



Centrum pro výzkum
toxických látek
v prostředí

Ecotoxic effects - Introduction -

Luděk Bláha, PŘF MU

Tento projekt je spolufinancován Evropským sociálním fondem a státním rozpočtem České republiky.



INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

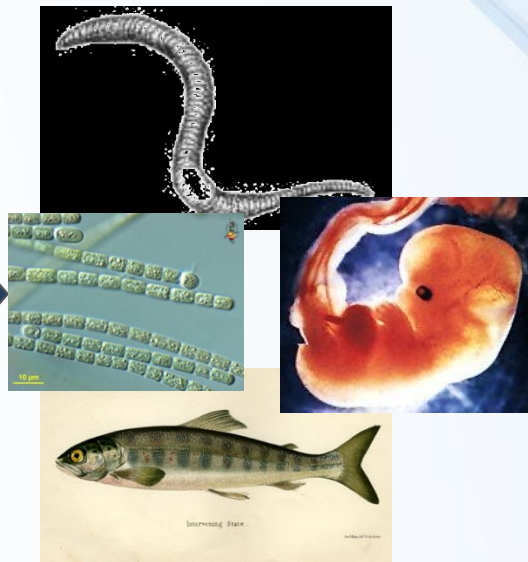
**CHEMICAL
ENTERS THE
ENVIRONMENT**



**LEVELS, FATE,
PROCESSES**



**Bioavailable
fraction**



"EXPOSURE"

acute



chronic



**CHEMICAL ENTERS THE
ORGANISM**

biomonitoring



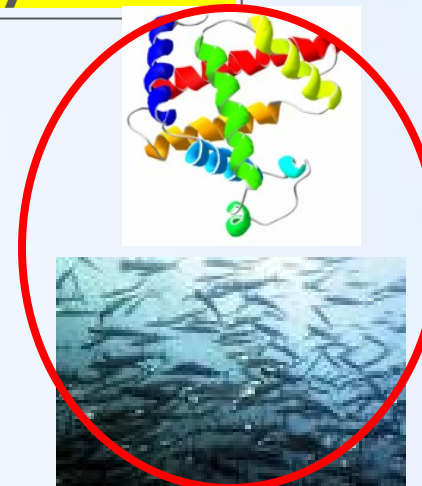
Toxicokinetics

*biotransformation
bioactivation
excretion / sequestration*



Target site

**"EFFECT"
toxicodynamics**



WHAT IS LIFE ?

Characteristics & properties of a living entity ?

- Structure
- Functioning



1 Atoms

2 Molecules and macromolecules

3 Cells

4 Tissues

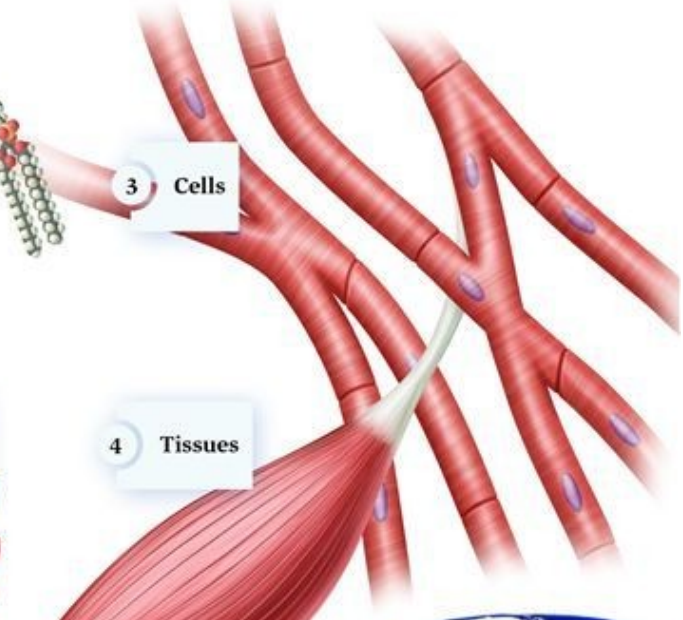
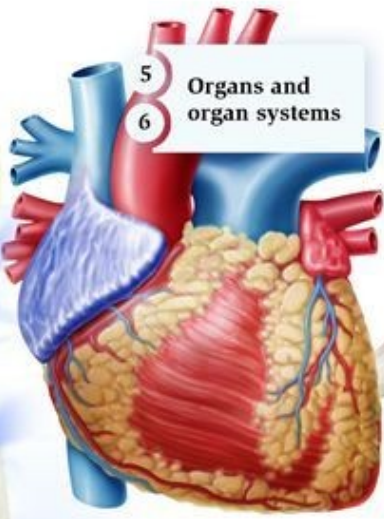
5 Organs and organ systems

12 Biosphere

11 Ecosystem

8 Species form populations

10 Community



WHAT IS **LIFE** ?

WHAT IS **ECOTOXIC EFFECT** ?



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Energy
hv
food



Losses
heat
faeces



Life
(maintenance)



Metabolism



Control,
Interactions
with environment



Defence
against pathogens
predators ...



Defence against
toxicants



Chemical
stress



Growth
to sexual
maturity



Reproduction



Chemical stress
→ energy re-allocation
→ „insufficient“ resources elsewhere

Energy
hv
food



Losses
heat
faeces



Life
(maintenance)



Metabolism



Control,
Interactions
with environment



Defence
against pathogens
predators ...



Defence against
toxicants



Chemical stress

Growth
to sexual
maturity



Reproduction



Chemical stress

**+ ... another stress
(food scarcity)**

Energy
hv
food



Losses
heat
faeces



Life
(maintenance)



Metabolism



Control,
Interactions
with environment



Defence
against pathogens
predators ...



Defence against
toxicants



Growth
to sexual
maturity



Reproduction



**Chemical
stress**



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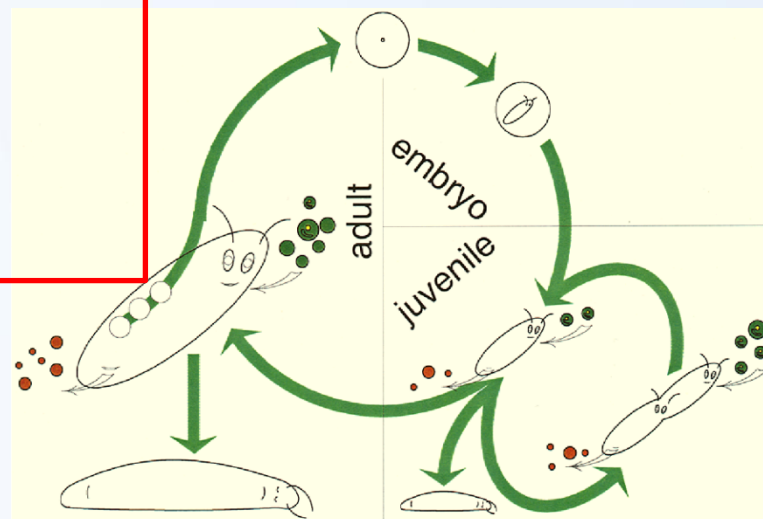
Effects at different levels - ORGANISM

Ecotoxicological effects (see also [Bioassays](#))

- Effects on structure
- Effects on metabolism (maintenance)
- Effects on regulation

→ Changes in functions (e.g. hormones, EE2)
→ Repair, survival, **growth**
→ **Death (lethality)**
→ Proliferation = **Reproduction**

3 key apical endpoints
(reflected e.g. in regulations)



WHAT IS LIFE ?

WHAT IS ECOTOXIC EFFECT ?

WHAT HAPPENS „**BEFORE**“ EFFECT MANIFESTATION ?

WHAT ARE THE **CONSEQUENCES** OF THE EFFECT ?



Exposure → TK → TD → Effects

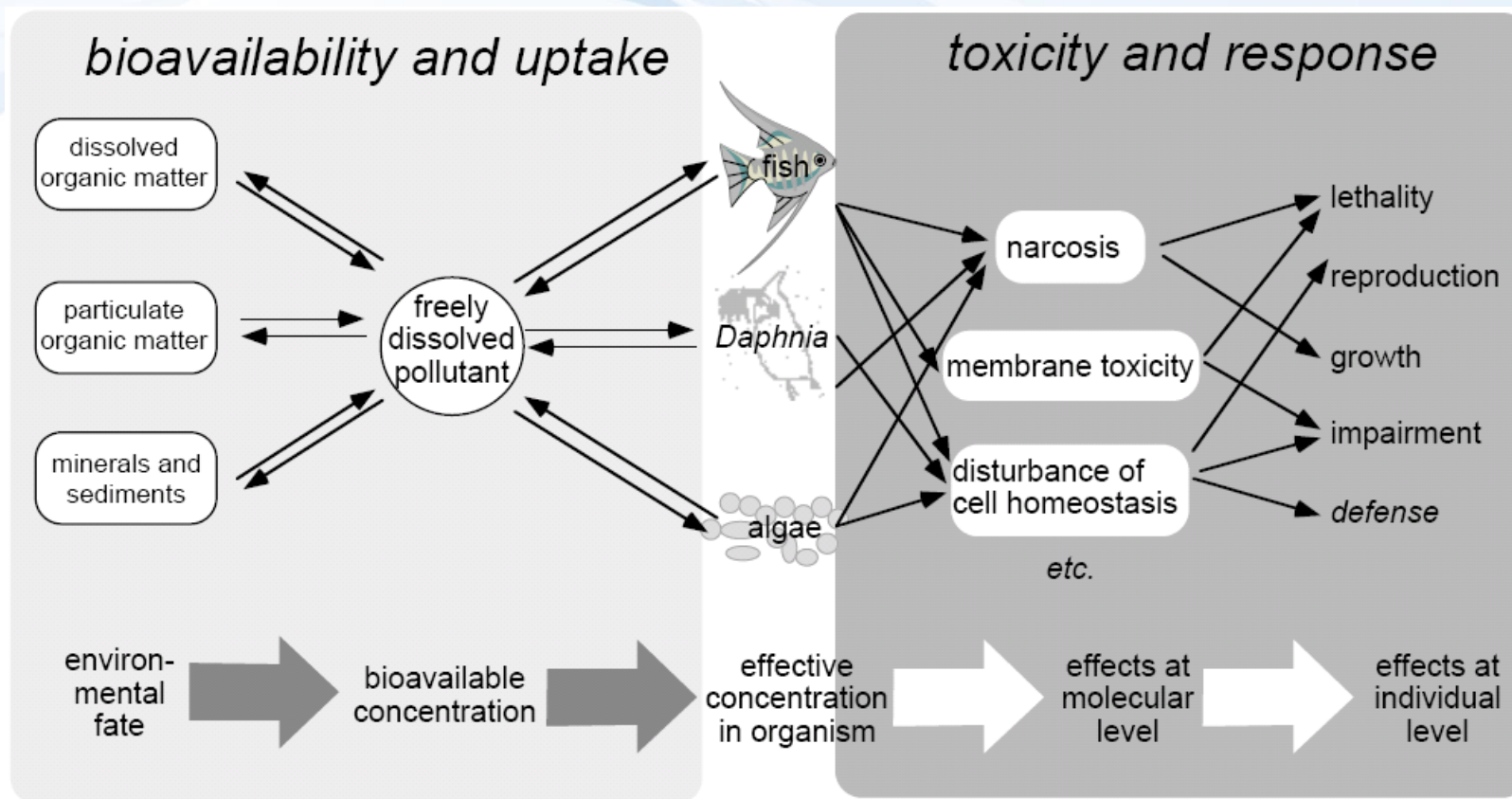
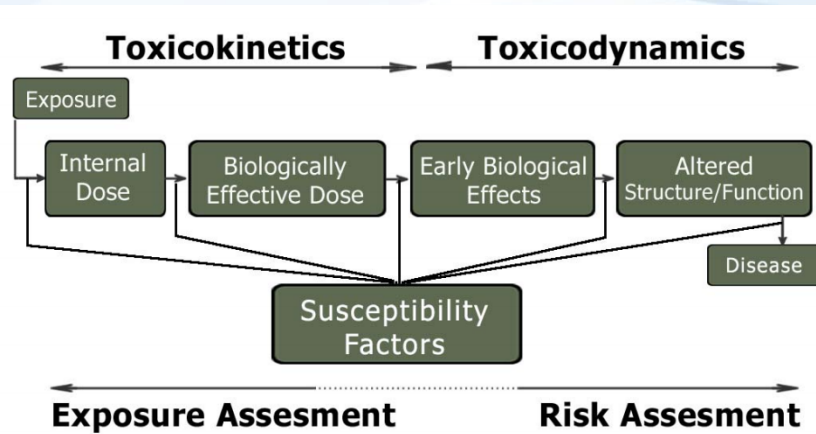


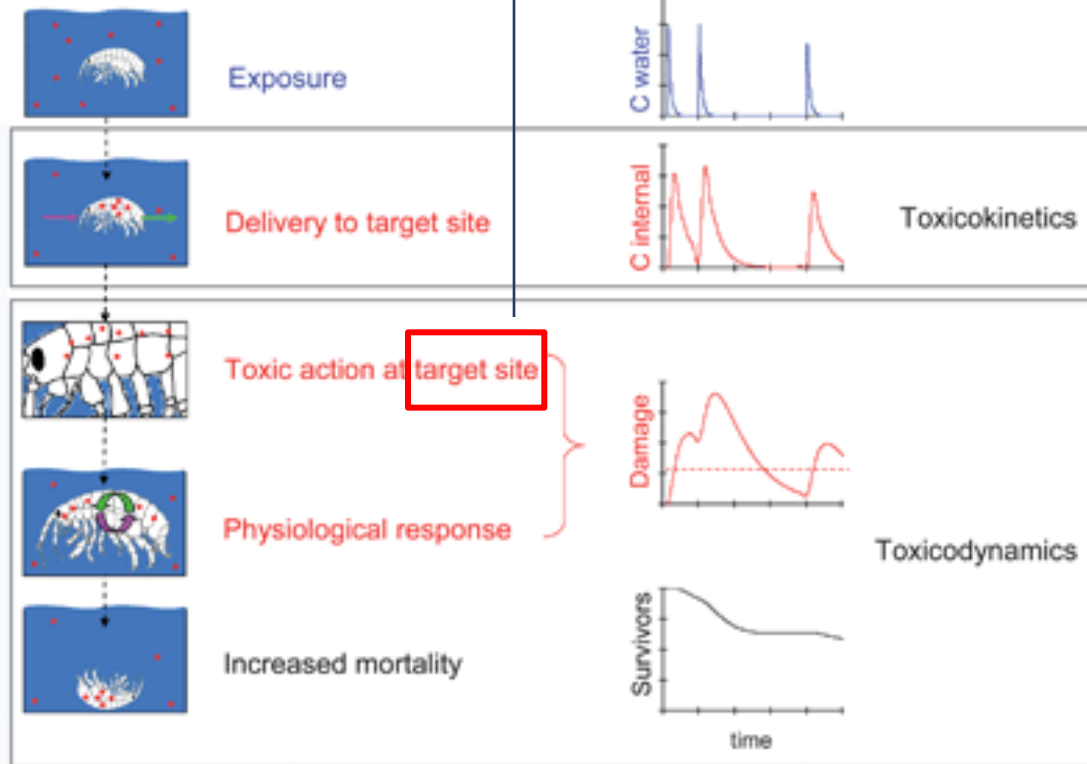
Figure 1 The effective concentration of a pollutant in an organism (e.g. fish, daphnia, algae) or at the target site inside the organism is the link between the environmental fate of a pollutant and its toxic effect.

Escher, B. I., Behra, R., Eggen, R. I. L., Fent, K. (1997), "Molecular mechanisms in ecotoxicology: an interplay between environmental chemistry and biology", *Chimia*, 51, 915-921.

Toxicokinetics → Toxicodynamics



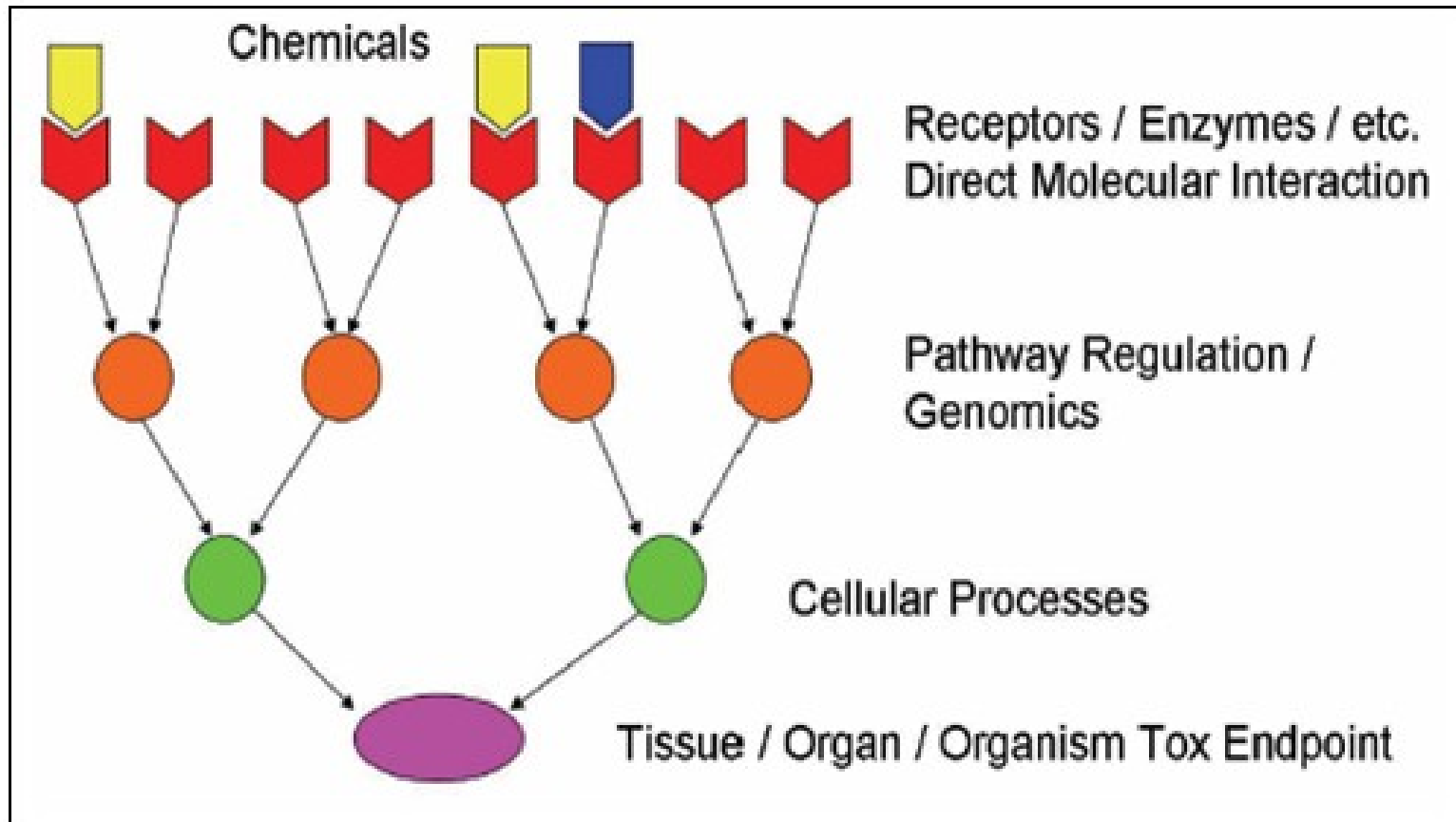
TARGETS = macromolecules (DNA/RNA, proteins, membrane lipids)



MoA →
 ↓
 ... and measurable EFFECTS →

Target sites = molecules

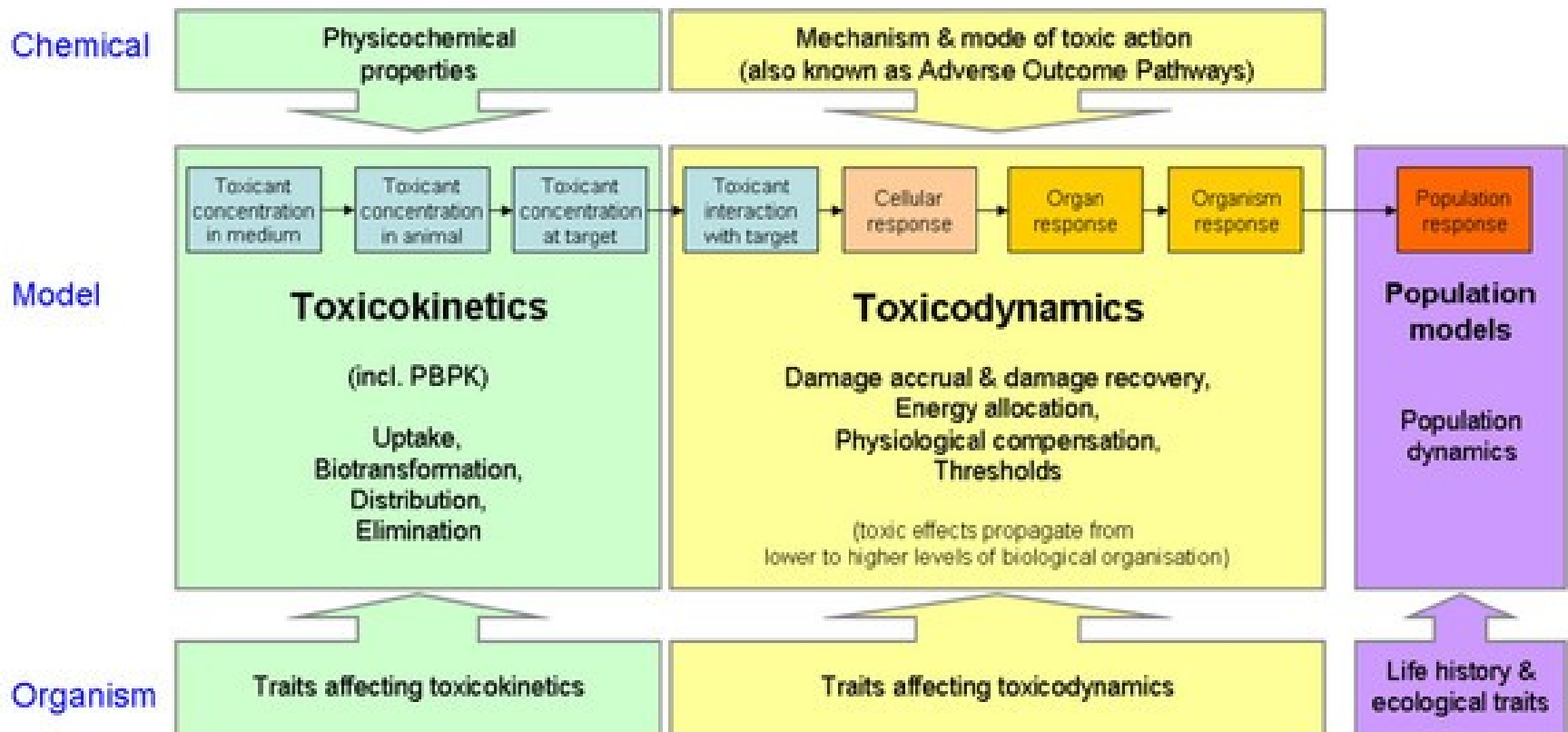
MECHANISMS OF TOXICITY



From molecules to individuals → to populations

ADVERSE OUTCOME PATHWAYS

Mechanistic effect models for ecotoxicology



→ Arrows indicate a causal relationship

See also: Ashauer & Escher *JEM* (2010), Rubach *et al.* *IEAM* (2011), Jager *et al.* *ES&T* (2011), Ashauer *et al.* *ET&C* (2011)

www.ecotoxmodels.org

It all starts with MoA = Mechanisms of Action (MoA)

- According to **target molecules** (next slide)
 - Mechanisms primarily targeting different
 - **BIOLOGICAL MACROMOLECULES**
 - i.e. PROTEINS and/or NUCLEIC ACIDS and/or PHOSPHOLIPIDS
 - **SMALL BIOLOGICAL (ORGANIC) MOLECULES**
 - E.g. Antioxidants or scavengers (vit.E, GSH)
- According to **INTERACTION** between toxicant/target (next slide)
 - Non-covalent interactions
 - Partitioning (v d Waals, H-bonds, hydrophobic interactions) → [1] below
 - Partitioning with **specific steric fit** → [3] below
 - Formation of covalent bonds
 - ... with proteins / DNA-RNA / P-lipids / small molecules → [2] below
- According to **“STERIC SPECIFICITY”** of the interaction
 - NON-SPECIFIC MECHANISMS
 - the interaction between the toxicant and the target occurs “generally” with any target of certain general properties (e.g. toxicant is able to bind to ANY protein having e.g. SH- group), it does not require specific steric (structural) properties of the target
 - **mechanisms [1] and [2] below**
 - SPECIFIC MECHANISMS
 - the toxicant interacts only with certain and specific structural properties (e.g. specific binding of a pesticide into the active site of enzyme acetylcholinesterase)
 - **mechanism [3]**



Target (receptor) in MoA / toxicodynamic = BIOMOLECULE

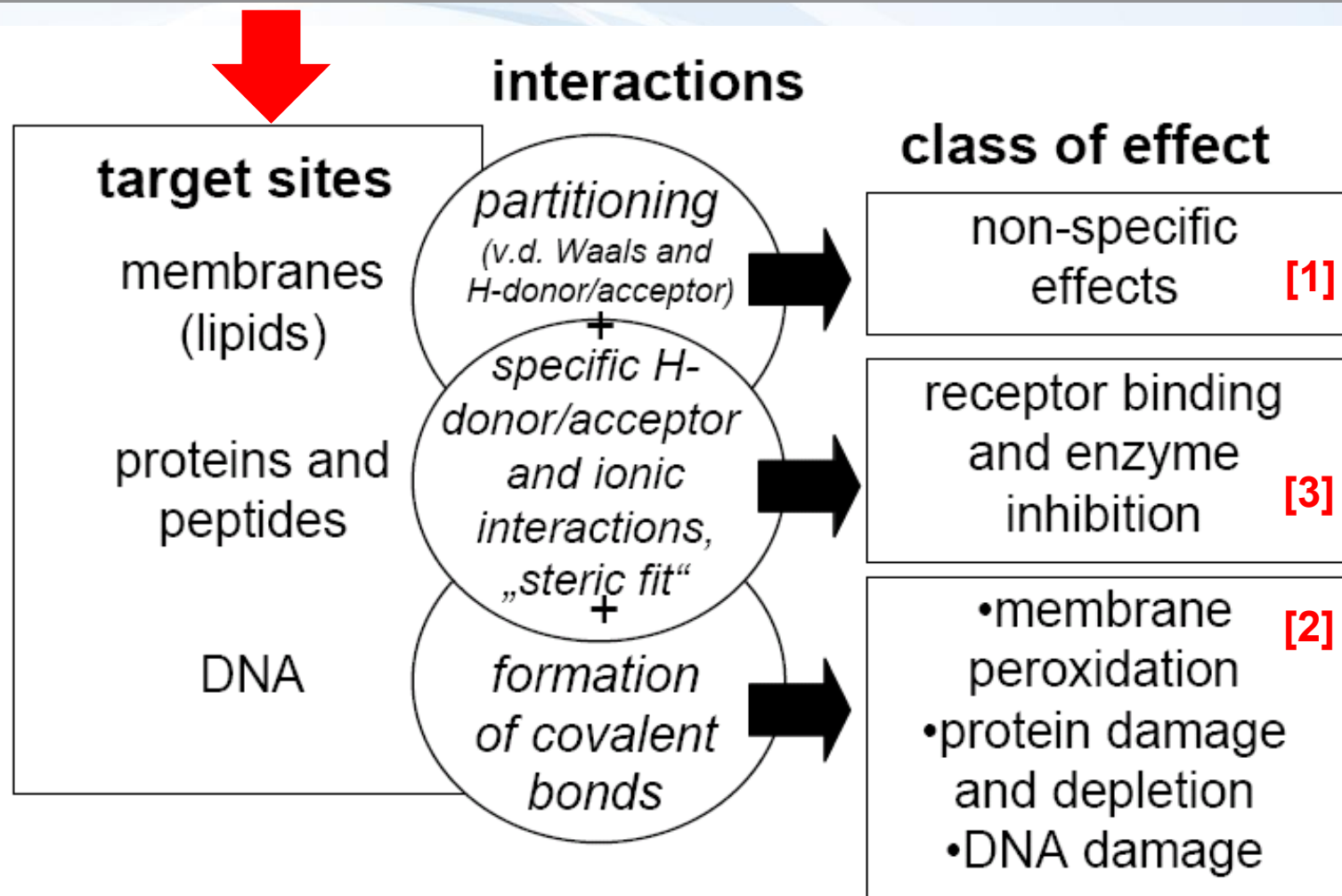
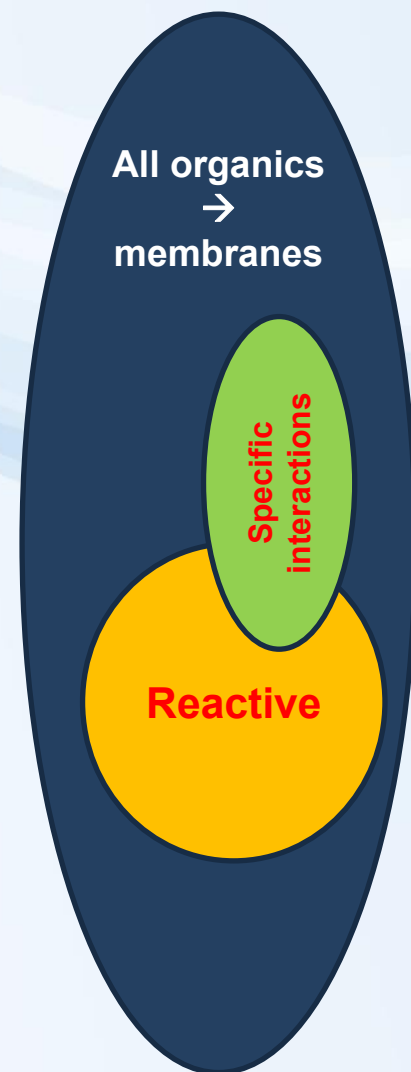


Figure 2 Rationale behind the classification of chemicals according to mechanism: target sites and type of interaction.



Categorizations of MoAs

- **[1] non/specific membrane toxicity**
 - Involves ALL ORGANIC compounds
 - Affinity to non-polar environment (membrane phospholipids)
 - Two types can be discriminated
 - nonpolar basal / narcotic toxicity
 - effects observed at relatively high concentrations, depends on hydrophobicity (Kow)
 - polar narcosis
 - more polar compounds may affect also membrane proteins (effects at lower concentrations than expected from Kow)
- **[2] nonspecific reactive toxicity**
 - some compounds with “reactive” properties may directly modify biological macromolecule (lipids, proteins, nucleic acids) causing thus toxic effects
 - reactive chemicals are mostly „electrophiles“ (reacting with „nucleophiles“ in cells – i.e. electrone-rich sites - nucleotides, -NH₂, -SH and others), and also toxic (heavy) metals
- **[3] specific steric interactions**
 - only certain specific compounds selectively affect specific targets
 - E.g. enzyme inhibitions (drugs, insecticides); receptor interactions (e.g. Estrogens)
 - Can be non-covalent as well as covalent
 - Effects at **very low** concentrations



MoA(s) - toxicity mechanisms - overview

Student is expected to know principles and some examples of the following main types of toxicity mechanisms

- **Membrane** nonspecific toxicity (narcosis)
- **Proteins** and inhibition of enzymatic activities
- Ligand competitions – **receptor mediated toxicity**
- **DNA** toxicity (genotoxicity)
- **Complex** mechanisms
 - Oxidative stress – redox toxicity

The molecular and cellular effects
propagate → **ORGANISM**

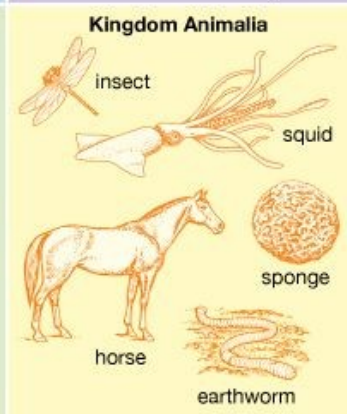
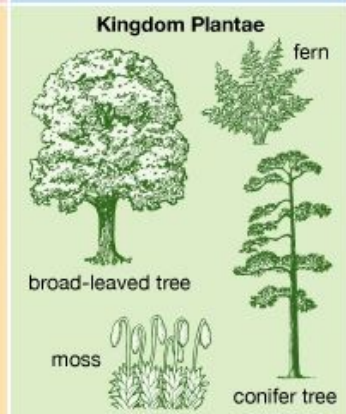
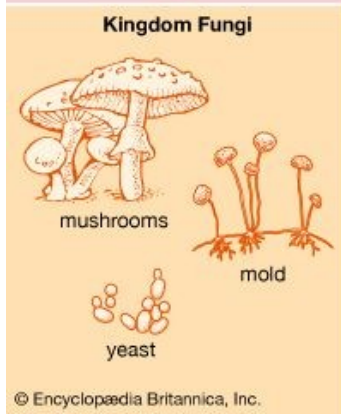
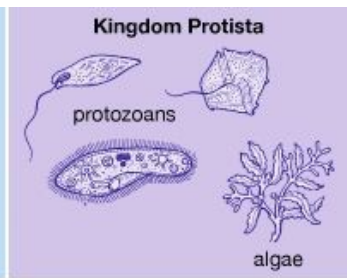
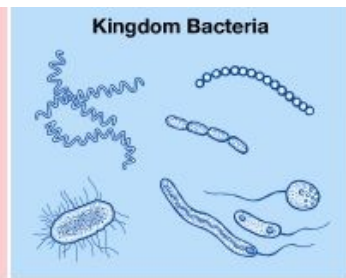
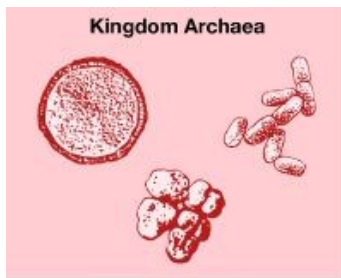
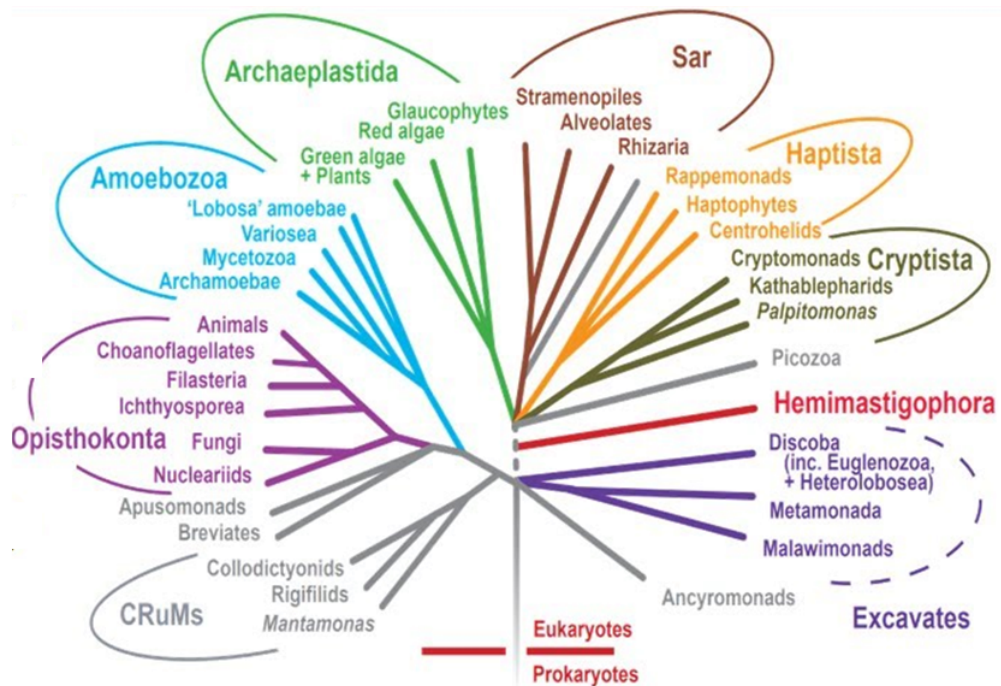
WHAT (types of) „**ORGANISMS**“
can be affected by ecotoxicants ?

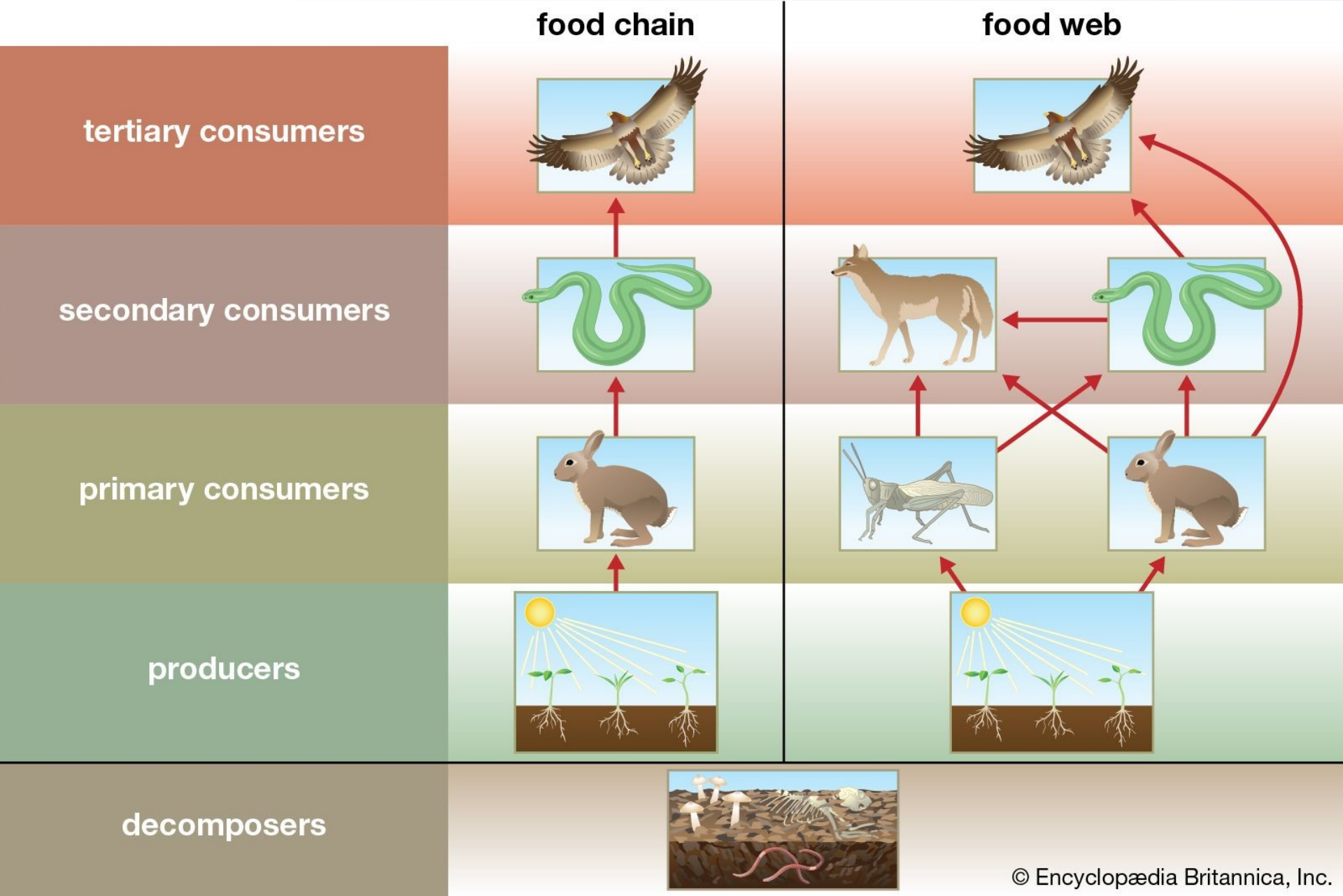


WHAT (types of) „**ORGANISMS**“ can be affected by ecotoxicants ?

- Structure = TAXONOMY
- Functioning = ECOPHYSIOLOGY







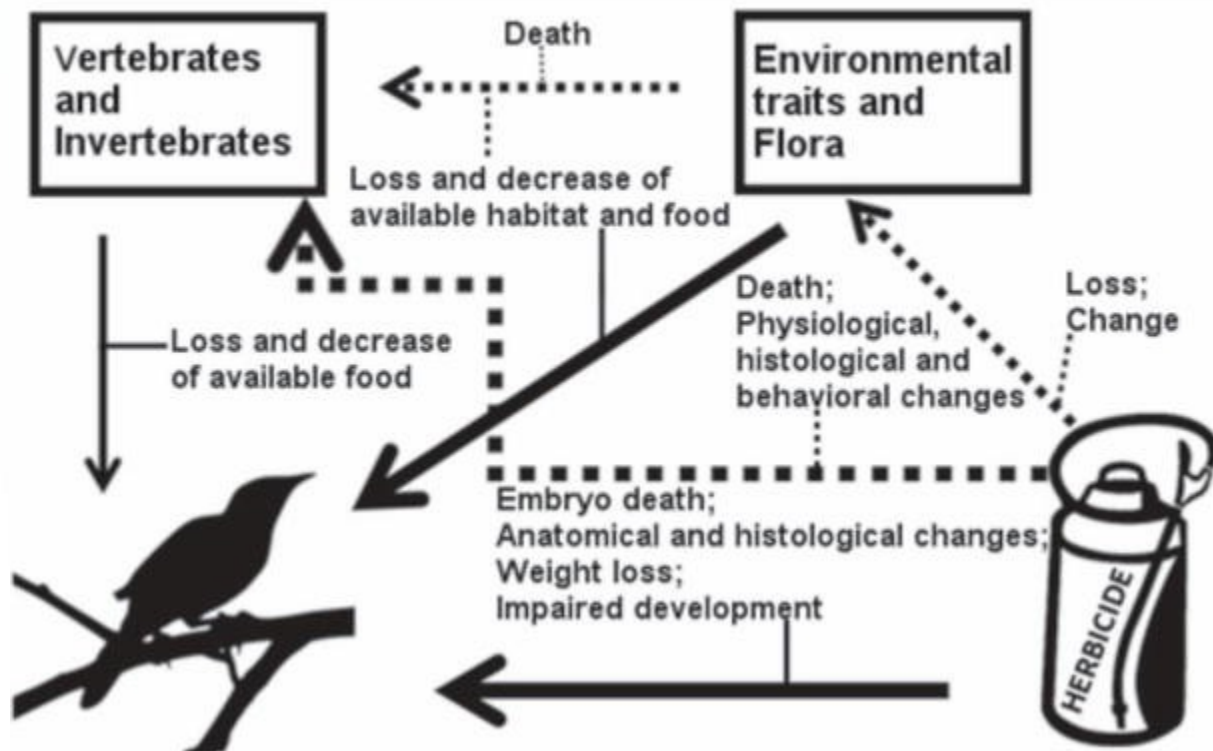
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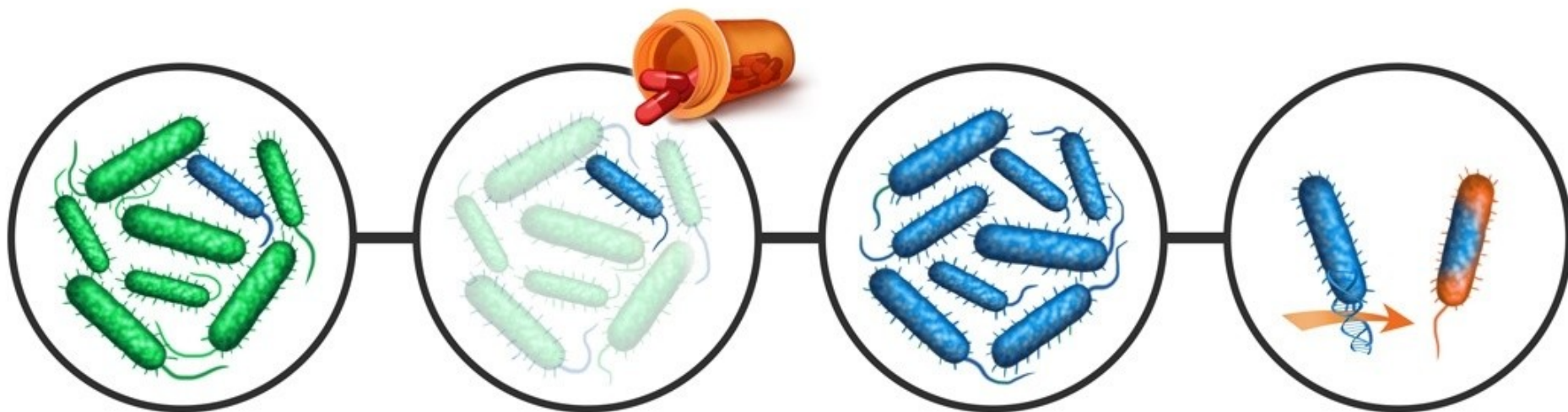
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Ecotoxicity of glyphosate-based herbicide (GBH) to aquatic birds. Direct (continuous arrows) and indirect (dashed arrows) effects of GBH on birds.

Direct and Indirect effects of herbicides on birds



Antibiotic Resistance in Bacteria



Step 1

In a population of bacteria, one bacterium mutates and becomes antibiotic resistant.

Step 2

Antibiotic kills off all bacteria except for the antibiotic resistant bacterium.

Step 3

Antibiotic resistant bacterium multiplies, forming a population of antibiotic resistant bacteria.

Step 4

Antibiotic resistant bacteria can transfer their mutation to other bacteria.

WRAP UP = TAKE HOME MESSAGE

Ecotoxicology aims to understand effects of stressors (chemicals) in biological systems

- Be aware of **life (biological systems) in all types and dimensions**
- (Eco)toxicological effects are captured (organized) in **Adverse Outcome Pathways** – from Exposures to TK to MoA to „in vivo“ (and beyond)
- The 3 most important biological endpoints in vivo (**apical endpoints**) reflected in pragmatic approaches (biotesting) are ...

Effects at different levels - ORGANISM

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