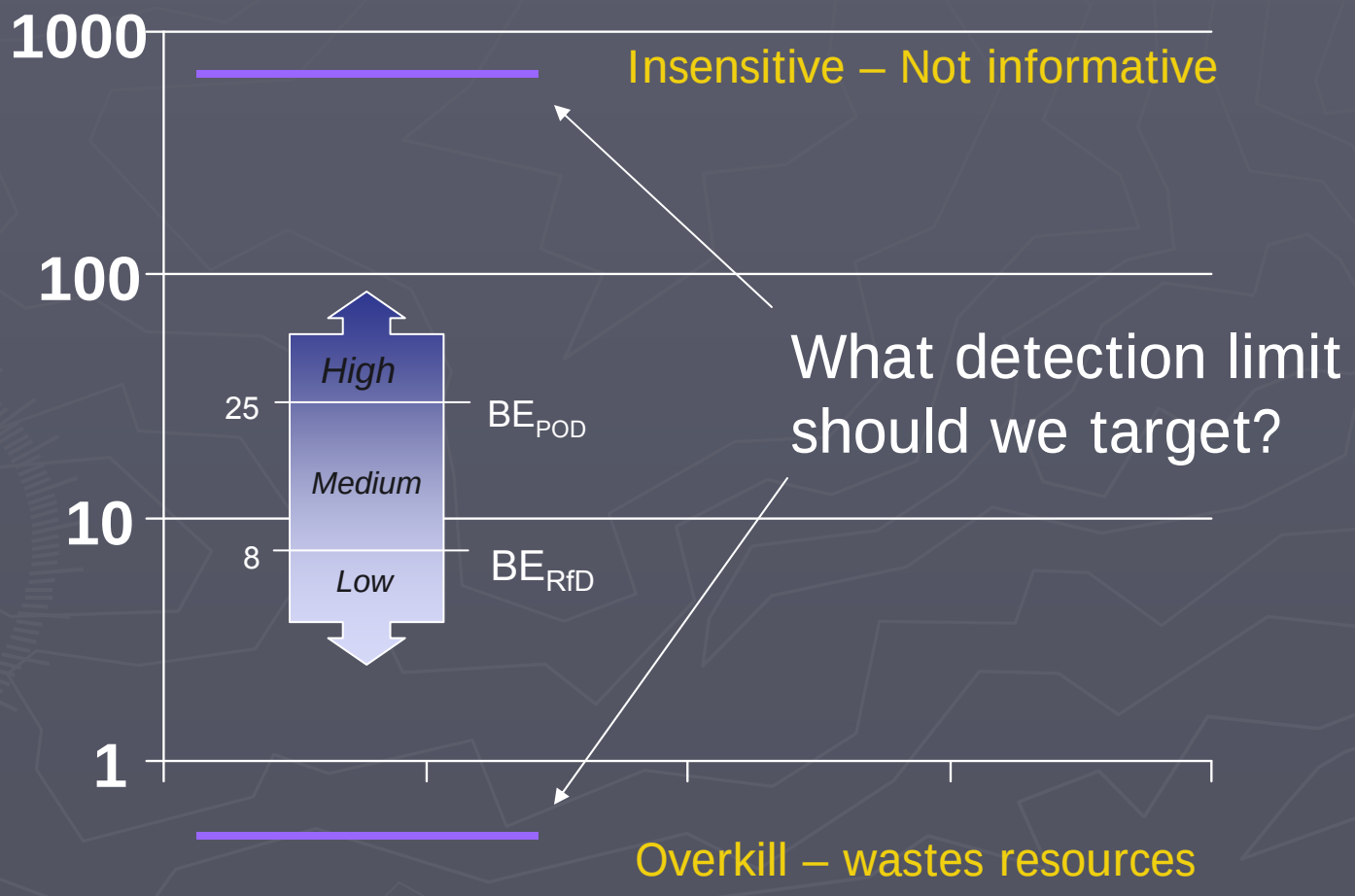
Compound	MOS	Priority for Risk Assessment Follow-up
Acrylamide	<1	High
Dioxins	~1	Medium
Cadmium	~2	Low - Medium
Chloroform	>10	Low
Toluene	>50	Low
2,4-D	>100	Low

- Risk prioritization screening tool

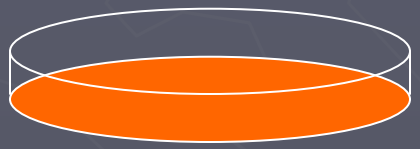
Additional Benefits of BEs

- Inform potential risk assessment improvements (mode of action, internal dose)
- Inform biomonitoring study design
  - Identify preferred biomarker(s)
  - Identify concentrations of interest (LOD)

Application of BEs in Study Design

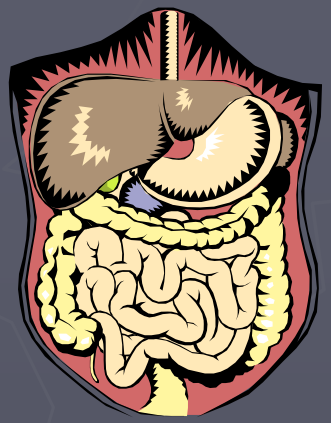


Application of BE Concept to 21st Century Tox Initiatives



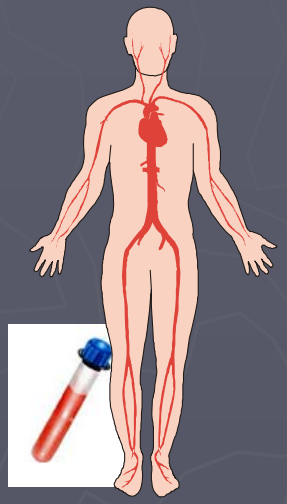
In vitro benchmark concentration

Partition coefficient

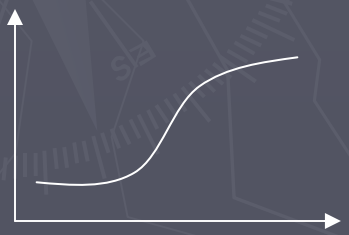


In vivo organ concentrations

Partition coefficient

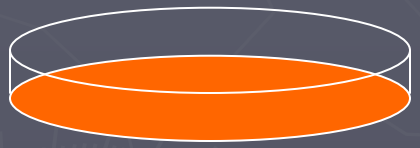


In vivo blood concentrations



- Dose-response data are important for setting screening levels
- Only limited toxicokinetic data may be needed for screening – fully-developed PBPK models may not be required

Biomonitoring Data and BEs Can Help Inform Concentration Selections for 21st Century Tox Initiatives



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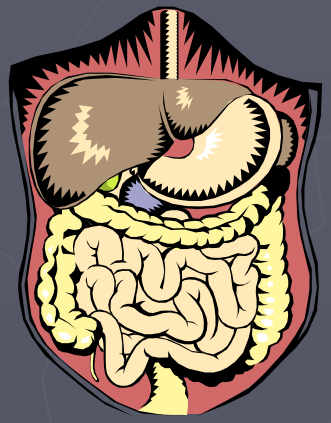
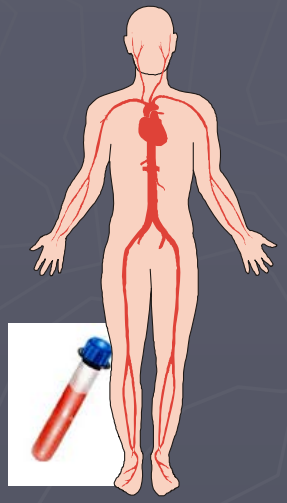


In vivo organ concentrations

Partition coefficient



In vivo blood concentrations

Relevant exposures (internal doses) can help bound and BEs can help to "anchor" concentrations of interest in *in vitro* tox test systems

Conclusions

- Biomonitoring Equivalents leverage existing chemical risk assessments
  - Reproduces risk assessment based on internal dose, mode of action considerations
- BEs provide a tool for prioritization for risk assessment follow-up
- BEs can inform study design
  - Selection of biomarkers, detection limit targets
- The BE concept may be applicable to "21st Century Tox" approaches

Resources

- www.biomonitoringequivalents.net
  - Home of Registered Biomonitoring Equivalents
  - Information on the BE concept and interpretation of biomonitoring data
  - Information for physicians
  - Chemical-specific information for BE case study compounds (in progress)
- *Regulatory Toxicology and Pharmacology* BE Pilot Project Supplement (2008)