The ILSI Key Events Dose Response Framework: Improving Hazard Characterization of Chemicals

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Risk assessment

Hazard ID
Hazard characterisation

Uncertainty factor

Reference value (e.g. ADI)
[RV] = RP/UF

Exposure assessment
Risk characterisation

Use of science to underpin the use of reference values (ADIs, etc)

- The RV approach is based on the premise that most toxicological endpoints have a true biological threshold, although this is not identifiable with precision
- Risk assessment would be improved if the existence of such thresholds could be established mechanistically

Traditional approach to hazard characterization

- Identify point of departure (NOAEL/BMDL), from epidemiological or experimental evidence, to serve as reference point, and apply default uncertainty factors
- The RP is not a no-effect level and derivation of “acceptable” doses requires assumptions about thresholds and variability in those thresholds
- In studies of inherently limited power, it is implicit that there is uncertainty as to the magnitude of the response, if any, at the RP
- Are the assumptions in risk assessment conservative overall?

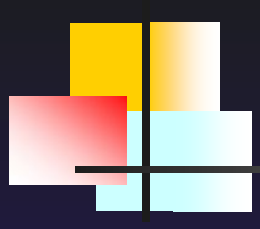
Key Events Dose-Response Framework

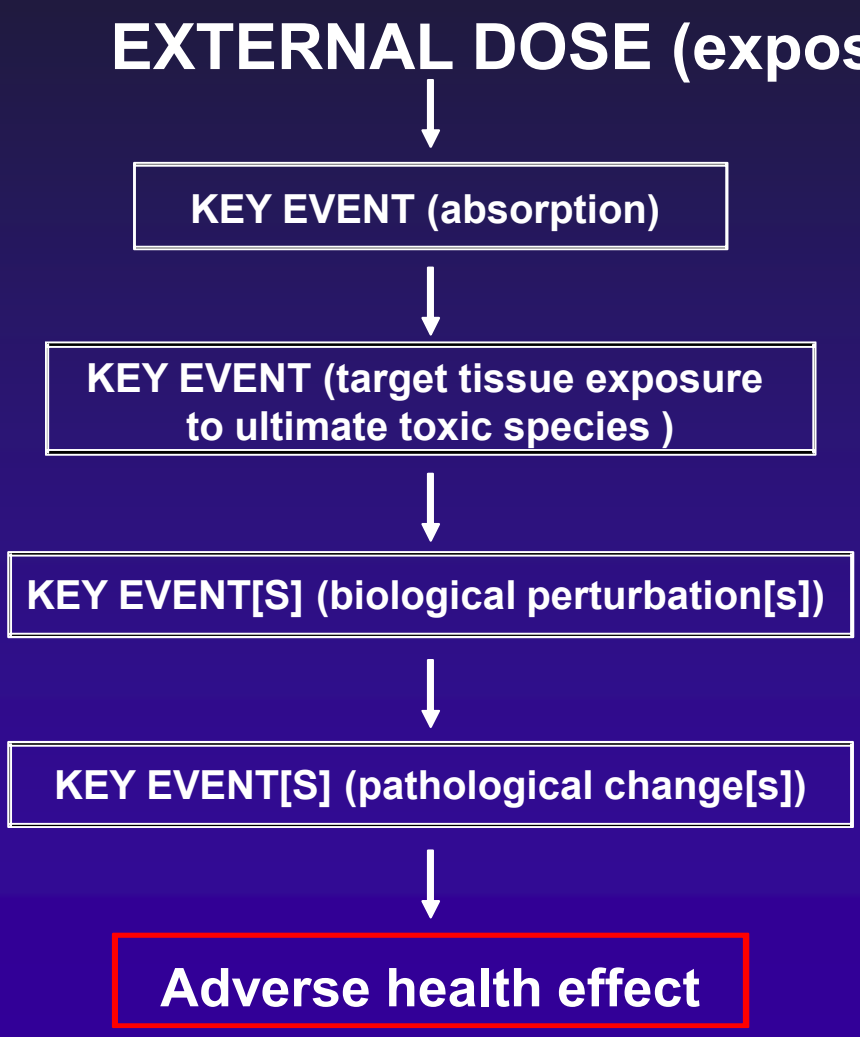
- ILSI Research Foundation established a tripartite, multidisciplinary activity to develop an integrated framework to incorporate advances in scientific knowledge to support sound scientific decisions
- Based on mode of action concept, with focus on understanding the fundamental biology and dose-response (including possible thresholds) at each key event, to inform hazard characterization and risk assessment
- *Crit. Rev. Food Sci. Nutr.* **49**(8), September 2009 – open access

ILSI RF Threshold Working Group

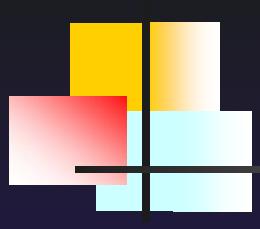
- Chemical Group: Alan Boobis (Imperial College London), George Daston (Procter & Gamble), and Julian Preston (EPA)
- Nutrient Group: Sanford Miller (U Maryland), Joseph Rodricks (ENVIRON), Ian Munro (CANTOX), A. Catharine Ross (Pennsylvania State), Robert Russell (Tufts), and Elizabeth Yetley (retired NIH)
- Allergen Group: Steven Gendel (FDA CFSAN), Geert Houben (TNO), and Steve Taylor (U Nebraska)
- Pathogen Group: Bob Buchanan (U Maryland), Arie Havelaar (RIVM), Mary Alice Smith (U Georgia), and Richard Whiting (Exponent)
- ILSI RF: Stephen Olin and Elizabeth Julien

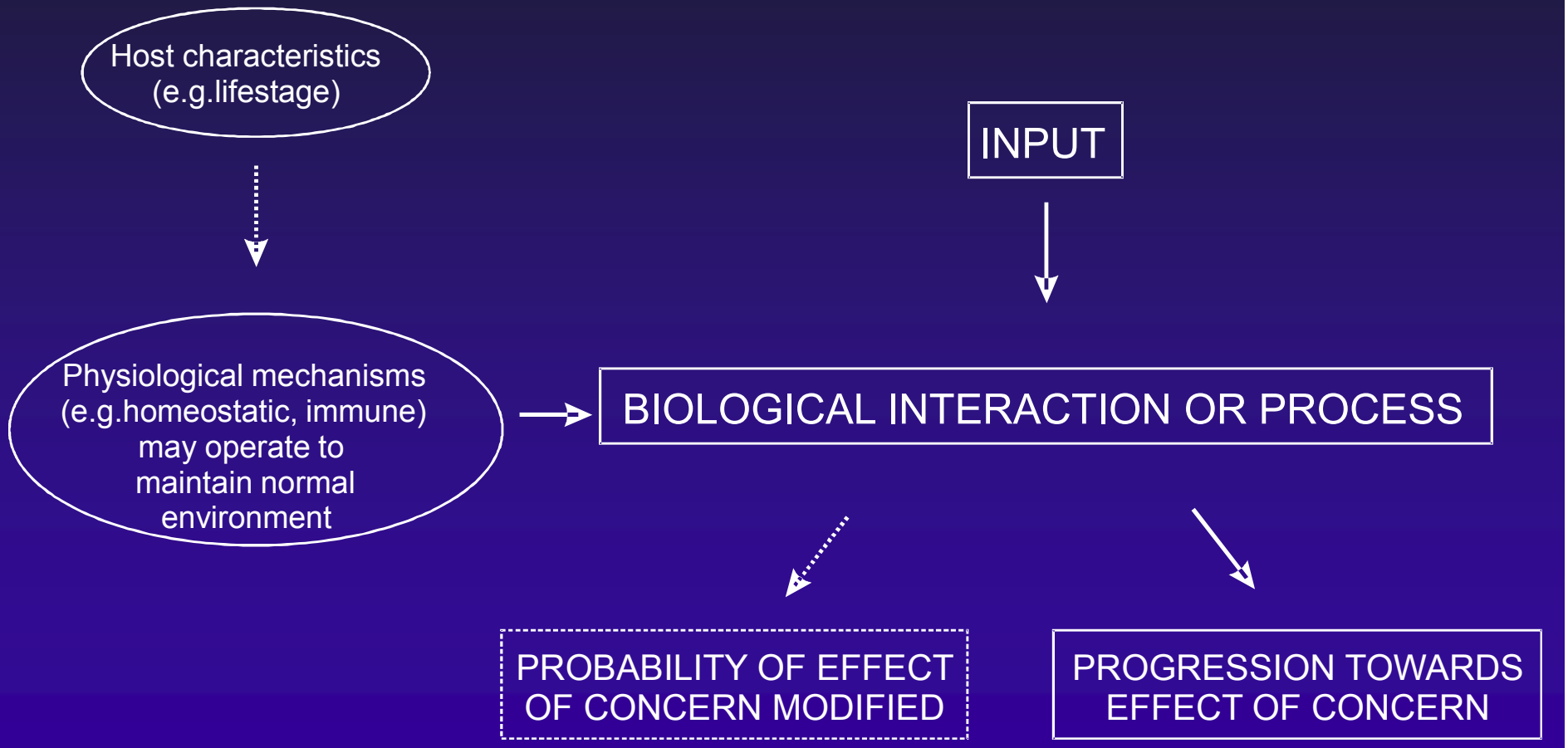
Mode of action and key events





Factors operating at the level of a key event





Address each key event systematically

- Is a minimum dose level [input] required in order for this key event to occur? What data would be needed to demonstrate this?
- Is any one key event rate limiting, driving the shape of the overall dose-response curve?
- What response mechanisms (e.g. homeostasis, repair) are involved? At what dose [input] would these be overwhelmed?
- What modifying factors (e.g. lifestage, disease state, nutritional status) can potentially reduce the effectiveness of response mechanisms? What factors can increase the effectiveness of response mechanisms?
- Do such modifying factors change the dose level at which response mechanisms become overwhelmed? What data would be needed to demonstrate this?

Case studies

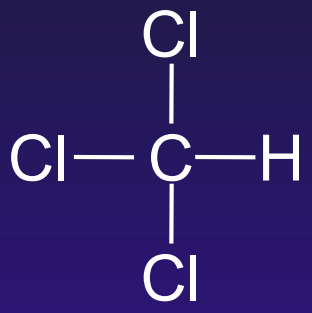
- Chemicals
  - Non-DNA-reactive carcinogen (chloroform)
  - DNA-reactive carcinogens
  - Endocrine active (binding to estrogen receptor)
- Nutrients
  - Vitamin A (retinol) toxicity
- Pathogens
  - General discussion of toxigenic, toxicoinfectious, and invasive bacteria
  - *Listeria monocytogenes*
- Food Allergens
  - General discussion of key events for elicitation

Postulated MOA for $CHCl_3$

Oxidative CYP2E1 Metabolism

Phosgene

Chloroform



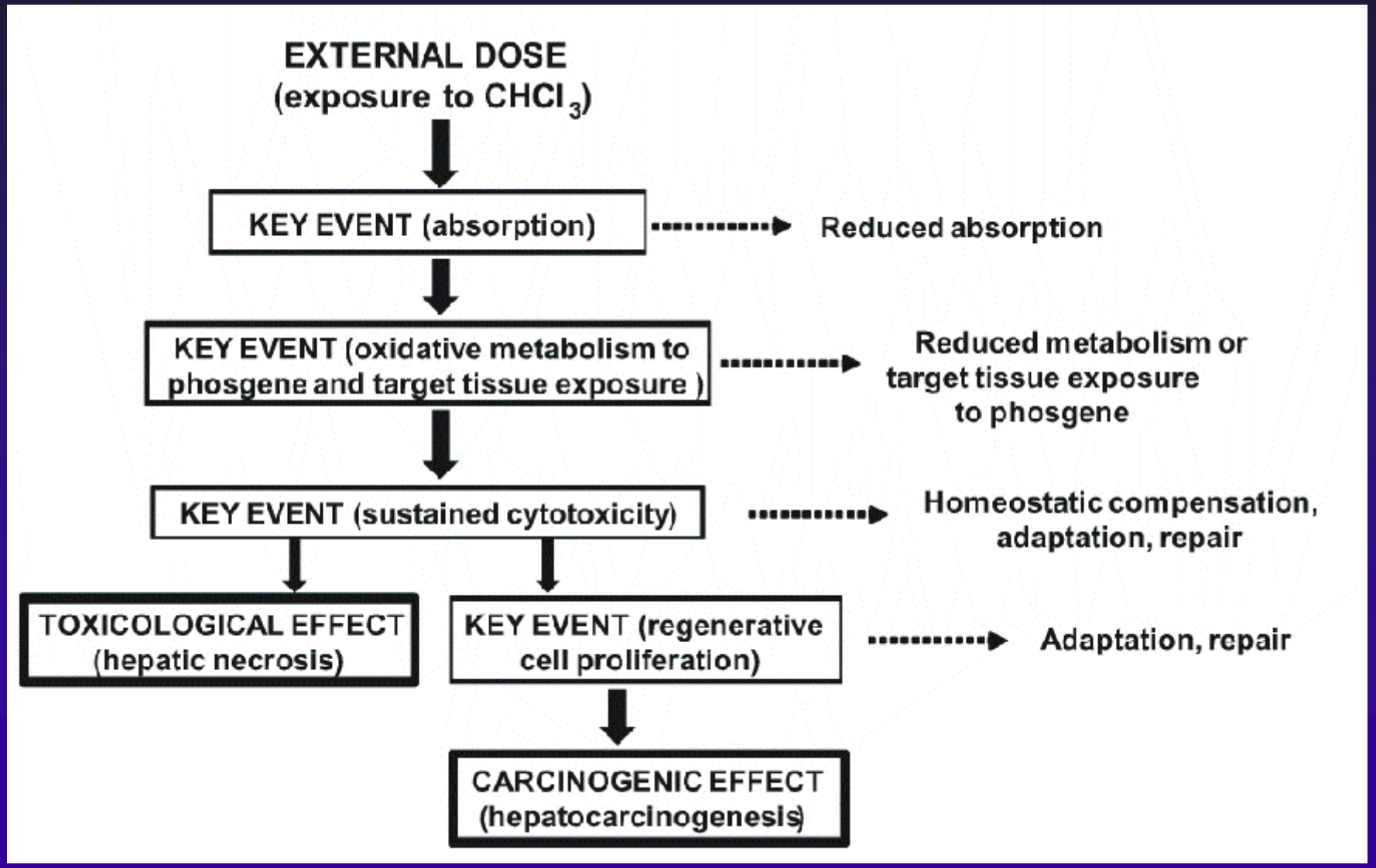
Sustained cytoxicity

Regenerative cell proliferation

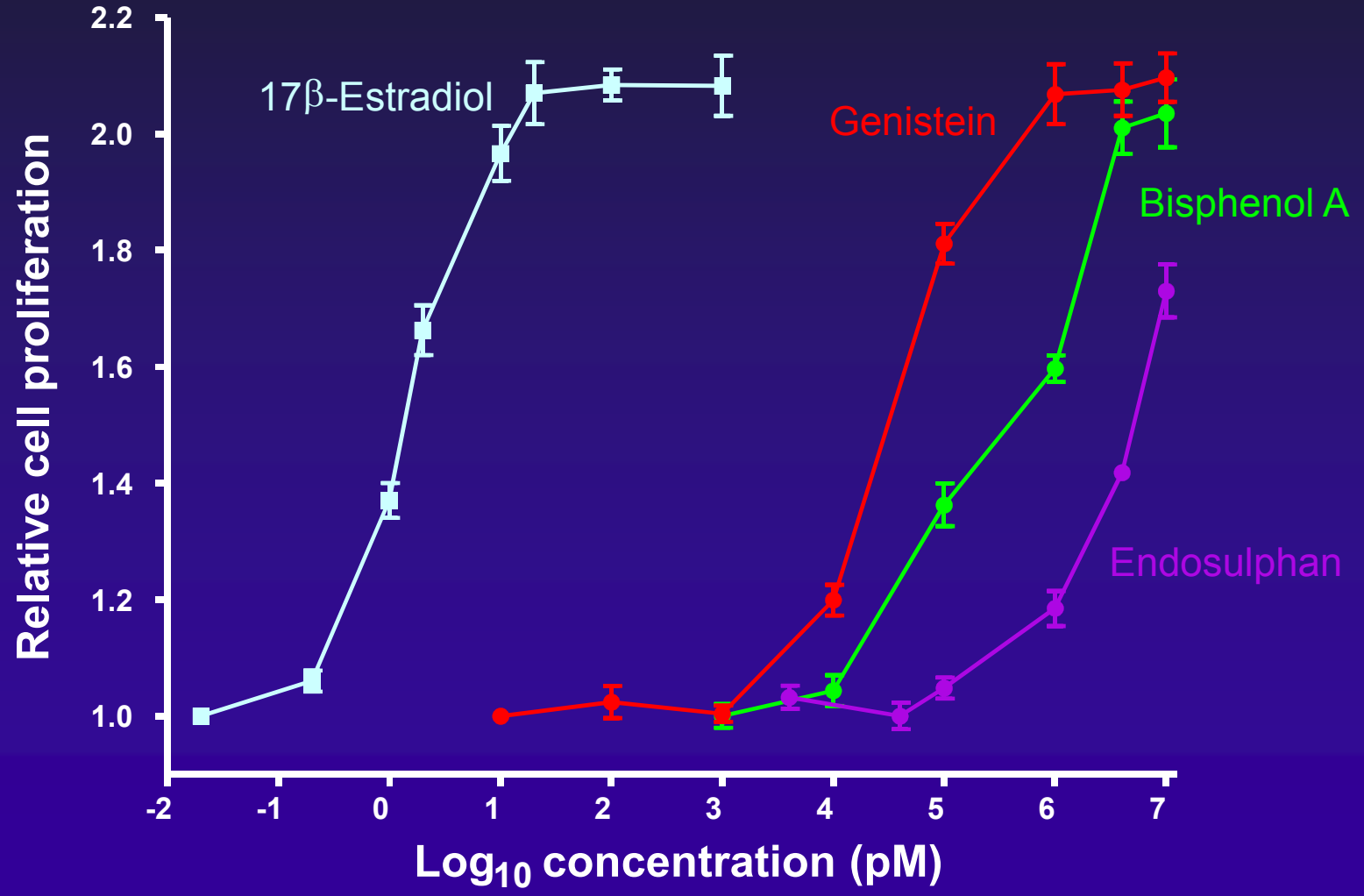
Key events

Tumour development

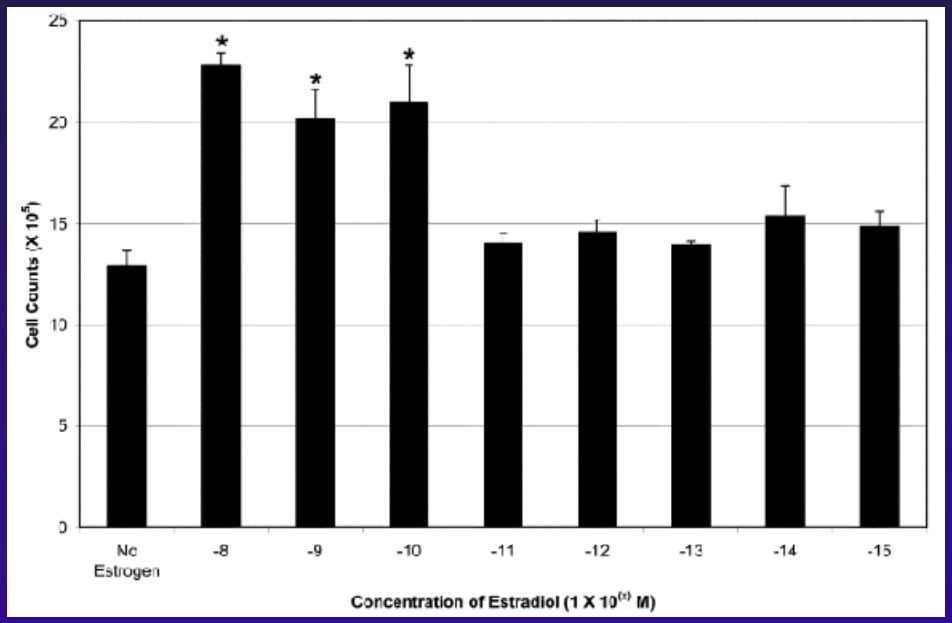
Key events for chloroform carcinogenicity

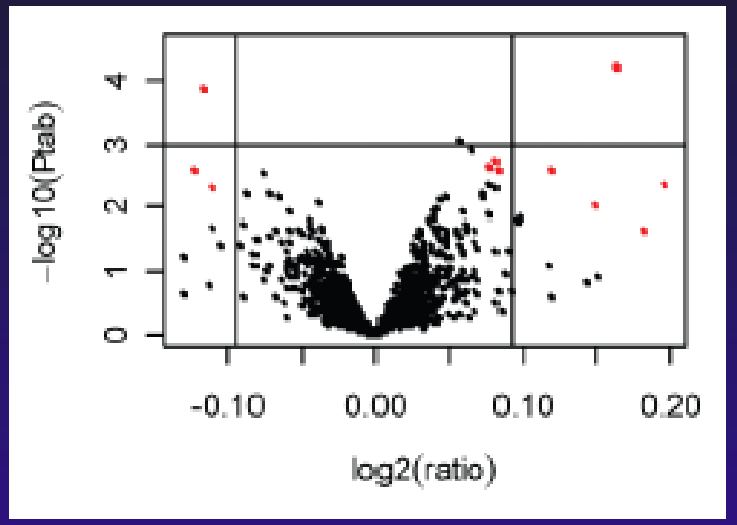


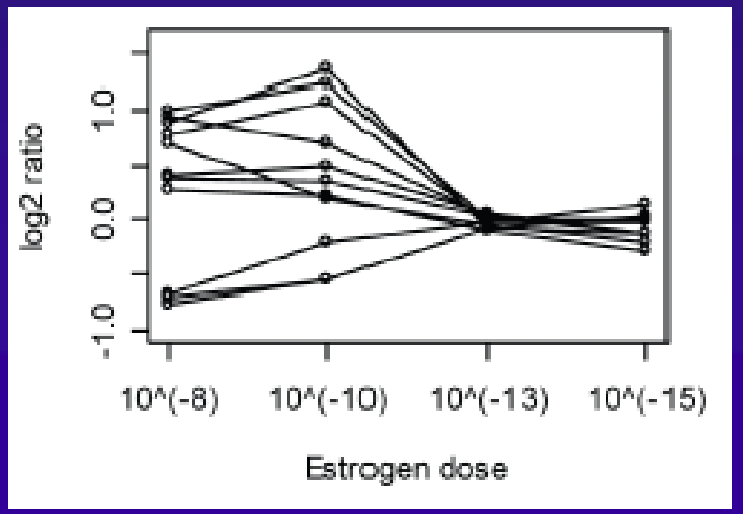
Concentration-effects of estrogens on MCF-7 cells (n=8)



Thresholds for transcriptional response of MCF-7 cells to oestradiol

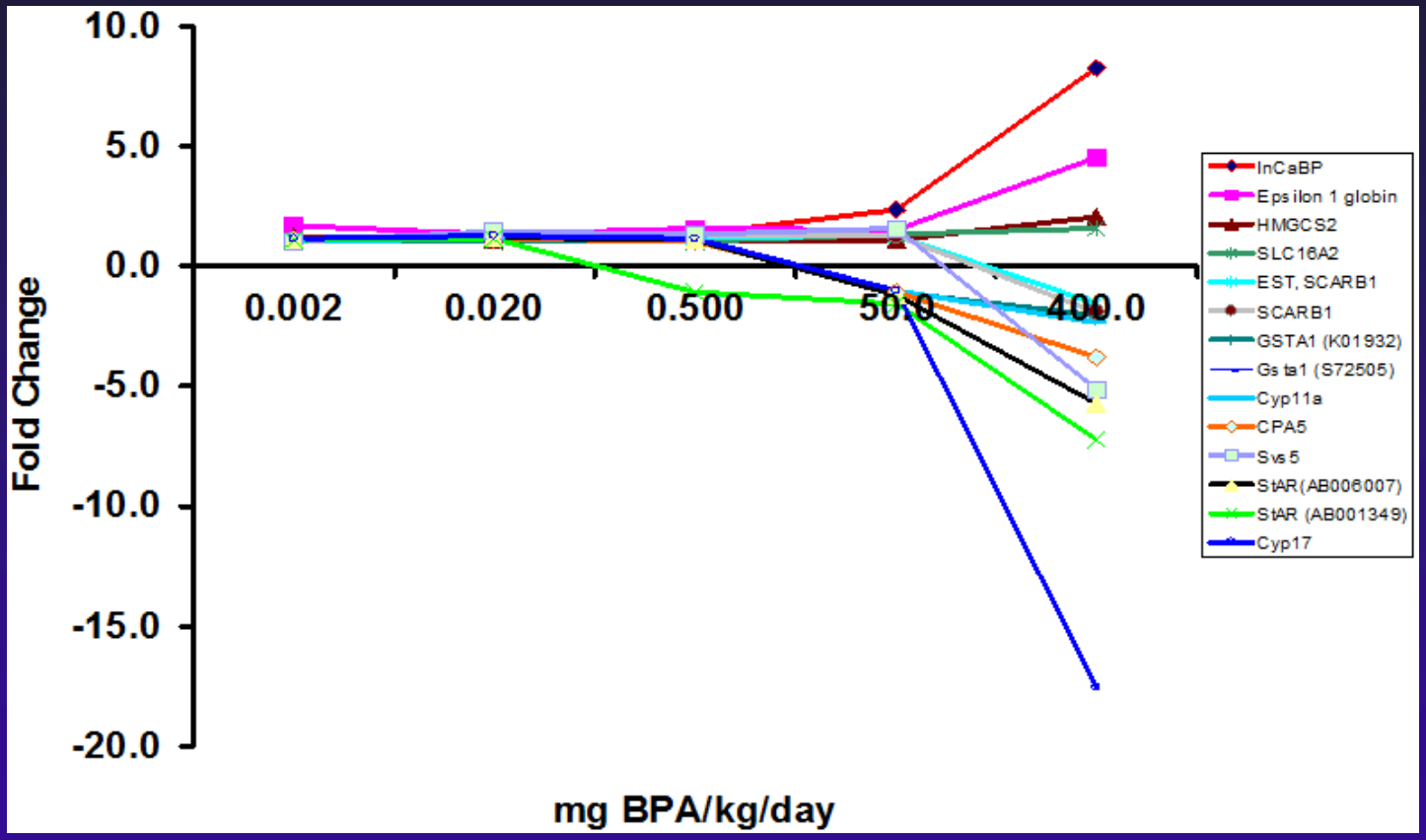






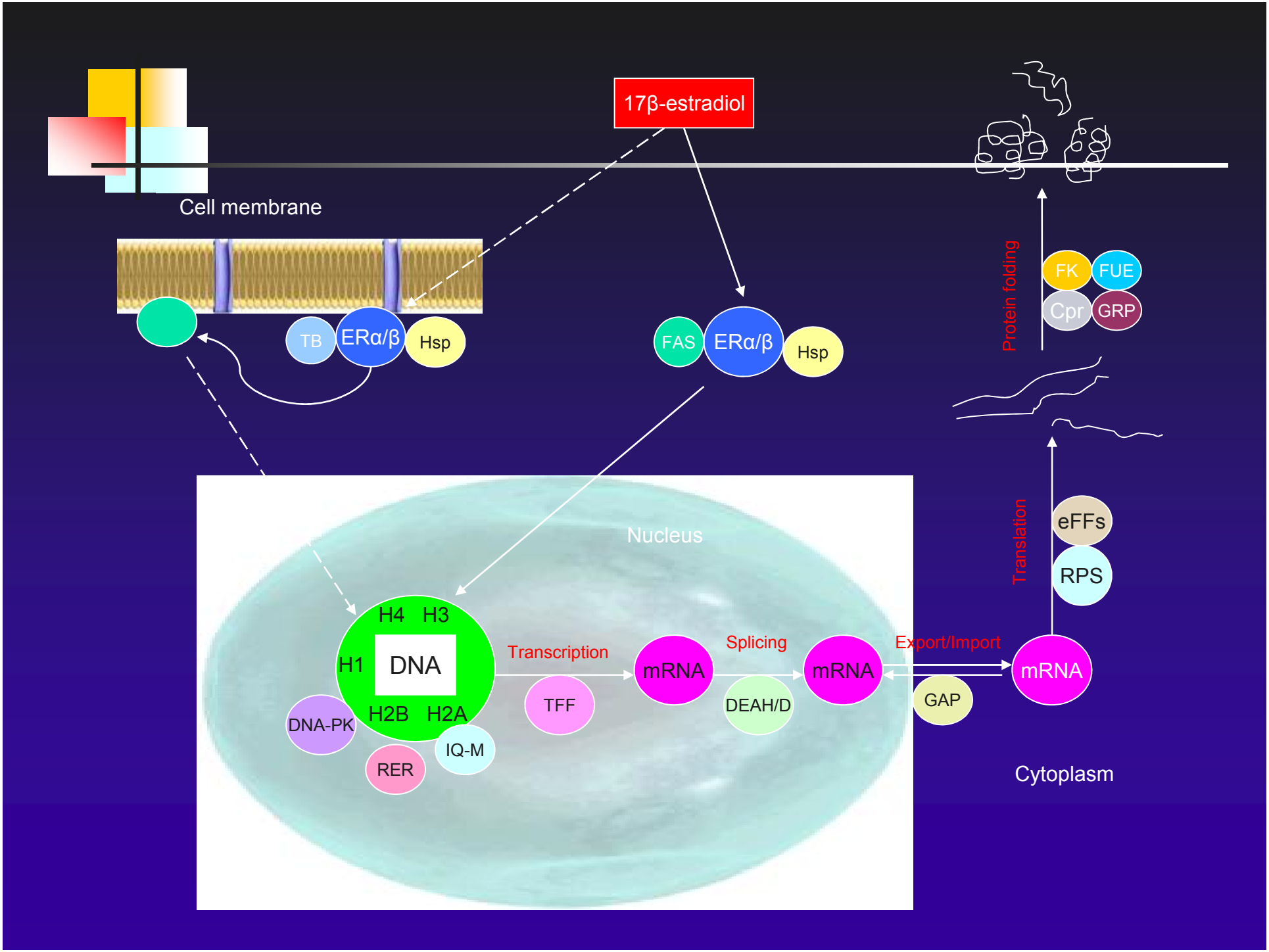
Lobenhofer *et al* (2004)
Tox Pathol 32: 482-92

Threshold dose-response in gene expression in rat fetal testis

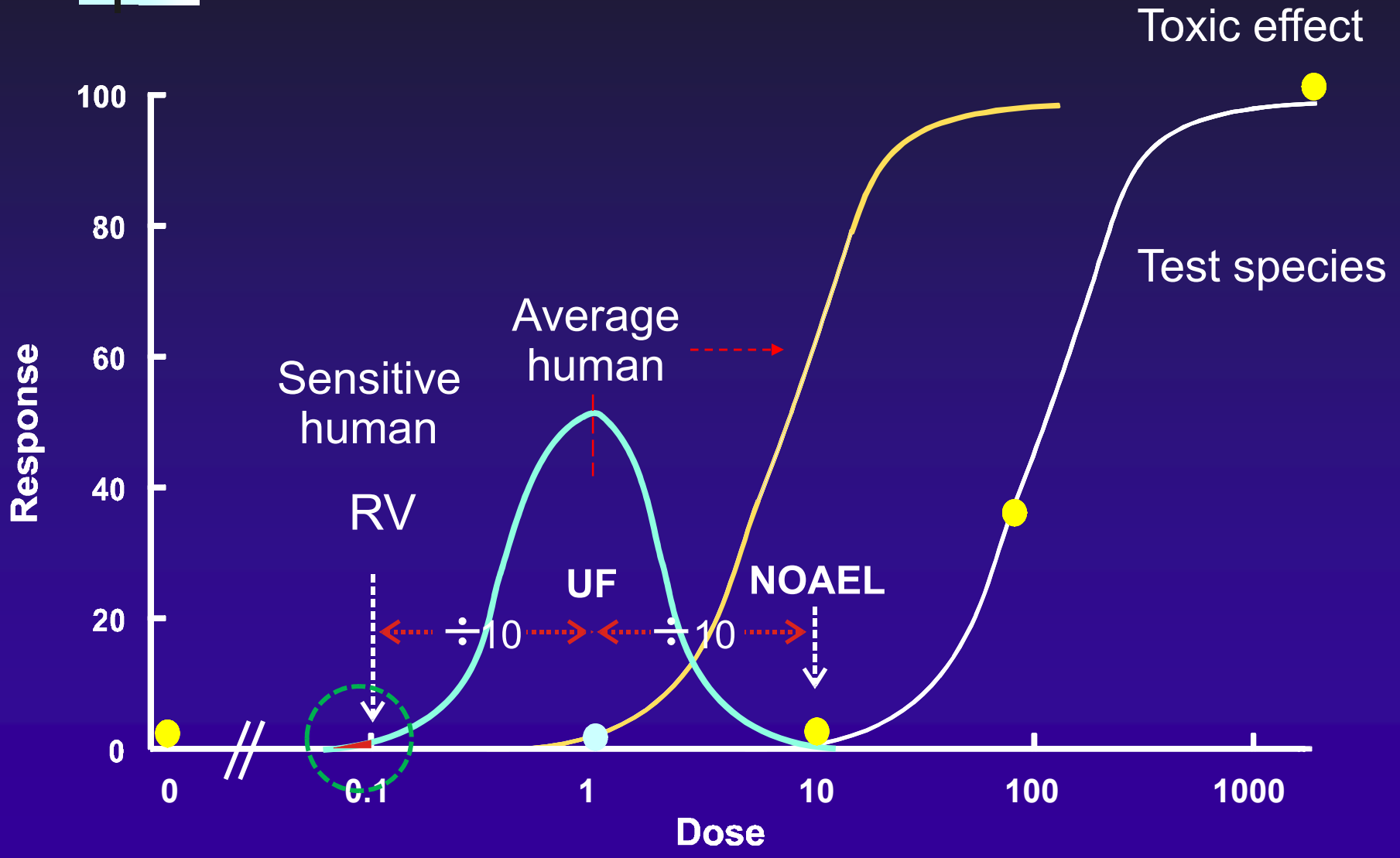


- Estradiol and genistein also show threshold
- Gene responses were monotonic
- Morphological changes were not observed

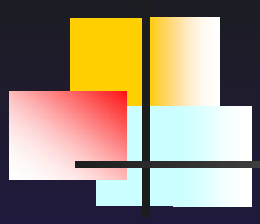
Naciff et al 2005
Tox Sci 86:396


17β-estradiol
Cell membrane
TB
ERα/β
Hsp
FAS
ERα/β
Hsp
Protein folding
FK
FUE
Cpr
GRP
Nucleus
H4
H3
H1
DNA
H2B
H2A
DNA-PK
IQ-M
RER
Transcription
TFF
mRNA
Splicing
DEAH/D
mRNA
Export/Import
GAP
mRNA
Translation
eFFs
RPS
Cytoplasm

Individual v population thresholds



Individual vs. population thresholds



- Thresholds will vary among individuals
- Once the determining key events are understood, research to study contributions to population variability (including identification of susceptible subpopulations) can be targeted on those events
- The goal is to understand how various factors (age, gender, disease state, nutritional status, etc.) may quantitatively affect the doses at which those determining events occur
- Some key events are likely to show absolute population bounds, thus determining population thresholds

Advantages of the KEDRF

- Mechanistic support for TTC values
- Integration of toxicogenomics data
- Development and application of mechanism-based biodynamic models to identify rate-limiting processes in modes of action
- Understanding interindividual variability in the rate determining events may enable a true population threshold(s) to be identified
- Characterisation of the population dose-response curve and identification of susceptibility factors
- Development of new testing strategies, enabling reduction, refinement and eventual replacement of animals in toxicity testing
- Biomarker development