



UNIVERSITÀ DEGLI STUDI DI MILANO
DIPARTIMENTO DI SCIENZE
FARMACOLOGICHE E BIOMOLECOLARI

RISK ASSESSMENT- - REACH

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STRUCTURE OF RISK ANALYSIS



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HAZARD



Hazard is the potential capacity of producing harm.



RISK



Risk is proportional to both the hazard and the extent of exposure.



STRUCTURE OF RISK ANALYSIS



RISK ASSESSMENT

✓ Hazard identification

- ❖ Inherent biological activity

✓ Hazard assessment

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

EXPOSURE ASSESSMENT

- ◆ Active principle
 - ◆ Dose of toxicant
 - ◆ Dose in individuals
 - ◆ Dose in special population groups
 - ◆ Max/min chronically/occasionally

HAZARD IDENTIFICATION

- ◆ Identification of adverse health effects
 - ◆ In silico methodologies
 - ◆ *In vitro* toxicology data
 - ◆ Animal-based toxicological studies
 - ◆ Human observation

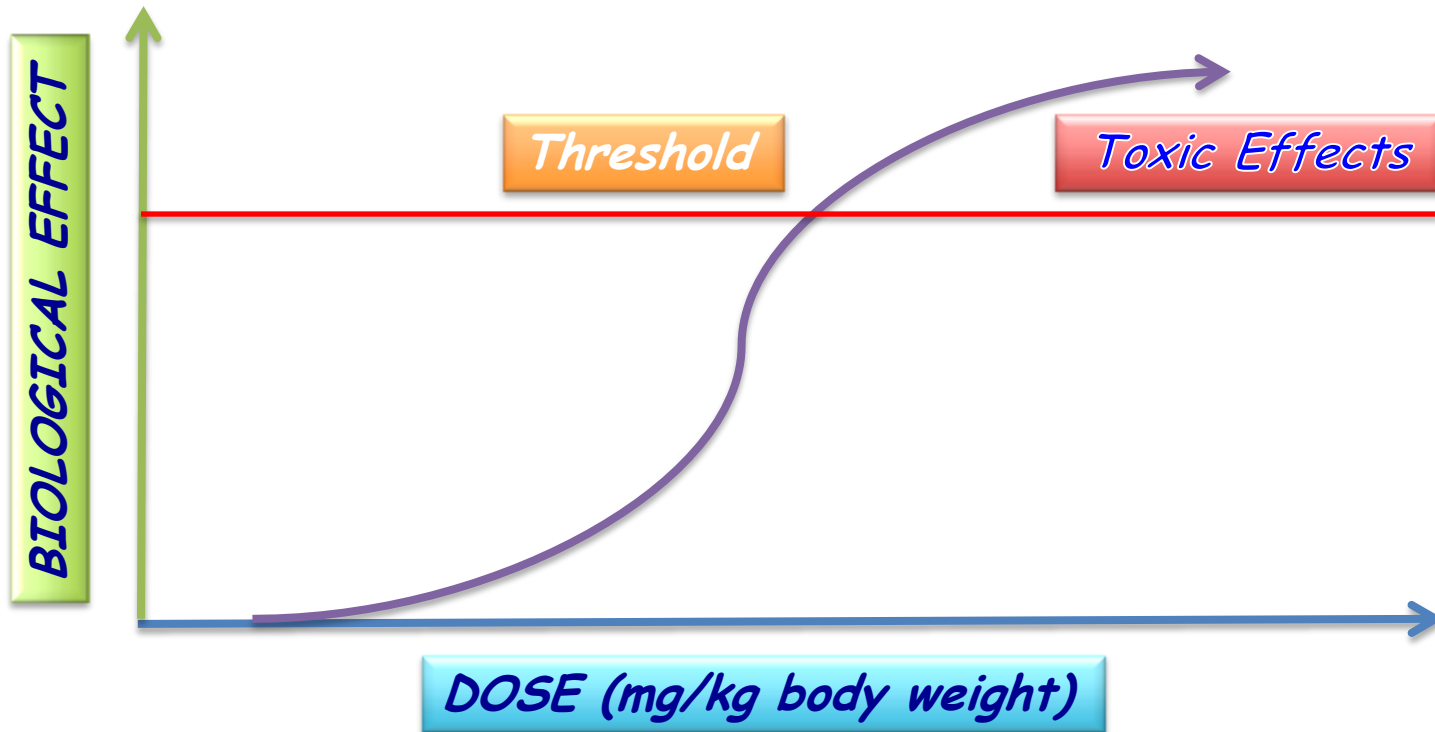
HAZARD ASSESSMENT

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

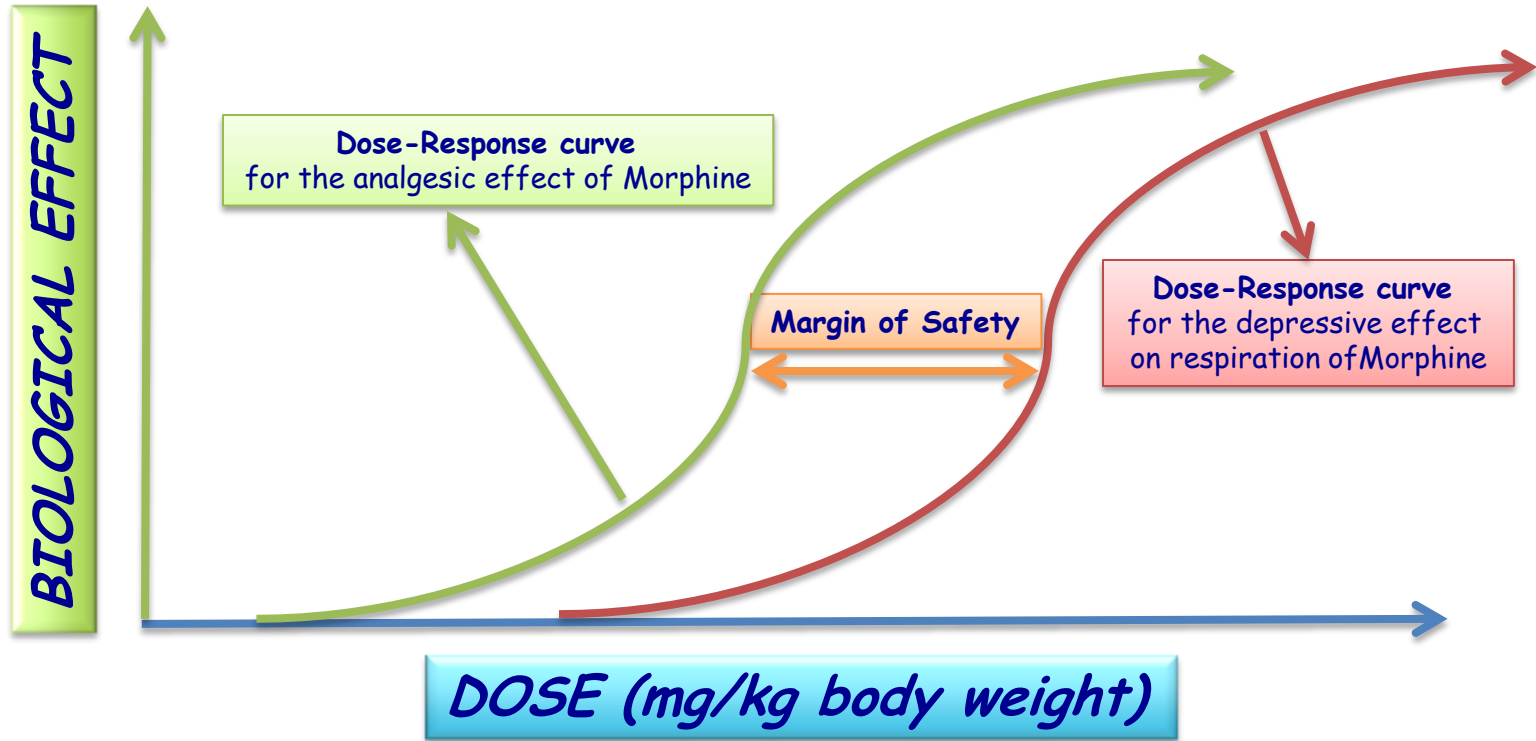
RISK CHARACTERISATION



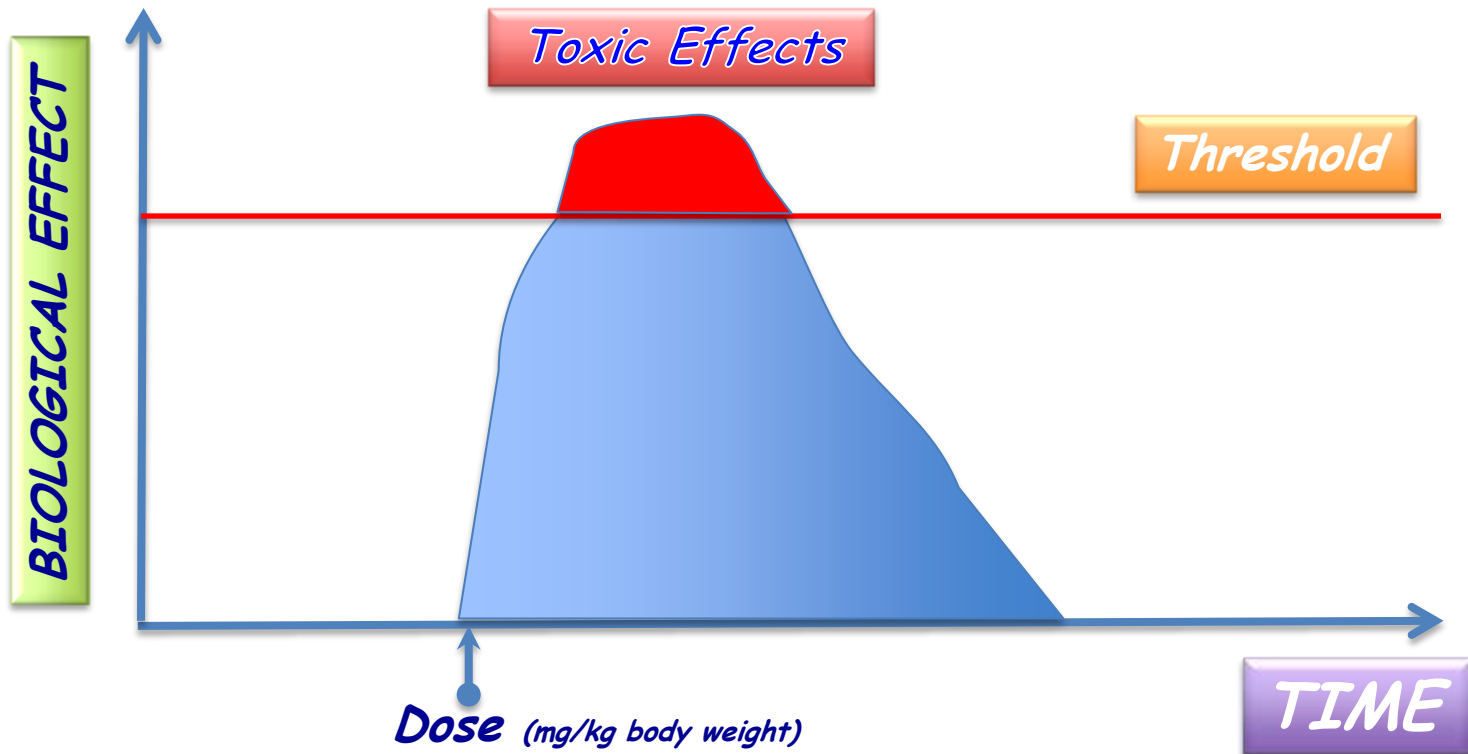
DOSE - RESPONSE - CURVE



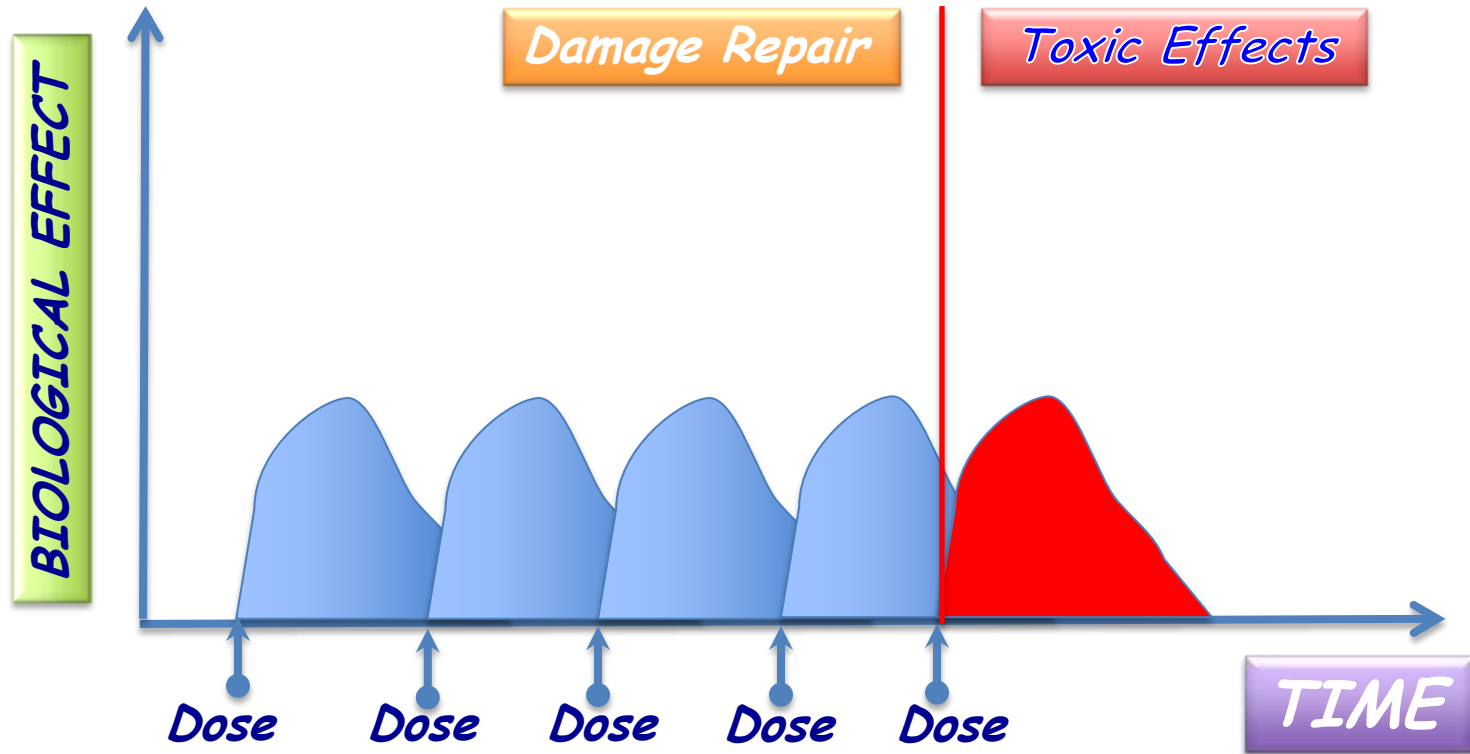
DOSE-RESPONSE CURVES FOR THE ANALGESIC AND DEPRESSANT EFFECTS OF MORPHINE



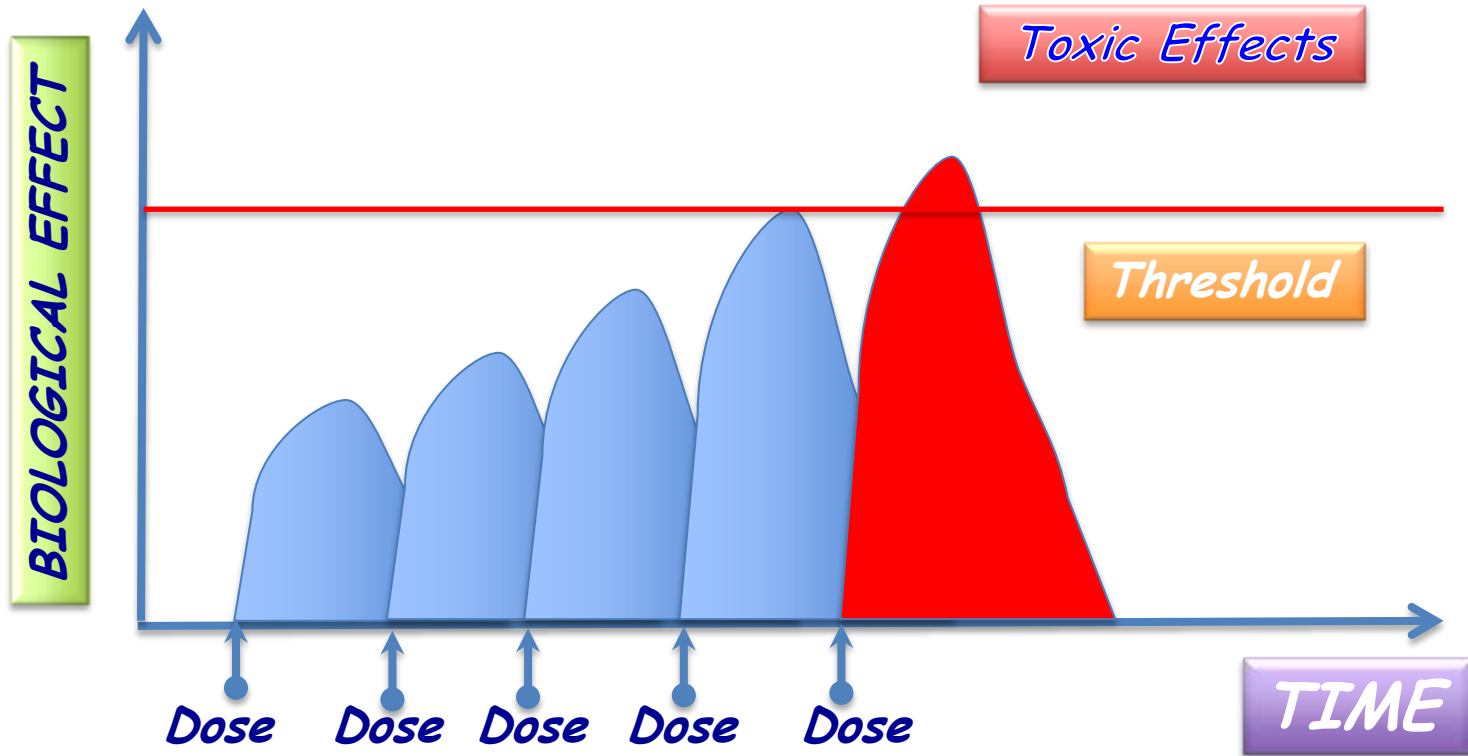
DOSE - RESPONSE - ACUTE EFFECT



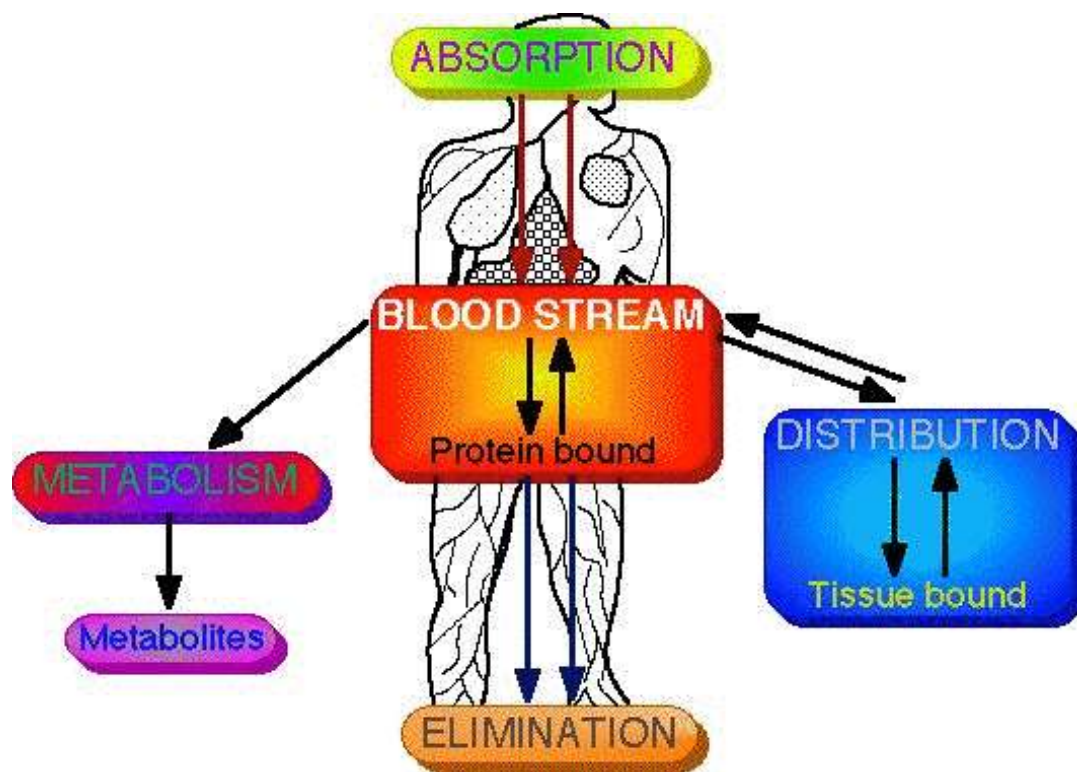
DOSE - RESPONSE - CHRONIC EFFECT



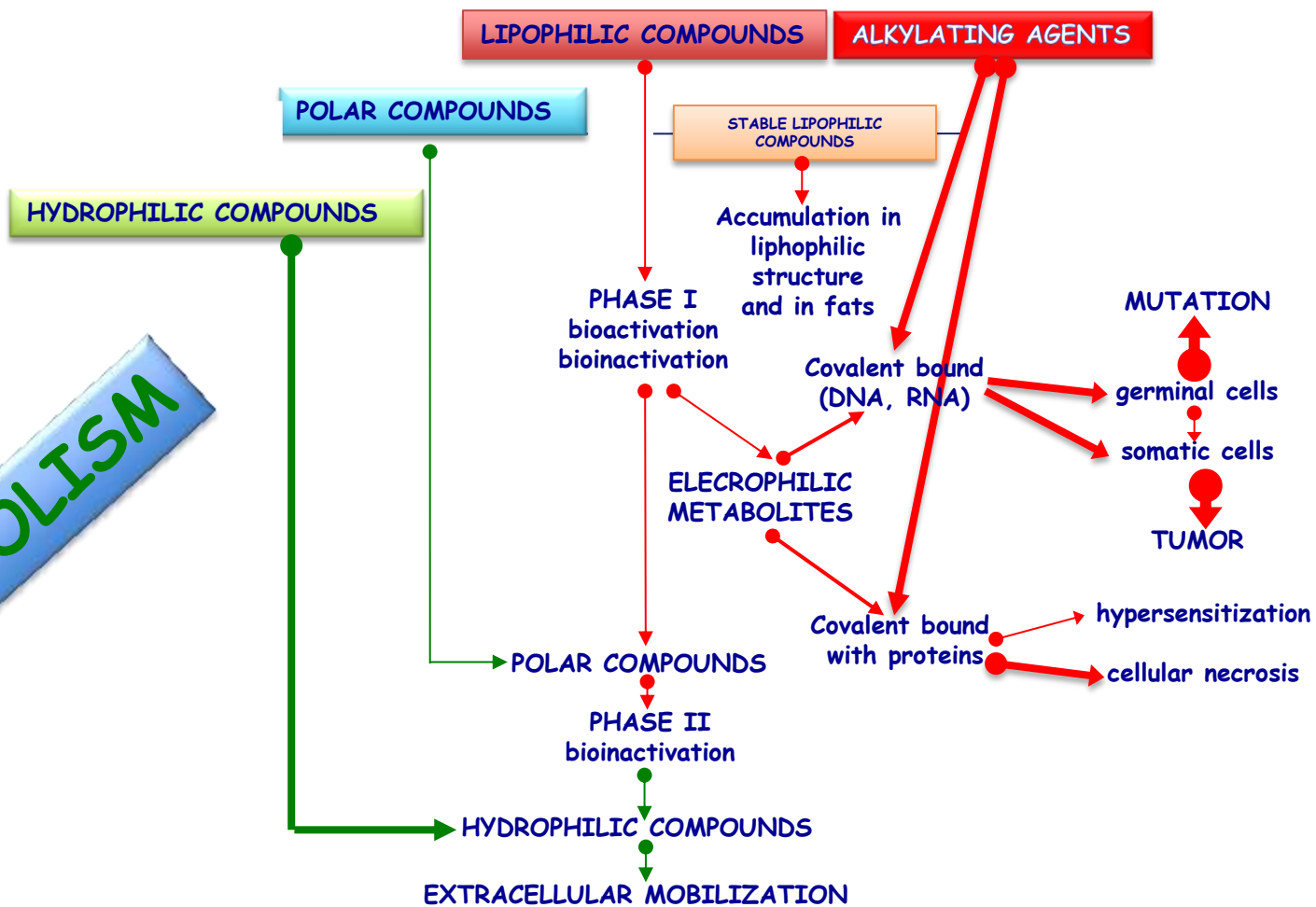
DOSE - RESPONSE - CUMULATIVE EFFECT



ADME



METABOLISM



TOXICOKINETIC/TOXICODYNAMIC

TOXICOKINETIC

Exposure → Dose to target → Interaction with target

Interaction with target → Toxic effect

TOXICODYNAMIC

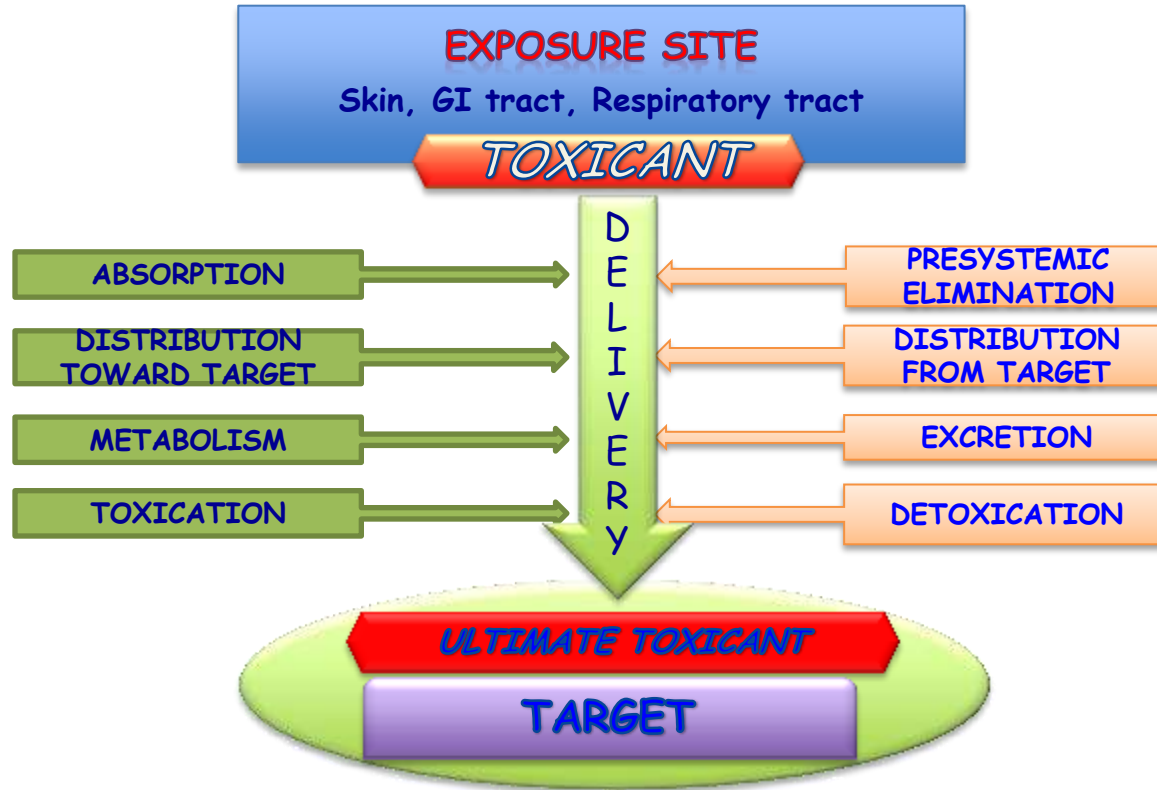


TARGET and TOXIC RESPONSE

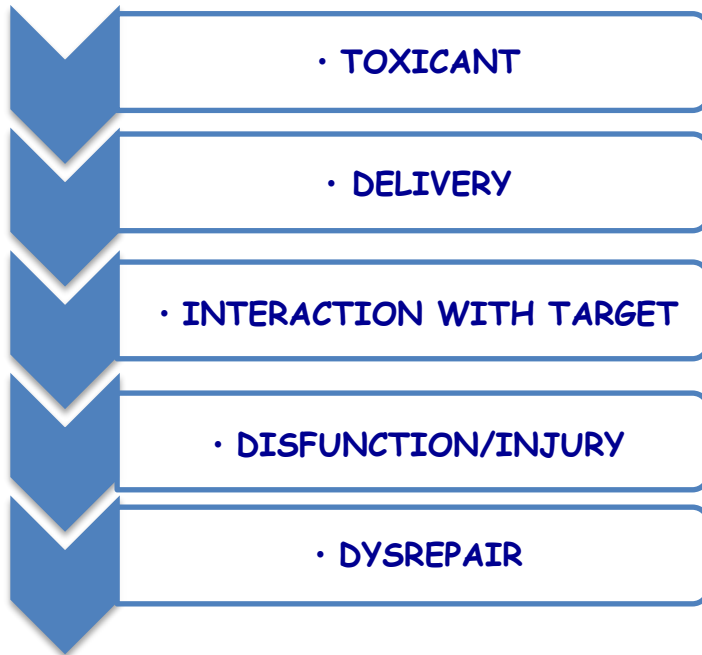
- ❖ The presence of a **TARGET** is essential, so that the toxic agent could interact and to get the toxic response
- ❖ **The concentration at the target** of the toxic agent and/or its metabolites and/or its degradation products is strictly related to the external dose
 - ◆ *mg/kg body weight of the administered toxic agent or the one present in the environment*
- ❖ **The toxic effect**, either qualitative or quantitative, is strictly related to the internal dose
 - ◆ *mg/kg body weight of the administered toxic agent or the one present in the environment and or its metabolites and or its degradation products reaching the target*



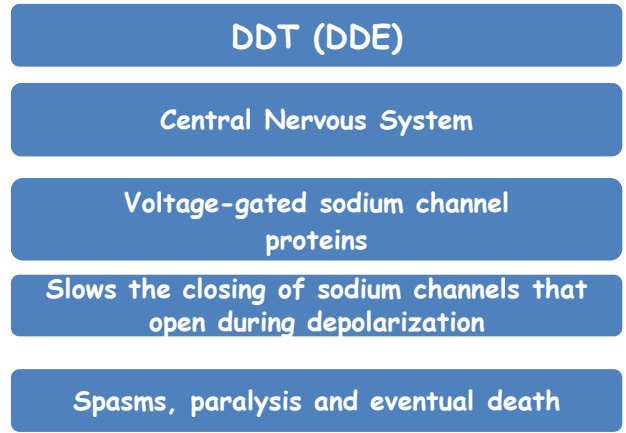
TARGET- TK - TD - TOXIC RESPONSE



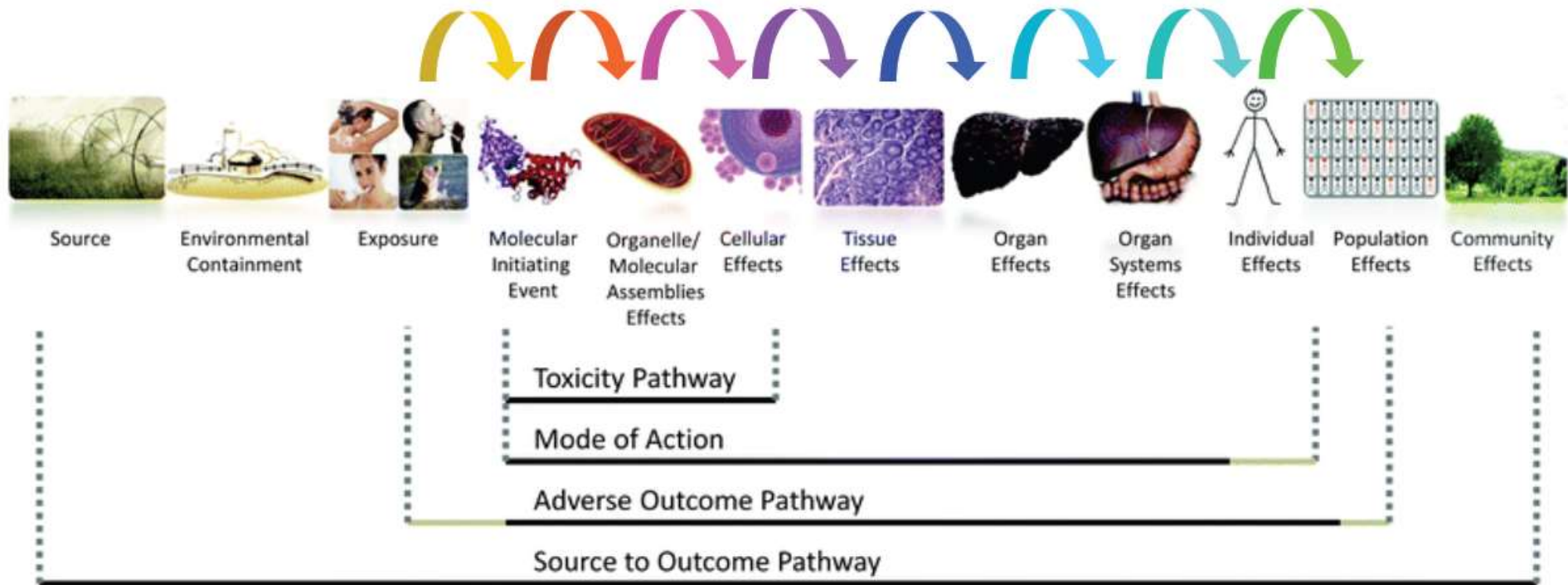
TARGET- TK - TD - TOXIC RESPONSE



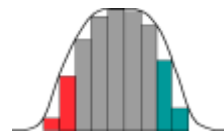
TOXICITY



THE ADVERSE OUTCOME PATHWAY (AOP)

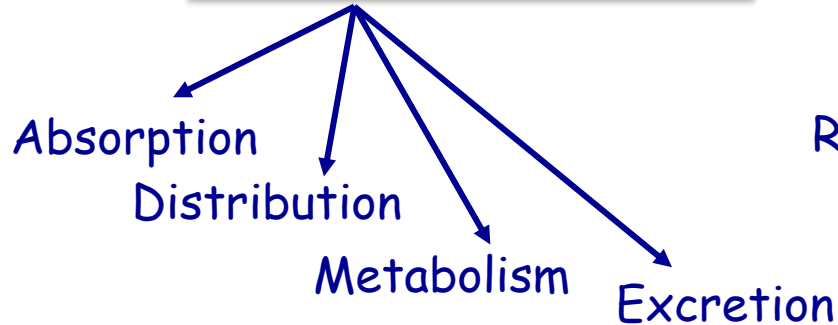


TOXICITY AND INDIVIDUAL SUSCEPTIBILITY (GENETIC POLYMORPHISM)

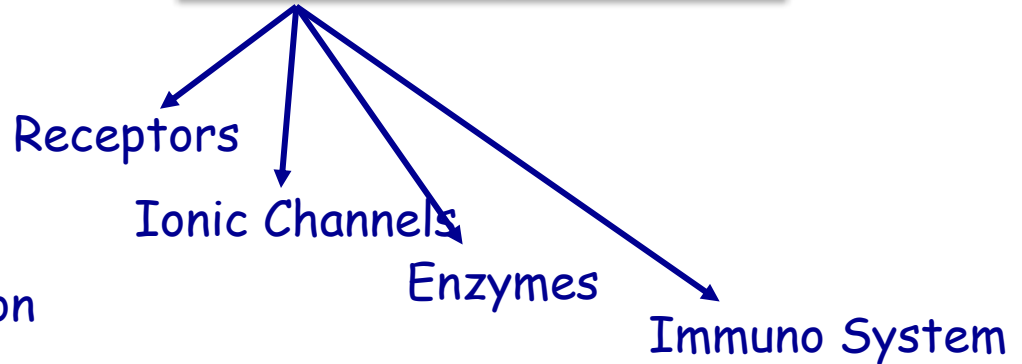


GENETIC POLYMORPHISM

Toxicokinetic



Toxicodynamic



HEALTH BASED GUIDANCES

Non - Carcinogens

- ☑ **ADI** (Acceptable Daily Intake)
- ☑ **TDI/TWI** (Tolerable Daily/Weekly Intake)
- ☑ **MoE** (Margin of Exposure)

Carcinogens

- ☑ **TTC** (Threshold of Toxicological Concern)



ADI - TDI

(HEALTH BASED GUIDANCES)

ADI - Admissible Daily Intake

- ☑ represents the amount of a **food additive, a pesticide or a veterinary drug residue**, expressed on a body weight basis, that can be ingested daily **over whole lifetime** without appreciable health risk.

TDI - Tolerable Daily Intake -

- ☑ represents the amount of a **contaminant or other foreign chemicals**, expressed on a body weight basis, that can be ingested daily **over whole lifetime** without appreciable health risk.



RISK ASSESSMENT

Hazard Assessment



Genotoxic Carcinogen



Toxicant and/or
NON Genotoxic Carcinogen



RISK CHARACTERIZATION

Hazard Assessment



Genotoxic Carcinogen



Toxicant and/or
NON Genotoxic Carcinogen



REFERENCE POINTS

Reference points (RPs) in toxicology studies used to calculate a safe level for human intake:

- ◆ ***NO-OBSERVED-ADVERSE-EFFECT-LEVEL (NOAEL):***
- ◆ **Benchmark Dose (BMD)**



HAZARD IDENTIFICATION

(HEALTH BASED GUIDANCES)

ALLOCATION



ADI - TDI



TOXICOLOGICAL PROTOCOL



ANIMAL-BASED TOXICOLOGICAL STUDIES

TOXICOKINETIC

- Absorption
- Distribution
- Metabolism
- Excretion

ACUTE TOXICITY

- LD₅₀ oral
- LD₅₀ dermal
- LC₅₀ 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

NOAEL/BMD



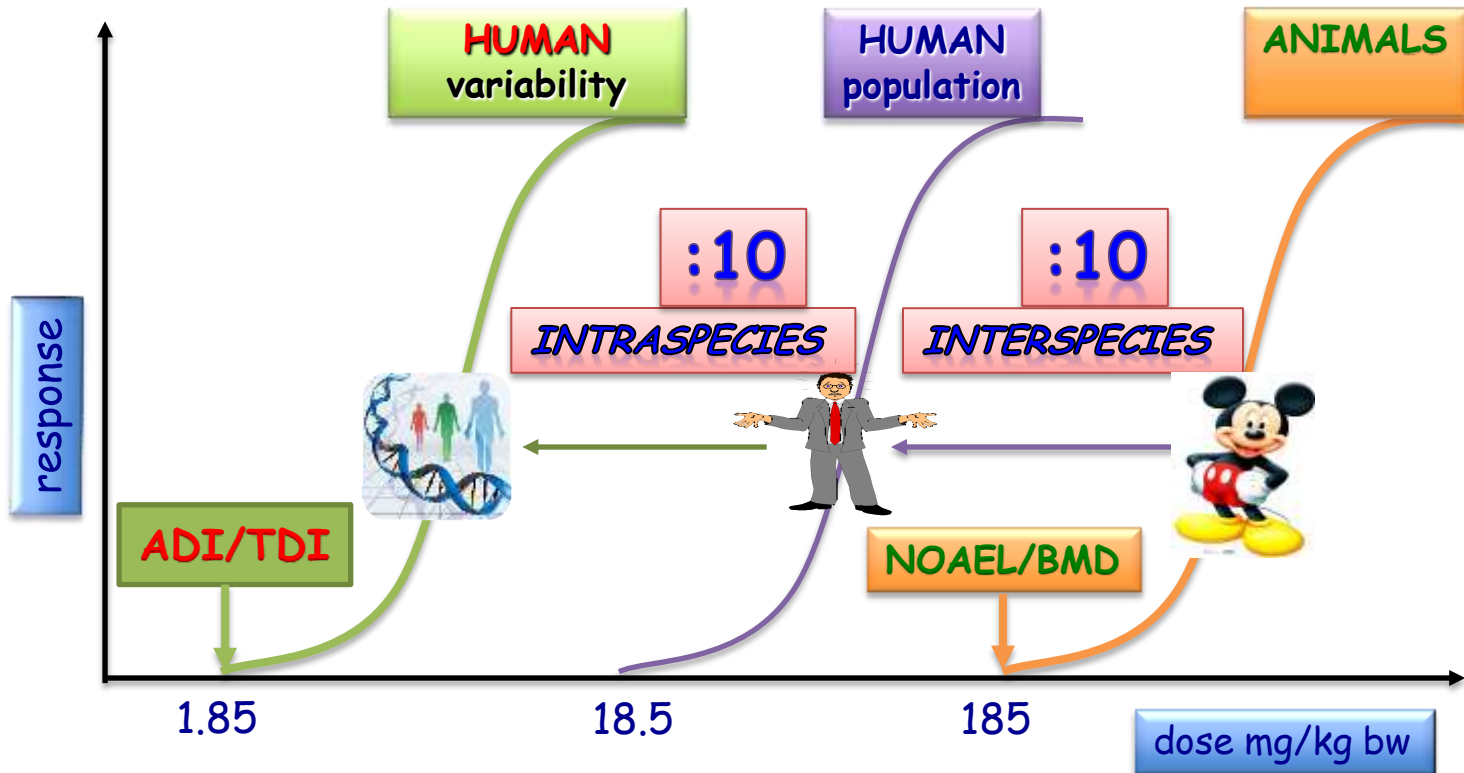
NO-ADVERSE-OBSERVED-EFFECT-LEVEL (NOAEL)

- The greatest concentration or amount of an agent, found by study or observation that causes detectable, usually adverse (or toxic?) alteration of morphology, functional capacity, growth, development or lifespan of the target



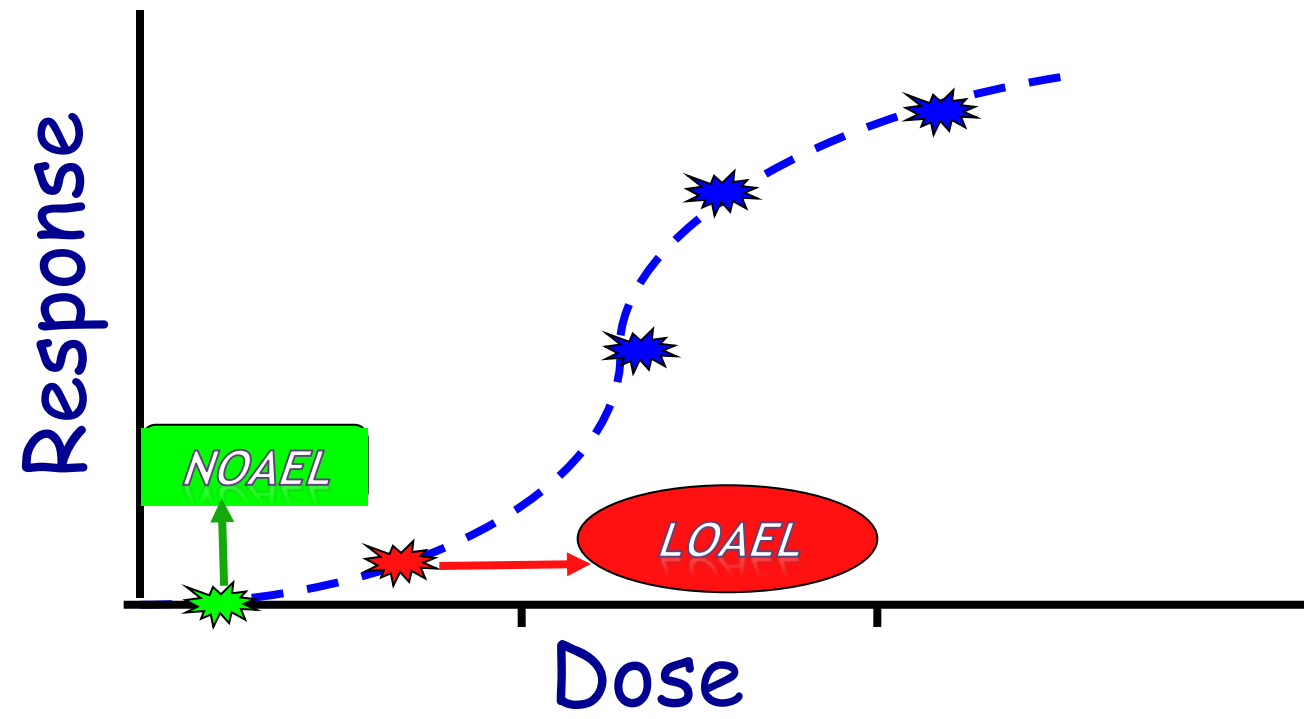
ANIMAL-BASED TOXICOLOGICAL STUDIES

(QUANTIFICATION OF ADVERSE HEALTH EFFECTS)



DOSE - RESPONSE FOR CRITICAL EFFECTS

(TO ESTABLISH A DOSE WITHOUT ADVERSE EFFECTS IN ANIMALS)



ADMISSIBILE/TOLERABLE DAILY INTAKE

$$\text{ADI/TDI} = \frac{\text{NOAEL}}{\text{SF}}$$

ADI/TDI = Admissible (Tolerable) Daily Intake mg/kg b.w.

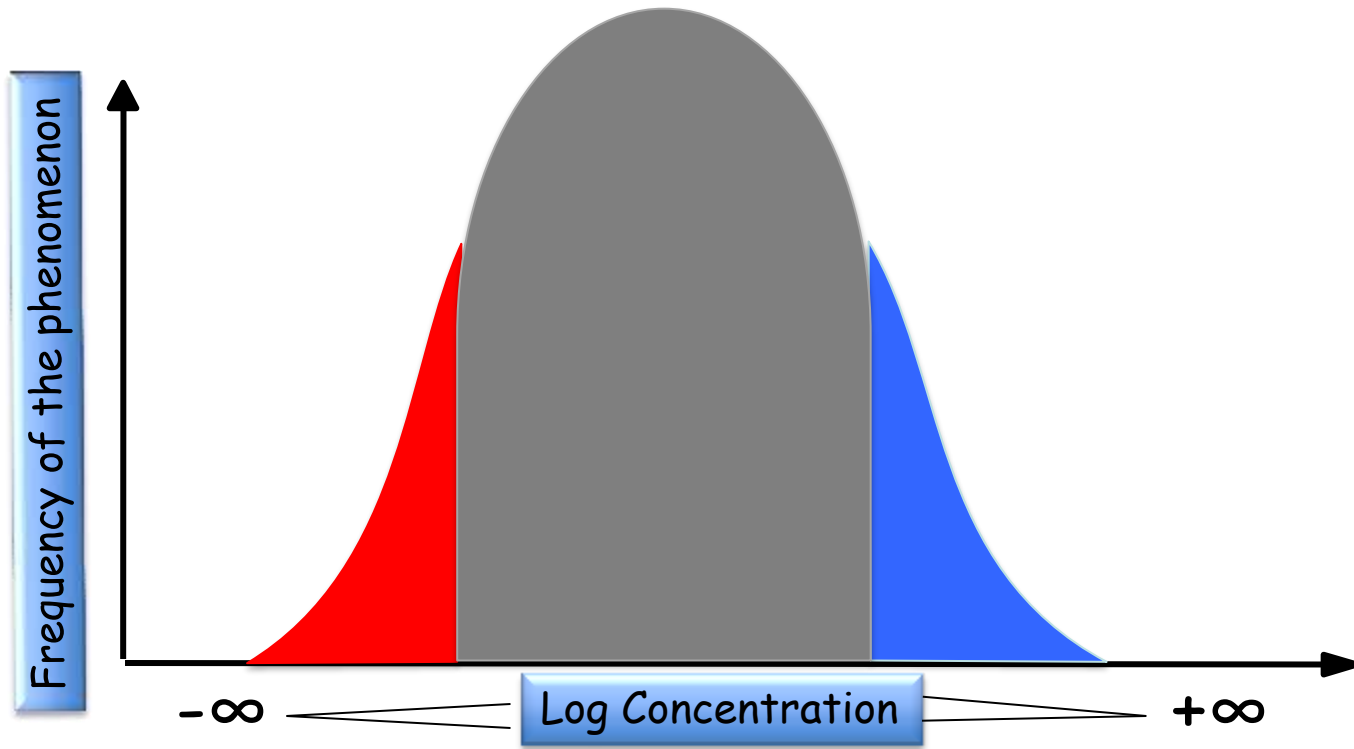
NOAEL = No Observed Adverse Effect Level (mg/kg b.w.)

SF = Safety Factor (10, 100, n)



INDIVIDUAL SUSCEPTIBILITY

(GENETIC POLYMORPHISM)



REFERENCE POINTS

Reference points (RPs) in toxicology studies used to calculate a safe level for human intake:

◆ *NO-OBSERVED-ADVERSE-EFFECT-LEVEL (NOAEL):*

◆ *BENCHMARK DOSE (BMD).*

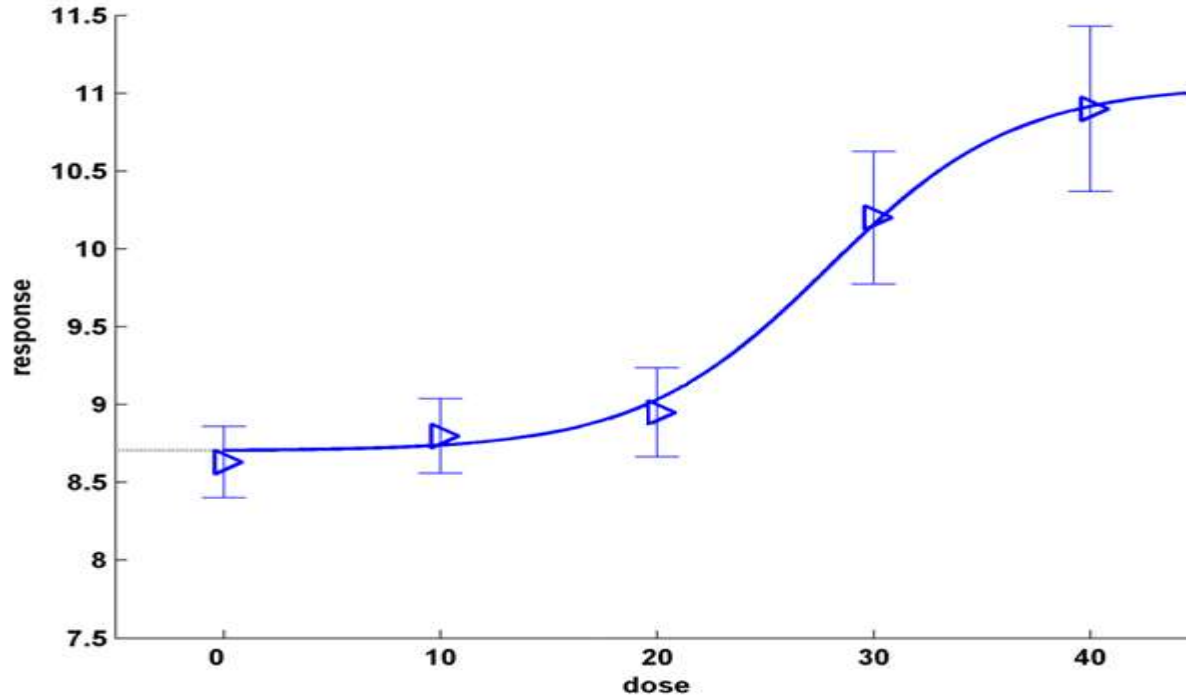


BENCHMARK DOSE - (BMD)

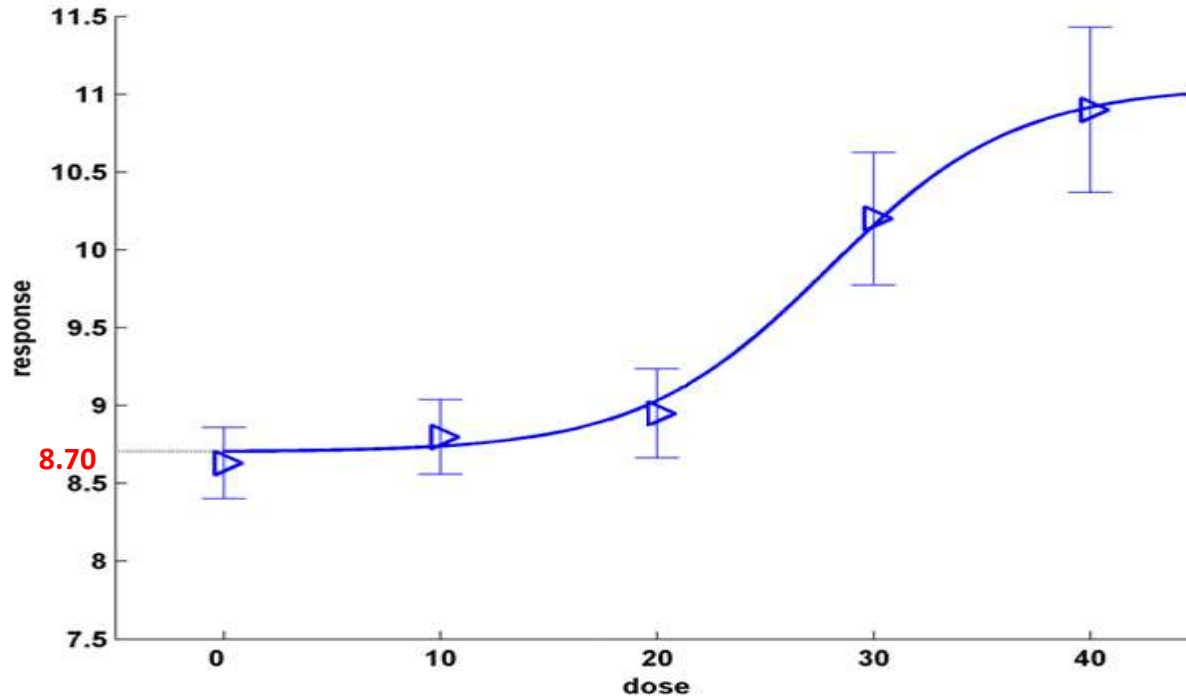
- The BMD (Benchmark Dose) approach is applicable to any biological effect.
- All available data are exploited to estimate the dose-response curve for a particular target.
- The BMD is a dose derived from a calculated dose-response curve, associated with a peculiar change in the response: the Benchmark Response (BMR).
 - Ex. BMR = 5%, means change of 5% of the relative response to the background.



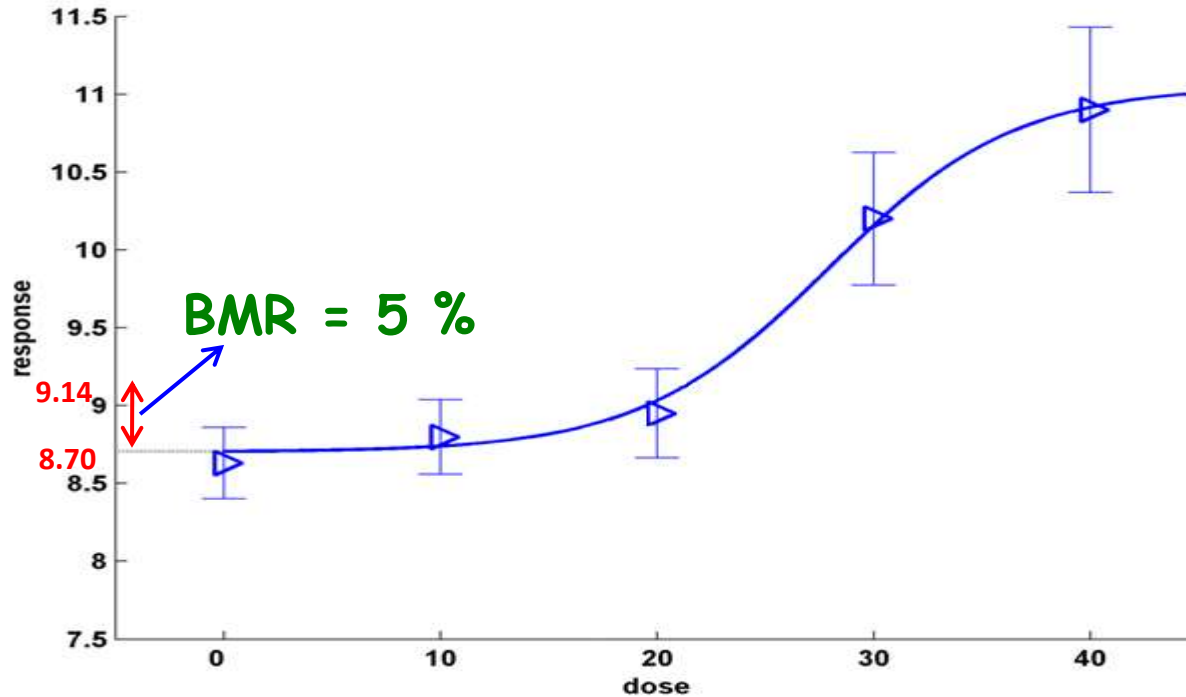
BENCHMARK DOSE - (BMD)



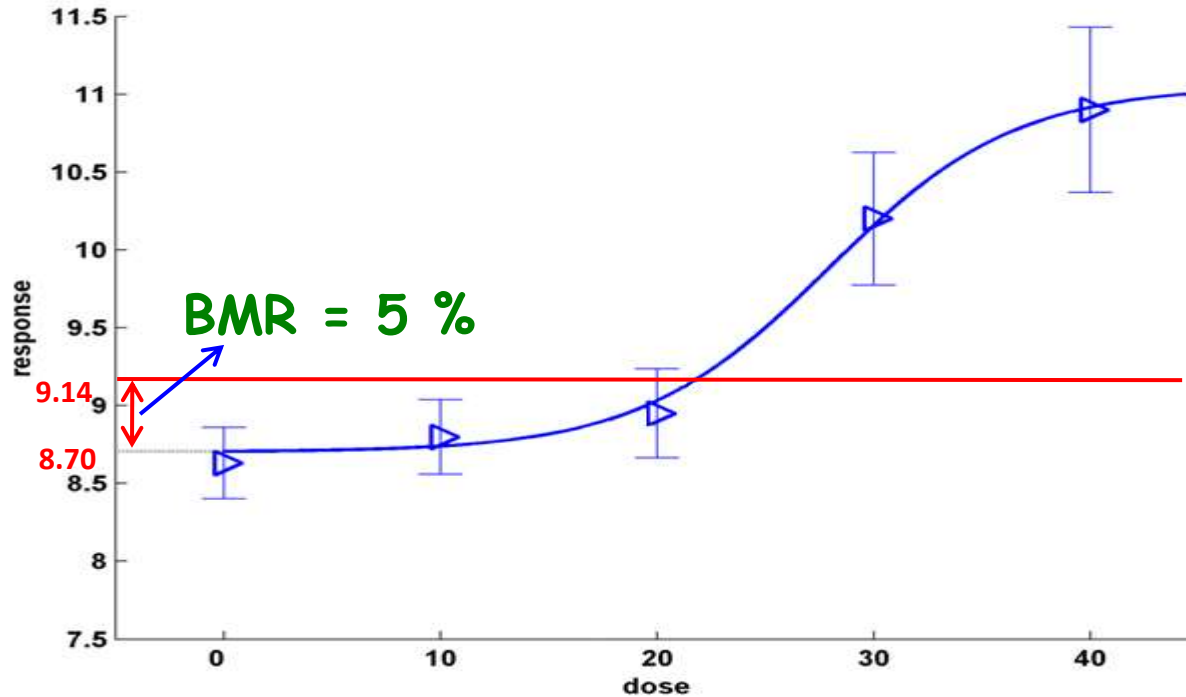
BENCHMARK DOSE - (BMD)



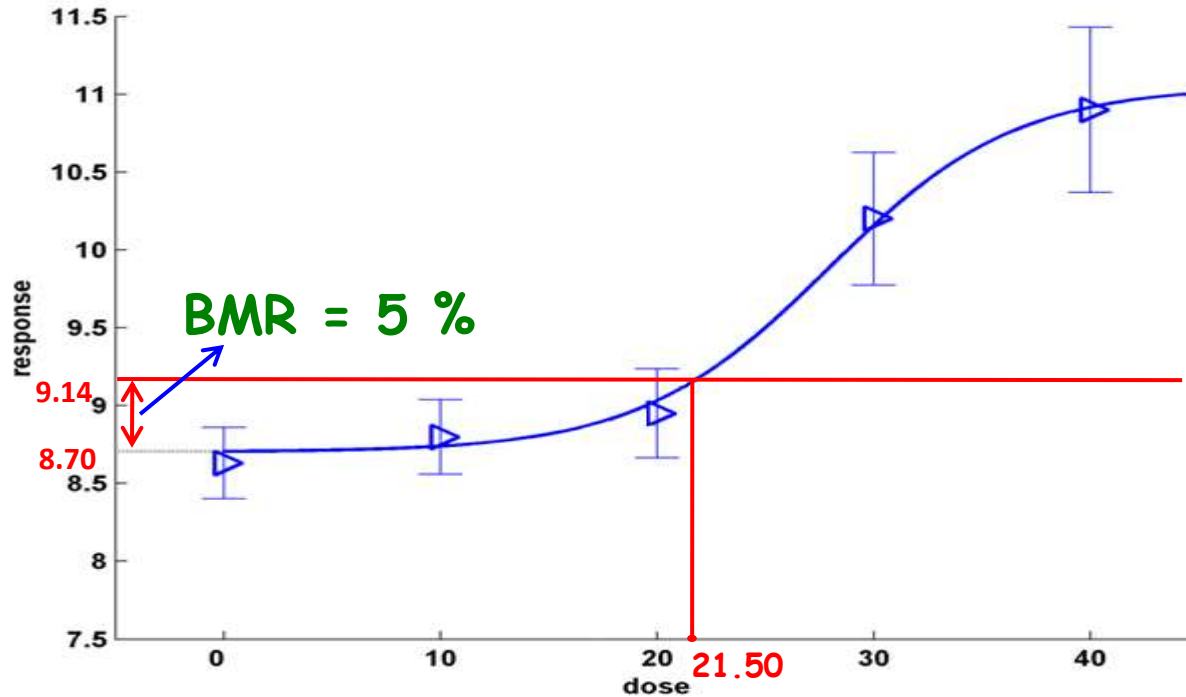
BENCHMARK DOSE - (BMD)



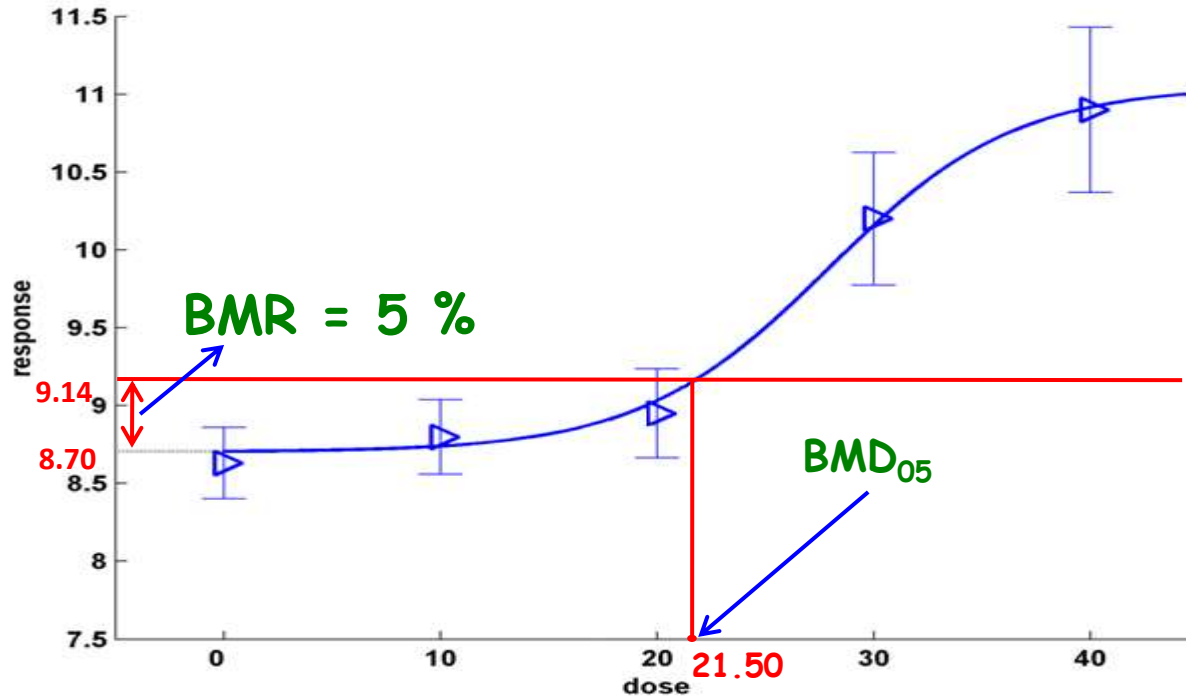
BENCHMARK DOSE - (BMD)



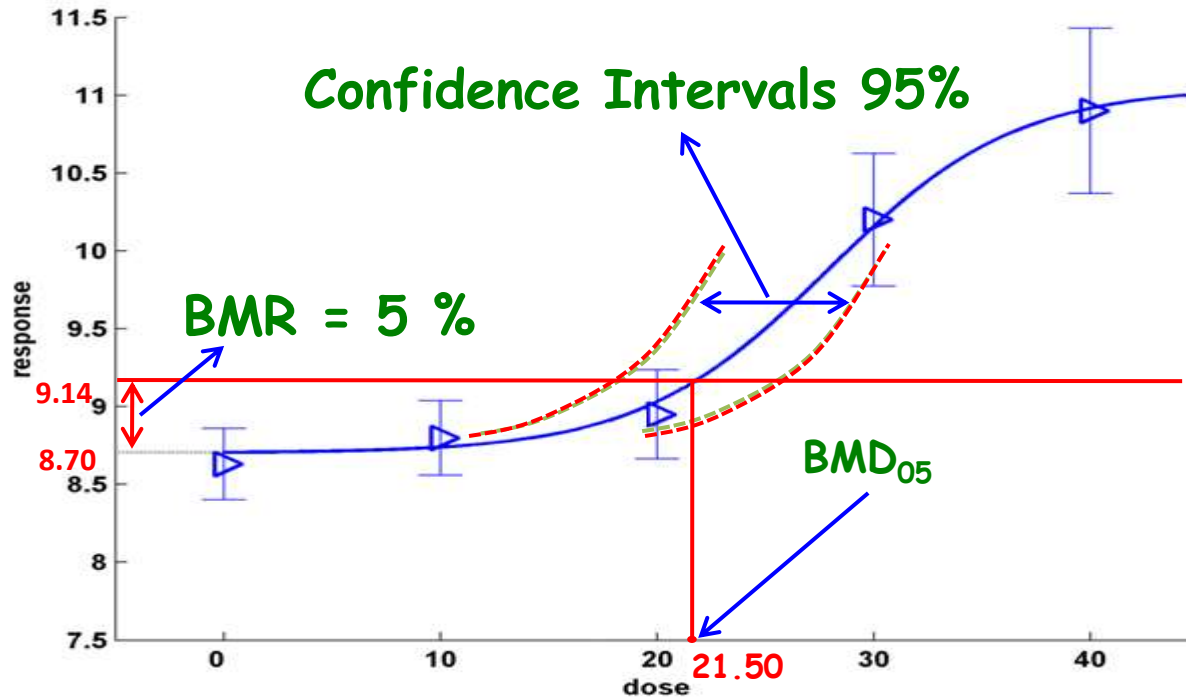
BENCHMARK DOSE - (BMD)



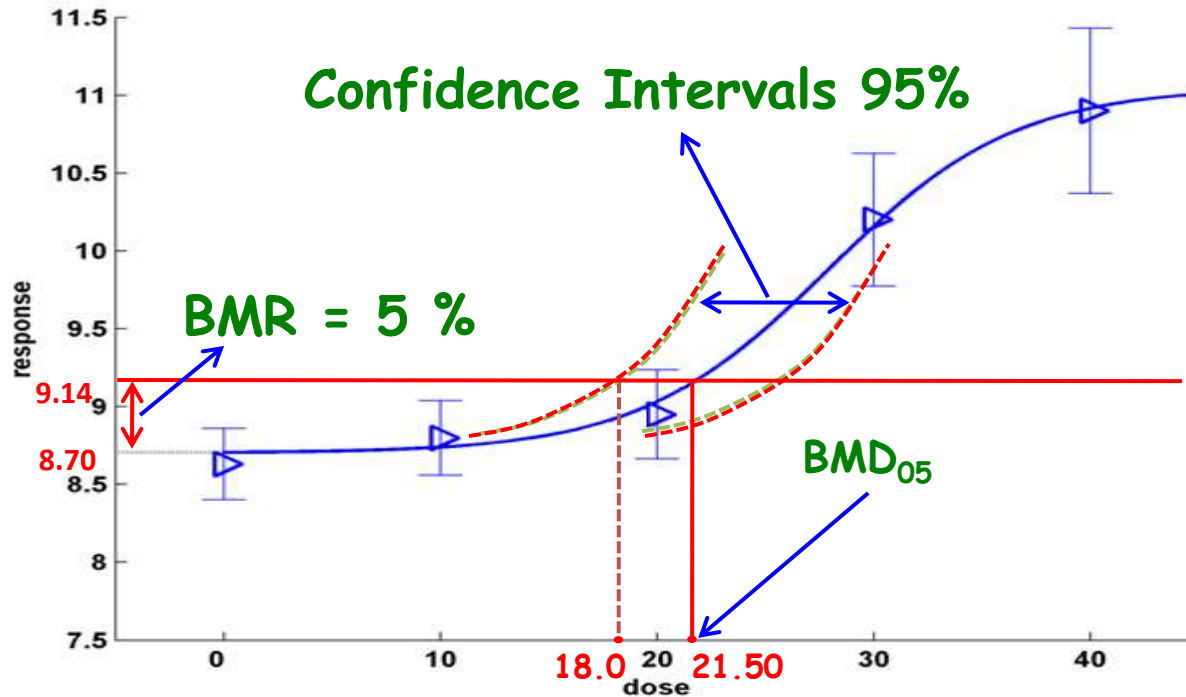
BENCHMARK DOSE - (BMD)



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BENCHMARK DOSE - (BMD)



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