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Consulting & Research Services

Uncertainty vs. Certainty in Cumulative Risk Assessment: *Anti-Androgens*

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Summary

- Dose additive (Hazard Index) cumulative effects have not been demonstrated except at doses near the observable effect range.
- Dose addition is NOT a generalized phenomenon; there is no scientific basis for extrapolation to lower doses.
- It is impossible to be protective without accuracy.
- A more rationale and protective approach would employ a Human-Relevant Potency-Threshold.

Background

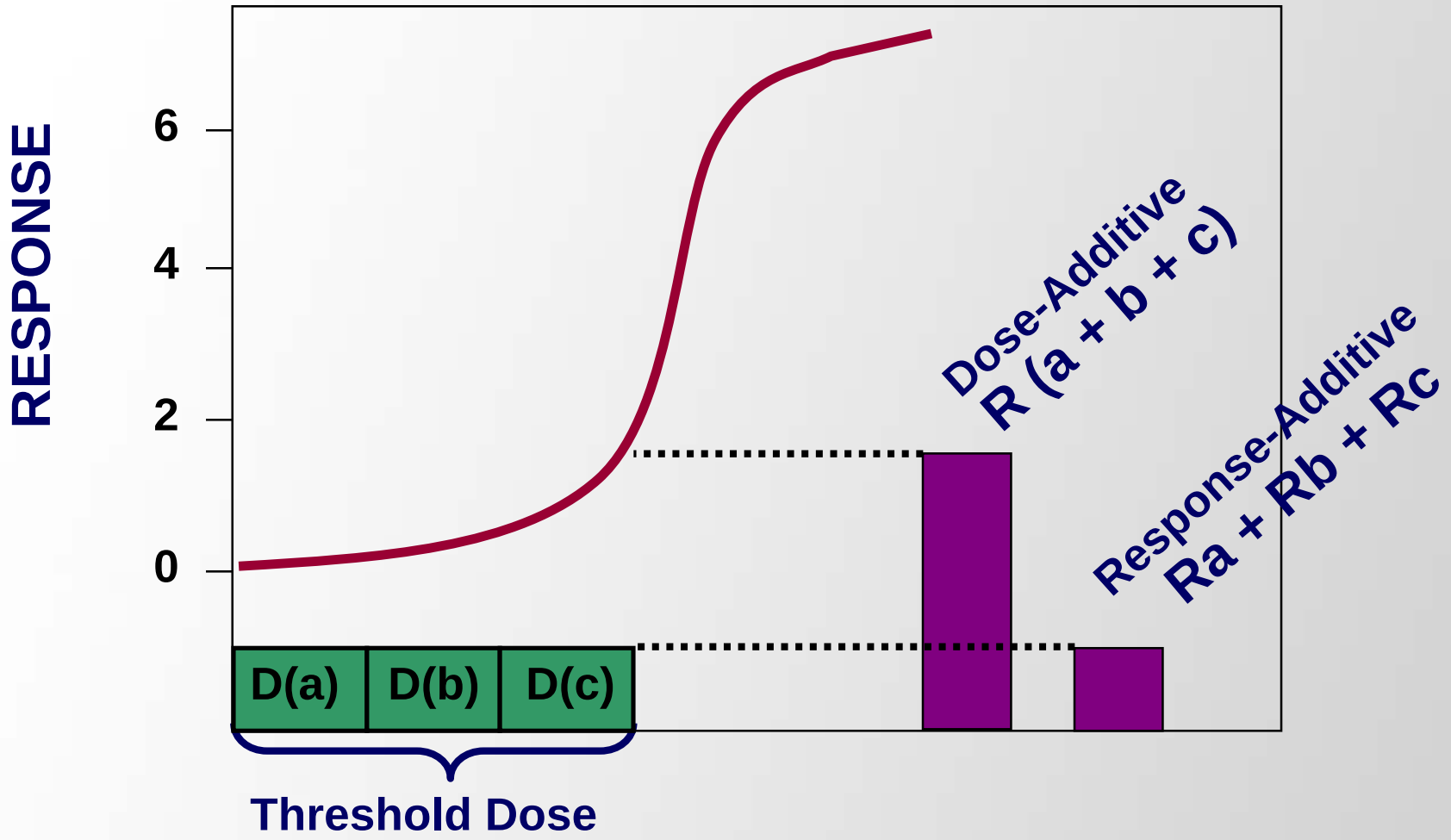
- Gray and Kortenkamp have independently reported cumulative effects of anti-androgenic chemicals (drug, pesticides, phthalate esters) on male reproductive tract malformations, testosterone levels, and secondary sex characteristics in the rat.
- Based on these results, a cumulative risk approach is proposed that utilizes a Hazard Index calculation for anti-androgenic chemicals that affect the male reproductive tract.
- The approach is based on a precautionary preference for the concentration-addition (dose addition) model of combined action.

Uncertainties

1. Both Gray and Kortenkamp evaluated a single ratio of mixture components across a dose range near the No Effect Level. However, mixture effects vary with both the concentrations *and* ratios of the constituents.
2. Both Gray and Kortenkamp evaluated scored endpoints for their mixture analysis, which makes quantification of variance very difficult. Both groups segregated mild malformations into the "no malformation," i.e., zero effect group. This could bias the mixture analysis toward rejecting response addition near the NOEL.
3. Gray reported that the response addition model of combined action did not predict mixture effects; Kortenkamp generally found that both concentration addition and response addition predicted mixture effects, but also found some evidence for synergism.
4. Both Gray and Kortenkamp combined scored endpoints for some analyses; statistical methods for assessing variance unclear.
5. Borgert, Casella, Golden working on statistical models to understand uncertainties and certainties and exploring how a HRPT might be developed.

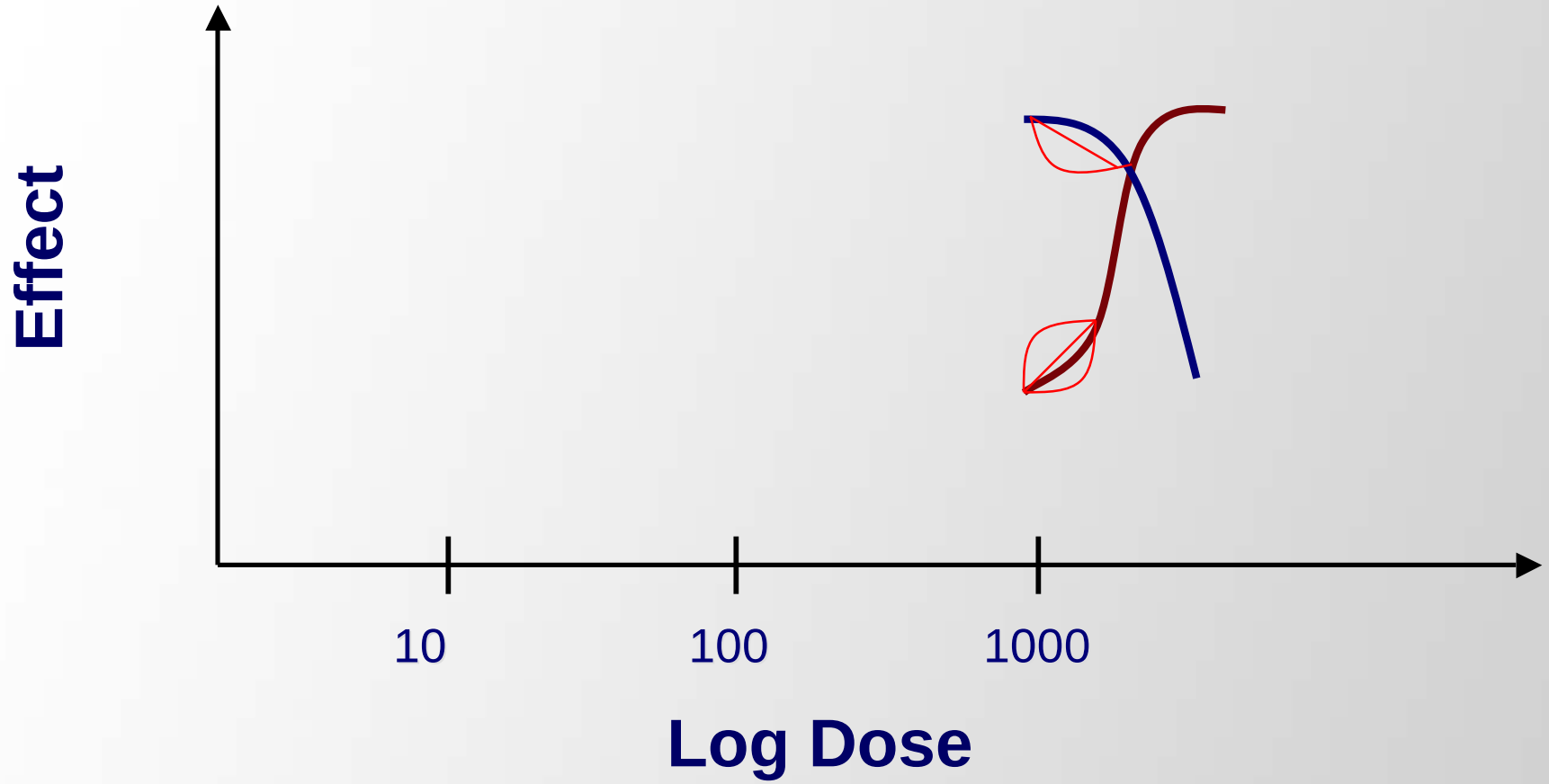
Impact of the No-Interaction Model

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



Extrapolation of the No-Interaction Model

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



Progress ?

Examples of Mechanisms With Dose-Dependent Transitions

Slikker et al. 2004. TAAP Vol *201*(3): 203-225.

- Absorption / Distribution / Excretion
- Metabolic handling
- Efficiency
  - DNA repair
  - Cell killing
  - Rate of cell replication
- Detoxifying enzyme systems
  - Modifying factors
- Co-substrate depletion
- Chemical transformation / activation
- Altered homeostasis
  - Essential nutrients
  - Hormones
- Repair mechanisms
- Blood flow and diffusion limitation

Charles et al. 2007. *Toxicol. Appl. Pharmacol. 218: 280-288*

Question-

- Are mixtures of estrogenic synthetic chemicals (SC) dose additive in combination with phytoestrogen (PE) mixtures?
- Determined dose of SC mixture necessary to produce an estrogenic response greater than PEs alone.

Results-

- No increase in response due to the addition of SC mixture at 0.02μM and 0.2μM.
- Very slight increase with addition of SC mixture at 1.0μM and 2.0μM.
- Clearly significant increase (p=0.006) at 3.0μM

Conclusion- **SC mixture increased estrogenic response over PE background only when each chemical in the mixture was ≥ 0.5x its individual NOEL in the estrogenic assay.**

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
- 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

Conclusions

- Dose additive (Hazard Index) cumulative effect models could be justified for high potency chemicals or at doses near the observable effect range.
- A Human-Relevant Potency-Threshold could be used to differentiate supportable from unsupportable applications of dose addition model.
- Developing a HRPT for anti-androgens should be possible based on data for human pharmaceuticals.