



Centrum pro výzkum
toxických látek
v prostředí

BIOMARKERS AND TOXICITY MECHANISMS 02 – MECHANISMS OVERVIEW

Luděk Bláha, PŘF MU, RECETOX
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

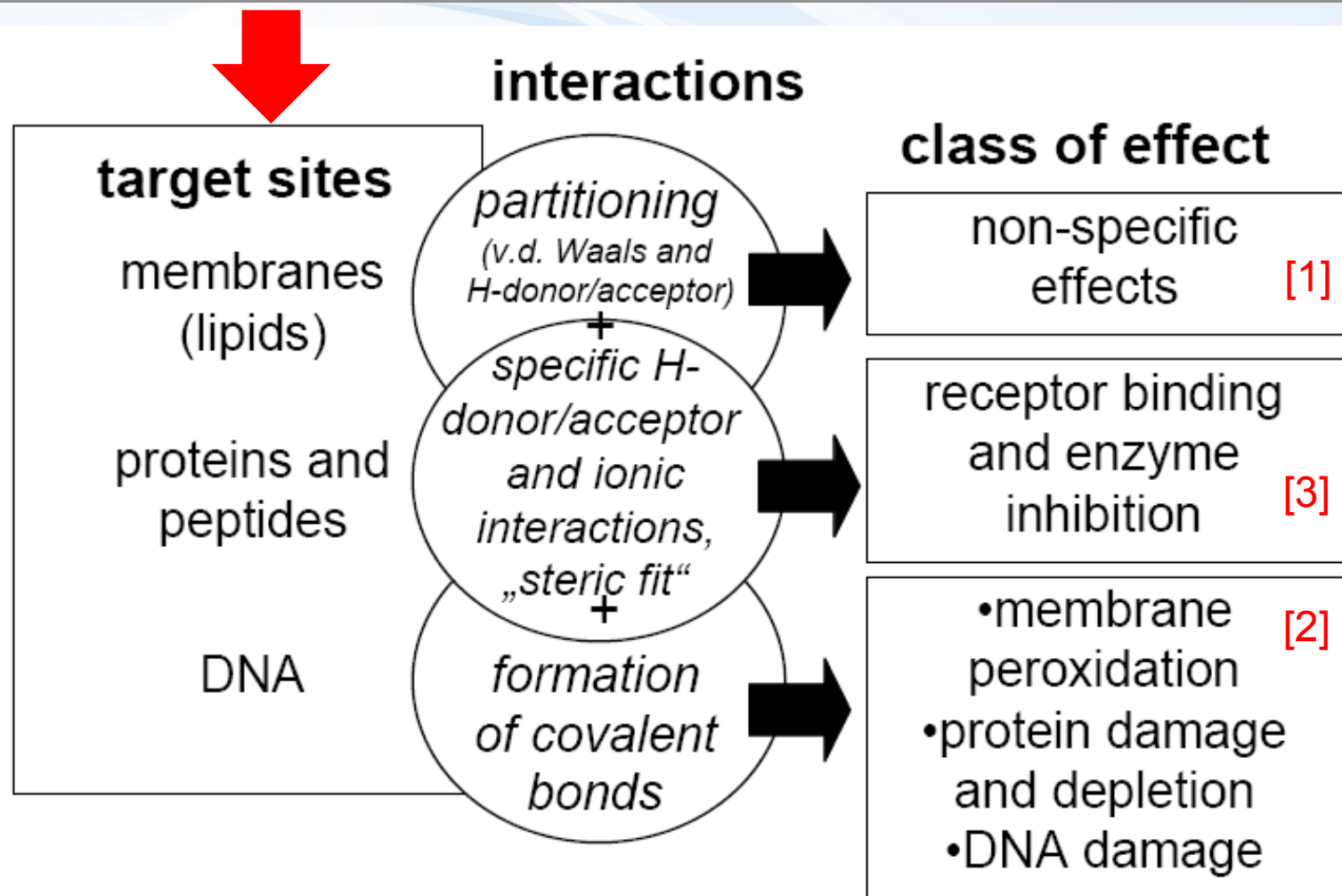
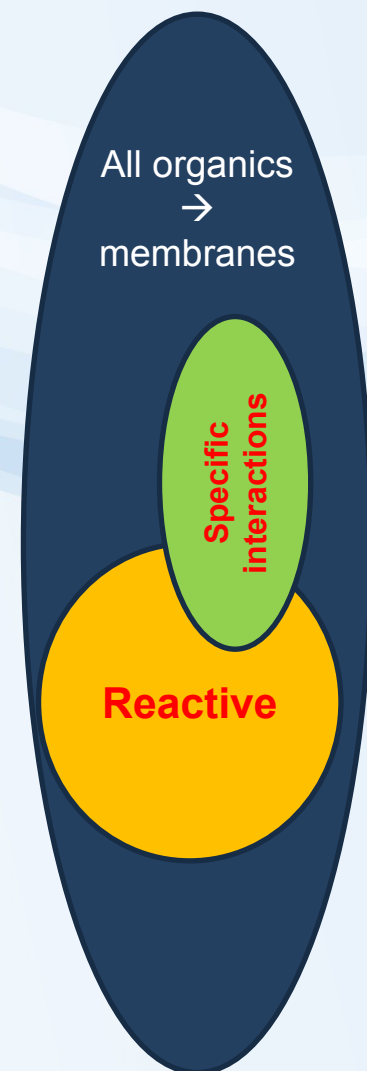


Figure 2 Rationale behind the classification of chemicals according to mechanism: target sites and type of interaction.



Possible categorizations of MoA

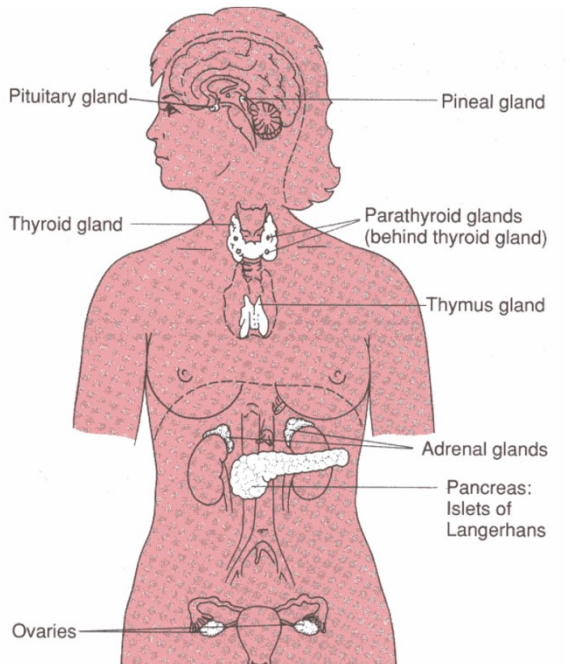
- **[1] non/specific membrane toxicity**
 - Involves ALL ORGANIC compounds
 - Affinity to non-polar environment (membrane phospholipids)
 - Two types can be discriminated
 - nonpolar basal / narcotic toxicity (
 - effects observed at relatively high concentrations, depends on hydrophobicity (Kow)
 - 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, -NH₂, -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*



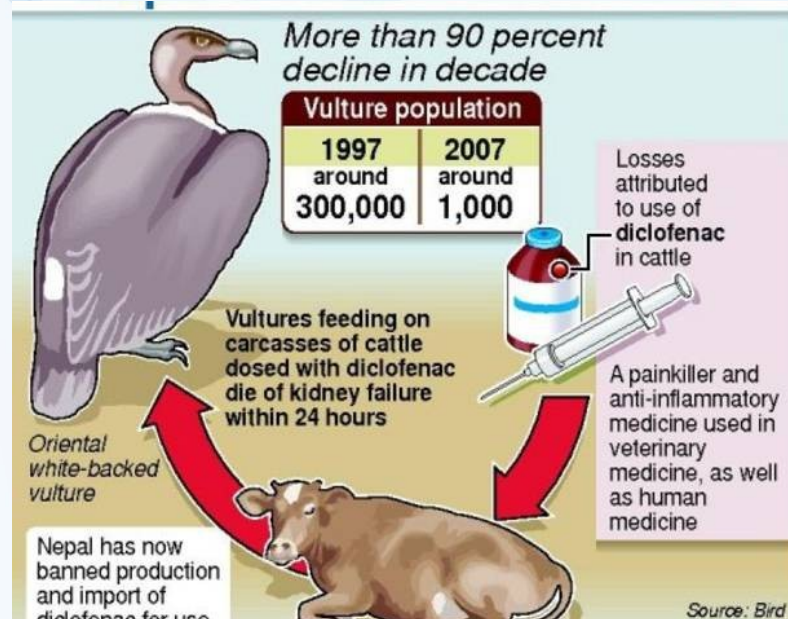
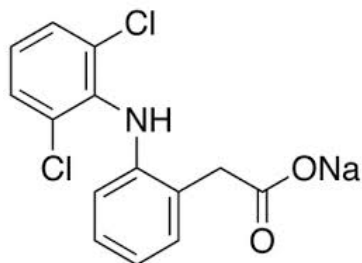
Growth in invertebrates ecdysis (moulting) - *ecdysteroids*



Possible categorizations of MoA

- Tissue-specific mechanisms (& effects)

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



Developmental stage-specific mechanisms

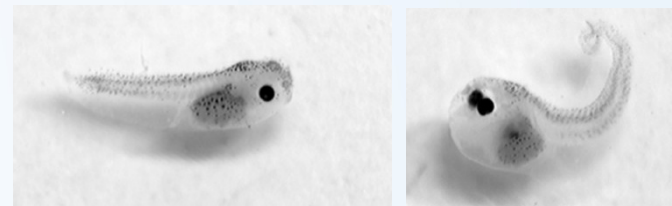
- embryotoxicity/teratogenicity: toxicity to cell differentiation processes

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