European Food Safety Authority

Scientific Conference
"*Challenging boundaries in risk assessment – sharing experiences*"

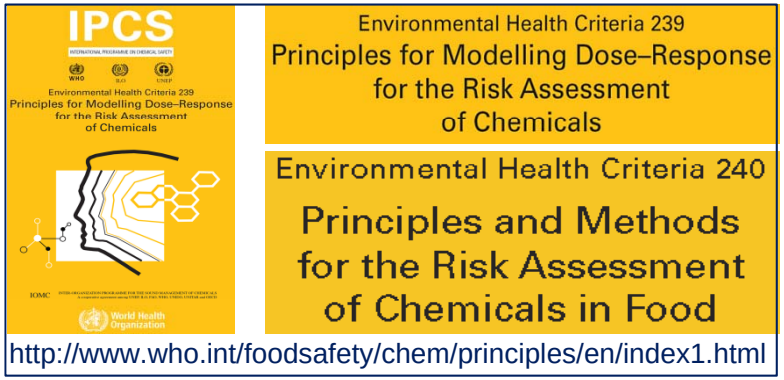
Trends in chemical risk assessment and integration of new methodologies

Josef Schlatter

Overview

- Background / Introduction
- Optimising hazard characterisation
  - Issues with genotoxic and carcinogenic compounds
- Improving Risk characterisation
  - Consideration of uncertainties in RA
- Newer methodology needs
- The future of RA ?
- Further information:

EFSA JOURNAL
http://www.efsa.europa.eu/en/publications.htm



http://www.who.int/foodsafety/chem/principles/en/index1.html

EFSA's risk assessment remit

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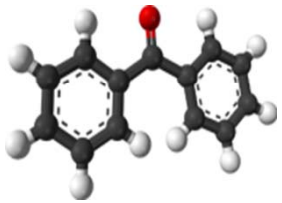
Chemicals in Food and Feed



Botanicals

Whole food and feed

Organisms (plants & animals), microorganisms

Genetically modified foods, crops and organisms

Chemicals in Food and Feed

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Natural constituents

additives

pesticides

Food processing

animal drugs

packaging materials

biotech-nology

Environmental contaminants

overfeeding, deficiencies

nutrients

Dietary fibers…

Risk assessment paradigm

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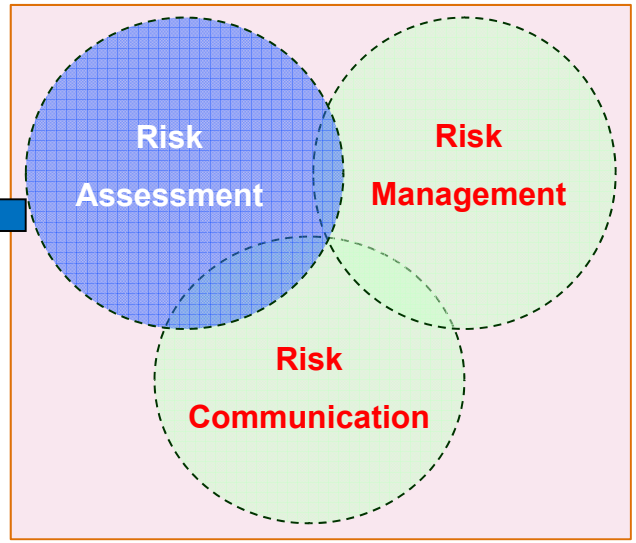
Hazard characterisation (dose-response)

Hazard identification



Risk characterisation

Exposure assessment

IPCS
Environmental Health Criteria 240
Principles and Methods for the Risk Assessment of Chemicals in Food

EHC 240: http://www.who.int/foodsafety/chem/principles/en/index1.html

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Extrapolation from Animals to Man

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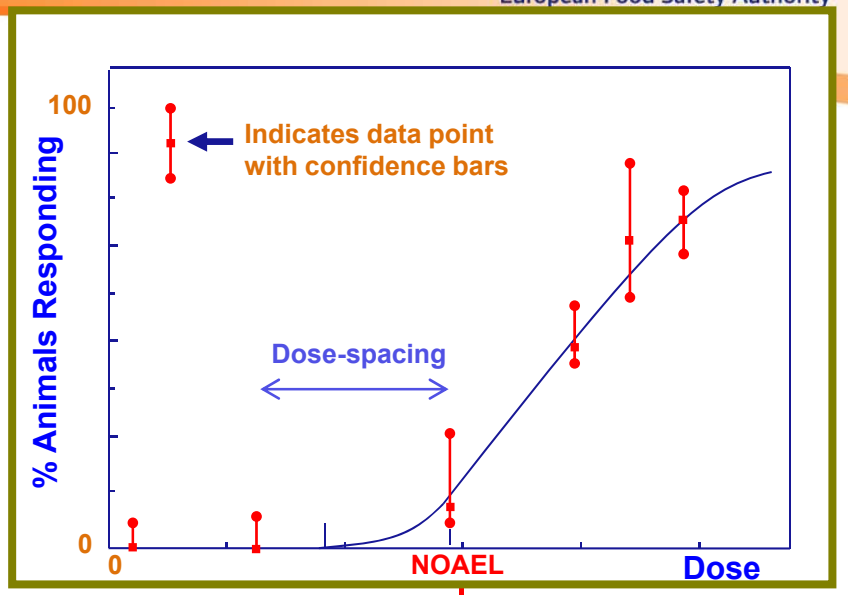
- Most sensitive species
- Lowest NOAEL
- Apply uncertainty factors (UF)



Establishing a Health Based Guidance Value

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

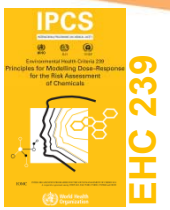
animals

man

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

Optimising hazard characterisation

Dose-response analysis : moving from NOAEL to Benchmark Dose approach (EFSA 2009)



➢The BMD approach offers a more scientific way of defining a reference point on the dose-response curve that can be used as the point of departure for risk characterisation

✓Use of the whole does-response data and no NOAEL is needed

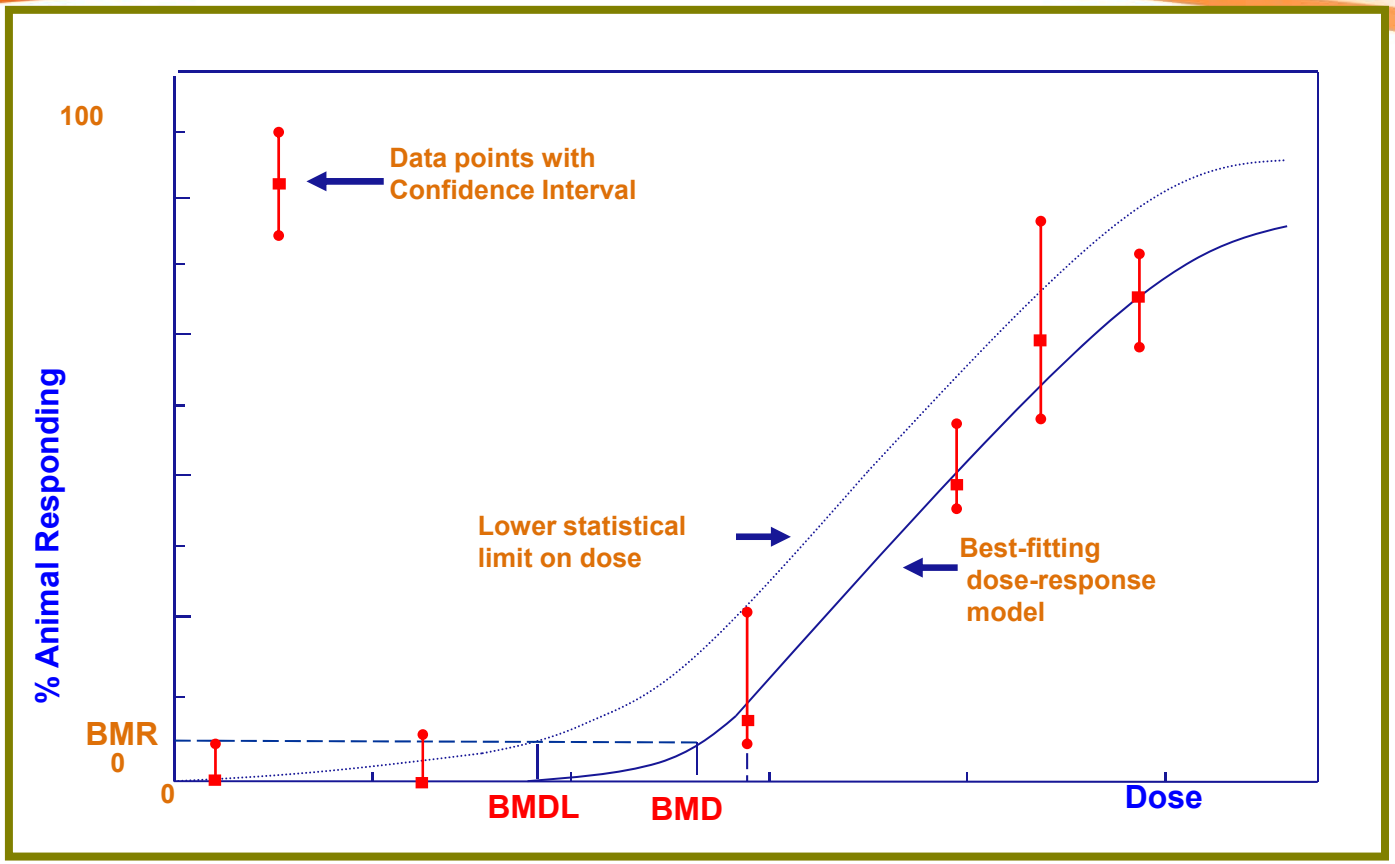
✓Not dependent on dose-spacing

✓Evaluates the uncertainty in the calculated BMD

e.g.

- **Derivation of health-based guidance values for substances with thresholded effects**
- **Calculating margins of exposure for substances with non-thresholded effects – i.e. genotoxic & carc. compounds**

The Benchmark Dose (BMD)



- Different Species
- Different Endpoints (organ-specific Tumour incidence, Total Tumours)
- Different Models

➢ Use lowest BMD(L) as reference point? Central estimate?

Extrapolation from observed range to Low-Dose Exposure

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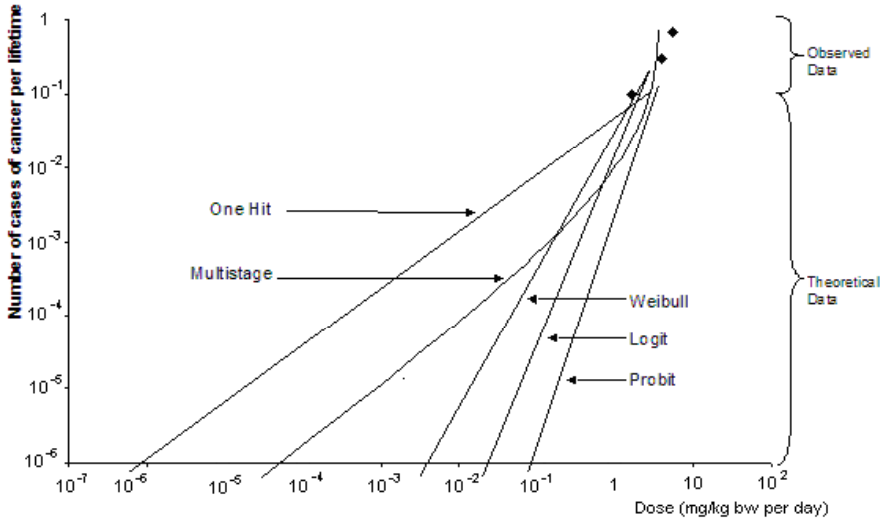
EFSA 2005:

has serious reservations about extrapolating outside the observed dose range using mathematical modelling



„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

http://www.efsa.europa.eu/etc/medialib/efsa/science/sc_commitee/sc_opinions/1201.Par.0002.File.dat/sc_op_ej282_gentox_en3.pdf

The MOE approach

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Moving from ALARA To MOE

$$\text{MOE} = \frac{\text{dose producing tumours in animals}}{\text{human exposure dose}}$$

- to provide additional scientific advice to risk managers taking into account available scientific information
  - Potency of compound
  - Extent of human exposure
- Selection of a reference point (point of departure): $BMDL_{10}$

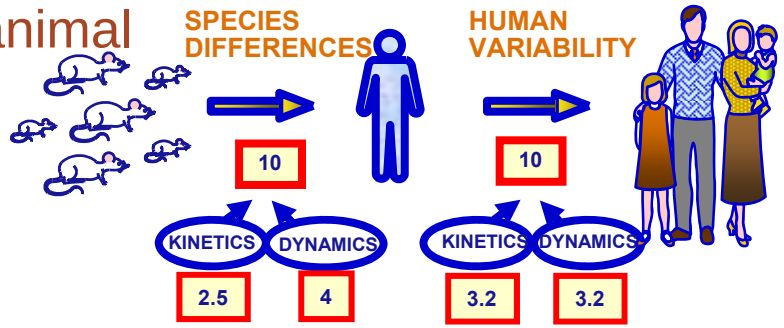
- ✓ Magnitude of a MOE can be used for priority setting: a small MOE represents a higher risk than a larger MOE
- ✓ Magnitude of MOE which is acceptable is a societal judgment and is the responsibility of risk managers
- ✓ MOE makes no implicit assumptions on a "safe" intake

64. JECFA 2005, EFSA 2005

Improving risk characterisation

Default values (EFSA 2012)

- Use of harmonised default values across EFSA Panels
  - e.g. body weight; human & animal food & liquid intake;
  - rounding figures
  - uncertainty factors when using animal data for human risk assessment



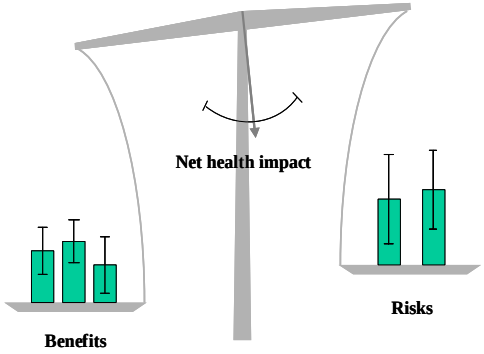
- Will result in more consistency and transparency in opinions

Expression of uncertainties in dietary exposure assessments (EFSA 2006)

- **Systematic examination of sources and types of uncertainty**
- **Quantitative or semi-quantitative expression of uncertainties**

Improving risk characterisation

Risk/benefit analysis (EFSA 2010)



➢Improving the human health assessment of foods with **both risks and benefits**

e.g. fish containing both
- toxic chemicals (methylmercury, PCBs, pesticides)
- and beneficial nutrients (n3-LCPUFAs, Se, I, vit D)

Step-wise approach

➢Do health risks outweigh benefits?

➢Semi-quantitative or quantitative assessment of risks and benefits at same exposure using common metric

➢Comparison of risks and benefits on a comparable scale

Chemical RA methodology

NEWER METHODOLOGY NEEDS

Improvement of methods within the standard RA paradigm

- Methods that facilitate assessment of large groups of chemicals over a short time

- **Methods enabling advice to be given on chemicals with few or no data**

- **Methods to assess cumulative risks from co-exposure to chemicals with similar and dissimilar MOAs**

- **Methods to assess risks of aggregate exposure to one chemical from all routes of exposure**

Chemicals with few or no data: the TTC approach

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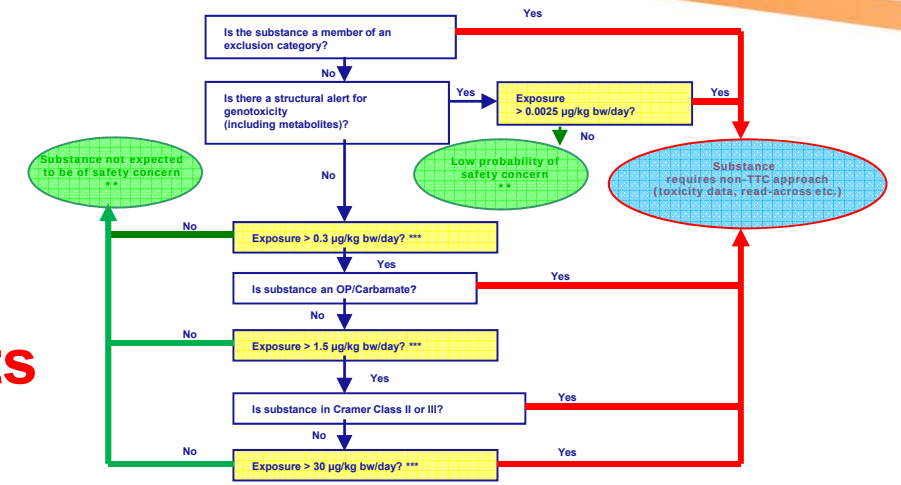
Data and expertise needed:

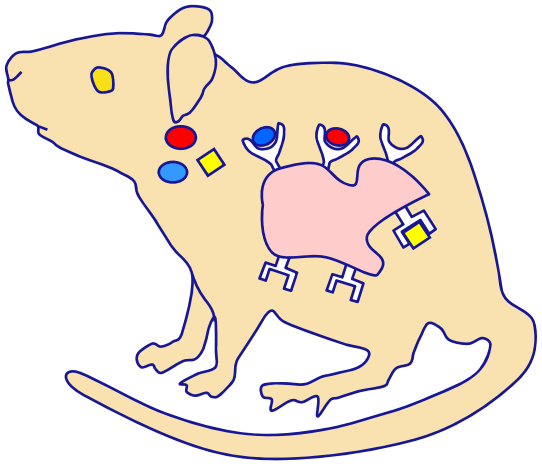


- **Chemical structure**
- **Good exposure assessments or 'worst-case'**
- Ability to use Cramer Structural Class Decision Tree (broad knowledge of metabolic pathways desirable)
- Ability to use decision trees or QSAR software to identify alerts for genotoxicity

  e.g. Ashby and Tennant et seq.; DEREK, TOPKAT, CASE, Multicase, ADAPT, QSAR-ES, COMPACT, COREPA

See EFSA 2012 http://www.efsa.europa.eu/en/efsajournal/doc/2750.pdf

Combination Effects



Dose Addition

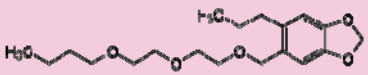
- •Dioxins, Furans, PCB
- •Organophosphates
- •N-Methyl-Carbamate
- •Triazine
- •Group ADI e.g. for different salts of an additive

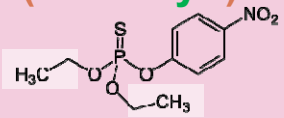
Effect Addition

- •Many

Interaction

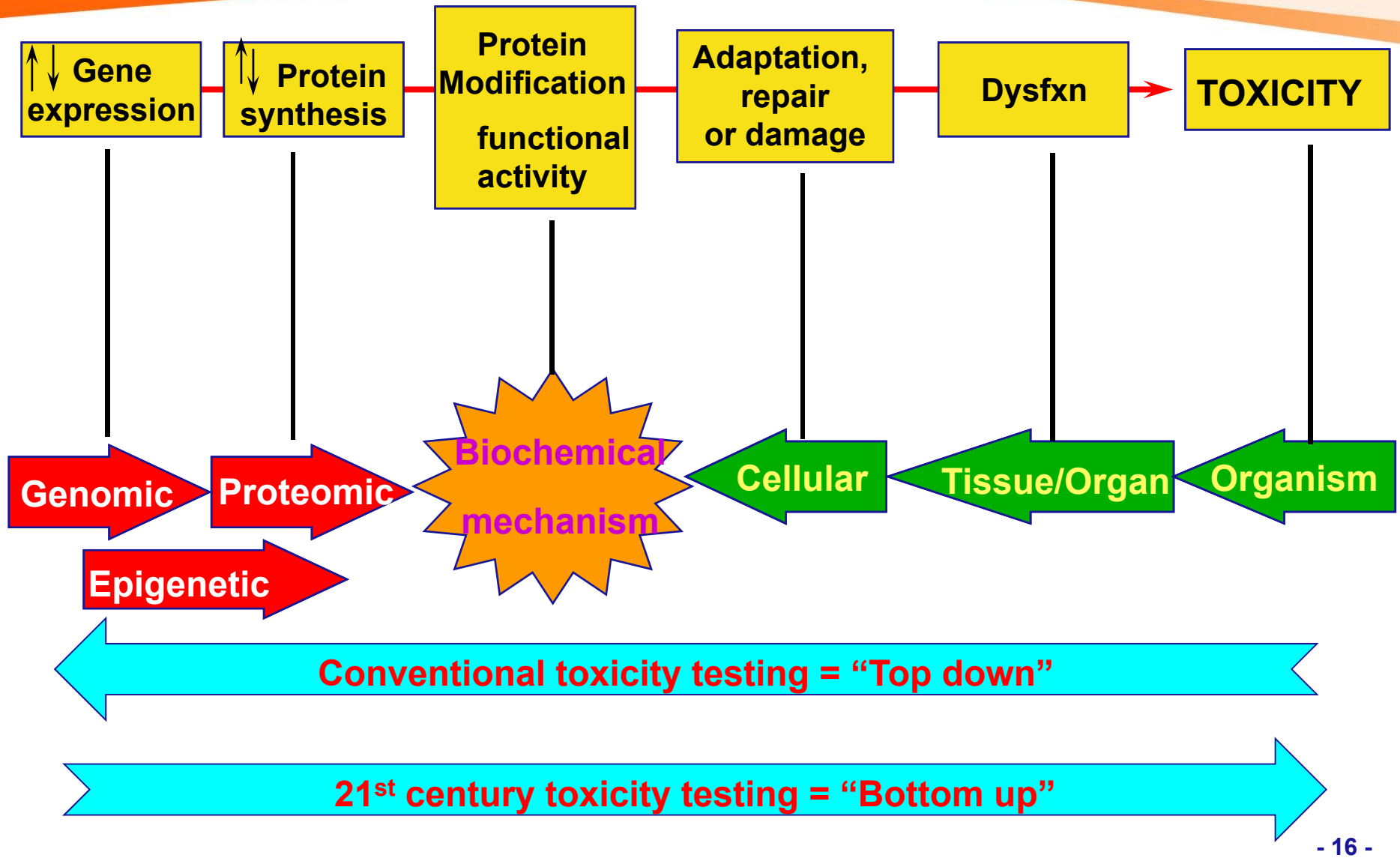
- •Piperonylbutoxid as Synergist (diethyl-) or Antagonist (dimethyl-) of Phosphorothionate Insecticides (e.g parathion↑↑, methylparathion↓↓)





How do we group chemicals ??

Toxicity data continuum



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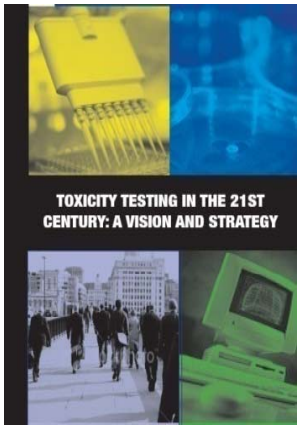
Perturbation of toxicity pathways



Exposure

Tissue Dose

Biologic Interaction

Perturbation

Low Dose

Higher Dose

Higher yet

Biologic Inputs

Normal Biologic Function

Early Cellular Changes

Adaptive Stress Responses

Cell Injury

Morbidity and Mortality

How do we distinguish adaptive versus adverse (toxic) responses?

Where next?

- Future specific tasks and challenges include
  - RA of low-dose effects, e.g. for endocrine-active substances
  - RA of mixtures
  - Environmental RA
  - Characterisation of uncertainties in RA
  - Implementing new technologies in RA

The future of risk assessment

- The basic principles of risk assessment will not change
  - **Make the best use of all available information to inform policy to protect human health**
- The **nature of the information** for risk assessment will change to a more bottom-up approach
- Assays will not be validated in conventional sense, but rather biologically justified
- **Uncertainty will increase**, at least initially, as new approaches are evaluated
- There is likely to be a move from “bright line” ***safety*** to ***levels of protection***
  - Need to bound uncertainty

Thank you very much for your attention !