Approaches to assessment of substances for which no safe threshold can be set

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Main Question in Food Toxicology

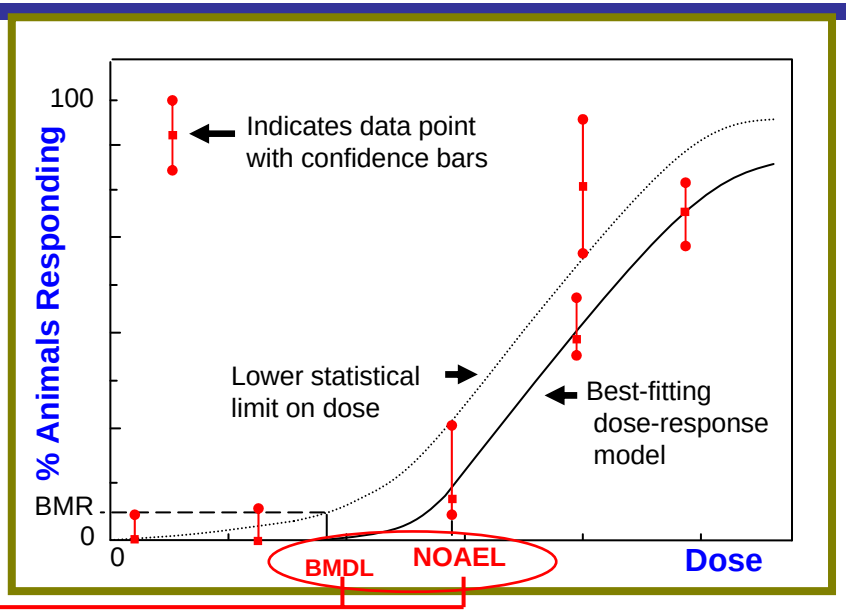
What is a „safe" human exposure dose over lifetime ? ?

e.g. a dose with "no appreciable or a negligible risk"

⟷ acute exposure

Extrapolation from animals to Man:

- Most sensitive species
- Lowest NOAEL [or BMD(L)]
- Apply uncertainty factors (UF)



NOAEL		ADI
BMDL (mg/kg bw) : UF	=	TDI (mg/kg bw)
BMD		PTWI

animals — man

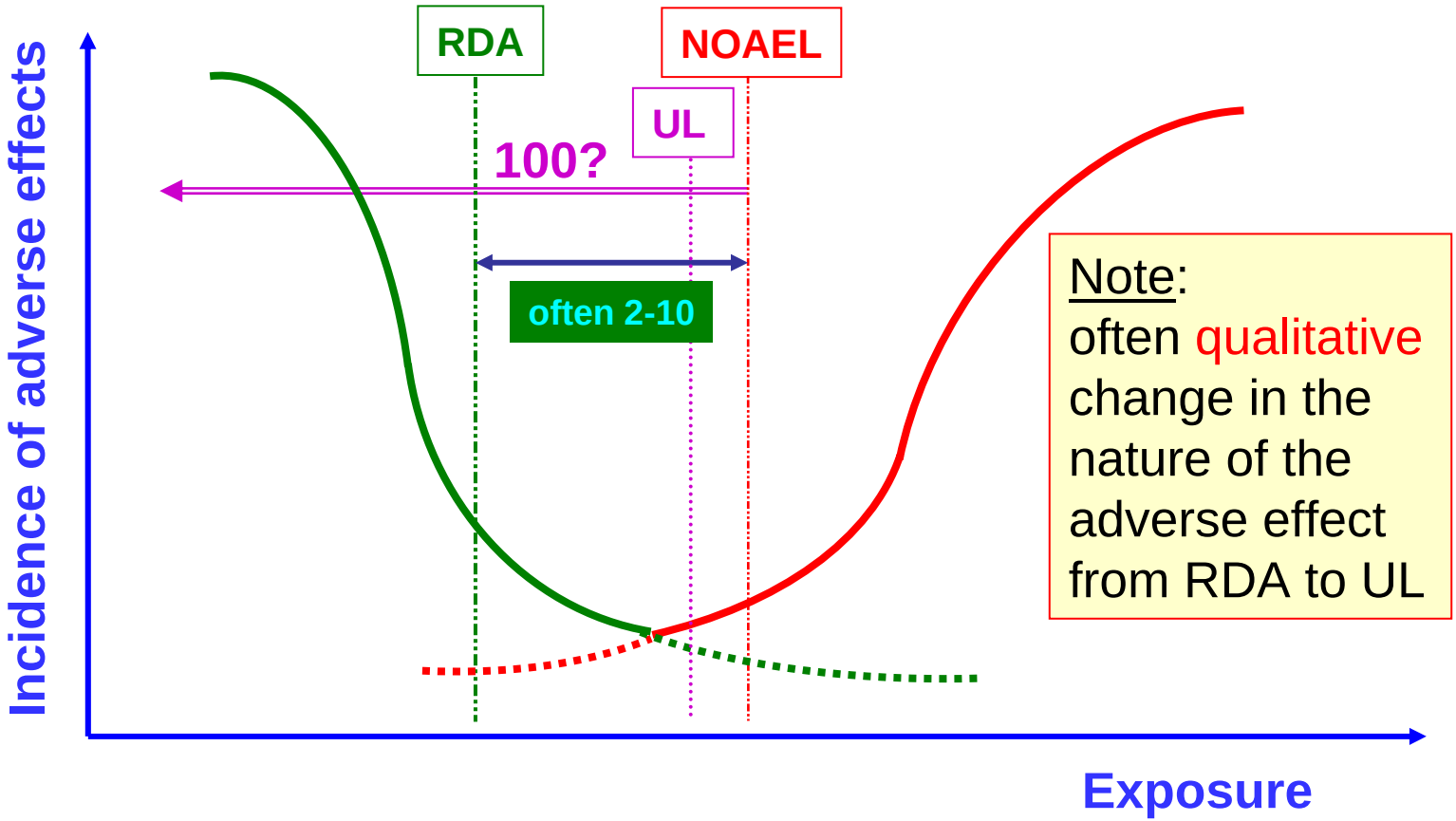
ADI: intentionally added compounds **TDI, PTWI: Contaminants**

Problematic areas:

- **Allergies and intolerances**
- **Non-monotonic dose-response curves (D-R)**
- **Assumption of a non-thresholded D-R**

NOTE:
the existence of a threshold cannot be proven or disproven experimentally

Hazard Characterization: Non-monotonic D-R



Irreversible toxic effects

- CNS Central nervous system damage (almost no regeneration)
- Cataracts
- Malformations (cell death during organogenesis)
- Carcinogenicity
  (DNA damage, disturbed cell-cell communication)
- Genotoxicity (DNA damage)

Most toxicological effects are thresholded

e.g. there is a dose without “appreciable” risk

Issues with genotoxic compounds

- Absence of a threshold in their mode of action is assumed, i.e. there is no dose without a potential effect
- No generally agreed paradigm for the risk assessment

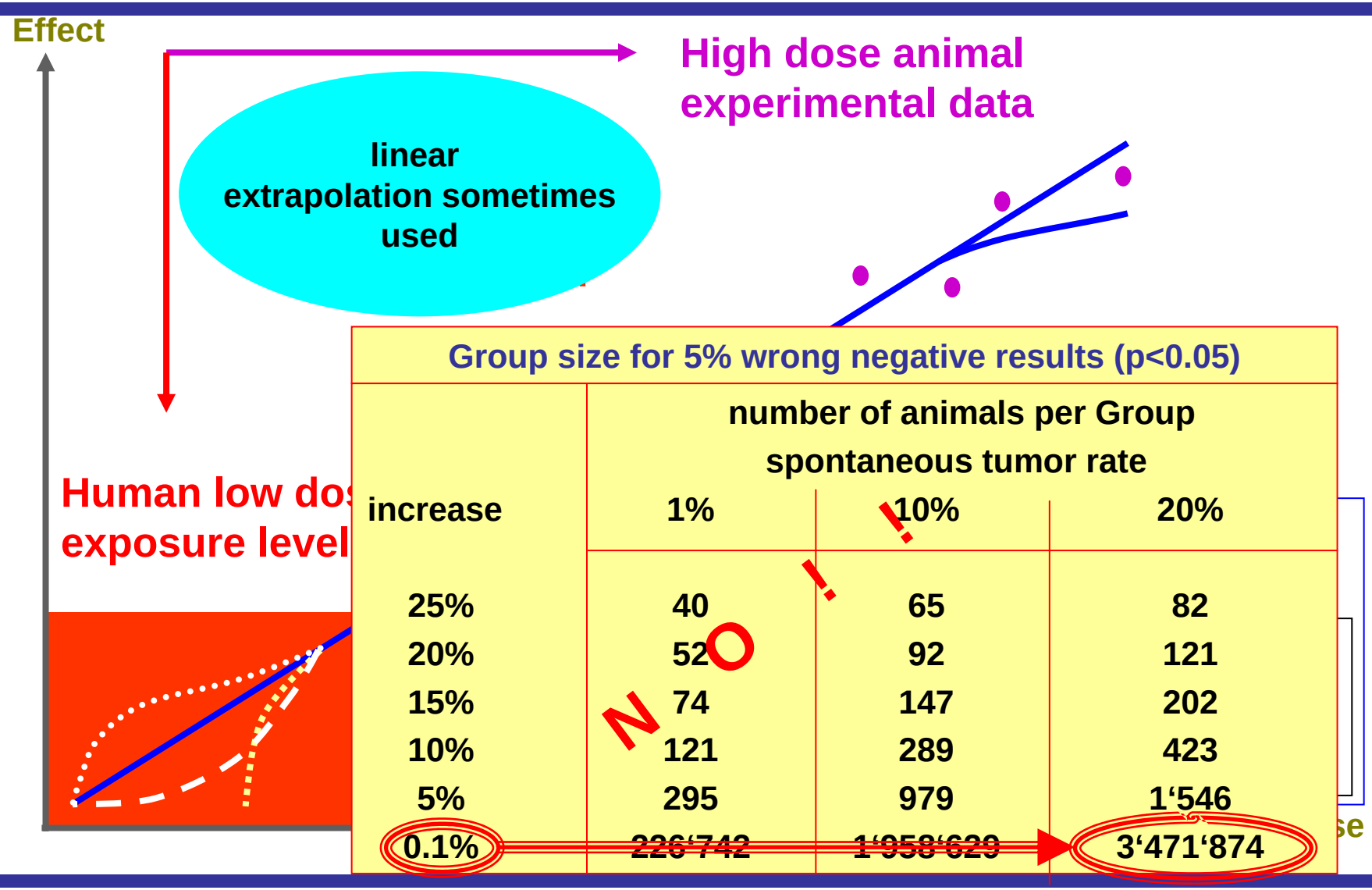
Most difficult issue in food safety is to advise on potential risks to human health for unavoidable compounds found in food, which are both genotoxic and carcinogenic

- As low as reasonably achievable (ALARA)
- Dose-response extrapolation outside the observed dose range

Limitation of ALARA approach

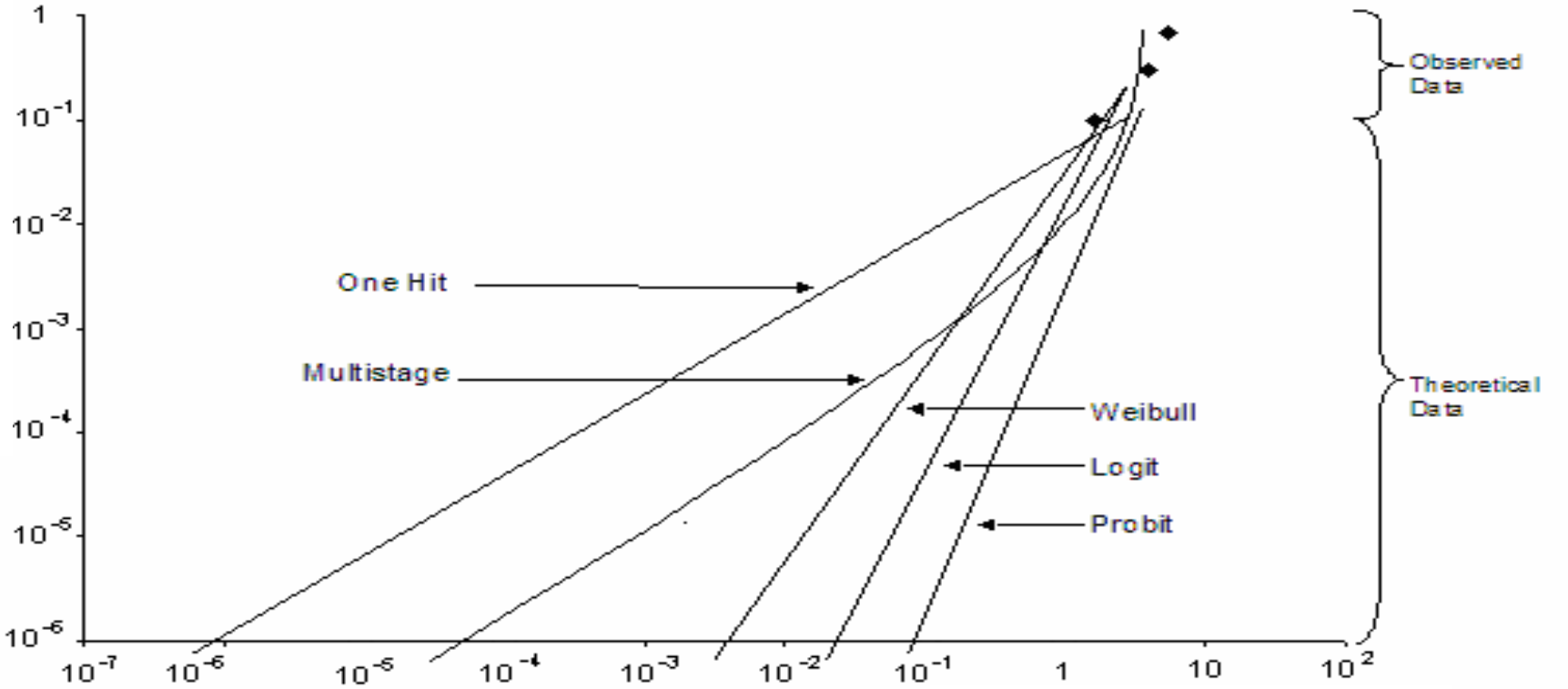
- Advice does not take into account available scientific information on potency of the compound and extent of human exposure
- Continuous improvement of analytical methods leads to lower detection limits and increases the number of genotoxic carcinogens detected in food
- ALARA does not provide risk managers with a scientific basis for setting priorities or for taking actions

Hazard Characterization: Non-thresholded D-R



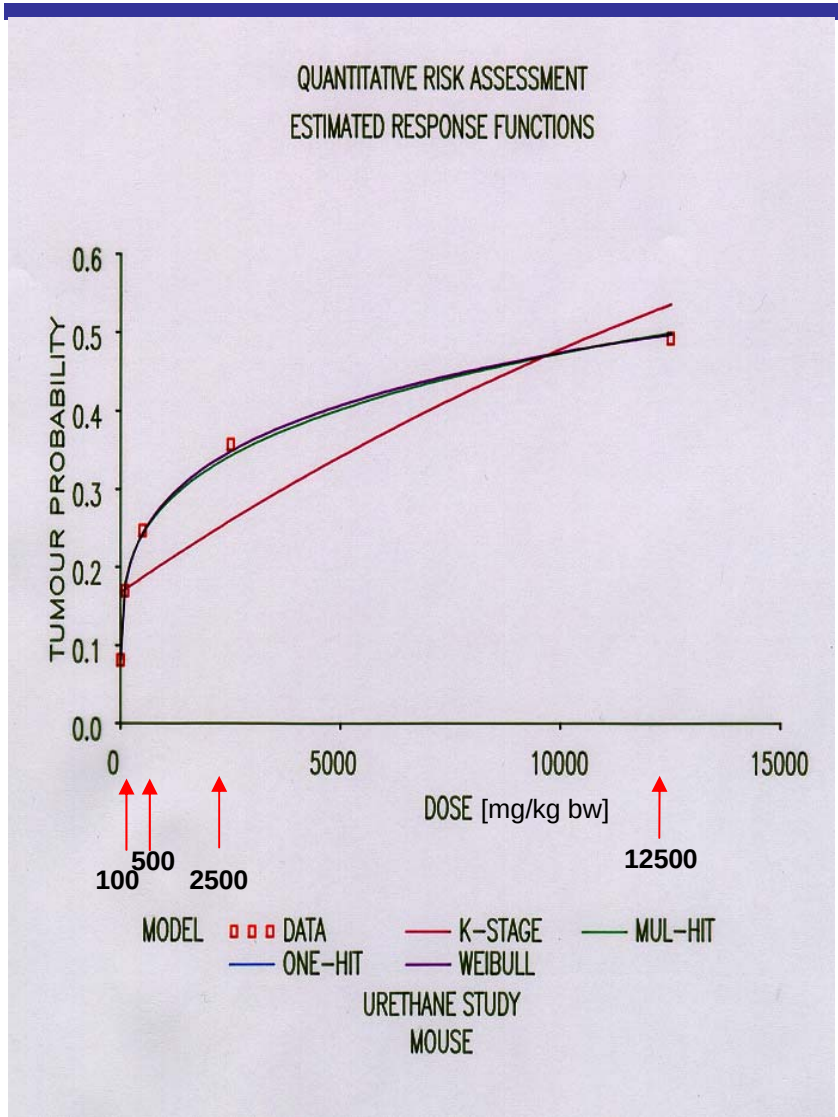
Extrapolation from observable range to low-dose exposure

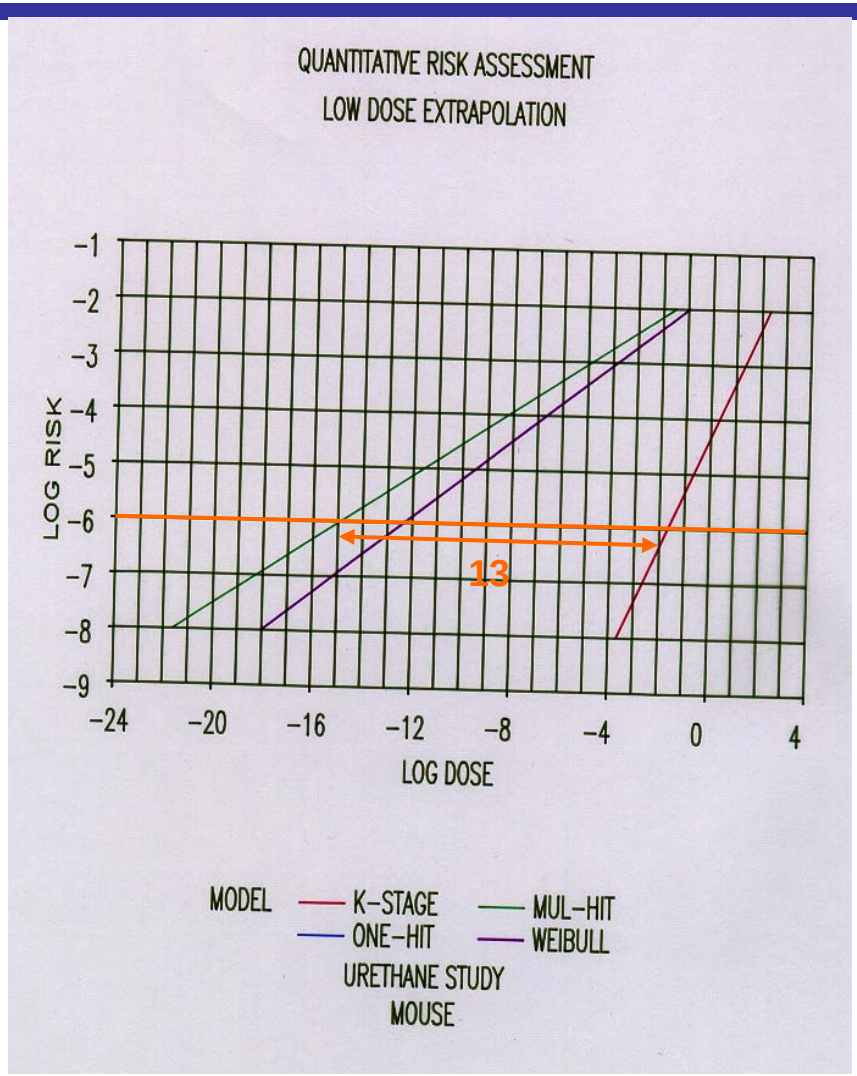
Number of cases of cancer per lifetime



Dose (mg/kg bw per day)

Ethyl Carbamate





Modelling by Dr. Felix Wächter, Ciba Geigy Basel (1986)

Extrapolation from observable range to low-dose exposure

EFSA Scientific Committee has serious reservations about extrapolating from animal tumour data at high doses using mathematical modelling to estimate risks to humans at low exposures for compounds that are both genotoxic and carcinogenic

„Model used more important than actual data“

- sign. non-linearities in toxicokinetics and mode of actions

- cytotoxicity at high doses may influence the D-R

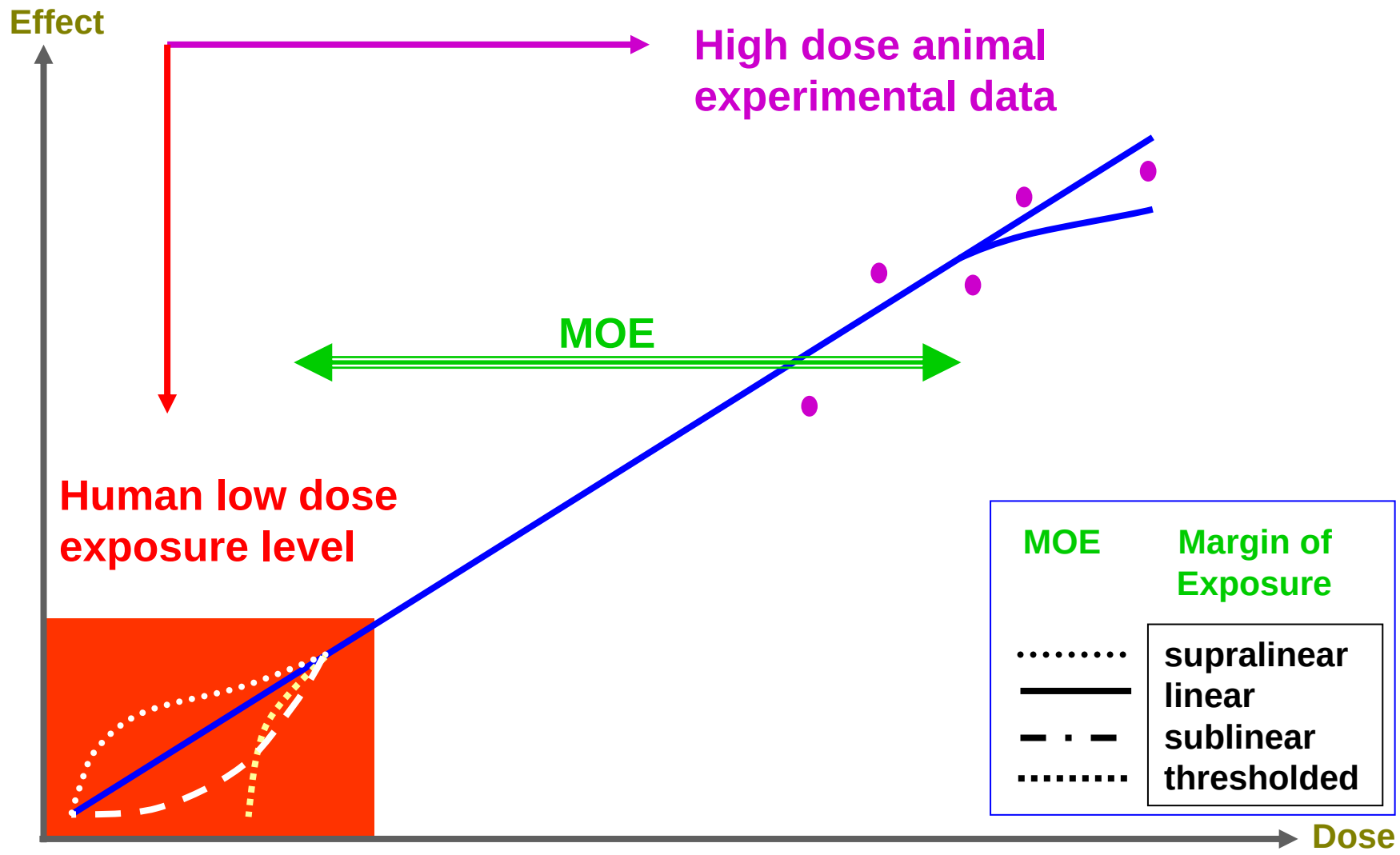
Extrapolation from observable range to low-dose exposure

- Homeostatic and cytoprotective mechanisms
- Abundance of cellular targets

⇒ minimum degree of interaction of the substance with the critical sites must be reached to elicit a toxicologically relevant effect

- Scientific Committee is of the opinion that there is a 'practical' threshold for genotoxic compounds
- Levels below which cancer incidence is not increased cannot be identified on scientific grounds
- Margin of exposure approach (MOE) was considered appropriate for genotoxic compounds

Hazard Characterization: Non-thresholded D-R



Chemicals in food and feed

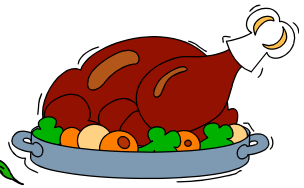
Natural constituents

additives

pesticides

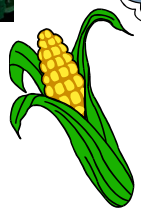
animal drugs

Food processing



packaging materials

biotech-nology



environmental contaminants

nutrients

overfeeding, deficiencies

Dietary fibers

Thank you for your attention !!