



Centrum pro výzkum  
toxických látek  
v prostředí

# BIOMARKERS AND TOXICITY MECHANISMS 02 – MECHANISMS OVERVIEW

Luděk Bláha, PŘF MU, RECETOX  
[www.recetox.cz](http://www.recetox.cz)

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



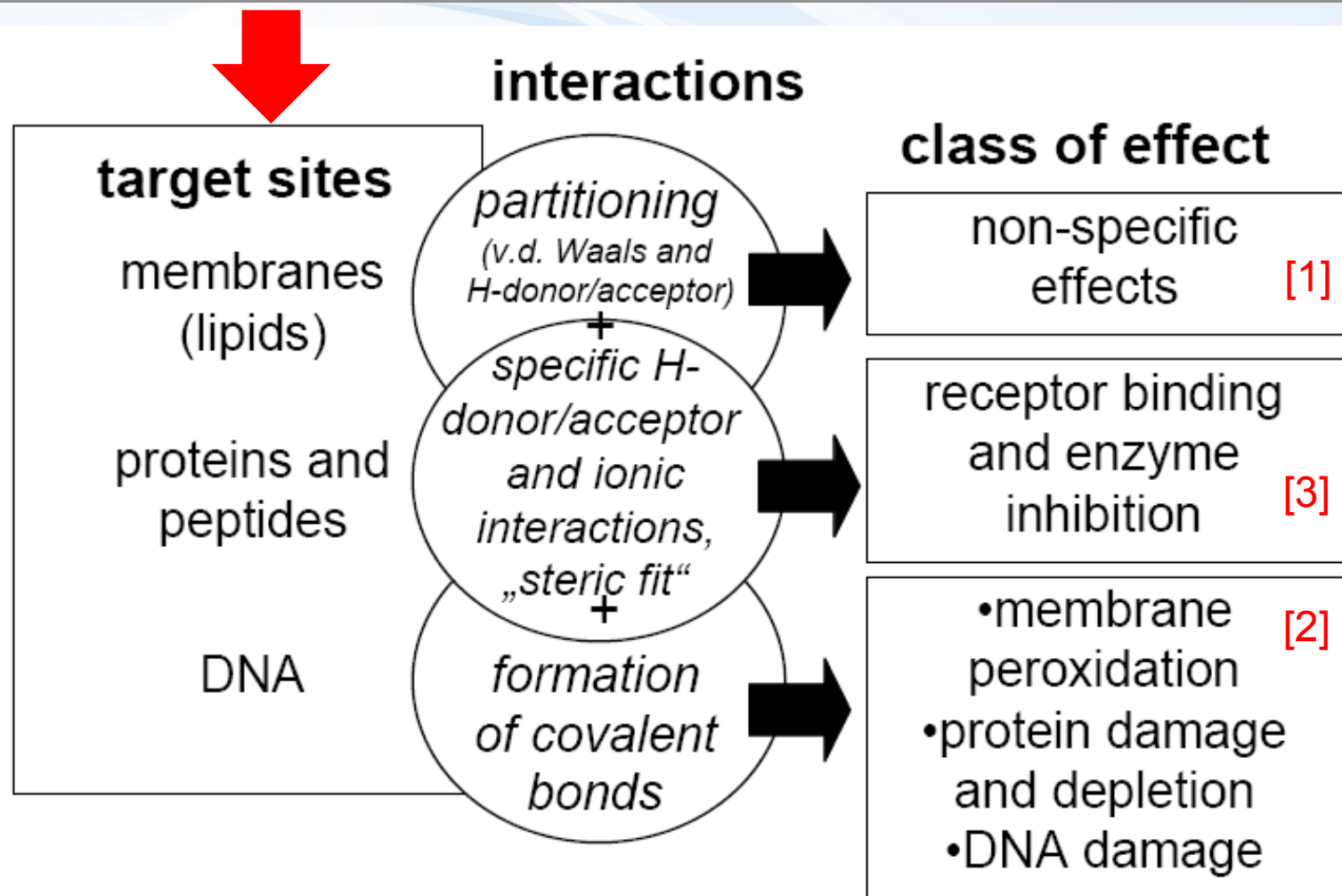
INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

# Different categorizations of 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.



# Possible categorizations of MoA

## • [1] non/specific membrane toxicity

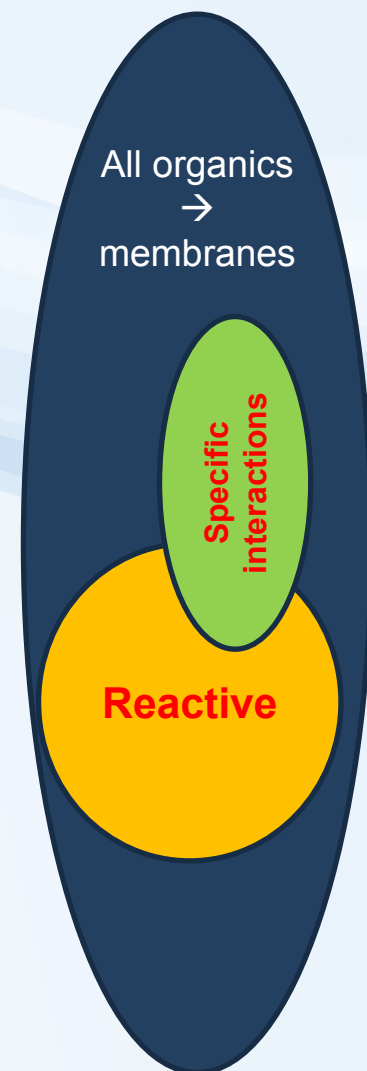
- Involves ALL ORGANIC compounds
- Affinity to non-polar environment (membrane phospholipids)
- Two types can be discriminated
  - nonpolar basal / narcotic toxicity (
    - effects observed at relatively high concentrations, depends on hydrophobicity (Kow)
  - polar narcosis
    - more polar compounds 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, -NH<sub>2</sub>, -SH and others)

## • [3] specific steric interactions

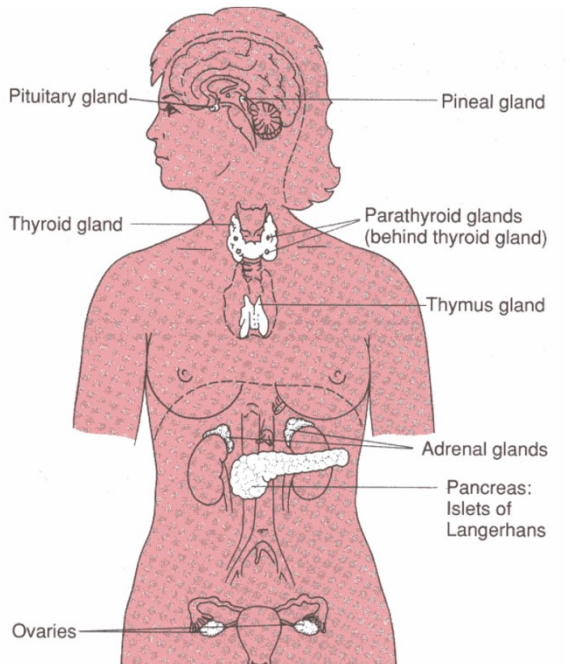
- only certain specific compounds selectively affect specific targets
- E.g. enzyme inhibitions (drugs, insecticides); receptor interactions (e.g. Estrogens)
- Can be non-covalent as well as covalent
- Effects at **very low** concentrations



# Possible categorizations of MoA

- **Species-specific mechanisms, examples**
  - photosynthetic toxicity (only in plants) vs. teratogenicity (only in vertebrates)
  - Endocrine disruption
    - different hormonal systems in invertebrates vs vertebrates  
→ different toxicity mechanisms

## Growth in humans *several hormones*



## Growth in invertebrates ecdysis (moulting) - *ecdysteroids*

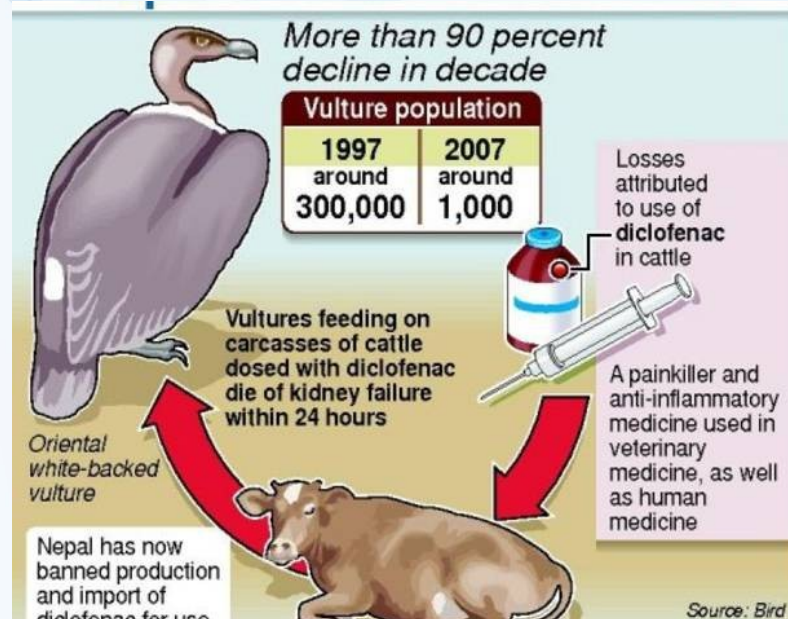
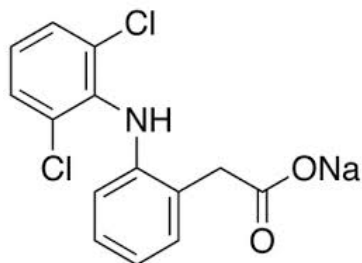




# Possible categorizations of MoA

## - Tissue-specific mechanisms (& effects)

- hepatotoxicity; neurotoxicity; **nefrotoxicity**; haematotoxicity
- toxicity to reproduction organs;
- immunotoxicity



## Developmental stage-specific mechanisms

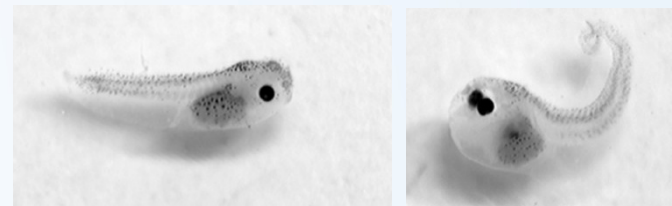
- embryotoxicity/teratogenicity: toxicity to cell differentiation processes

Thalidomide

**Cyanobacterial metabolites**



Malformations in frog tadpoles



# Keywords to remember and understand

- What is it MoA?
- Can you give examples of species-specific MoA?
- What are the biological targets for toxicants? How can they be classified?
- What are the possible interactions between toxicants and biological targets?
- What is it specific and non-specific toxicity mechanism?
- What biological molecules are likely to be affected (usually at relatively high concentrations) by ALL ORGANIC COMPOUNDS?

*.... and now let's look in detail on major MoAs  
and their toxic consequences*

# Toxicity mechanisms - overview

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

- **Proteins** and inhibition of enzymatic activities
- Mitotic poisons & microtubule toxicity
- Ligand competitions – receptor mediated toxicity
- **Membrane** nonspecific toxicity (narcosis)
- Toxicity to membrane gradients (*also includes proteins*)
- **DNA** toxicity (genotoxicity)
- **Complex** mechanisms
  - Oxidative stress – redox toxicity
  - Defence processes as toxicity mechanisms and biomarkers - detoxification and stress protein induction
  - Toxicity to signal transduction