Dose response relationships: biological and modeling aspects

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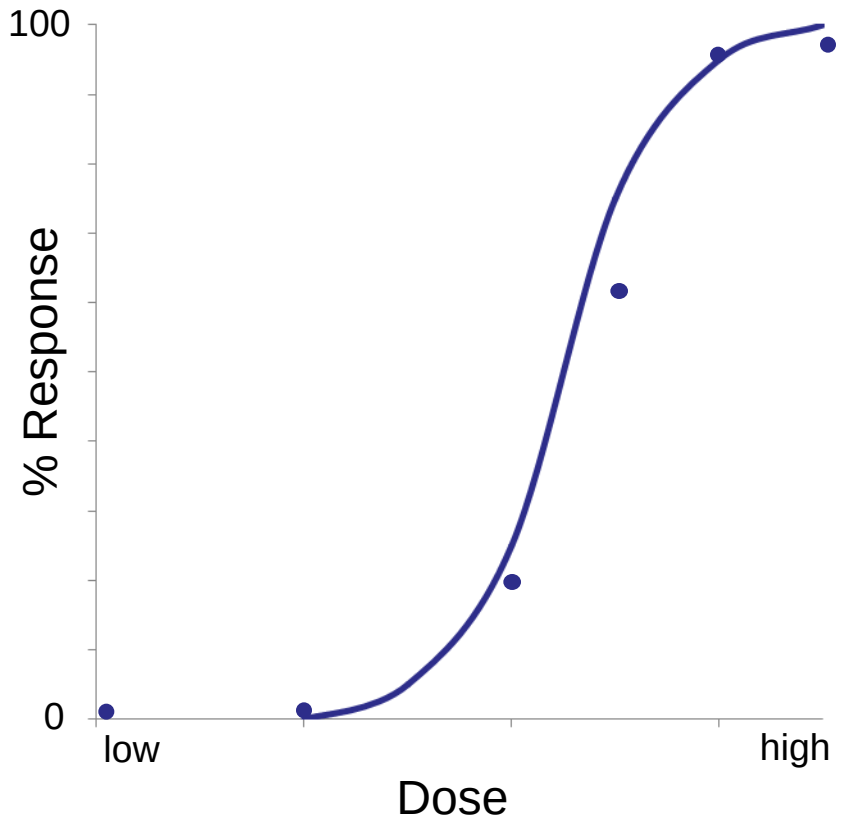
Dose Response Relationship

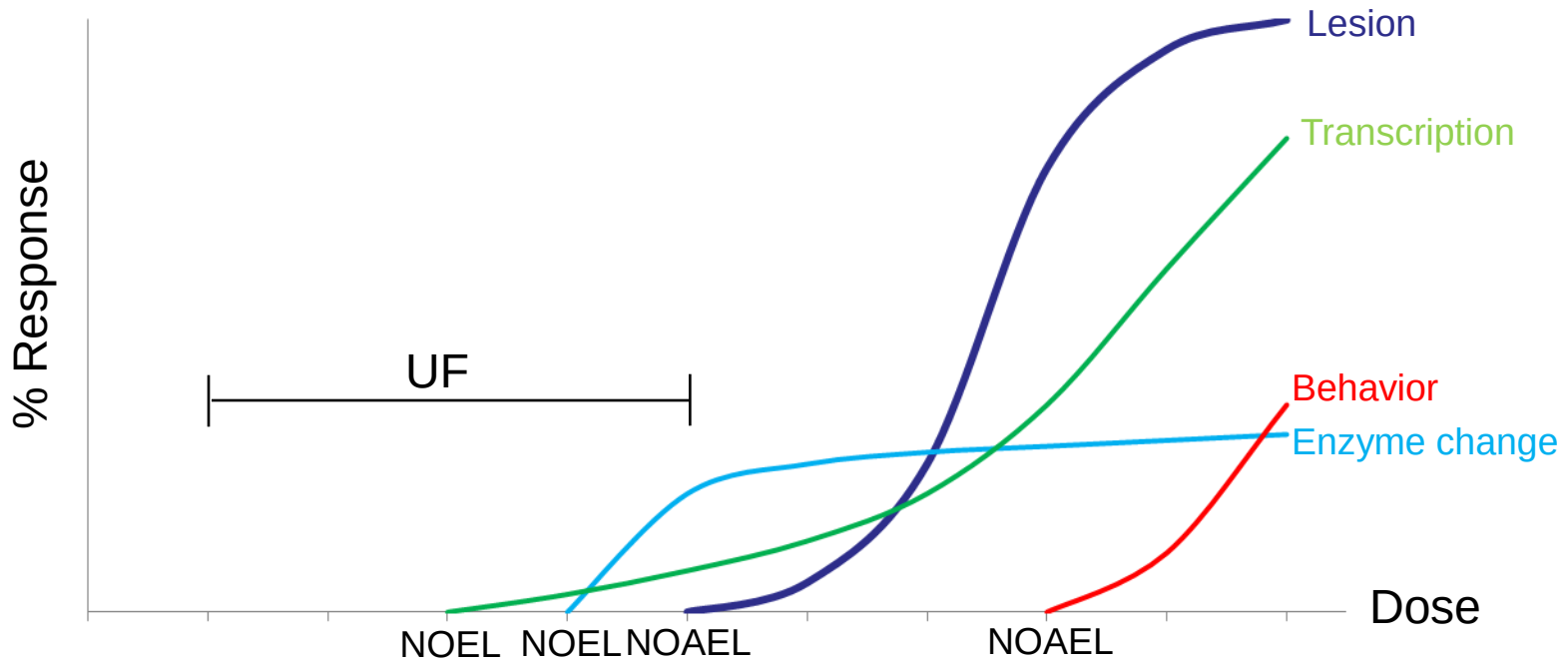
"The characteristics of exposure and the spectrum of effects come together in a correlative relationship customarily referred to as the *dose-response relationship*. Whatever response is selected for measurement, the relationship between the degree of response of the biological system and the amount of toxicant administered assumes a form that occurs so consistently as to be considered the most fundamental and pervasive concept in toxicology." - Casarett and Doull's Toxicology (6th Edition)

Dose Response



- Change in effect over a range of doses
- Regulatory safety assessment and testing examine multiple endpoints and doses
- Recommend 3-5 dose levels (e.g., Redbook, OECD)
- Dose selection related to biology, toxicity, and chemical properties

Biological Model



- Identify lowest non-neoplastic adverse effect or point of departure (NOAEL, BMD)
- Build a biological picture in whole organism
- Dose-response relationship builds biological context of a compound's (or class of compounds) action and permits extrapolation

Uncertainty

- Cannot test every dose, condition, species, or age
  - Analytical uncertainty and biological variability could increase errors at lower doses
- Uncertainty Factors (UF)
  - Intraspecies diversity (e.g., sensitivity, ages)
  - Interspecies extrapolation (e.g., rodent –human)
  - Dosing Duration Extrapolation (e.g., subchronic – chronic)
  - Dataset Deficiency (e.g., testing of a single species)
  - Additional modifying factor (e.g., testing conditions)
- Conservative default of 10 per UF, adjusted with additional testing and/or pharmacokinetic data
- UCR for carcinogenicity (linear no threshold response extrapolation)
- Reducing uncertainty leads to better biological models, risk characterization, and focused testing

Pharmacokinetics (PK)

- Reduce uncertainty, focus tox testing
- Characterize internal exposure (temporal, route, metabolites), age and species differences
- Combine with biomonitoring data to build physiologically based PK model (PBPK)
  - Extrapolation: route to route, species, dose

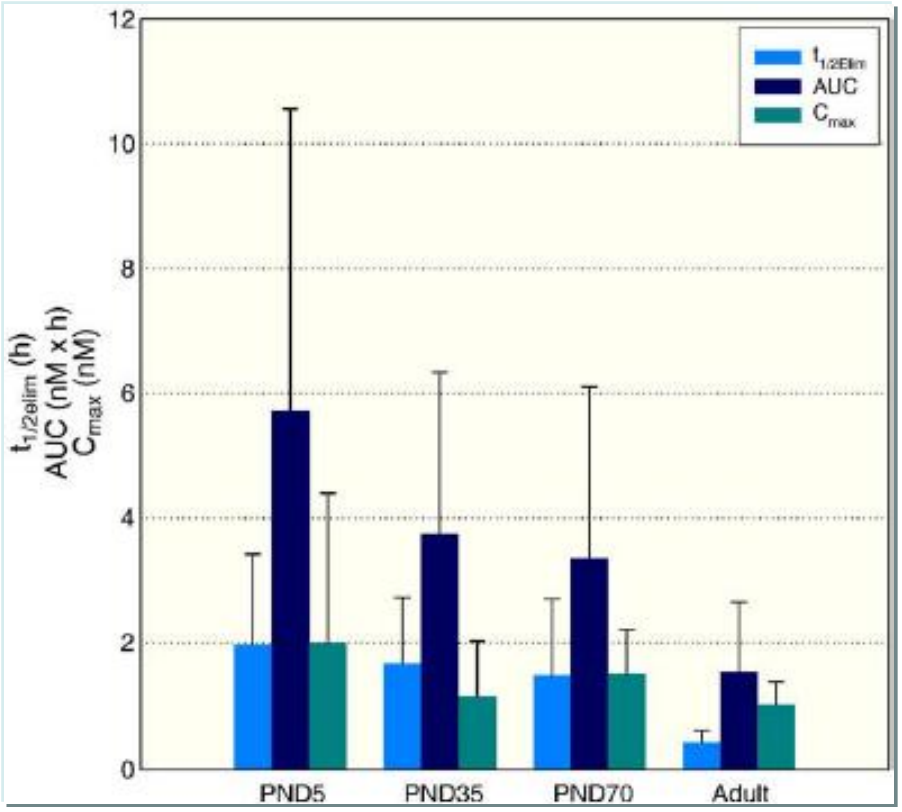
PK – Internal dose of active compound

	PND 3 (aglycone)	PND 3 (total)	PND 10 (aglycone)	PND 10 (total)	PND 21 (aglycone)	PND 21 (total)
$t_{1/2elim}$ (oral)[1]	8.5	6.7	4.0	4.7	1.9	2.9
$t_{1/2elim}$ (SC)	3.9	4.3	2.3	3.7	3.8	3.4
AUC (oral)	56	4030	21	2410	3.2	833
AUC (SC)	930	23,800	761	28,490	366	9820
C_{max} (oral)	29 ± 16	445 ± 230	6.7 ± 3.9	219 ± 87	0.70 ± 0.42	182 ± 37
C_{max} (SC)	1010 ± 290	5090 ± 1090	634 ± 249	5590 ± 2490	318 ± 43	1940 ± 730

Doerge et al., 2010a

- PK can address metabolism, development, and route of exposure
- Serum aglycone levels: Oral exposure <<< SC exposure
  - Substantial presystemic metabolism in gut and liver
- Age-related development of metabolic and excretory capacities in rodents

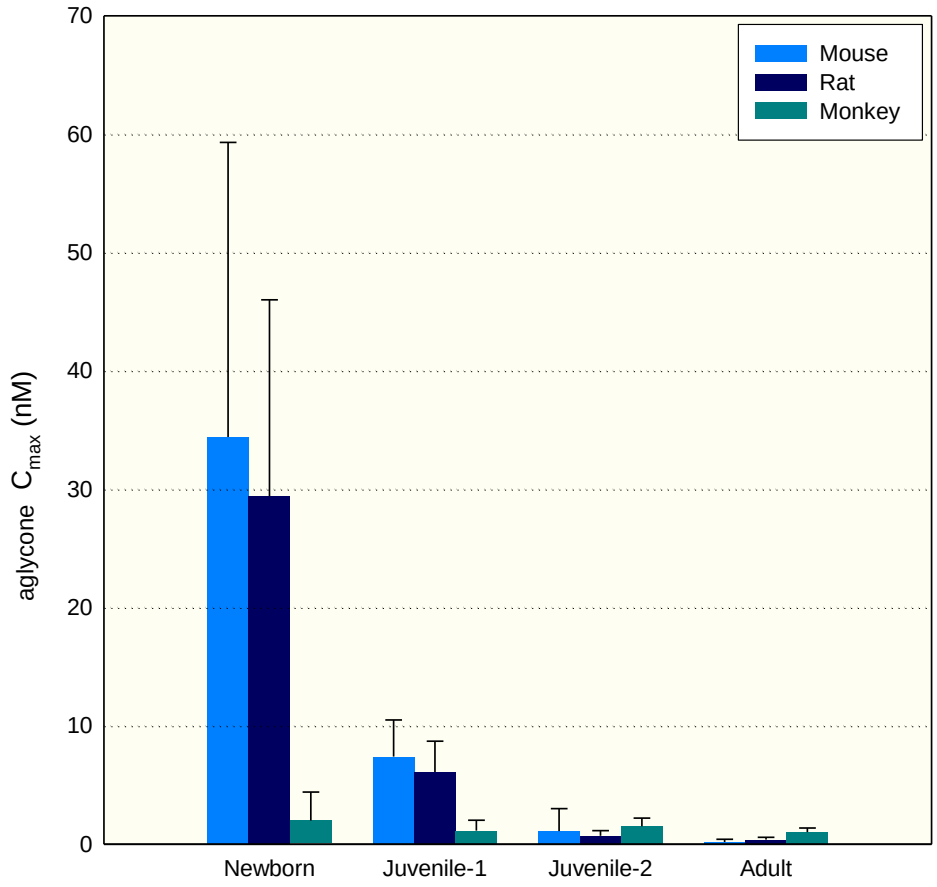
PK – Species-specific differences



Doerge et al., 2010b

- PK aids in extrapolation between species including humans
- Non-human primate metabolism: neonate ~ adult
- Neonate serum aglycone levels: rodent > primate
- Interspecies UF would overcompensate

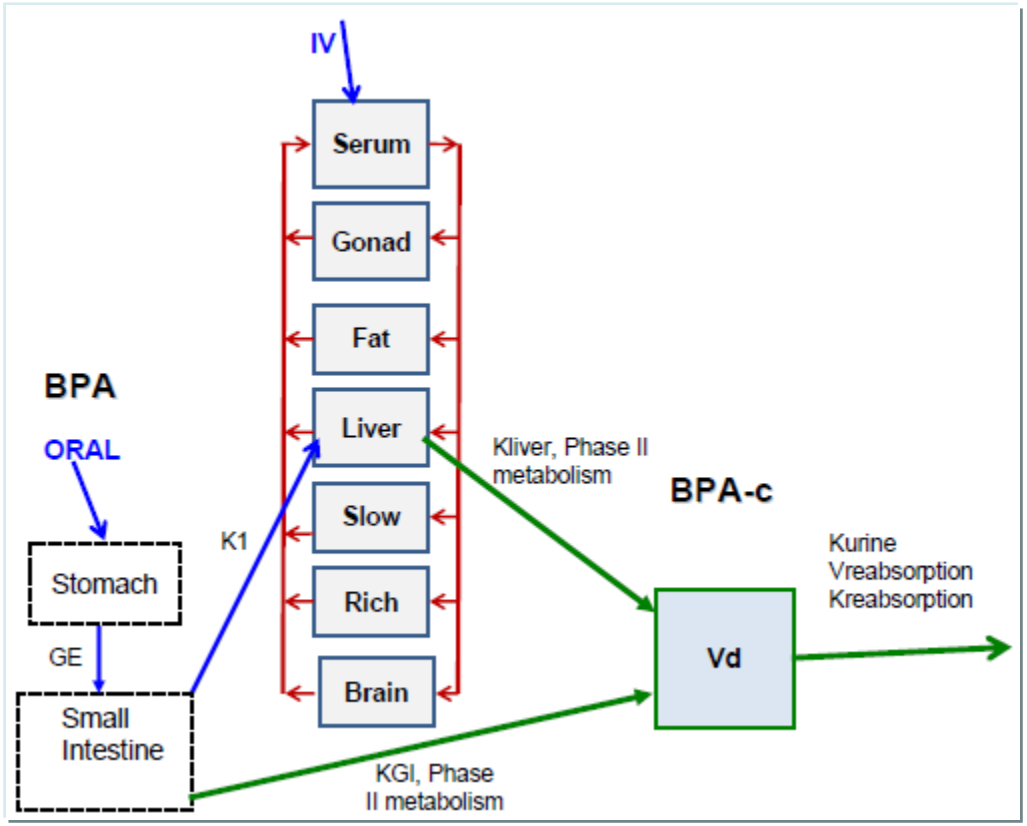
PK – Interspecies dosimetry and tissue distribution



Doerge et al., 2011

- Tissue distribution can be useful for interpretation and to focus testing
- Route of exposure may be important based on metabolism
  - IV: in vivo distribution ratios for aglycone from 5-0.7: adipose > mammary > brain, muscle, ovary > uterus > liver
  - Oral: metabolism and rapid elimination do not support sequestration or accumulation in tissues (including fetus and milk)

Physiologically based pharmacokinetic (PBPK) models



Fisher et al., 2011

- Connects the dose-reponse relationship to internal dose
- Tool for extrapolation
  - Route-to-route, species, age, dose
  - Combined with biomonitoring data to predict human dosimetry and ADME

PK and PBPK increases biological understanding

- PK and PBPK reduce uncertainty and support dose-response relationship
  - Internal dose of active compound (dose-response relationship) can be species, age, and route of exposure dependent
  - Allows comparison and interpretation across studies and endpoints
  - Can be used to focus testing (e.g., dose, tissue, TK/TD, route)
  - Identify/limit background contamination (e.g. labeled compound)
  - Refine UFs

- Contributes to extrapolation from dose-response and improve risk characterization

Quantitative Structure-Activity Relationship

- Chemical characteristics relate to toxicological activity
  - Similarities in physiochemical properties and correlations with toxicological properties support comparison and reproducibility between chemicals and dose-response relationships
  - Models available using read across methods and patterns in dose response data
- Hazard identification tool
  - Identify or fill data gaps, areas for specific toxicity testing, and prioritization
- Risk Assessment
  - Premarket: Identify structural analogs, extrapolate a unit cancer risk (UCR) from bioassay data, estimate worst case lifetime cancer risk
- Databases (in vivo, in vitro, high throughput, mechanistic data) and tools developing to increase dose-response predicitivity

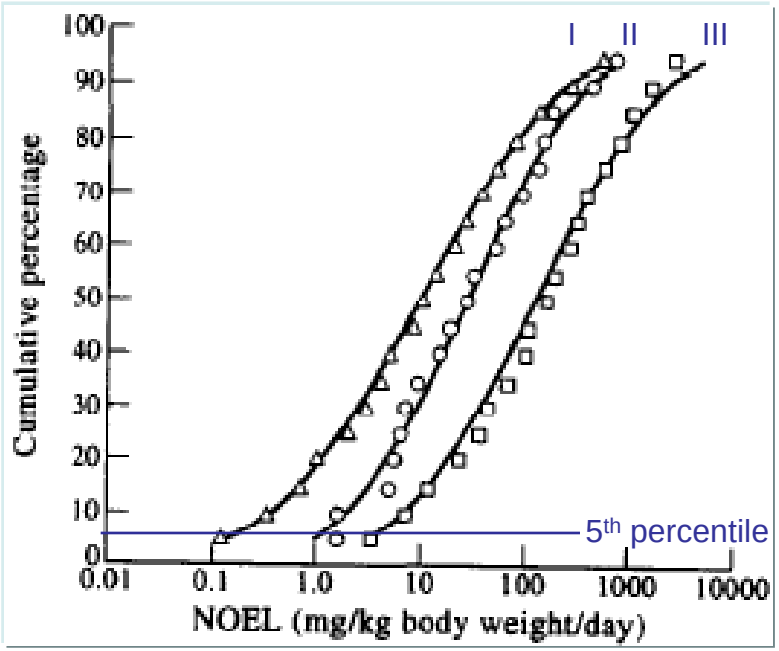
Threshold for Toxicological Concern (TTC)

- Predictive and reproducible pathways and thresholds based on structure and activity.

- "The basis of the Threshold of Toxicological Concern (TTC) concept is the assumption that a human exposure threshold for most chemicals exists below which there is negligible probability of any risk to human health." (ILSI.org)

- Current regulatory use
  - Joint WHO/FAO Expert Committee on Food Additives (JECFA) in evaluating flavouring substances
  - FDA Threshold of regulation (TOR)
  - EMEA genotoxic impurities in pharmaceuticals

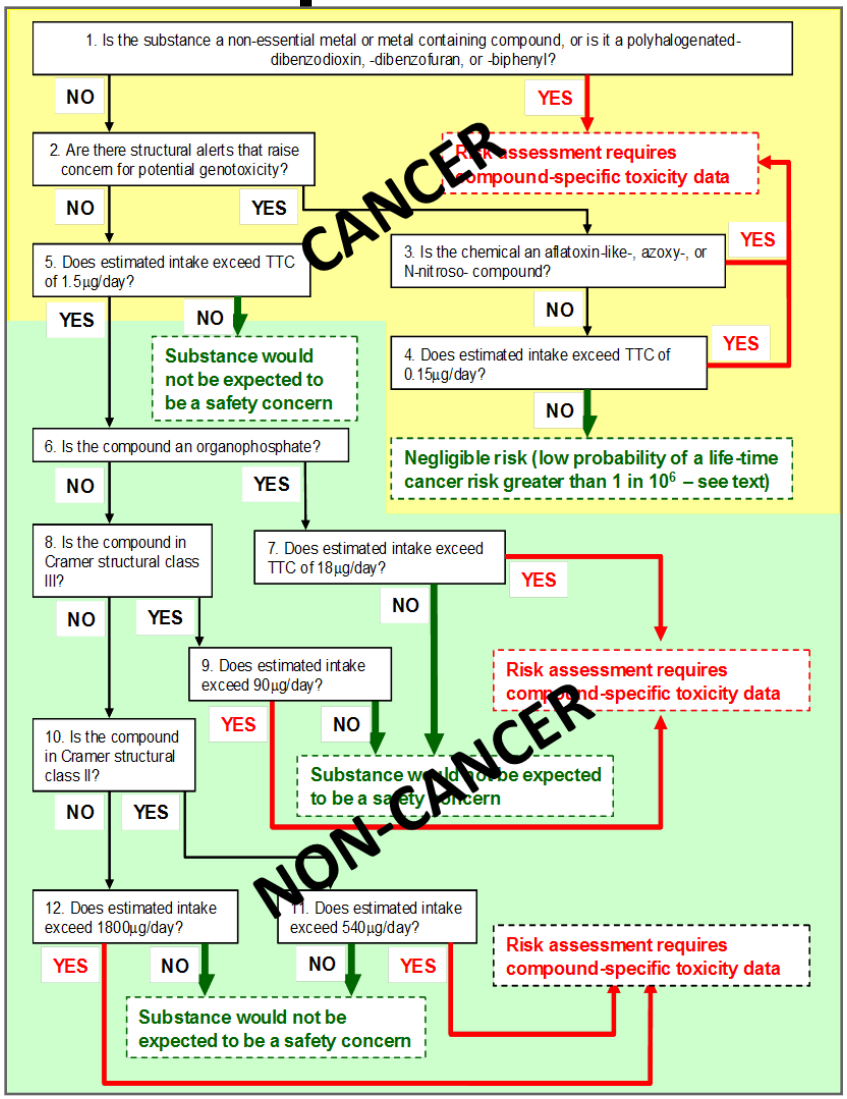
Threshold for Toxicological Concern (TTC)



Munro et al., 1996

- Based on analysis of large databases of repeat dose toxicity data
- Use of structural class decision trees “reflecting a presumption of low, moderate, or serious toxicity” (Cramer, 1978) to calculate thresholds
- 5th percentile NOAEL + 100 fold UF to define thresholds below which would not present a safety concern

TTC expanded classification



- Decision tree expanded to include additional classifications and toxicity data
  - Highly toxic or carcinogenic chemicals excluded
- Reinforces concept of similarities in structure, toxicological dose-response, thresholds, expectations in extrapolating to other doses, and safety measures
  - Suggests lower doses below which toxicity would not be expected

Kroes et al., 2004

Conclusions

- Dose-response is an integral component of a safety/risk assessment.
  - Multiple endpoints, reproducibility, biological based progression of effects, threshold identification, understanding mechanisms
  - Determination of treatment related effect

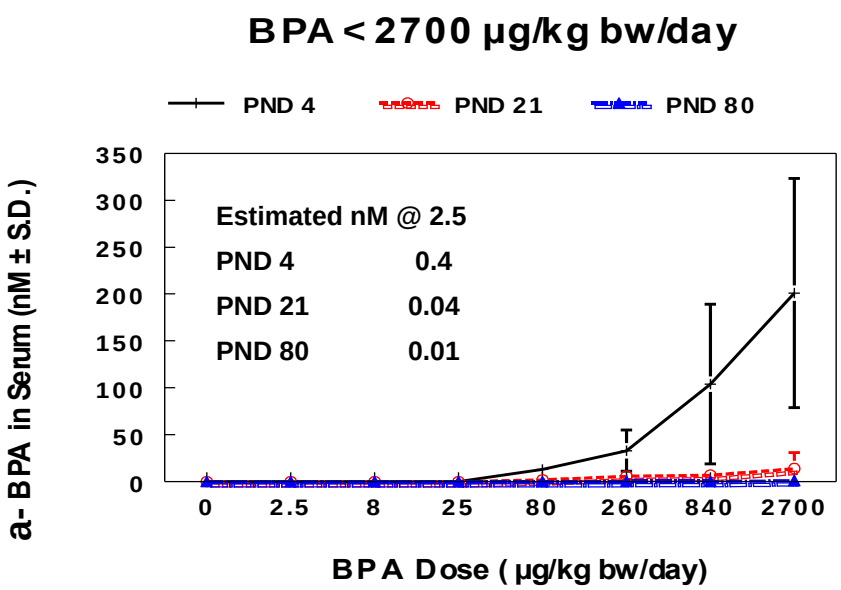
- Variability in biology and uncertainty in testing
  - Methods to reduce uncertainty and add confidence in understanding of a tox dose response
  - Enhance extrapolation from dose-response relationship and use of UFs

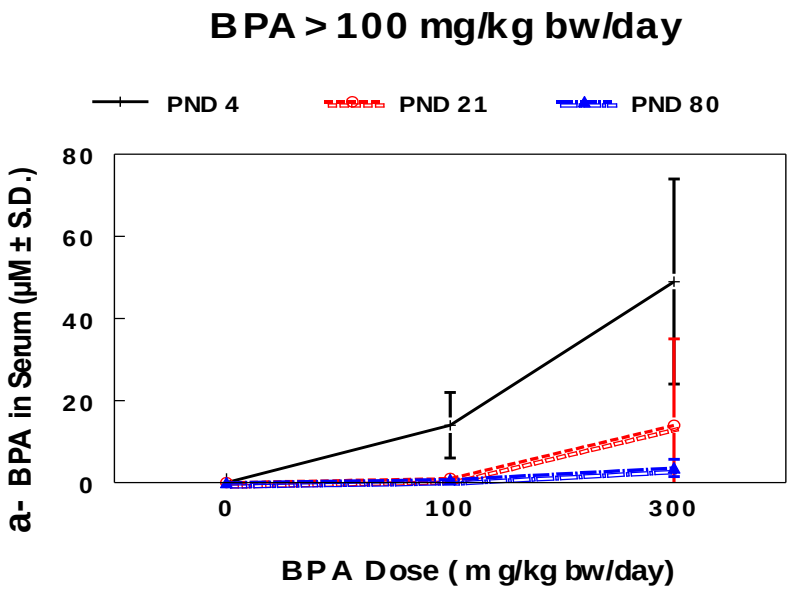
- Dose-response toxicity information can be combined and correlated with chemical and biological characteristics to identify probability of toxicity
  - Models function on integrating dose-response information across various endpoints, range of doses, and classes of chemicals
  - Predictive for thresholds and dose ranges for toxicity

References

- Pharmacokinetics of bisphenol A in neonatal and adult Sprague-Dawley rats Doerge D.R., Twaddle, N.C., Vanlandingham, M., Fisher, J.W. Toxicology and Applied Pharmacology 247 (2010a) 158–165
- Pharmacokinetics of bisphenol A in neonatal and adult rhesus monkeys, Doerge D.R., Twaddle, N.C., Woodling, K.A., Fisher, J.W. Toxicology and Applied Pharmacology 248 (2010b) 1–11
- Pharmacokinetics of Bisphenol A in neonatal and adult CD-1 mice: Inter-species comparisons with Sprague-Dawley rats and rhesus monkeys Doerge D.R., Twaddle, N.C., Vanlandingham, M., Fisher, J.W. Toxicology Letters 207 (2011) 298– 305
- Quantification of deuterated bisphenol A in serum, tissues, and excreta from adult Sprague Dawley rats using liquid chromatography with tandem mass spectrometry Twaddle, N.C., Churchwell, M.I., Vanlandingham, M., Doerge D.R. Rapid Commun. Mass Spectrom. 2010; 24: 3011–3020
- Lactational transfer of bisphenol A in Sprague–Dawley rats Doerge D.R., Vanlandingham, M., Twaddle, N.C., Delclos, K.B. Toxicology Letters 199 (2010c) 372–376
- Distribution of bisphenol A into tissues of adult, neonatal, and fetal Sprague–Dawley rats Doerge D.R., Twaddle, N.C., Vanlandingham, M., Brown, R.P., Fisher, J.W. Toxicology and Applied Pharmacology 255 (2011) 261–270
- Prediction and evaluation of route dependent dosimetry of bisphenol A in monkeys with extrapolation to humans Fisher, J.W., Twaddle, N.C., Vanlandingham, M., Doerge D.R. Toxicology and Applied Pharmacology 257 (2011) 122-36
- Correlation of Structural Class with No-Observed-Effect Levels: A Proposal for Establishing a Threshold of Concern. Munro, I.C., Ford, R.A., Kennepohl, E., Sprenger, J.G. Food and Chemical Toxicology 34 (1996) 829-867
- Estimation of toxic hazard—a decision tree approach. Cramer GM, Ford RA, Hall RL. Food Cosm Toxicol 16 (1978) 255–276
- Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. Kroes R, Renwick AG, Cheeseman MA, Kleiner J, Mangelsdorf I, Piersma A, Schilter B, Schlatter J, van Schothorst F, Vos JG, Wurtzen G. Food Chem Toxicol 42 (2004) 65–83

PK and low dose testing





- PK analysis incorporated into toxicity testing design
- Enhance dose-response interpretation