APPLIED PHARMACOLOGY AND TOXICOLOGY, INC.

Consulting & Research Services

The Human Relevant Potency Threshold (HRPT): Reducing Uncertainty by Human Calibration of Cumulative Risk Assessments

Alliance for Risk Assessment

Beyond Science and Decisions: From Problem Formulation to Dose-Response Assessment: Summary of Case Study

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What is "Expected"?
2 Classical Models for Non-Interaction

Loewe Additivity
[Dose Addition]

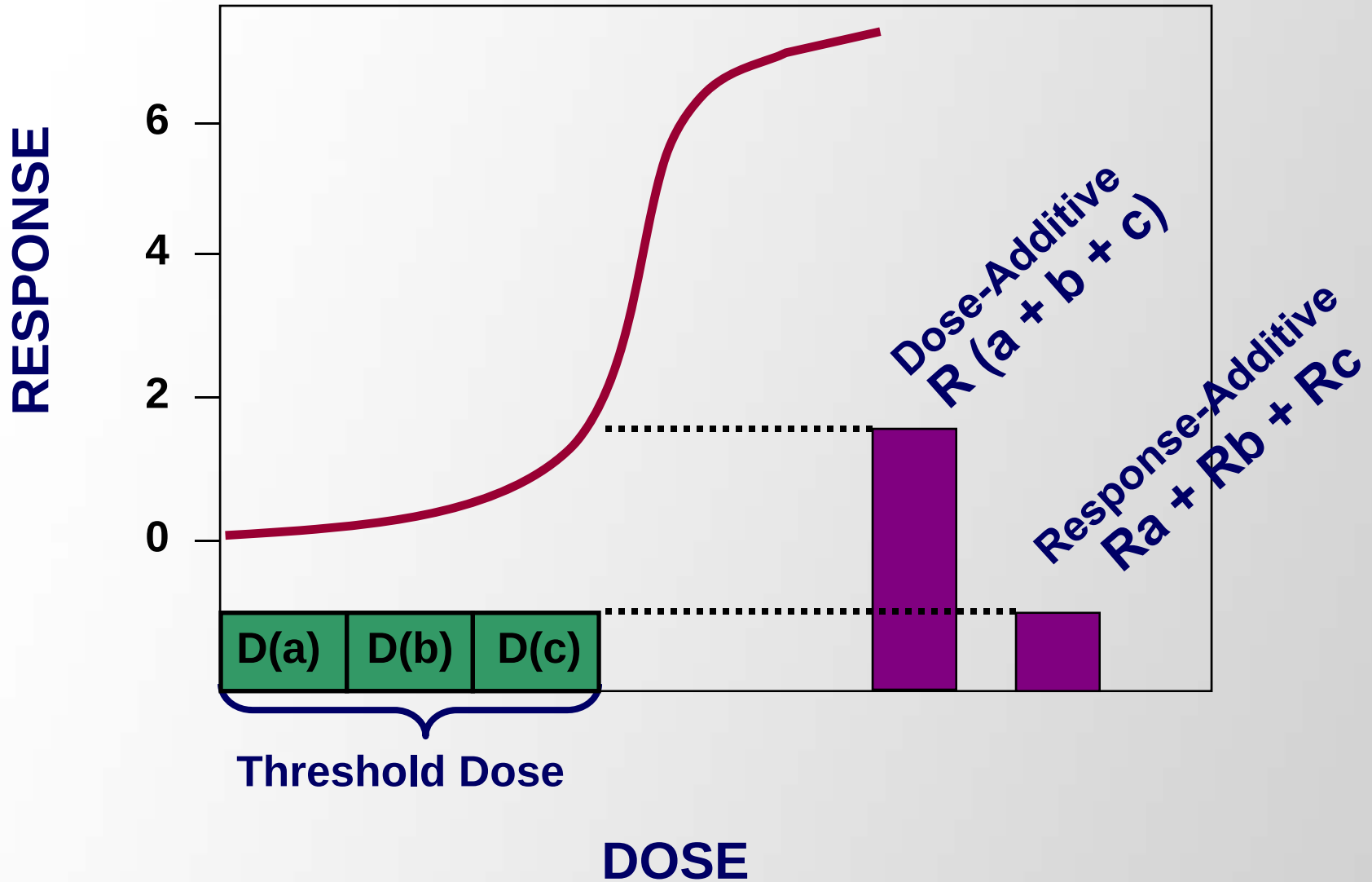
- No self-interaction
- Agents act as simple dilutions (potency, DRC)
- Sum doses & potencies of each agent
- $D_a/D_A + D_b/D_B = 1$

Bliss Independence
[Response Addition]

- Statistical independence
- Relative effect of A not influenced by B
- Sum effects of each agent
- $E_{A+B} = E_A + E_B - (E_A \times E_B)$

Impact of the No-Interaction Model

Borgert et al. 2004. TAAP Vol *201*(2): 85-96.



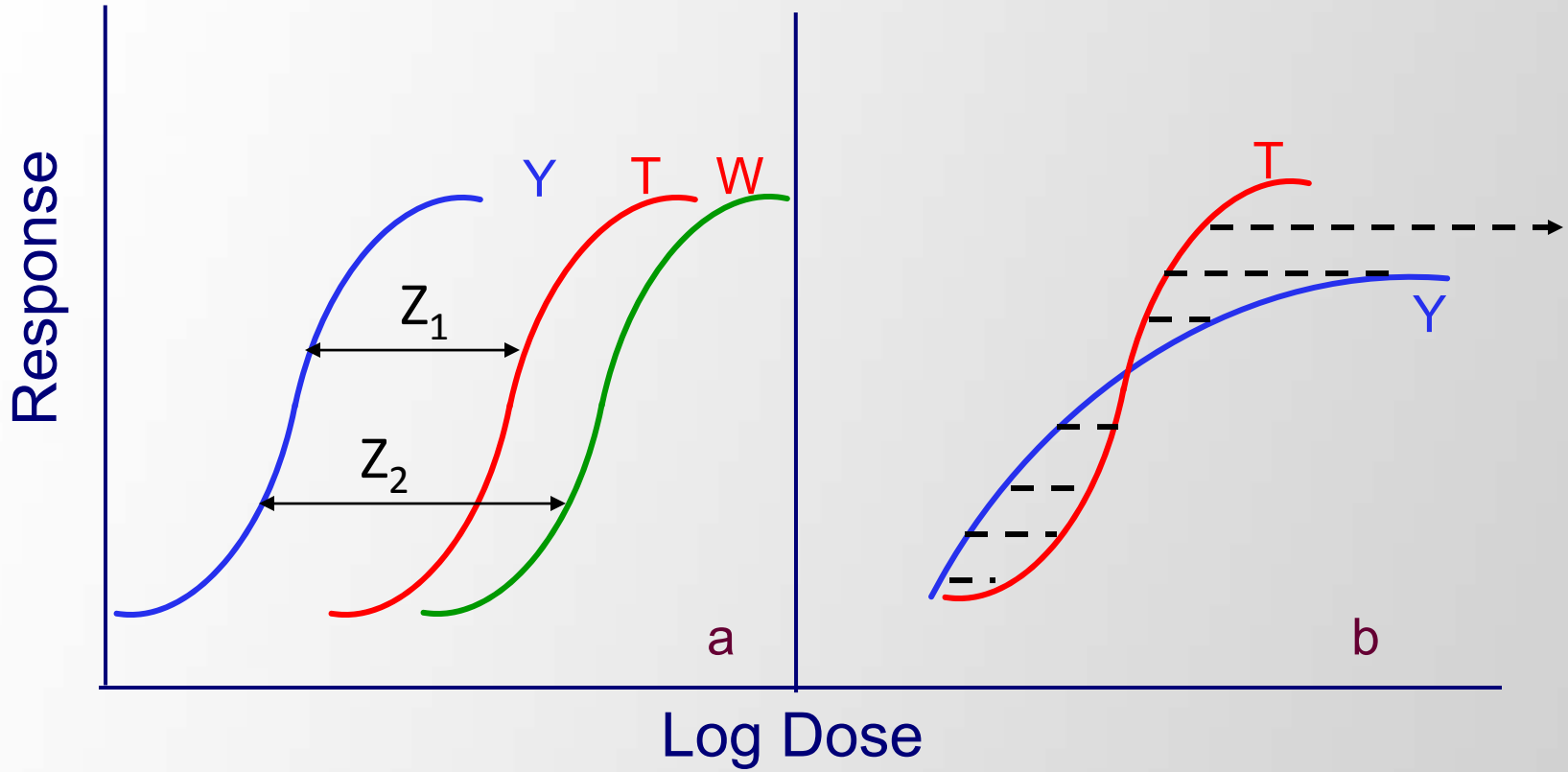
Assumptions of RPF/TEQ Approach

Safe, Environ. Health Persp. 106:1051-8.1998

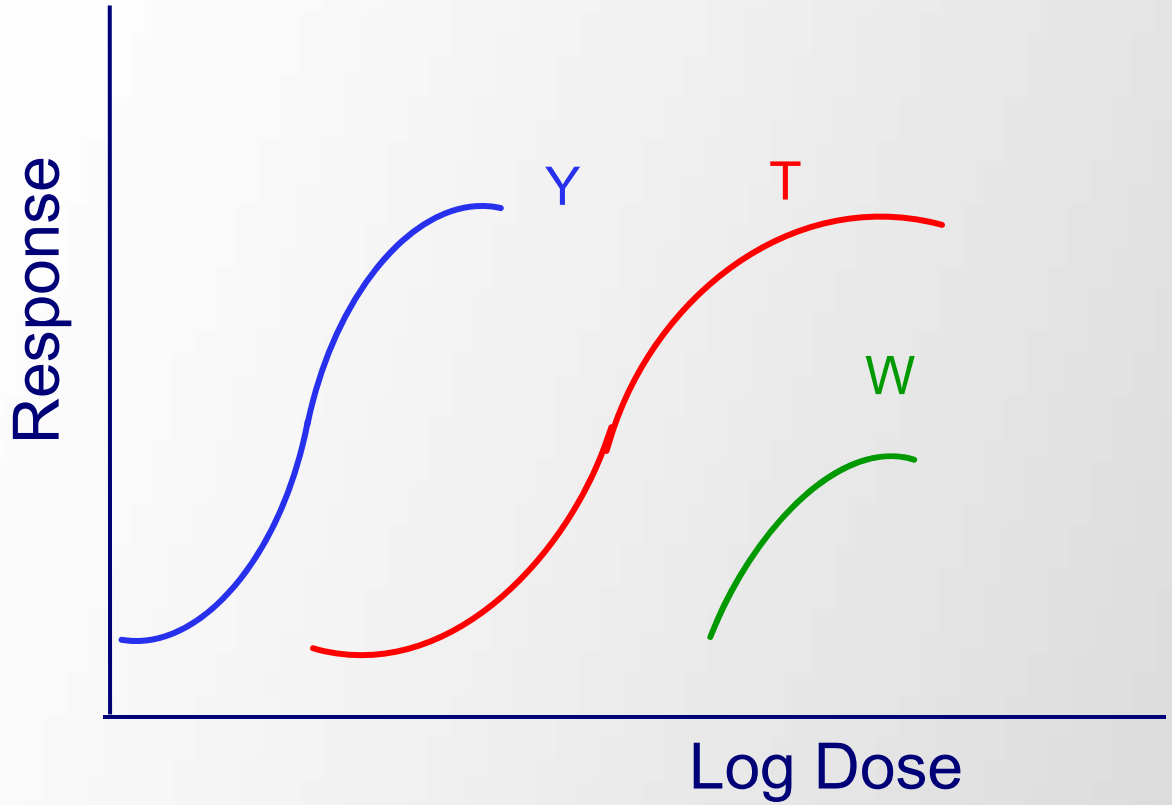
- Chemical congeners;
- Same molecular targets;
- Same biochemical pathways;
- Similar pharmacokinetic characteristics;
- Identical tissue- and organ-level toxic manifestations;
- Parallel log dose-toxicity curves;
- Non-interaction (dose additivity in mixtures);
- Simplifies mixture assessment.
- TEQ = ΣTEFs (i.e., RPF) of individual congeners X concentration (or dose) in the mixture

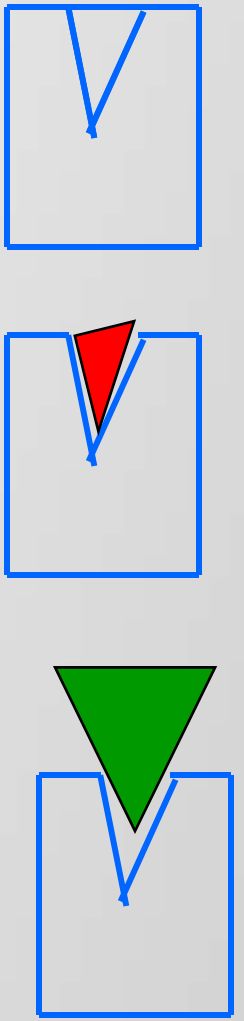
[Note Similarity to Hazard Index Approach]

Figure 1. Rationale for parallel DRC requirement



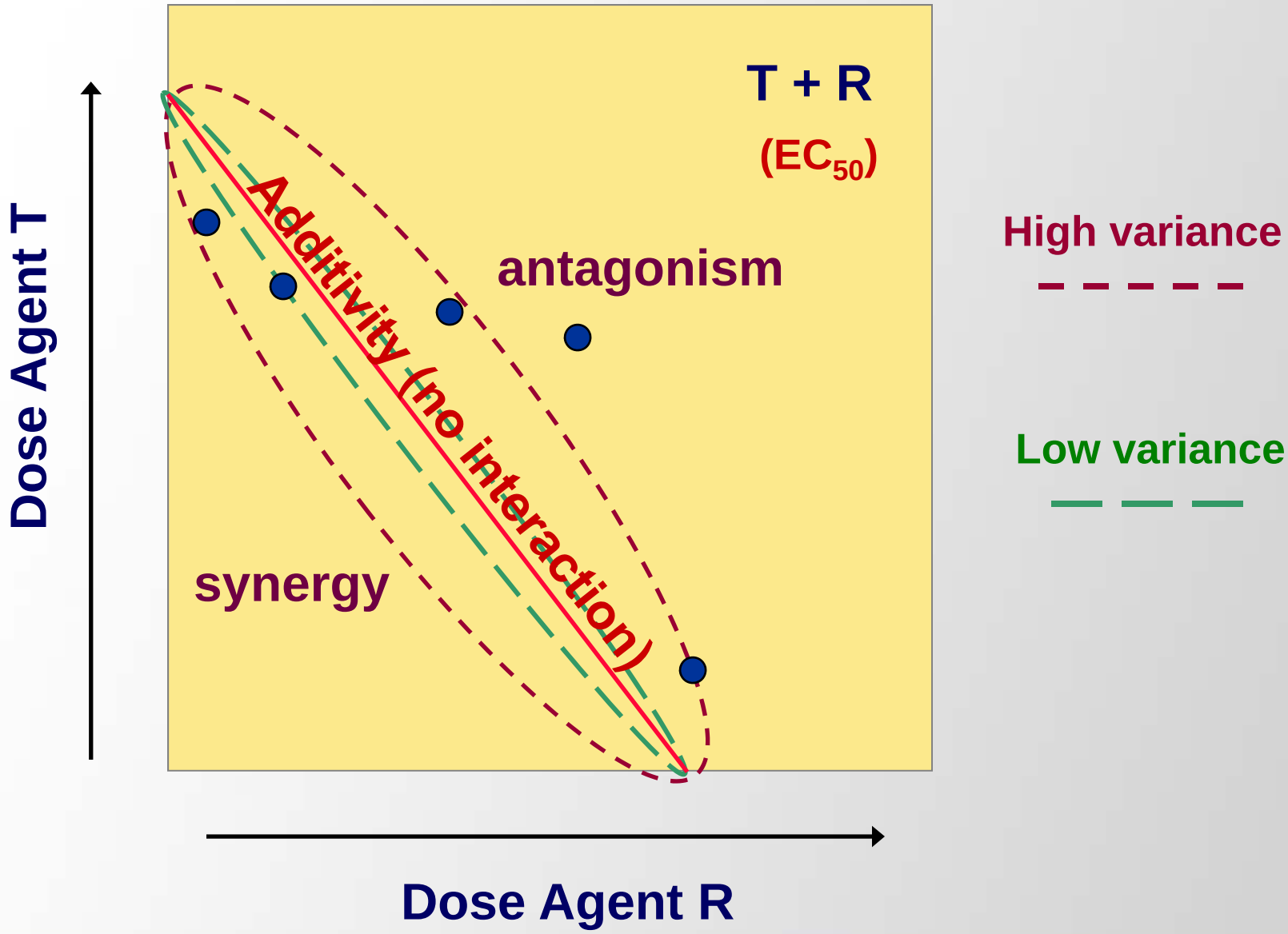
Affinity & Intrinsic Activity





Isobologram

Borgert et al. 2005.



Tallarida RJ. 2006. *Perspect. Pharmacol. 319(1): 1-7*

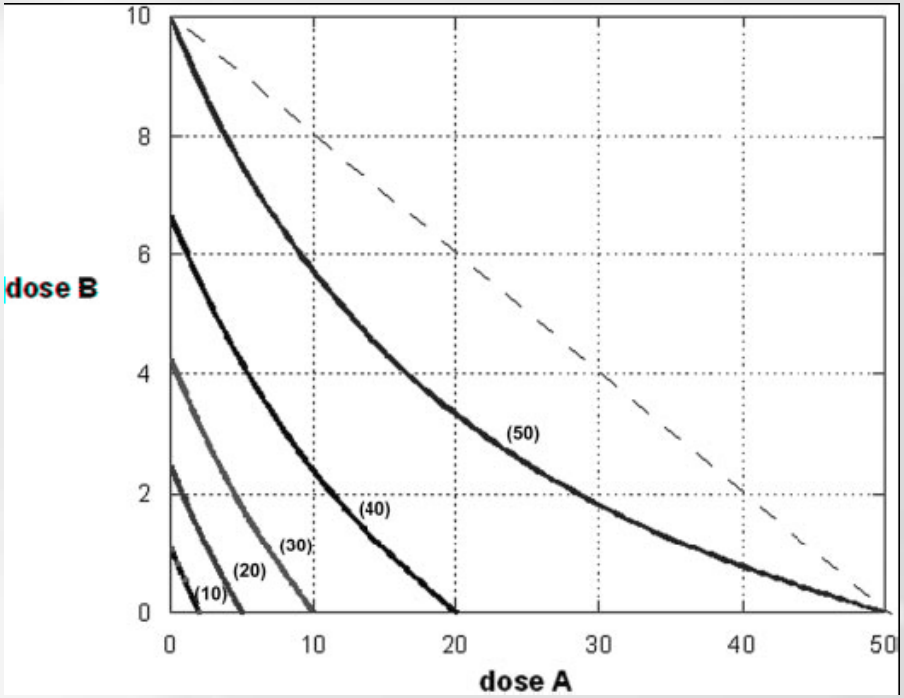


Fig 3: Additive isoboles for combinations of a full and a partial agonist at several different effect levels.

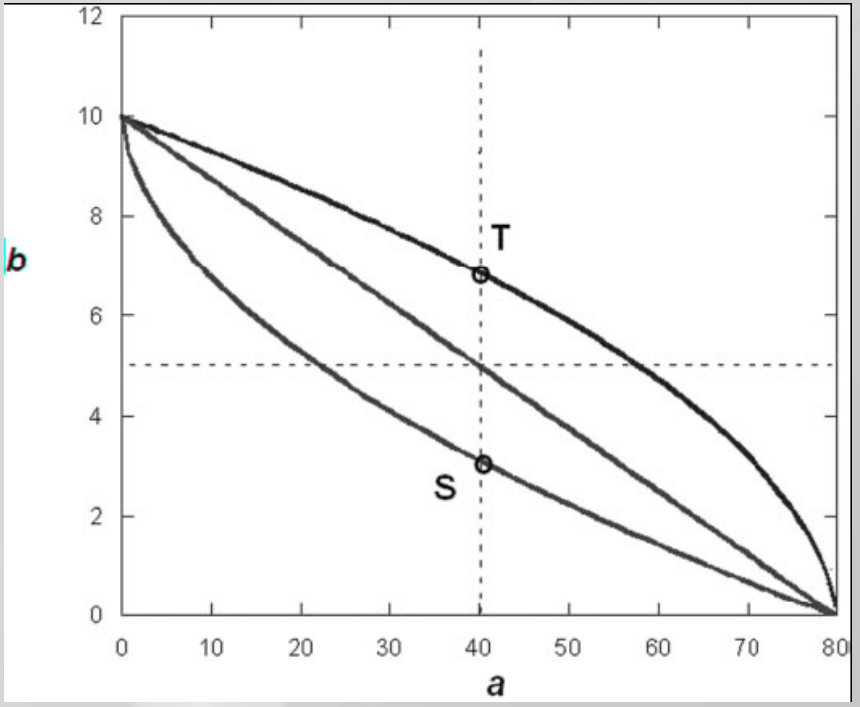
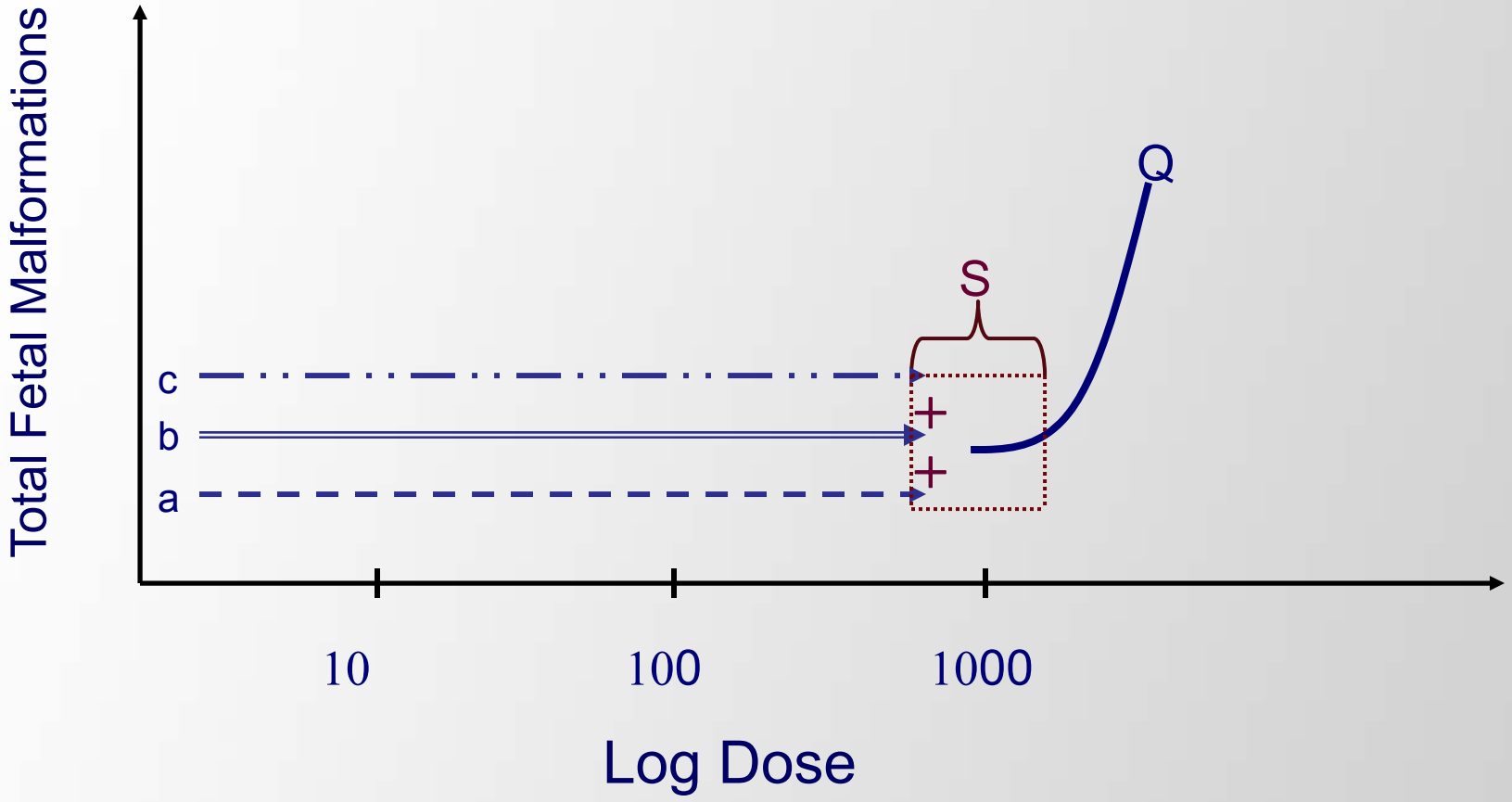


Fig 4: Additive isoboles at 50% effect level for two full agonists that have a variable potency ratio (non-parallel dose-response curves).

Figure 2a. Generation of dose addition data



Borgert et al. 2005. Thrombosis Research 117: 123-132.

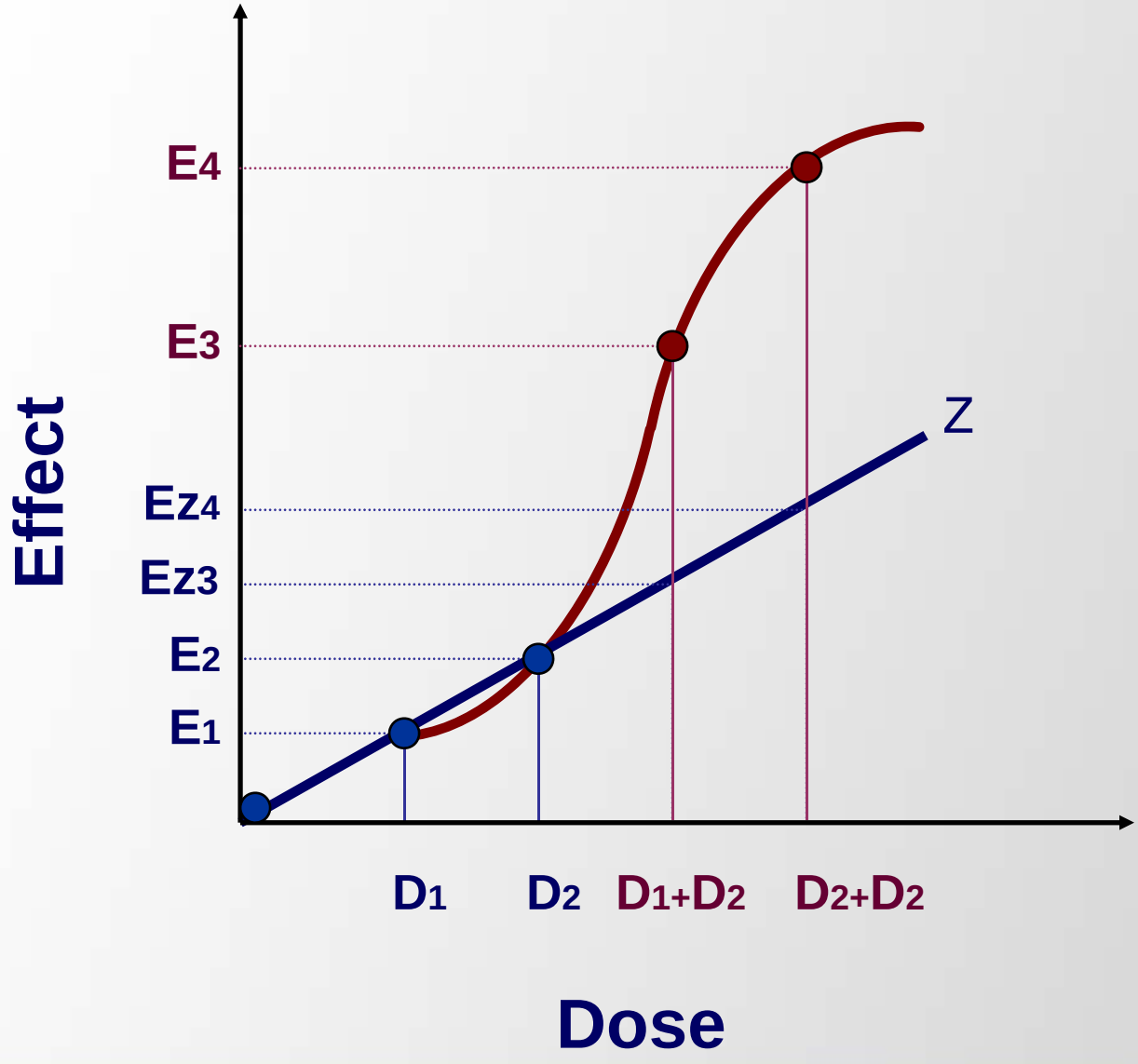


Figure 2b. Extrapolation of mixture data to DA-CAOS model

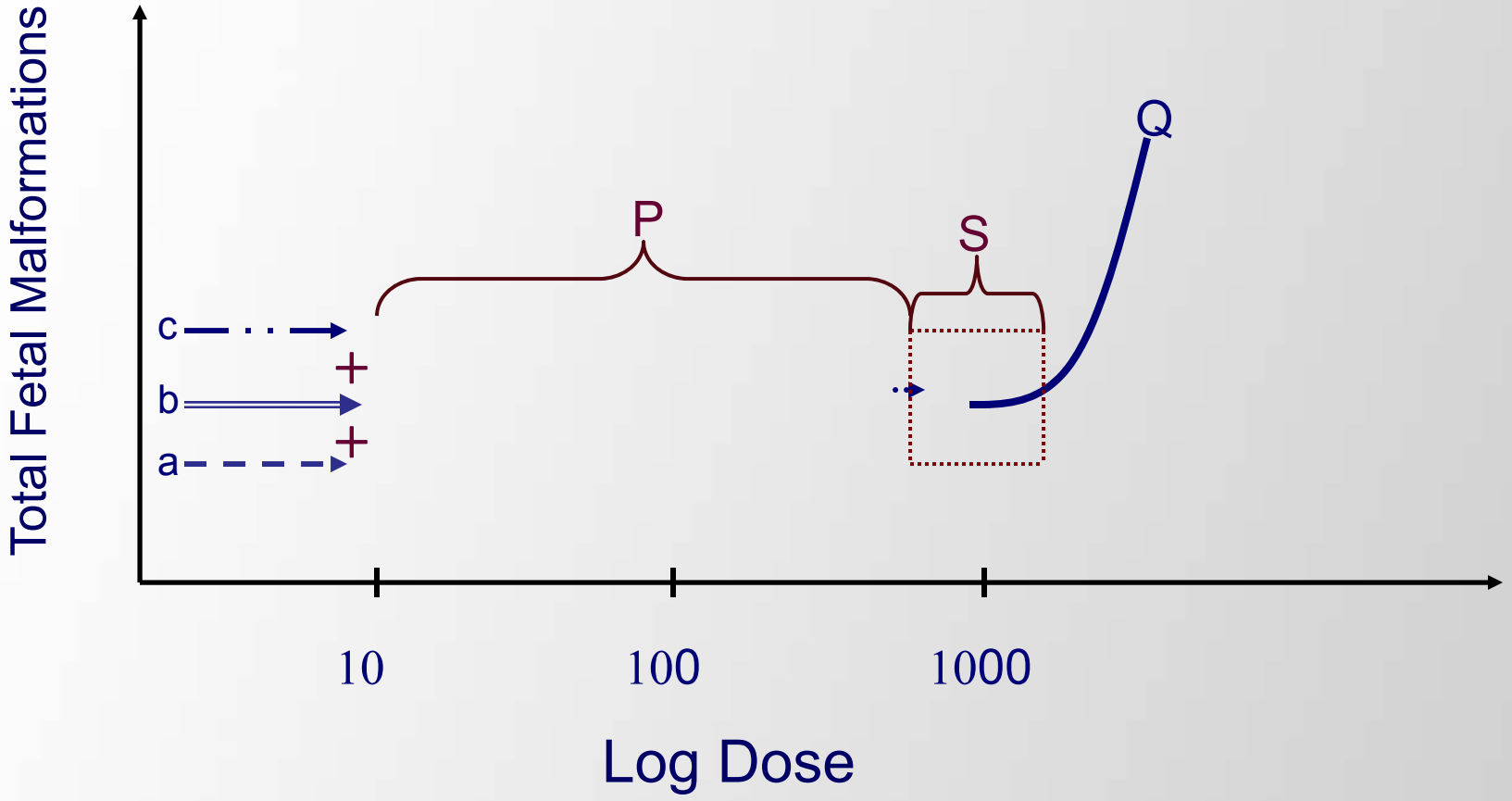


Figure 3-1. Statistical analysis of uncertainty; isoboles created from Bootstrap procedure

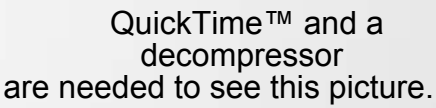
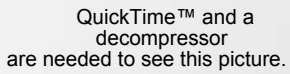


Figure 3-2. Statistical analysis of uncertainty; isoboles from Bootstrap procedure



Extrapolation of uncertainty in mixture data to DA-CAOS model

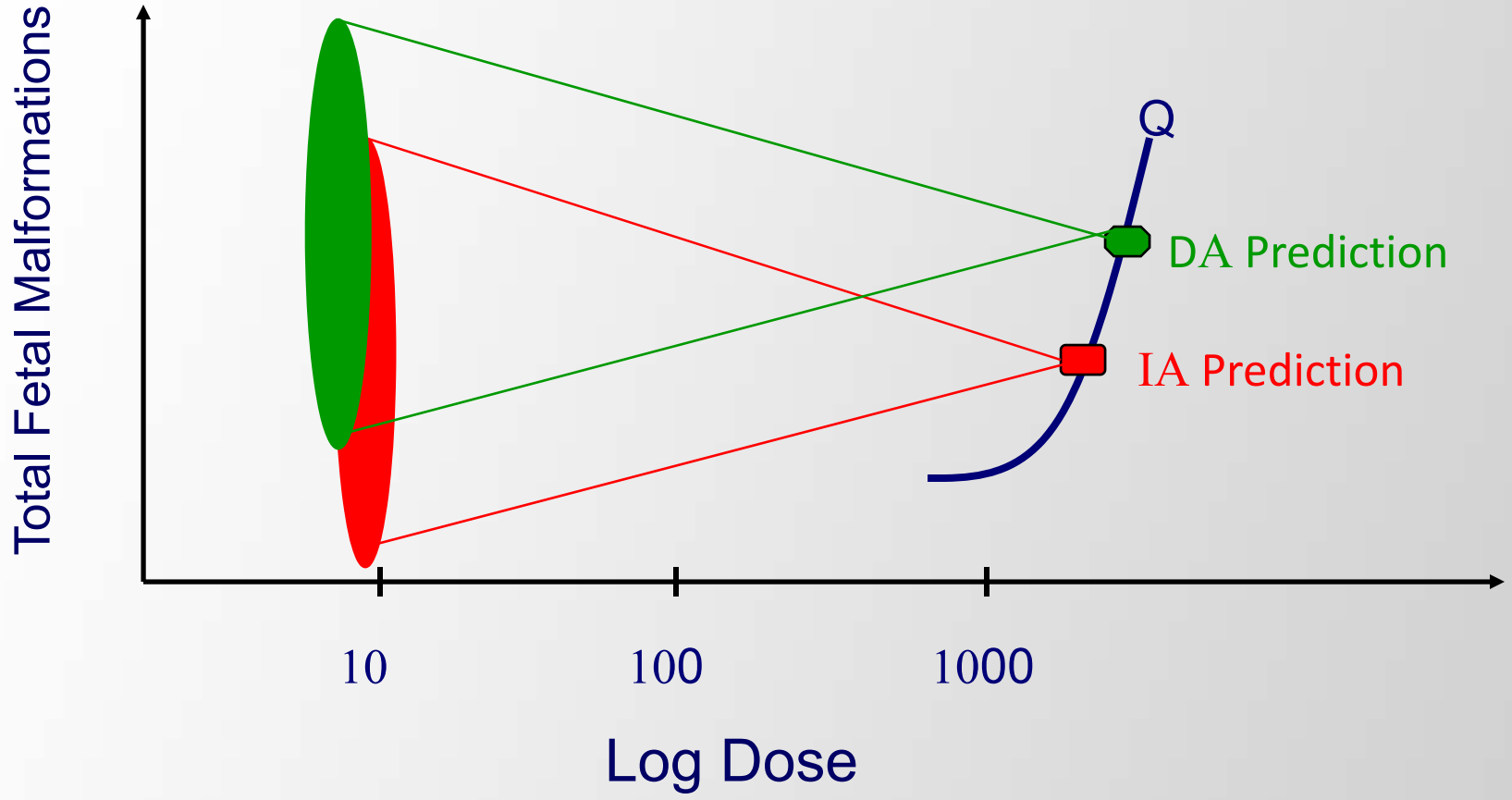
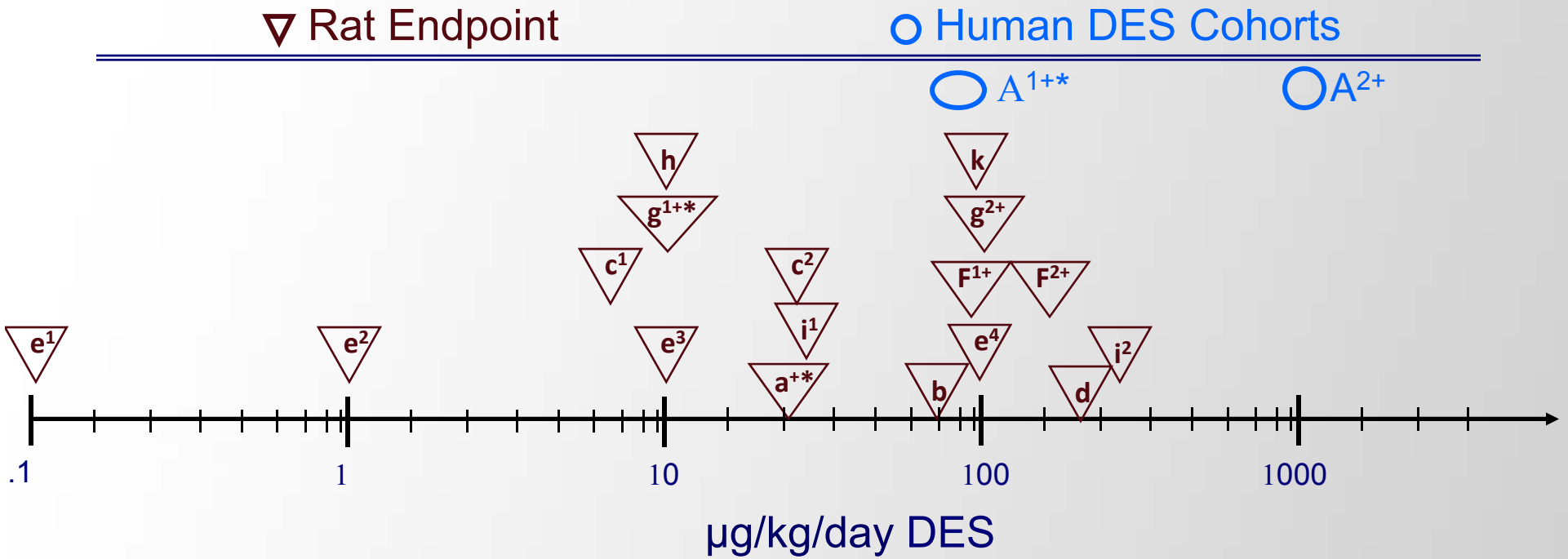


Figure 4. DES Potency Comparison for Male Reproductive Tract Parameters



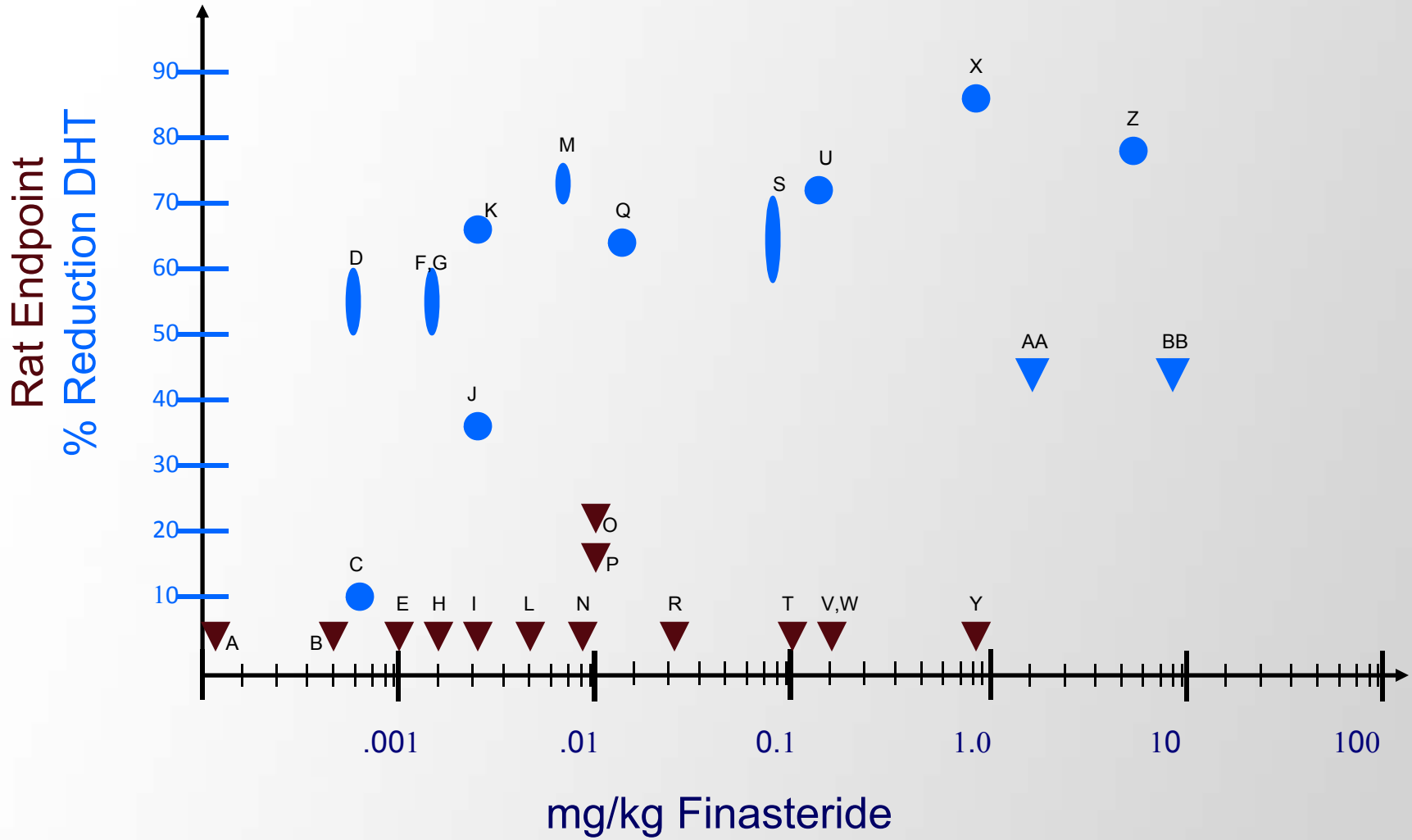
Thresholds for Human Repro Effects: DES

***Golden et al. 1998. Critical Reviews in Toxicology,* 28(2):109-227.**

- Widely prescribed to 4-5,000,000 pregnant women until 1972 in mistaken belief that it would prevent miscarriage.
- Large numbers of males & females exposed *in utero* to widely differing dosing protocols.
- Use discontinued in 1972 with discovery that small number of women developed vaginal adenocarcinoma; male malformations.
- 100s of clinical studies on DES-exposed men and women.

Institution	Estimated Mean Total Maternal Dose (g)	
Mayo Clinic	1.4	No effects in DES males
Stanford Univ.	3.5	
Boston Univ.	6.4	
DES Efficacy trial	10+	
Univ. Chicago	12	↓sperm counts, ↓penis size
British Medical Res. Council	18	cryptorchidism

Figure 5. Finasteride Potency Comparison for Human Clinical Suppression of DHT versus Rat Endpoints



Assertions of DA-CAOS Risk Assessment (Kortenkamp & Faust, 2010)

- 8% of all chemicals exhibit anti-androgenic potential; = “thousands of chemicals on the market in the EU.”

- Daily exposure to the 95% UCI of 15 anti-androgens combined exceeds an acceptable risk level and may be responsible for hypospadias and cryptorchidism from gestational exposure.

Logical Predictions of the DA-CAOS Model (Borgert et al. 2012)

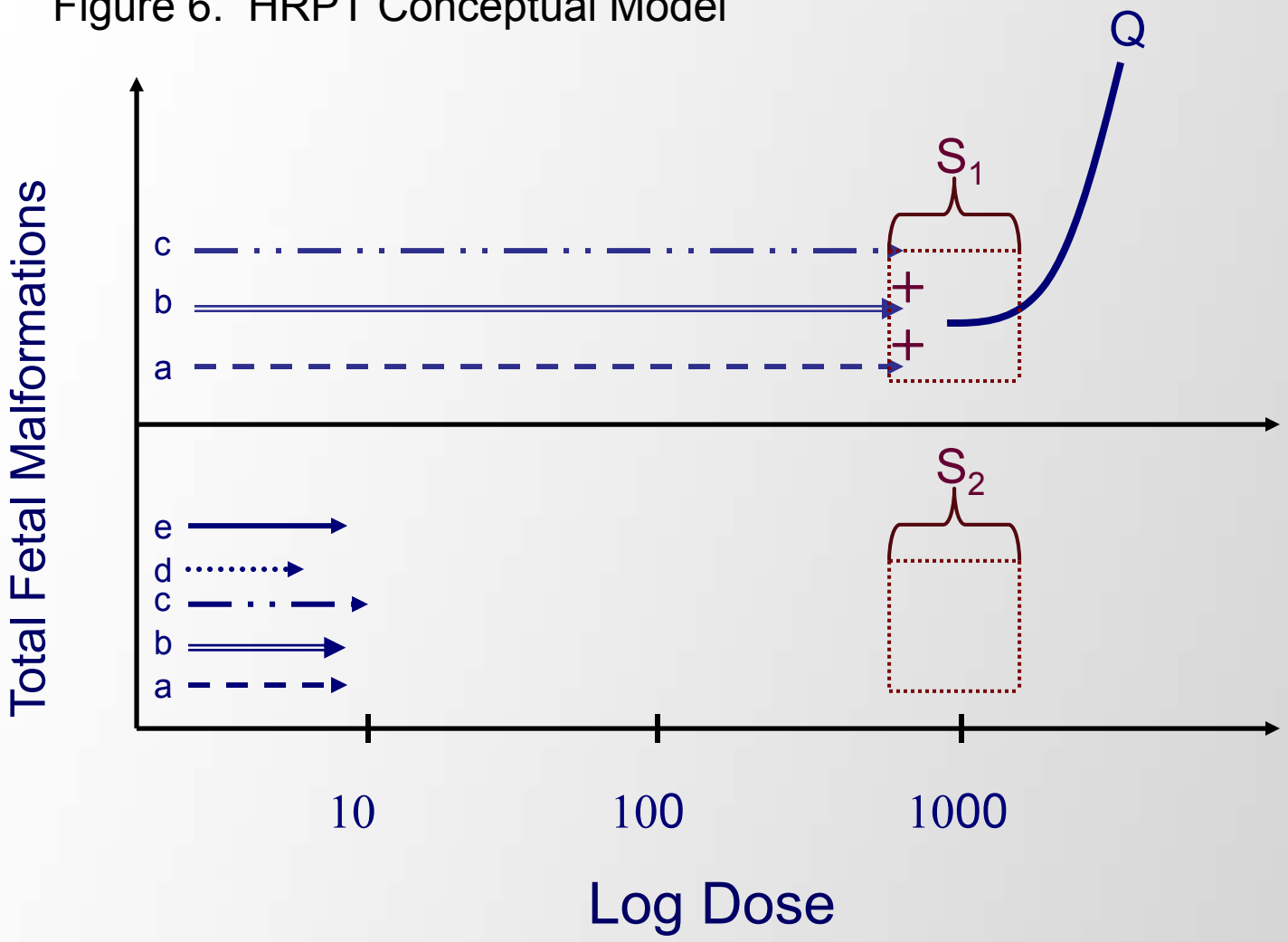
- Based on a 10% PoD, 0.5% may be expected to experience effects from exposure to 15 anti-androgens;

- Therefore, exposure to 1500 chemicals with anti-androgenic potential may be expected to produce effects in ~ 50% of the exposed population, and 3000 chemicals in ~ 100% of the exposed population.

BUT

. . . . the actual incidence of hypospadias (0.2-1%) and cryptorchidism (2-9%) is much lower.

Figure 6. HRPT Conceptual Model



HRPT Methodology

1. Define the common adverse outcome or target organ effect;
2. Identify the chemicals known to produce the common adverse outcome in the test species and data that demonstrate DA in mixtures;
3. Define, if possible, the modes of action that can lead to the adverse outcome in the test species;
4. Identify chemicals and drugs known to produce the adverse outcome in humans;
5. Identify chemicals for which the TEQ concept is justified;
6. Compare dose-response data for the chemicals and drugs of interest in humans and the test species;
7. Estimate the potency differential between species, and thus the potency threshold at which DA would be a conservative but tenable assumption for humans.

HRPTs for Anti-Androgens

- A conservative effect-based HRPT can be set at doses 1/5 the rat LOAELs / NOAELs for CAOS on the developing male reproductive tract.
- A conservative potency-based HRPT can be set 1 order of magnitude below the potency of finasteride for effects on the rat male reproductive tract from androgen deficiency via inhibition of 5-alpha-reductase.
- Independent Action (IA) should be applied as the most appropriate mixture model for human exposures to mixtures of potential anti-androgenic chemicals at concentrations lower than the derived HRPTs.

Strengths, Weaknesses, Data Requirments

- Leverages well-established TEQ approach and tenable elements of DA-CAOS approach.
- Uses human data for human risk assessment.
- Addresses and reduces uncertainty in dose-response model and species extrapolations.
- Generally applicable when data requirements are met (not available for all chemicals).
  - Human pharmaceutical or hormonal potency data
  - MoA data