UNIVERSITÀ DEGLI STUDI DI MILANO
FACOLTÀ DI FARMACIA

ESTABLISHING CAUSALITY AND MANAGING UNCERTAINTY.

"What evidence is needed to establish a causal relationship? How are uncertainty cause and quantitative uncertainty managed in assuring food safety"?

Corrado Lodovico Galli

University of Milan - Italy

CRN-I Scientific Symposium

July 3, 2010

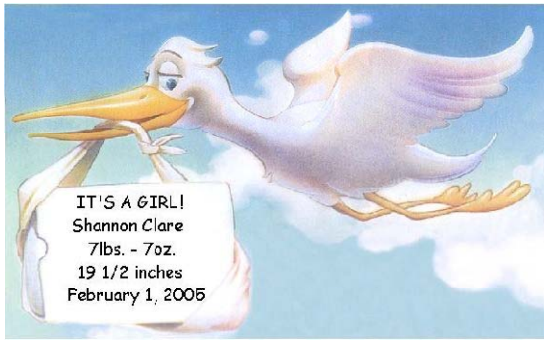
InterContinental Hotel Genève.

CAUSALITY

"**Causality** is the relationship between an event (the ***cause***) and a second event (the ***effect***), where the second event is a consequence of the first."

STATISTICAL CAUSALITY

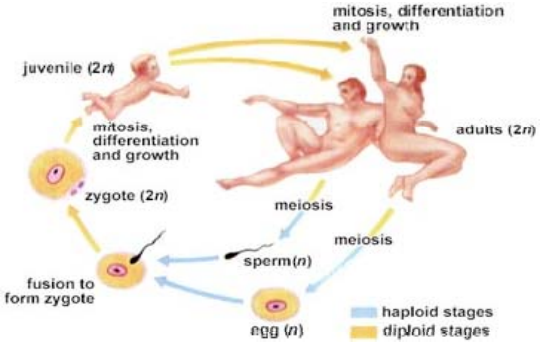
"**Causality** *may be* the relationship between an event (the ***storks***) and a second event (the ***birth rate***), where the second event is a consequence of the first."



Theory of the Storks (ThoS)

versus

Theory of Sexual Reproduction (ThoSR)



NEW EVIDENCE FOR THE THEORY OF THE STORK

Thomas Höfera, Hildegard Przyrembelb and Silvia Verleger
Federal Institute for Risk Assessment, Berlin,
Office of the National Breast Feeding Committee at BfR, Berlin, and Independent Midwife, Berlin, Germany

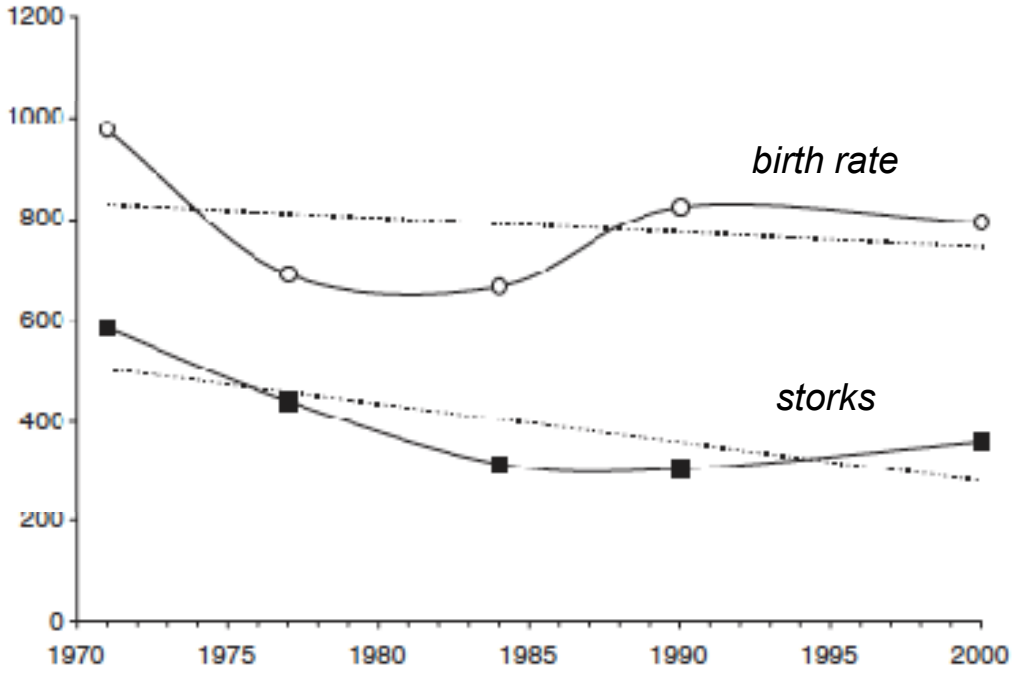


Figure 1. Storks and the birth rate in Lower Saxony, Germany (1971–2000). Open circles show yearly birthrates in hundreds in Lower Saxony. Full squares show numbers pairs of storks in Lower Saxony. Dotted lines represent linear regression trend ($y = mx + b$).

Paediatric and Perinatal Epidemiology 2004, **18**, 88–92

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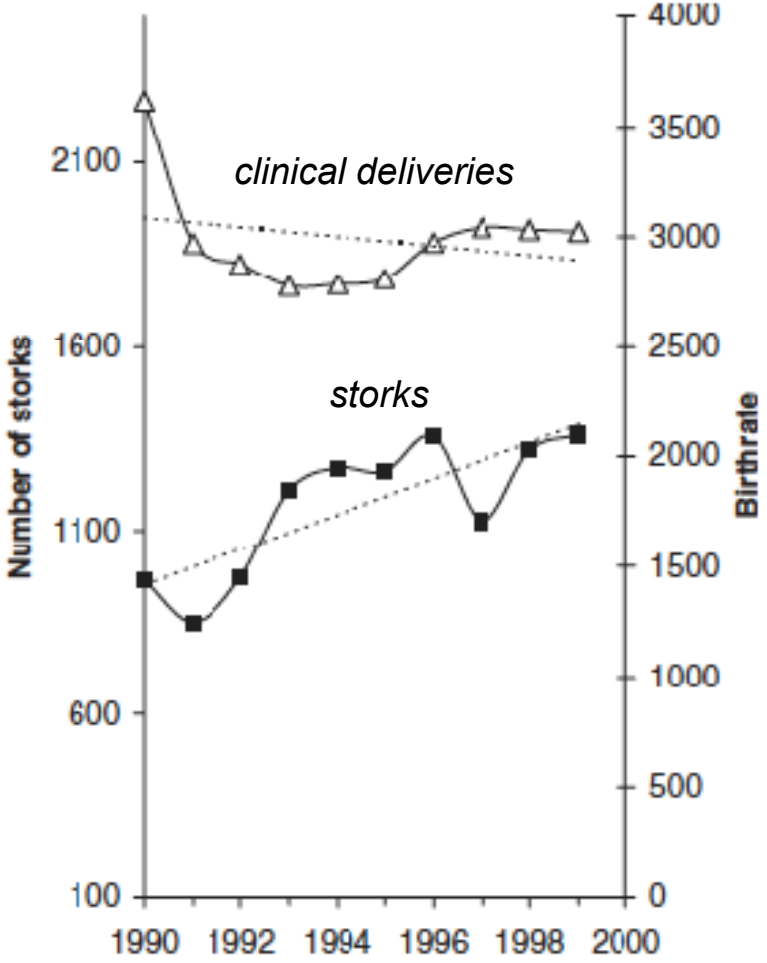

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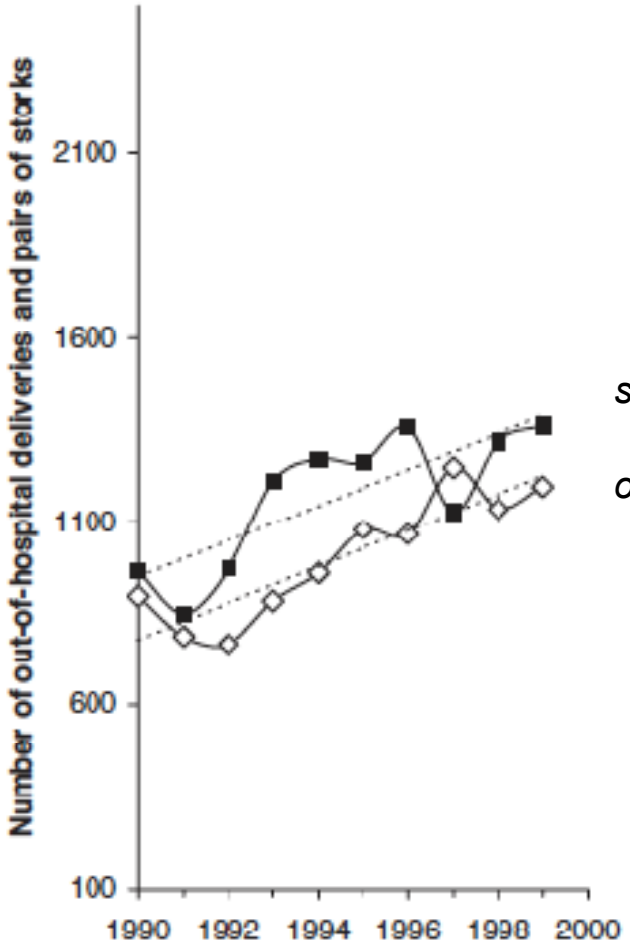


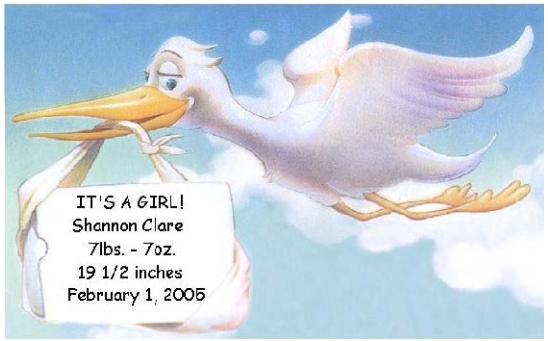
storks

out-of-hospital deliveries

Paediatric and Perinatal Epidemiology 2004, **18**, 88–92

CAUSALITY

"**Causality** is the relationship between an event (**storks**) and a second event (***out-of-hospital deliveries***), where the second event is a consequence of the first."



Theory of the Storks (ThoS)

Children are delivered by storks

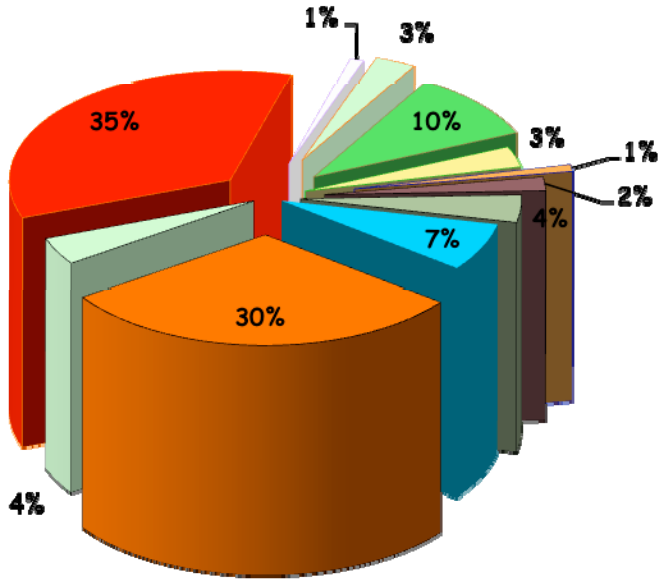
UNCERTAINTY

Uncertainty must be taken in a sense radically distinct from the familiar notion of risk

- **Risk**: A state of uncertainty where some possible outcomes have an undesired effect or significant loss.
  - **Measurement of Risk**: **A set of measured uncertainties** where some possible outcomes are losses, and the magnitudes of those losses – this also includes loss functions over continuous variables.

- **Uncertainty**: The lack of certainty, A state of having limited knowledge where it is impossible to exactly describe existing state or future outcome, more than one possible outcome.
  - **Measurement of Uncertainty: A set of possible states or outcomes** where probabilities are assigned to each possible state or outcome – this also includes the application of a probability density function to continuous variables

PROPORTION OF CANCER DEATHS
ATTRIBUTED TO VARIOUS ENVIRONMENTAL FACTORS

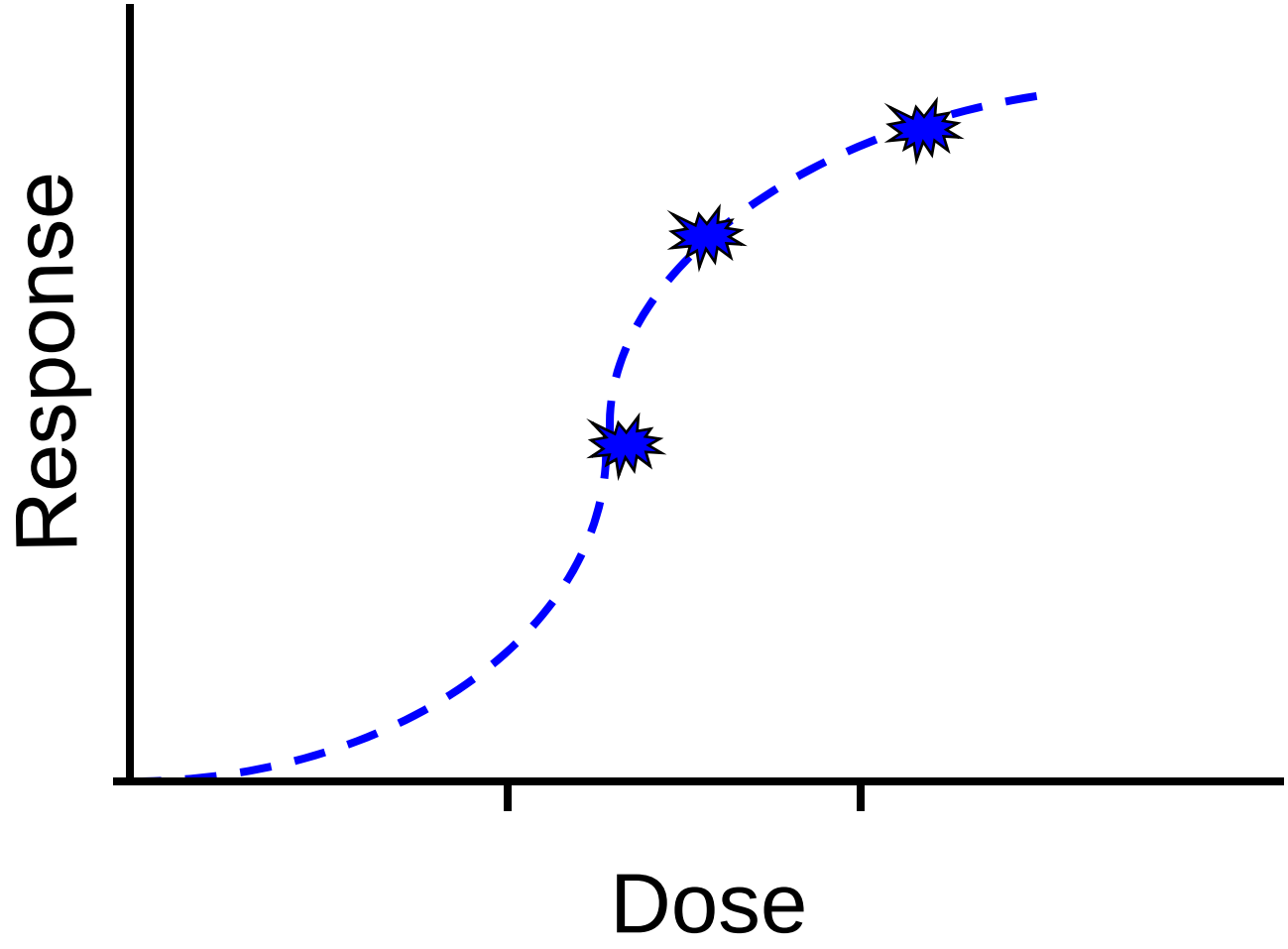


BIOLOGICAL CAUSALITY

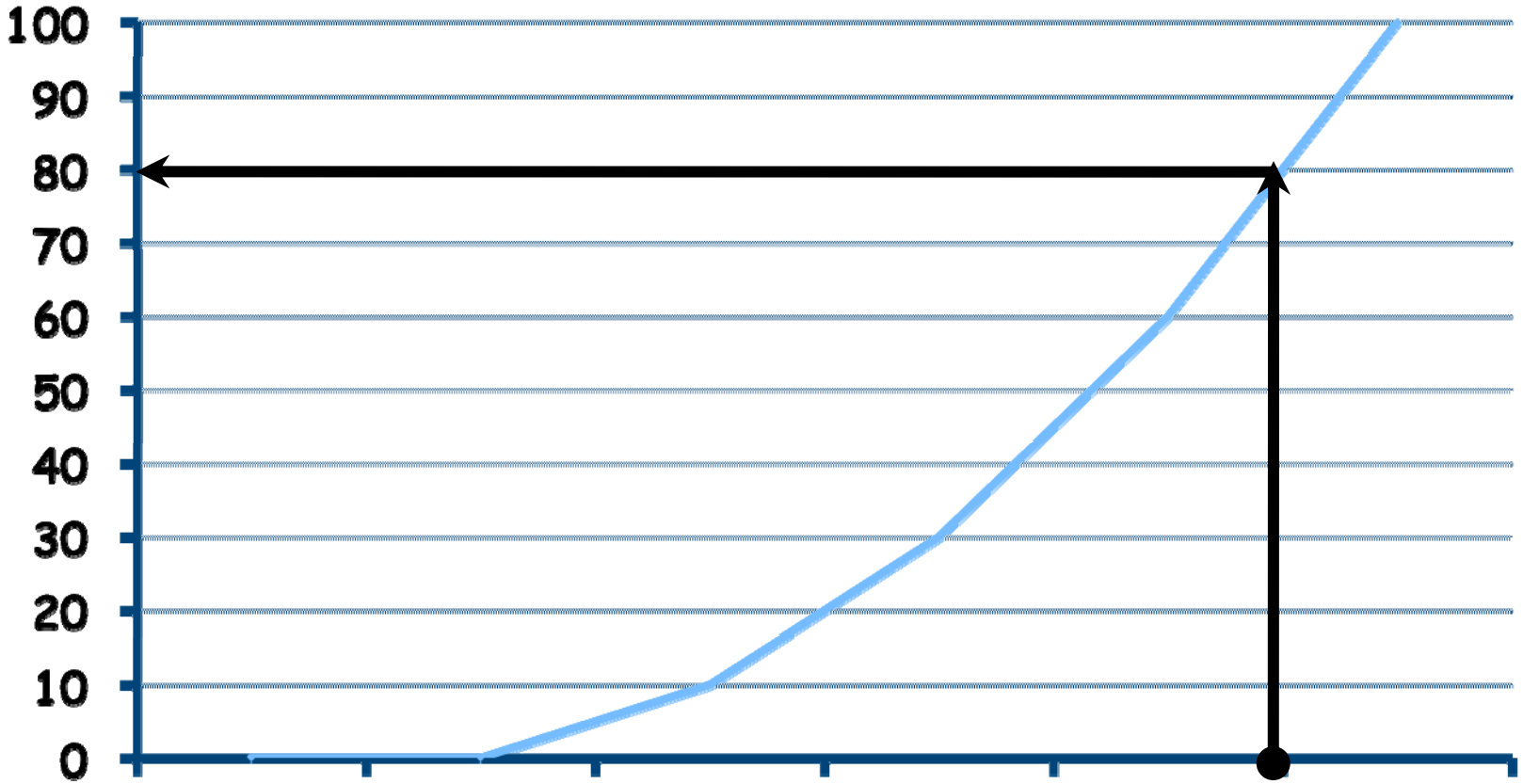
"**Causality** is the relationship between an event (the ***dose***) and a second event (the ***response***), where the second event is a consequence of the first."

DOSE - RESPONSE FOR CRITICAL EFFECTS

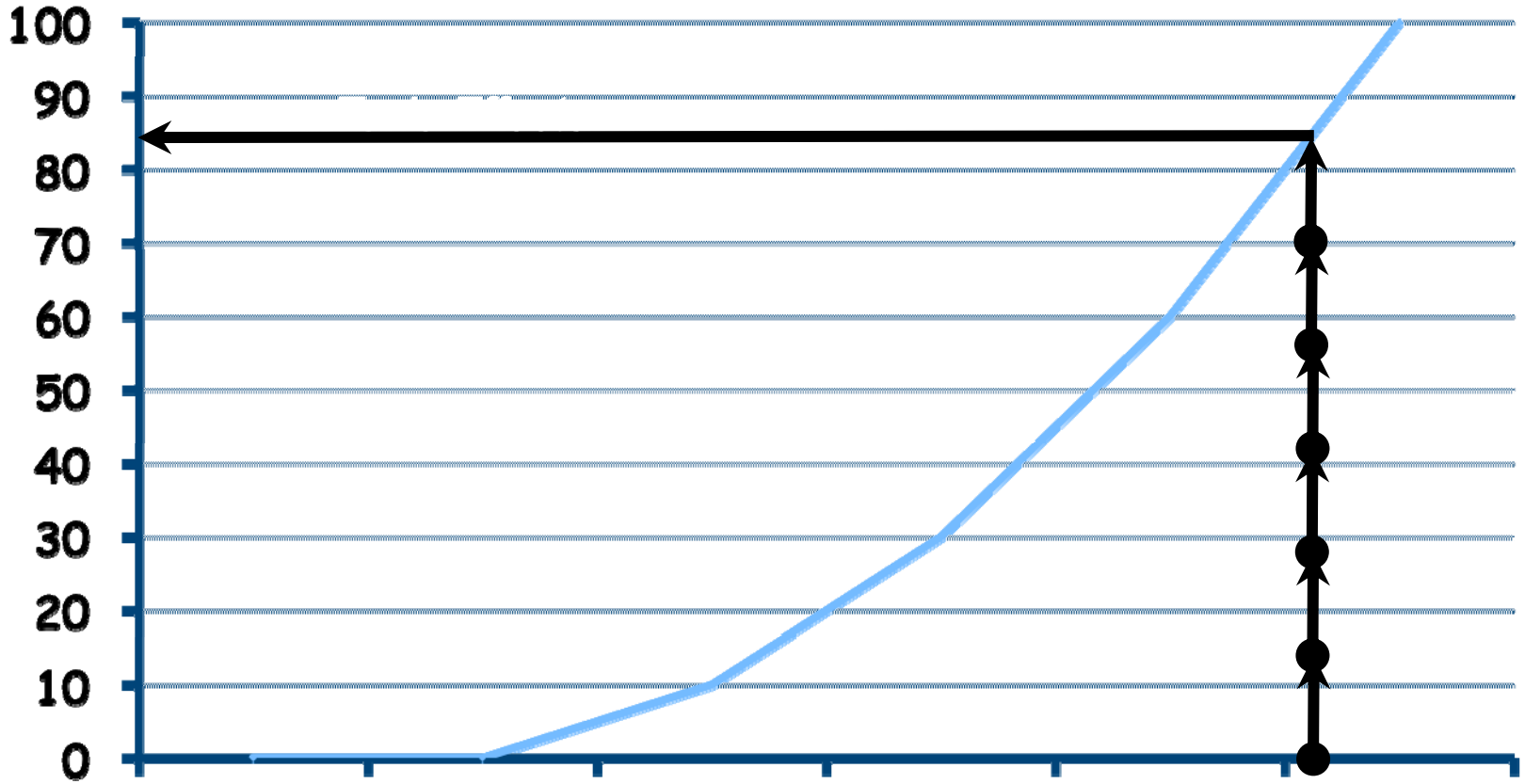
(to establish a dose without adverse effects in animals)



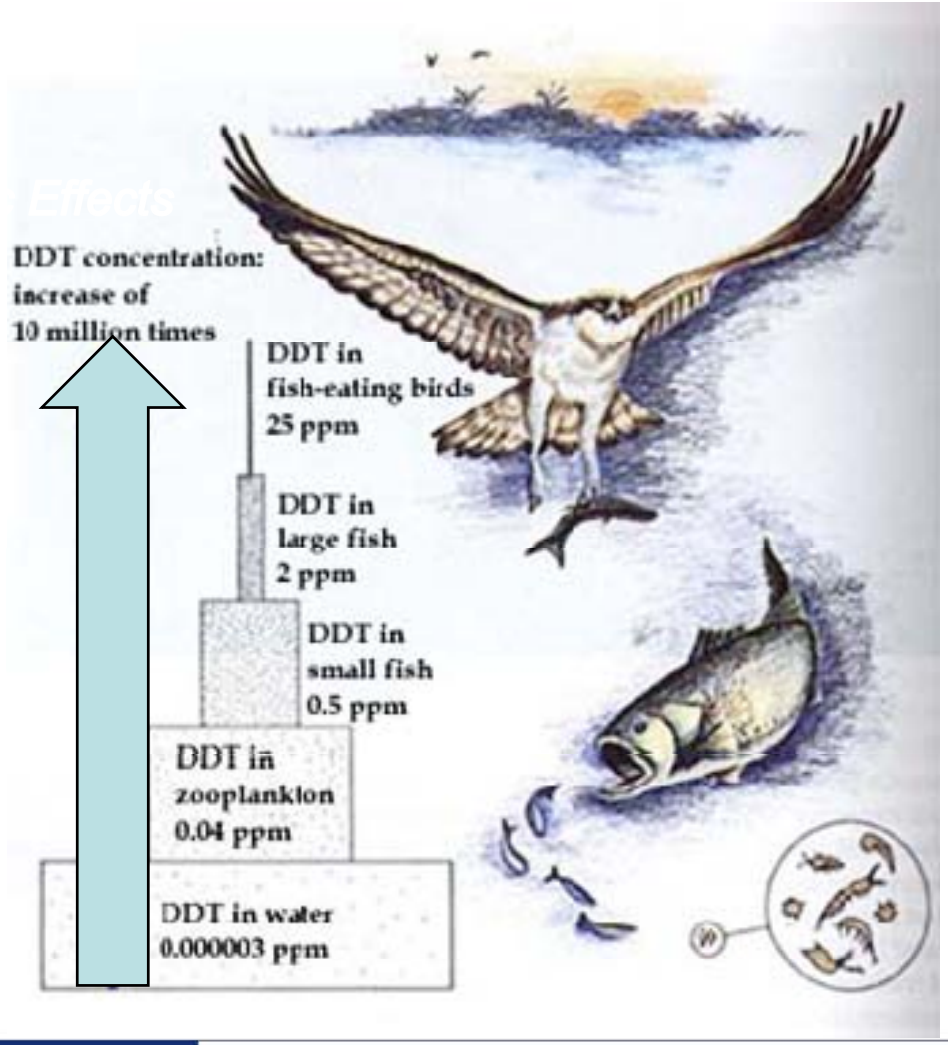
EXPOSURE (dose – acute)



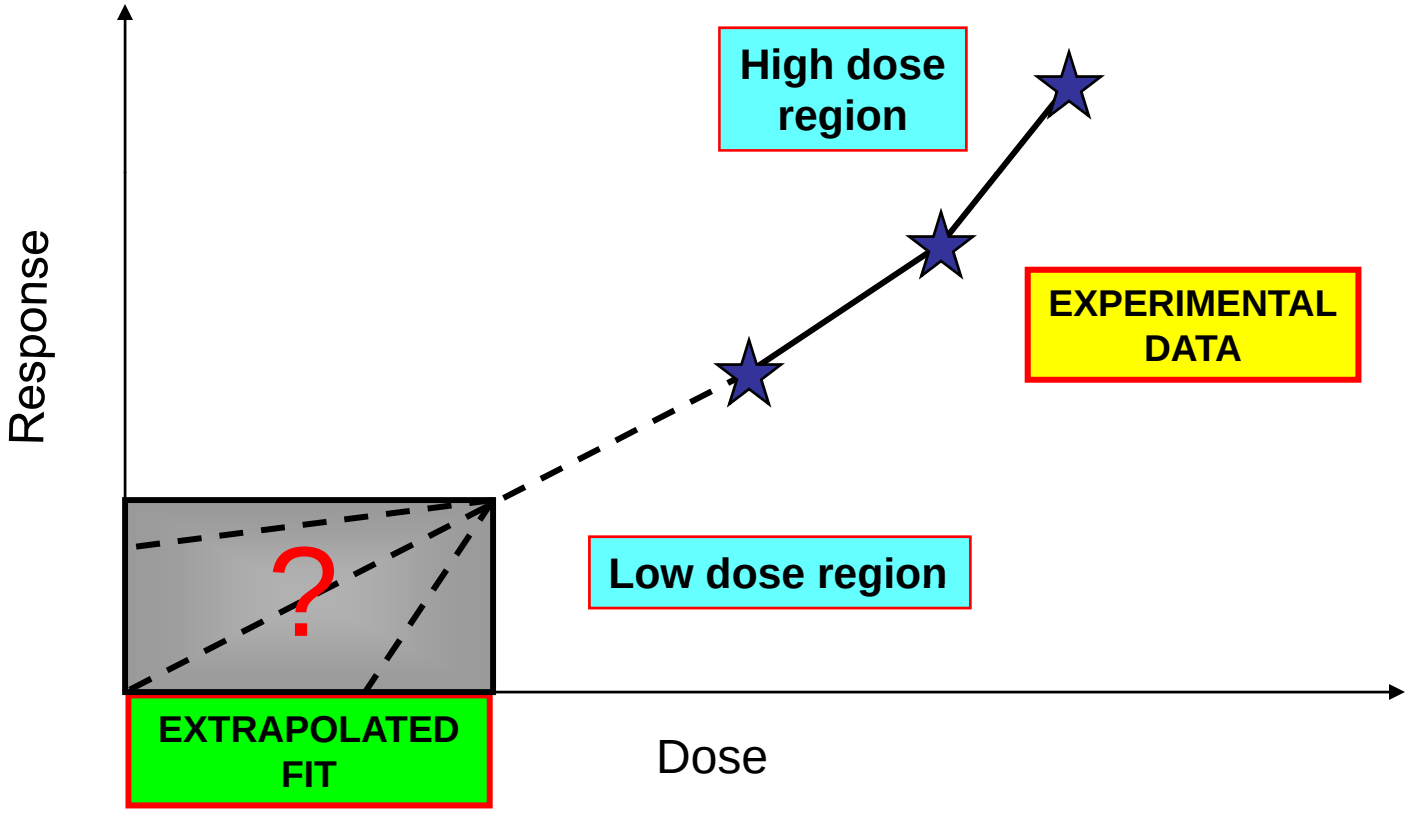
EXPOSURE (dose and time – additive)



EXPOSURE (dose and time – bioaccumulation)

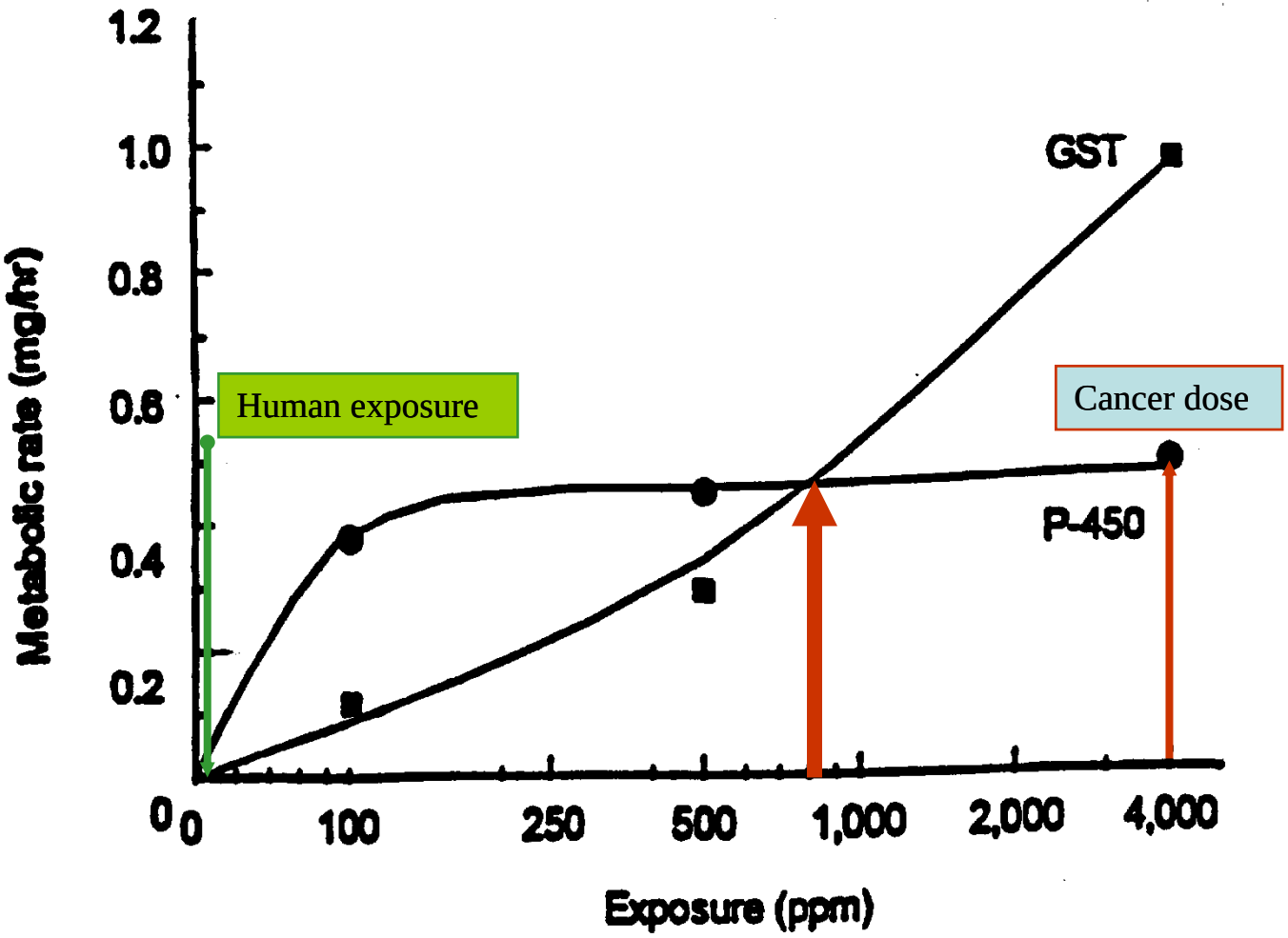


UNCERTAINTY FACTORS



KEY EVENT

Methylene Chloride



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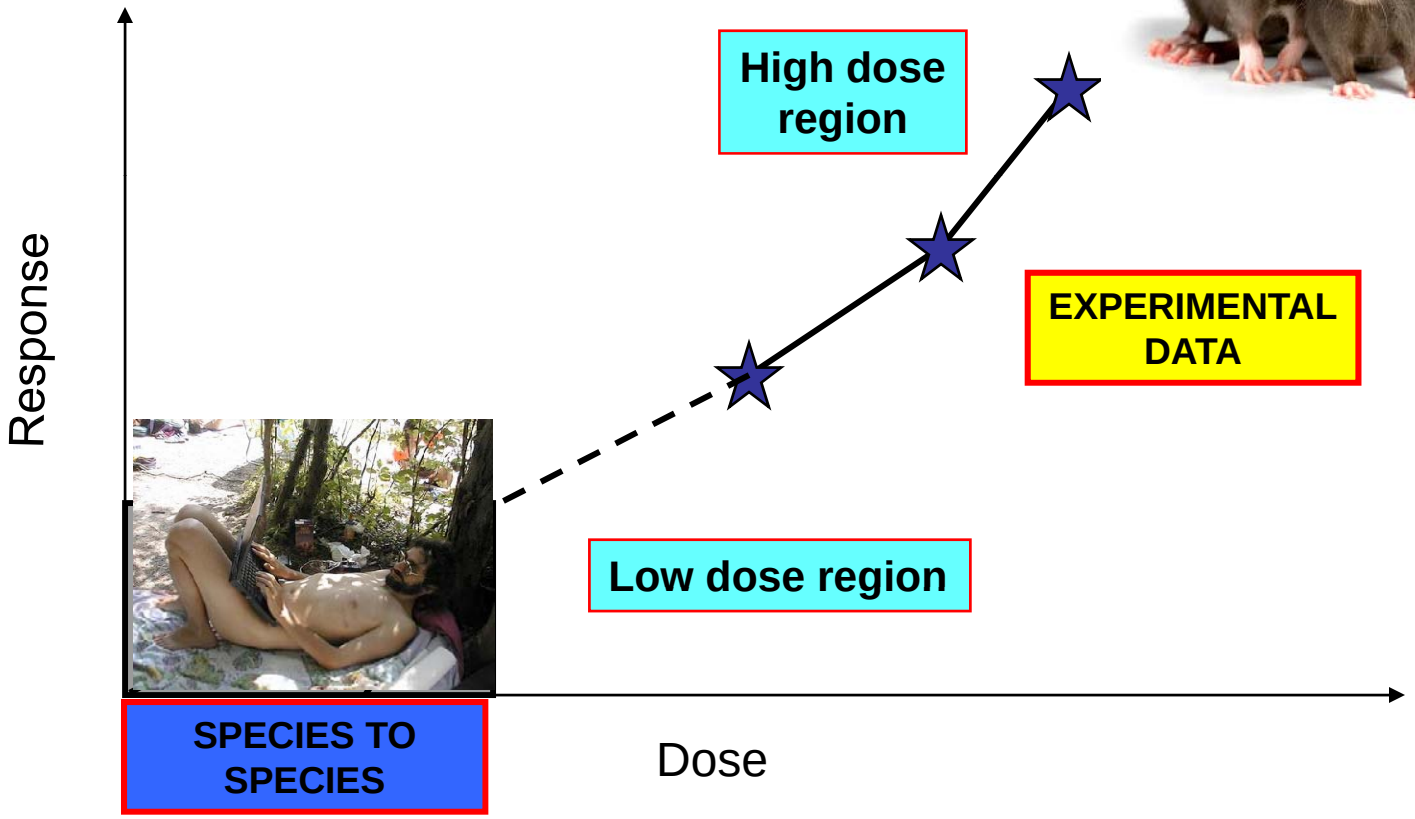
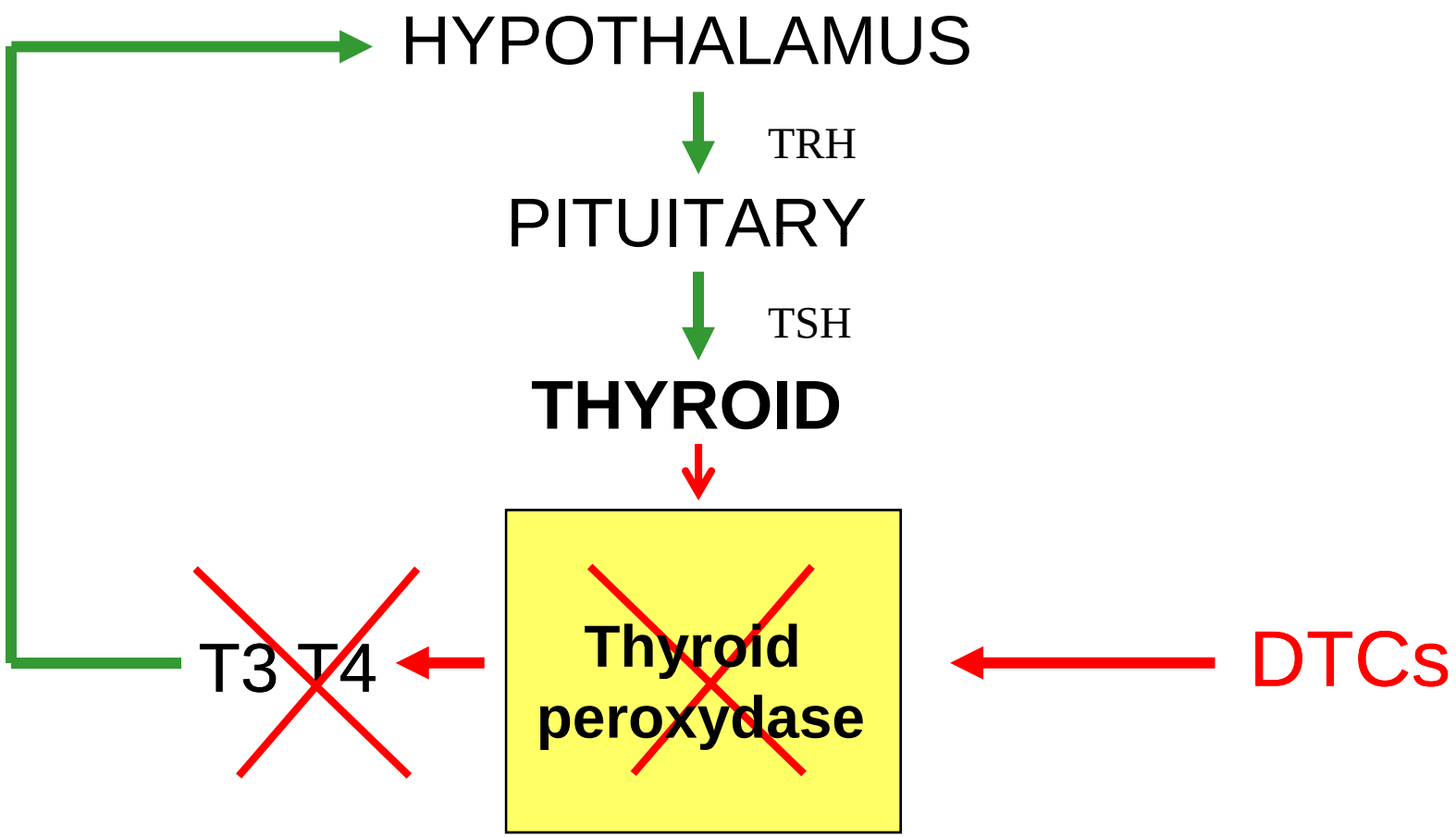


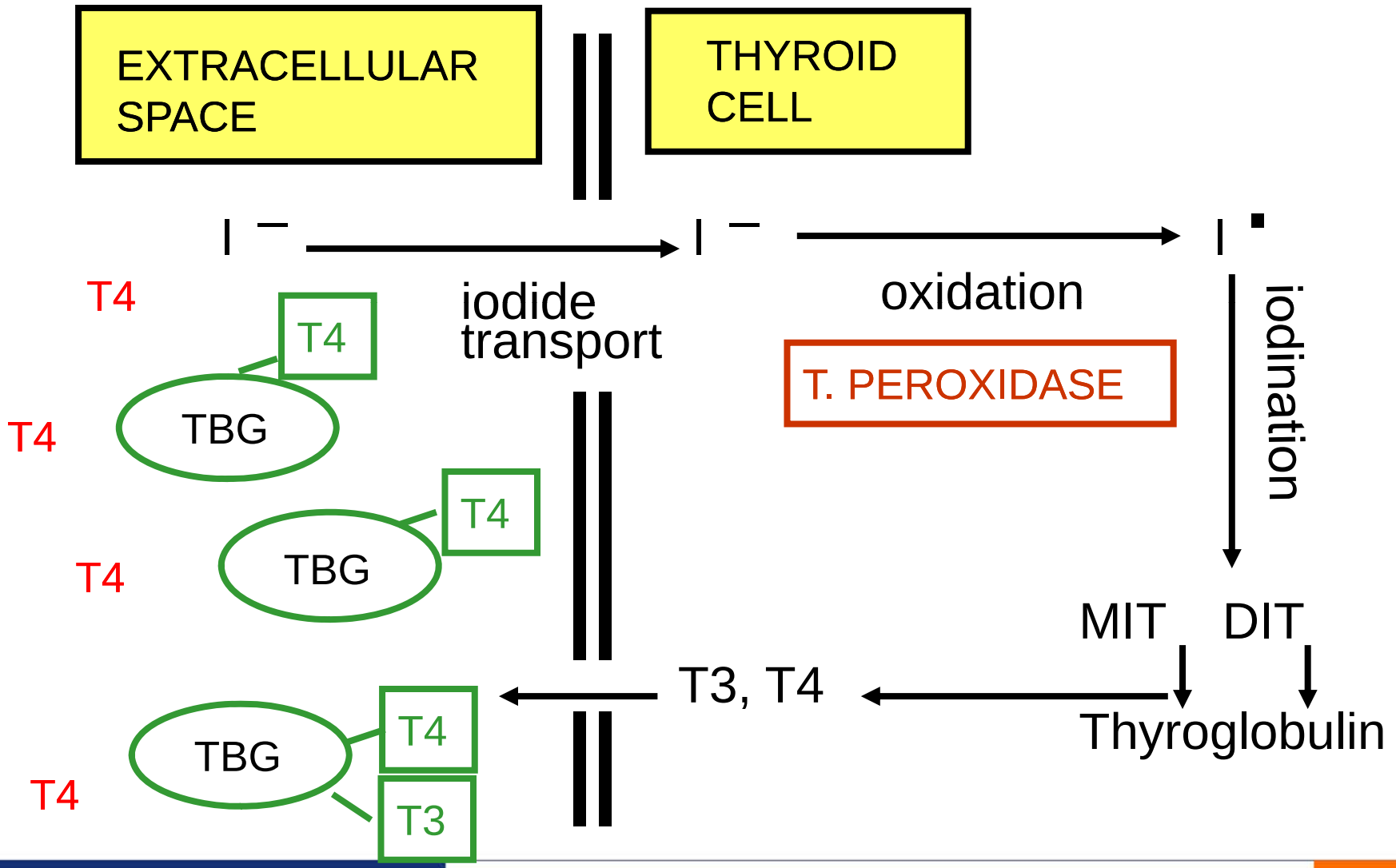
MECHANISTIC STUDIES

Dithiocarbamates (DTCs)



SPECIES DIFFERENCES

Dithiocarbamates



RISK CHARACTERIZATION

✓ **Hazard identification**

- **Inherent biological activity,**

HAZARD IDENTIFICATION
❖ Identification of adverse health effects ❖ Animal-based toxicological studies ❖ *In vitro* toxicology data ❖ Structure-activity consideration ❖ Human data

✓ **Hazard assessment**

- **Dose-response analysis**
- **Assessment of relevance for humans**

HAZARD ASSESSMENT
❖Quantification of adverse health effects ❖ Dose-response for critical effect ❖ Selection of critical data ❖ Mode/mechanism of action ❖ Kinetic variability ❖ Dynamic variability

EXPOSURE ASSESSMENT
❖ Active principle ❖ Dose of toxicant ❖ Dose in individuals ❖ Dose in special population groups ❖ Max/min, chronically/occasionally

→ RISK CHARACTERISATION

ANIMAL-BASED TOXICOLOGICAL STUDIES

TOXICOKINETIC

Absorption
Distribution
Metabolism
Excretion

ACUTE TOXICITY

LD_{50} oral
LD_{50} dermal
LC_{50} inhalation
Skin irritation
Eye irritation
Skin sensitization

GENOTOXICITY

Mutagenesis
Clastogenesis
Aneuploidy

SHORT-TERM TOXICITY

Mouse	90 day toxicity
Rat	90 day toxicity
Dog	90 day toxicity
Dog	1 year toxicity

DEVELOPMENTAL TOXICITY

Teratogenicity tests (Rat-Rabbit)

REPRODUCTIVE TOXICITY

Two generation reproductive toxicity

LONG-TERM TOXICITY and/or CARCINOGENICITY

Mouse 18 months
Rat 104 weeks

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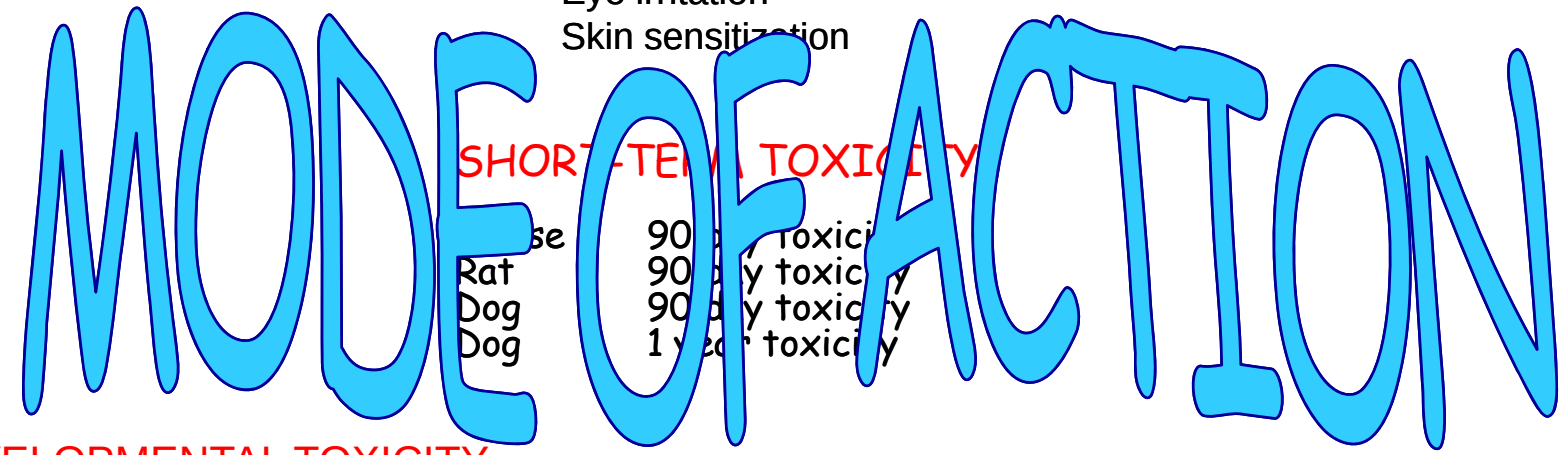

SHORT-TERM TOXICITY

se	90 [illegible] toxici
Rat	90 [illegible]y toxicity
Dog	90 [illegible]y toxicity
Dog	1 [illegible] toxicity

DEVELOPMENTAL TOXICITY

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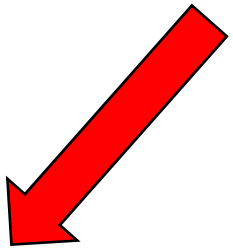
RISK CHARACTERIZATION

Hazard Assessment

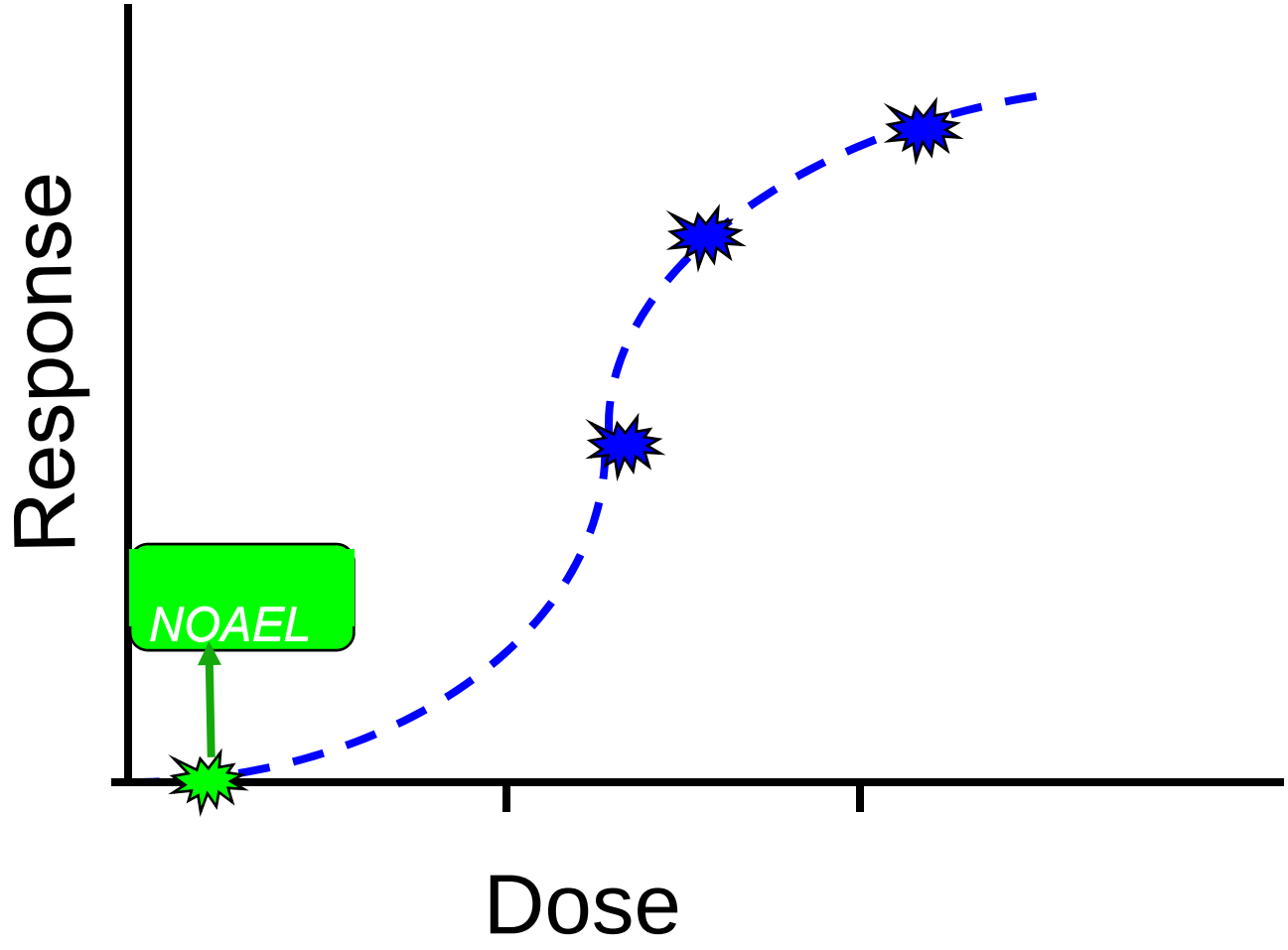


Genotoxic Carcinogen

Toxicant and/or
NON Genotoxic Carcinogen

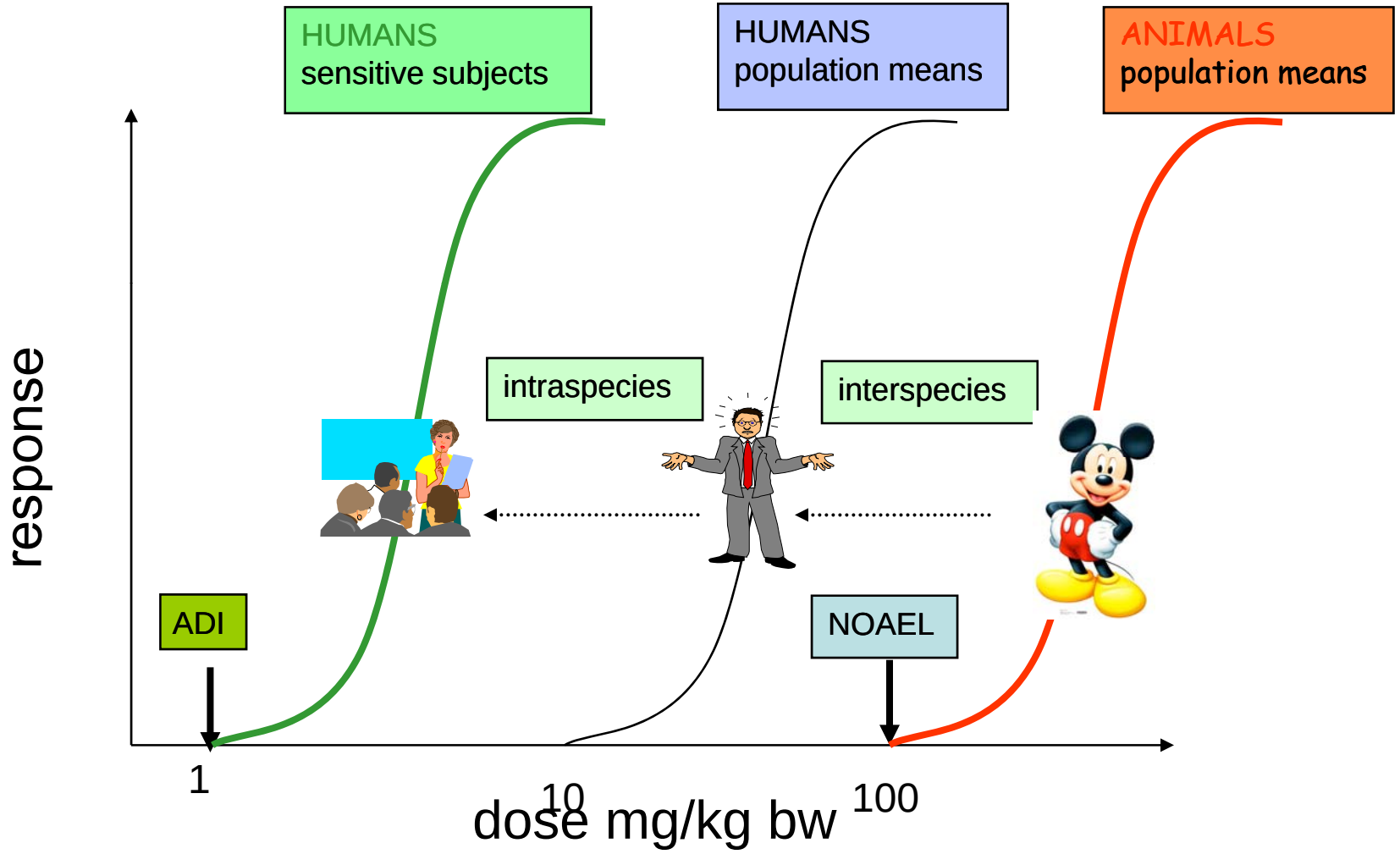
DOSE - RESPONSE FOR CRITICAL EFFECTS

(to establish a dose without adverse effects in animals)



ANIMAL-BASED TOXICOLOGICAL STUDIES

(quantification of adverse health effects)



ADMISSIBILE DAILY INTAKE

$$ADI = \frac{NOAEL}{SF}$$

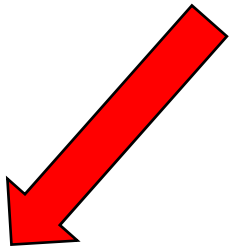
ADI = Admissible Daily Intake mg/kg b.w.

NOAEL = No Observed Adverse Effect Level (mg/kg b.w.)

SF = Safety Factor (10, 100, n)

RISK CHARACTERIZATION

Hazard Characterization

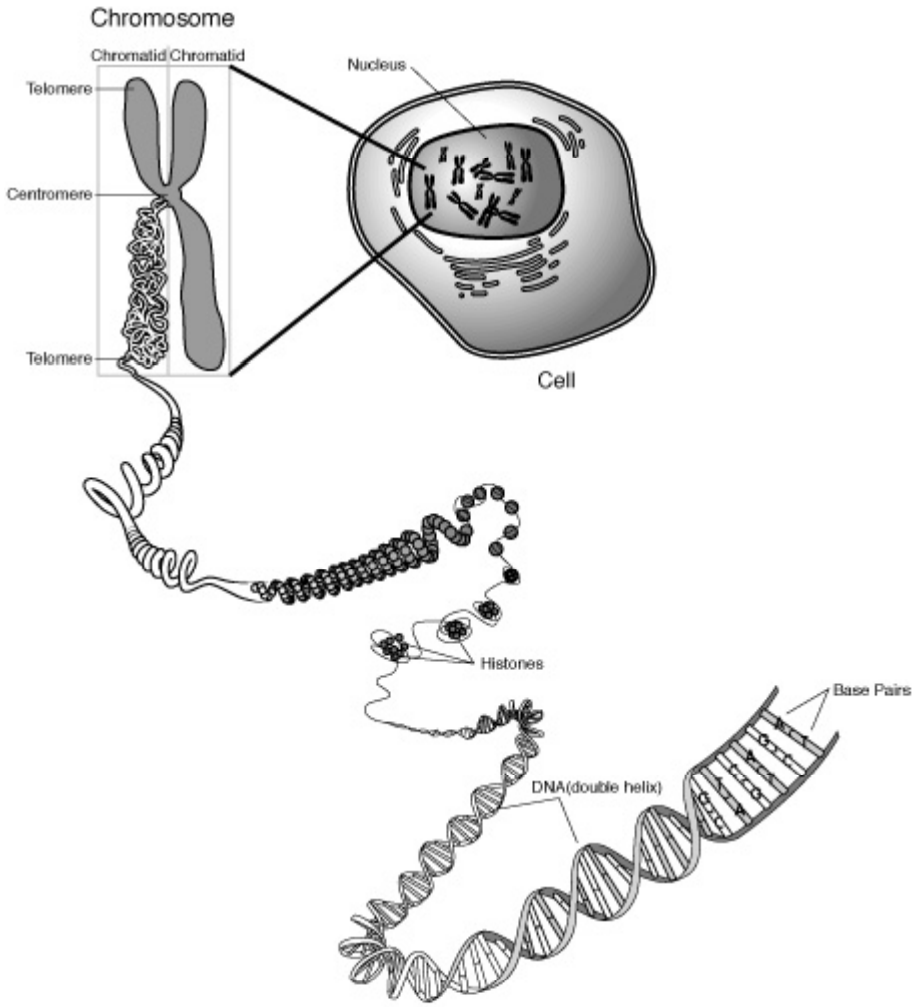


Genotoxic Carcinogen

Toxicant and/or

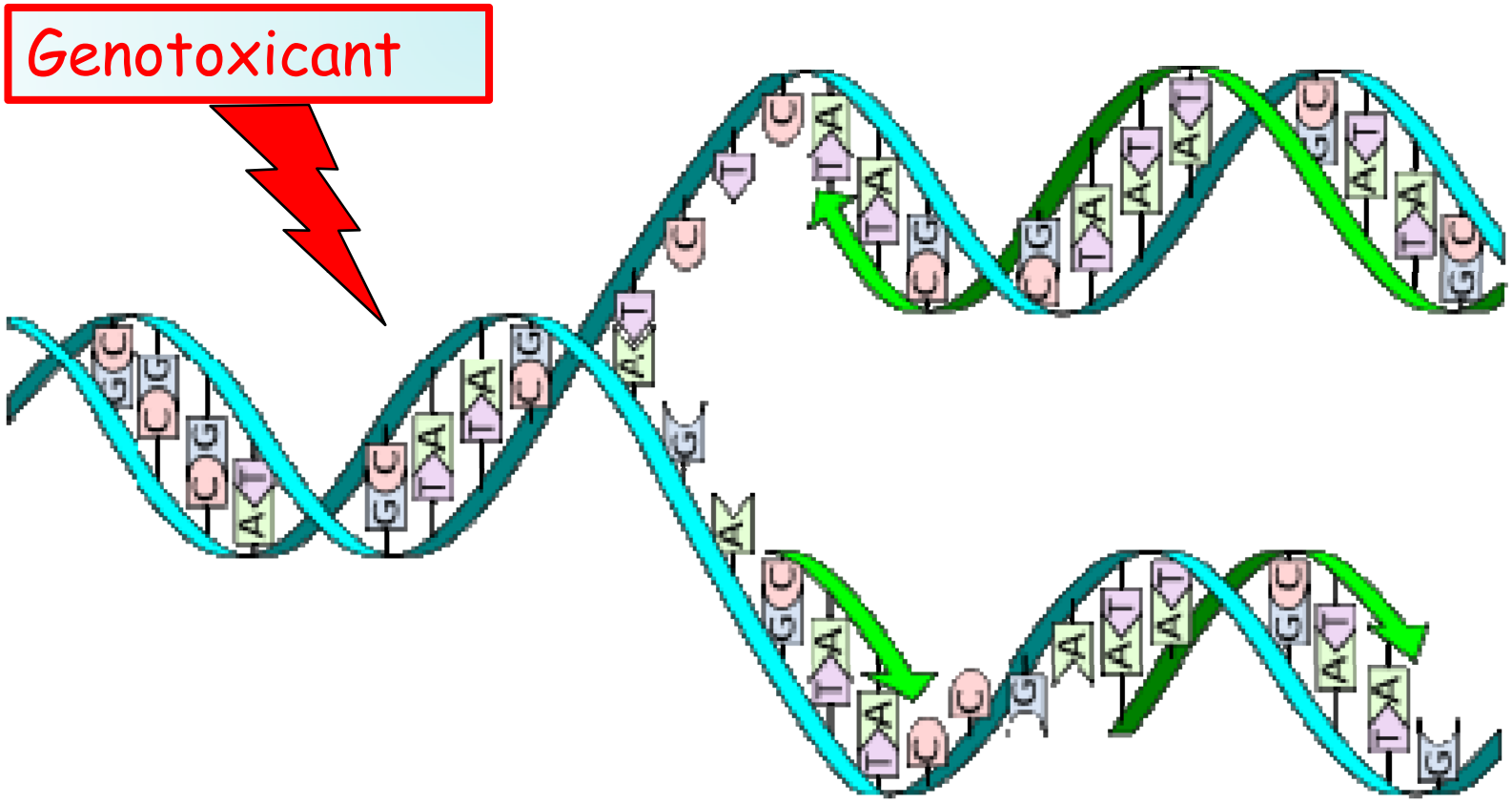
NON Genotoxic Carcinogen

DEOXYRIBONUCLEIC ACID (DNA)

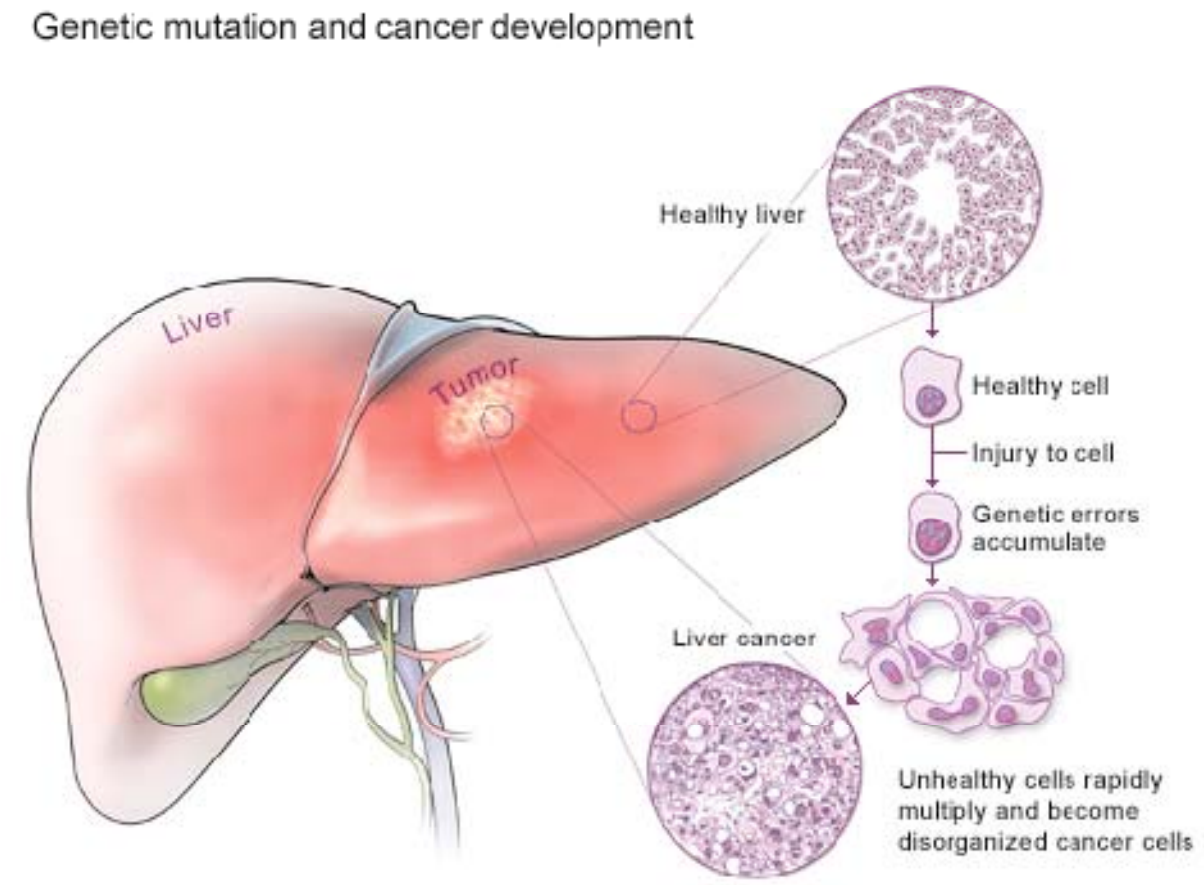


http://www.accessexcellence.org/AB/GG/chromosome.html

GENOTOXIC CARCINOGENS

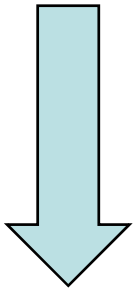


GENOTOXIC CARCINOGENS



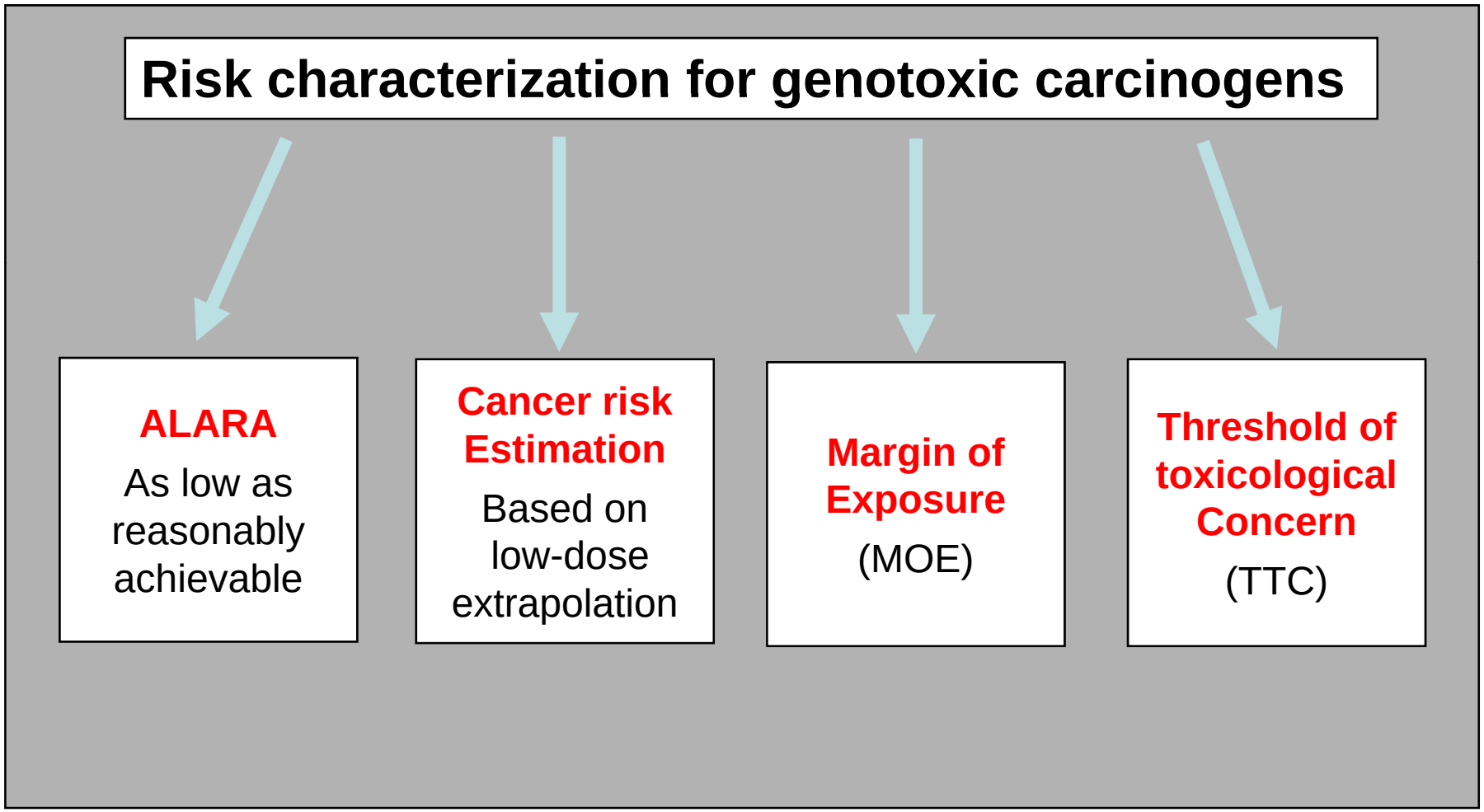
CARCINOGENS

DNA-reactive genotoxins



THRESHOLD ?

RISK CHARACTERIZATION
AND FORMULATION OF ADVICE TO RISK MANAGERS



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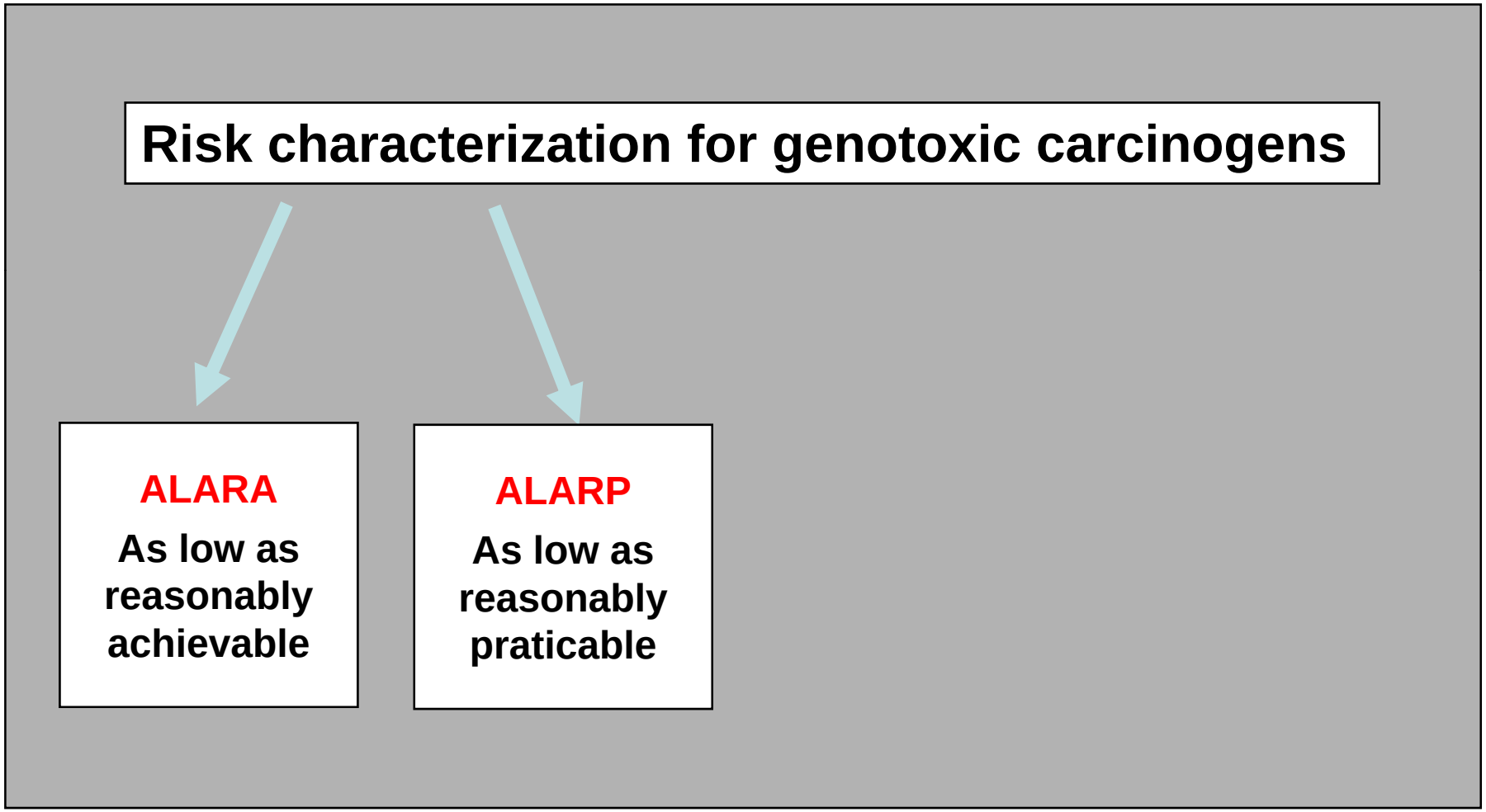


ALARA

- Based solely on **hazard identification**
- Does not take into account **human exposure**
- Does not take into account **potency**

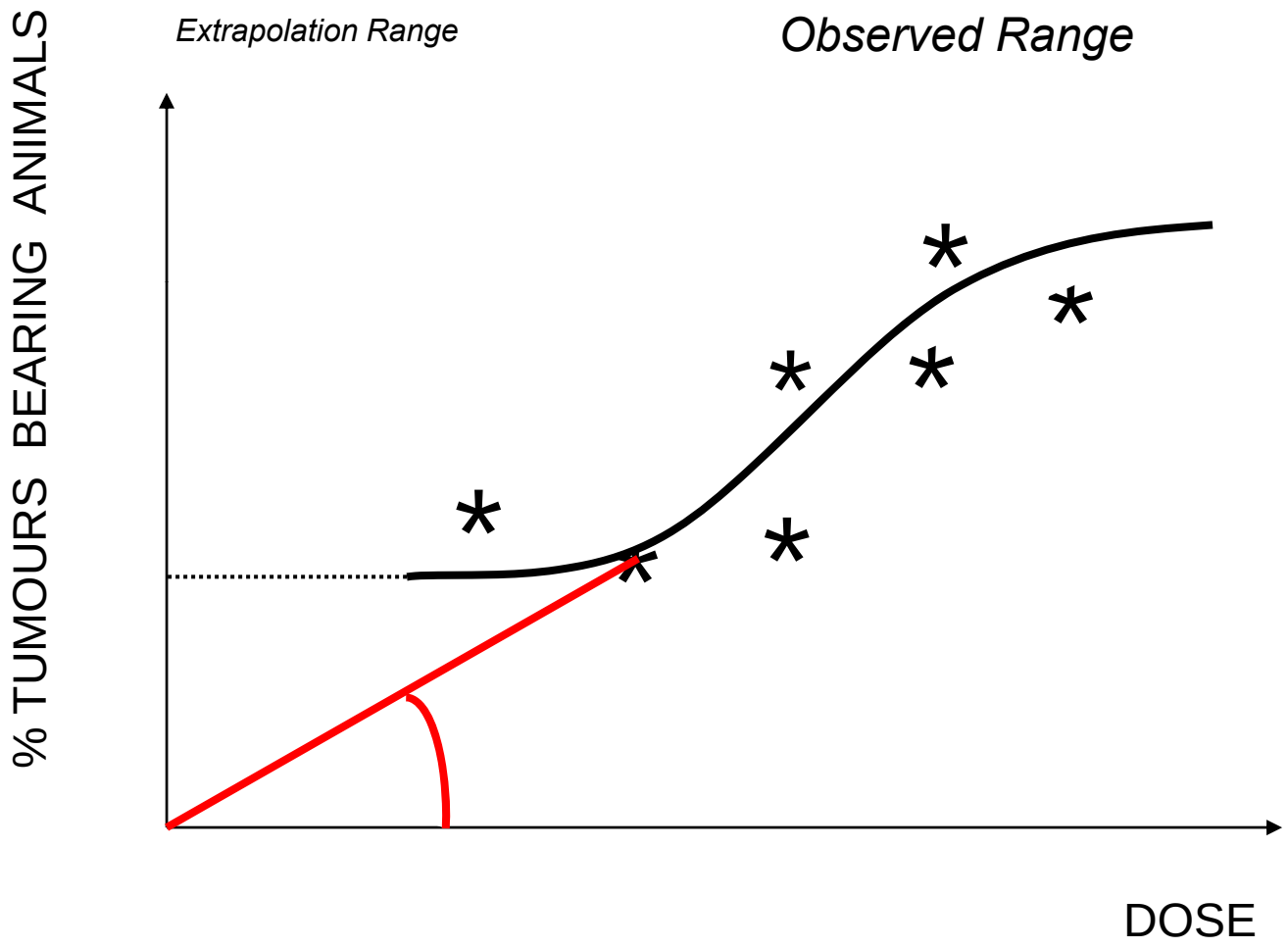
LOW-DOSE EXTRAPOLATION

Risk characterization for genotoxic carcinogens

Cancer risk Estimation

Based on low-dose extrapolation

RISK ASSESSMENT



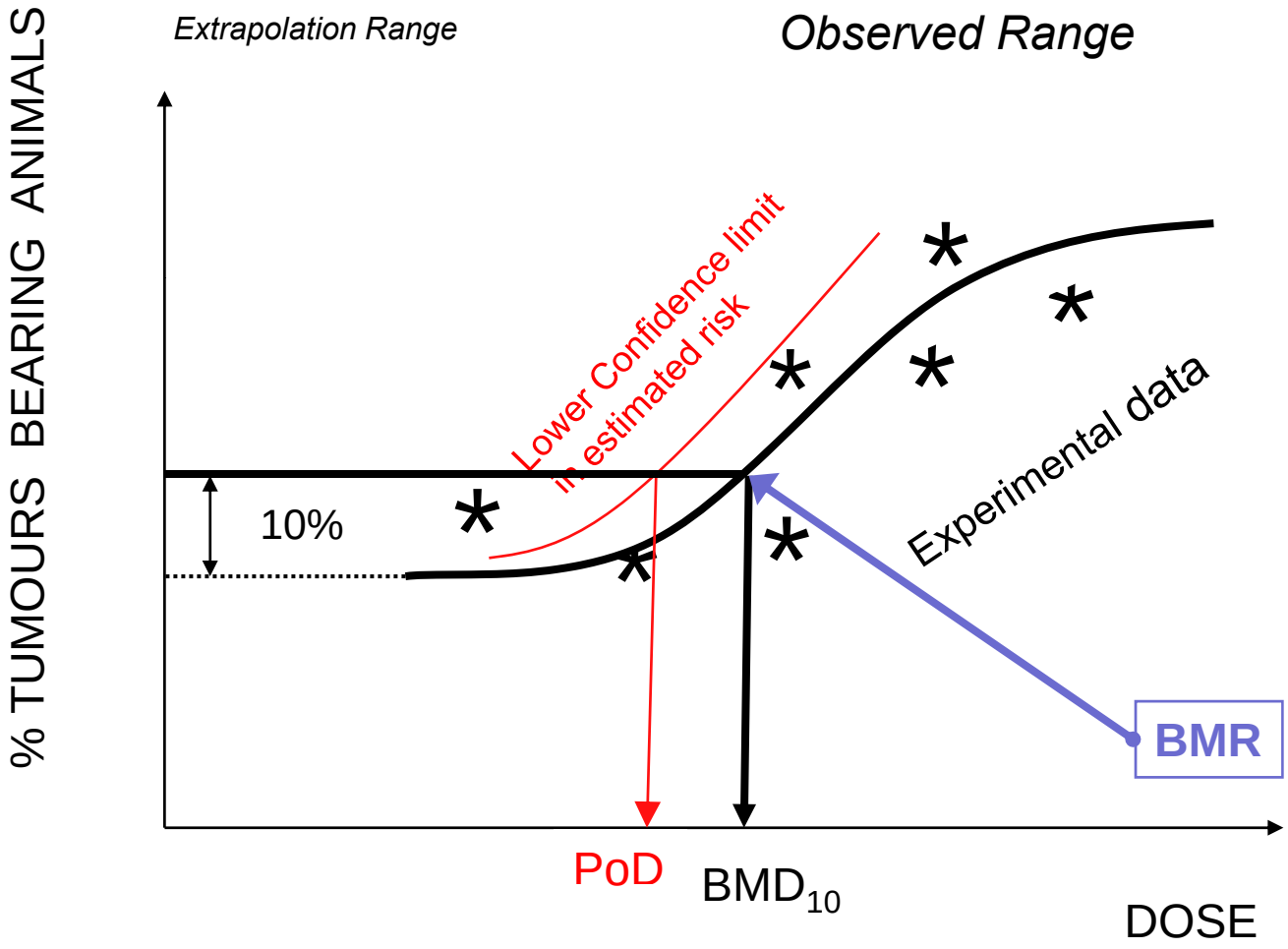
RISK CHARACTERIZATION
AND FORMULATION OF ADVICE TO RISK MANAGERS

Risk characterization for genotoxic carcinogens

Margin of Exposure

(MOE)

BENCHMARK DOSE



MARGIN OF EXPOSURE (MOE)

⌘MOE = PoD / HUMAN EXPOSURE

PoD = 25 mg/kg b.w.

EXPOSURE (Dietary Intake) = 0.00005 mg/kg/day

⌘MOE = 25 / 0.00005 = *58,000*

RISK CHARACTERIZATION
AND FORMULATION OF ADVICE TO RISK MANAGERS

Risk characterization for genotoxic carcinogens

Threshold of toxicological Concern

(TTC)

THRESHOLD OF TOXICOLOGICAL CONCERN (TTC)

IN RISK CHARACTERISATION

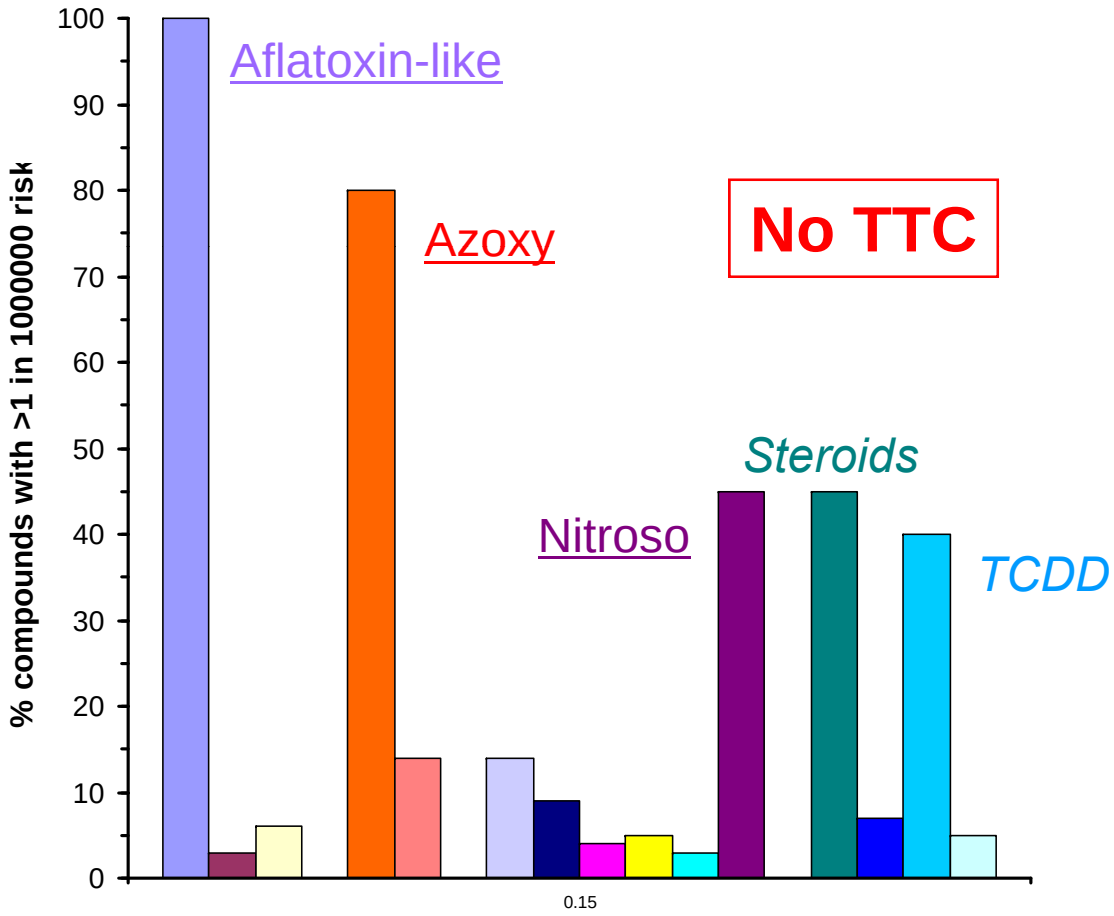
The threshold of toxicological concern (TTC)

is a pragmatic risk assessment tool that is based on the principle of:

establishing a human exposure threshold value for all chemicals (1.5 µg/person/day) below which there is a very low probability of an appreciable risk to human health.

COHORT OF CONCERN (CoC)

Compounds with a calculated risk >1 in 1,000,000



THRESHOLD OF TOXICOLOGICAL CONCERN (TTC) IN RISK CHARACTERISATION

HOW TO APPLY THE TTC ?

- **Stepwise approach on a case by case basis:**
  - **Cohort of Concern (CoC)? → NO TTC**
  - **Structural alerts but not CoC → 0.15 μg/person/day**
  - **Carcinogens → 1.5 μg/person/day**
  - **Class III chemical? → 90 μg/person/day**
  - **Class II chemical? → 540 μg/person/day**
  - **Class I chemical? → 1800 μg/person/day**

THANK YOU

COMPLEX MATRIX

The occurrence of an adverse health effect

resulting from the exposure

to group of substances

with same or different MOA

SAFETY ASSESSMENT OF BOTANICALS AND BOTANICAL PREPARATIONS USE IN FOOD AS SUPPLEMENTS

- **Level A: No testing required (assumed presumption of safety)**
  - long term history of food use
  - absence of adverse effect at the proposed level of use
  - no significant increase of in intake to be expected due to the in intended levels of use as food supplement
  - if presence of genotoxic and carcinogenic substances, MoE approach
  - if presence of otherwise toxic substances, comparison of the overall exposure with the existing safety levels (*e.g. ADI, TMDI) or Margin in of Safety approach*
- **Level B: Further testing and/or data required**
  - Toxicokinetics including metabolism
  - Genotoxicity testing (*in vitro testing + in vivo testing in case of (+) results)*
  - 90 days subchronic toxicity (to establish NOAEL)
  - Other studies based on previous info (target organs, structure activity…)

AGGREGATE AND CUMULATIVE EXPOSURE

Aggregate Risk

The likelihood of the occurrence of an adverse health effect resulting from all routes of exposure to a single substance.

Cumulative Risk

The likelihood of the occurrence of an adverse health effect resulting from all routes of exposure to a group of substance sharing a common mechanism of toxicity (MOA).

SIMPLE SIMILAR ACTION

– Synonyms

❖ **Similar joint action**

- **All chemicals in the mixture act by the same mechanism/mode of action (MOA) and differ only in their potencies**
- **Non-interactive (i.e. the chemicals in the mixture do not influence each other's toxicity)**

DOSE ADDITIVITY

SIMPLE DISSIMILAR ACTION

– *Synonyms*

- Simple independent action
- Independent joint action

- **The Mode of Action (MOA) and, possibly, the nature and site of the toxic effect differ among the chemicals in the mixture**
- **Non-interactive**

RESPONSE ADDITIVITY

TYPES OF COMBINED ACTIONS

- Simple similar action
- Simple dissimilar action
- **Interaction**
  - **Stronger than expected effect**
  - **Weaker than expected effect**

INTERACTION

- All forms of combined action deviating from the former two types of action
- The combined effect may be
  - stronger (synergy, potentiation, supra-addition)
  - weaker (antagonism, inhibition, sub-addition)
- than that expected on the basis of dose addition

INTERACTION

Available evidence is that interaction **does not occur** at doses that are at or below the No-Observable-Adverse-Effect-Level (NOAEL)

INTERACTION

ONLY DOSE ADDITIVITY SEEMS TO BE A PRIORITY IN RISK ASSESSMENT

i.e. only exposure to substances sharing a common MOA need to be cumulated