Mechanisms of toxicity - overview

- What is the "toxicity mechanism"

- interaction of xenobiotic with biological molecule
- induction of specific biochemical events
- in vivo effect

- Biochemical events induce in vivo effects *(mechanisms)*

- Changes of *in vivo* biochemistry reflect the exposure and possible effects *(biomarkers)*

Factors affecting the toxicity

Xenobiotic

- physico-chemical characteristics
  - solubility / lipophilicity
  - reactivity and redox-characteristics
  - known structural features related to toxicity (*organophosphates*)
  - structurally related molecules act similar way
- bioavailability & distribution (*toxicokinetics*)

Biological targets (receptors)

- availability (species- / tissue- / stage- specific effects)
- natural variability (individual susceptibility)

Concentration of both Xenobiotic and Receptor

Mechanisms of toxicity - specificity

- **Tissue-specific mechanisms (& efffects)**
  - hepatotoxicity; neurotoxicity; nefrotoxicity; haematotoxicity
  - toxicity to reproduction organs;
  - embryotoxicity, teratogenicity, immunotoxicity

- **Species-specific mechanisms**
  - photosynthetic toxicity vs. teratogenicity
  - endocrine disruption – invertebrates vs. vertebrates

- **Developmental stage-specific mechanisms**
  - embryotoxicity: toxicity to cell differenciation processes

Cellular toxicity mechanisms - overview

Membrane nonspecific toxicity (narcosis)

Inhibition of enzymatic activities

Toxicity to signal transduction

Oxidative stress – redox toxicity

Toxicity to membrane gradients

Ligand competition – receptor mediated toxicity

Mitotic poisons & microtubule toxicity

DNA toxicity (genotoxicity)

Defence processes as toxicity mechanisms and biomarkers
- detoxification and stress protein induction

Toxicity mechanisms in general

Two principal „types“ of toxic action

Non-specific toxicity
- nonpolar (narcotic) toxicity / basal toxicity
- polar narcosis
- reactive toxicity

Specific toxicity
- enzyme inhibition, interaction with specific receptor…

General concept – toxicity mechanisms

1) All ORGANIC compounds affect membrane phospholipids (organic/lipids attract organics) = nonpolar narcotic toxicity (membrane toxicity)
(effects at relatively high concentrations, depends on Kow)

2) Besides the nonpolar narcosis, more polar compounds may affect also „nonspecifically“ affect membrane proteins (polar narcosis)
(effects at lower concentrations than expected from Kow, molecular mechanisms not fully clear)

3) Further, some compounds with reactive properties may directly
- and nonspecifically (nonselectively) - react and modify any biological macromolecule (lipids, proteins, nucleic acids)
(effects at even lower concentrations than 1+2; reactive chemicals are mostly „electrophiles“ reacting with „nucleophiles“ in cells – i.e. electrone-rich sites (nucleotides, -NH2, -SH and others)

4) Only certain specific compounds selectively affect specific targets causing „specific“ toxicity (enzyme inhibitions – e.g. drugs, insecticides; receptor interactions – e.g. estrogens; effects at very low concentrations)

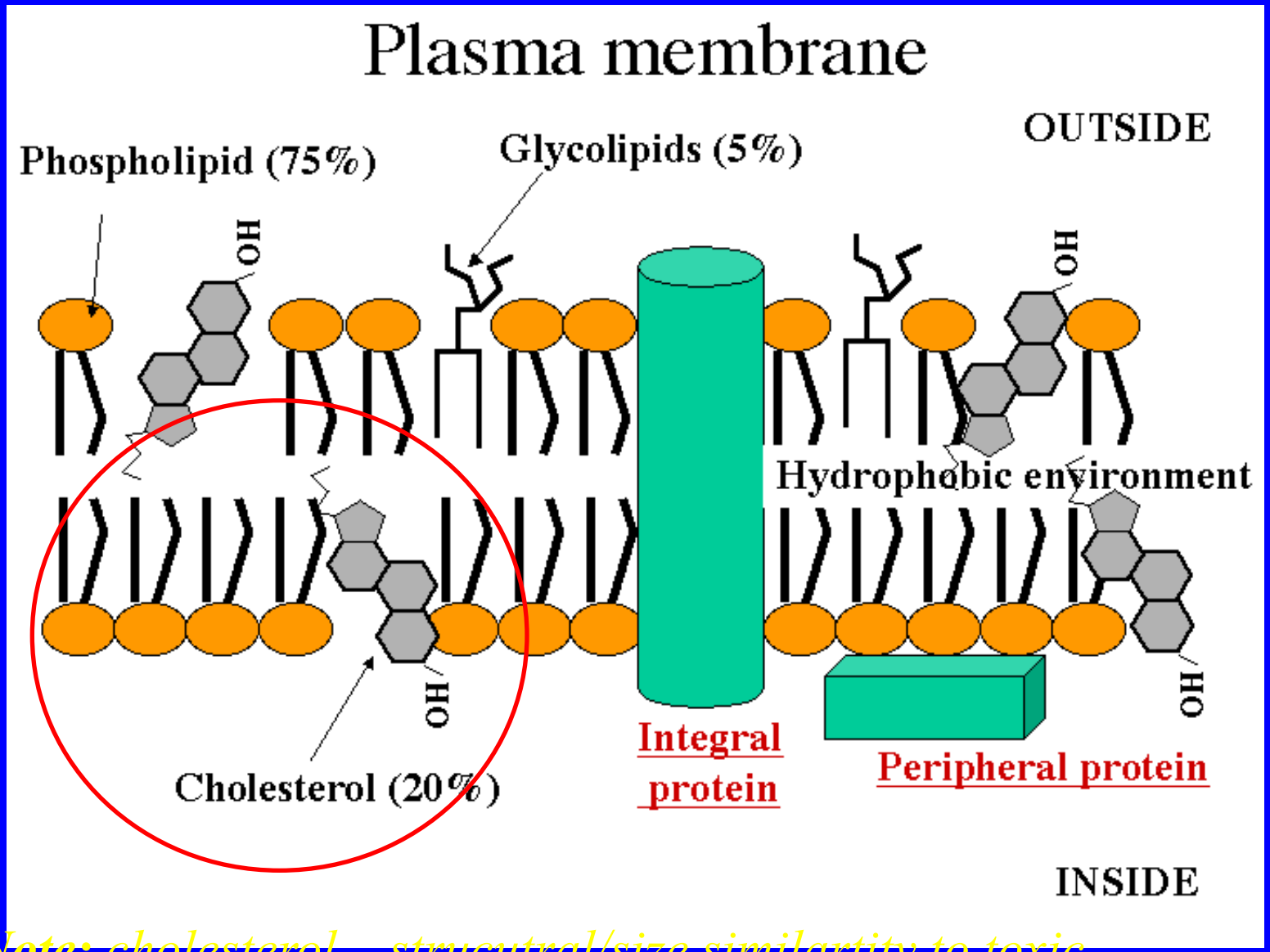
1-3 = nonspecific (large groups of chemicals, no specific target – reacts with „all“ biomolecules)
Vs. 4 = specific toxicity

Membrane and membrane toxicity

Cell membrane

Many key functions for life

- Primary barrier / separation of „living“ inside from „abiotic“ outside
- Semipermeability for nutrients / signals
- Reception of chemical signals & regulatory molecules
- Keeping gradients necessary for life
  - H+ - ATP synthesis(mitochondria / bacterial emambrane)
  - K+/Na+ - neuronal signals
- Proteosynthesis (ribosomes) depends on membranes
- Many other enzymes bound to membranes (e.g. signaling, detoxification, post-translational modifications)
- Etc.…



Note: *cholesterol – strucutral/size similartity to toxic organics e.g. PAHs*

NARCOSIS / nonspecific toxicity

- All organic compounds are narcotic in particular ("high") concentrations

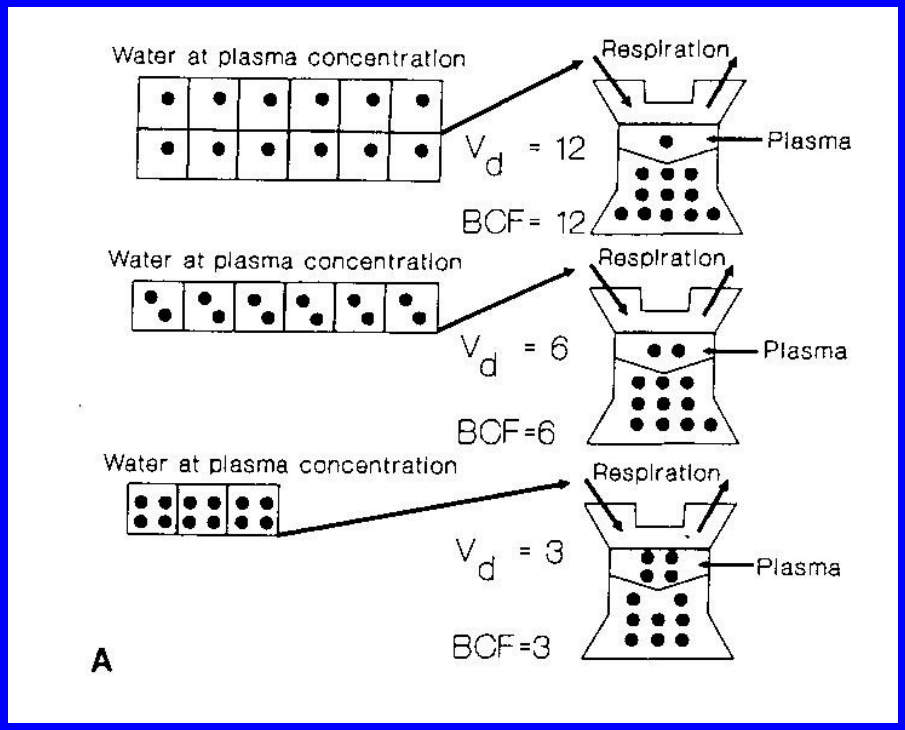
- Compounds are considered to affect membranes; nonspecific disruption of fluidity and protein function

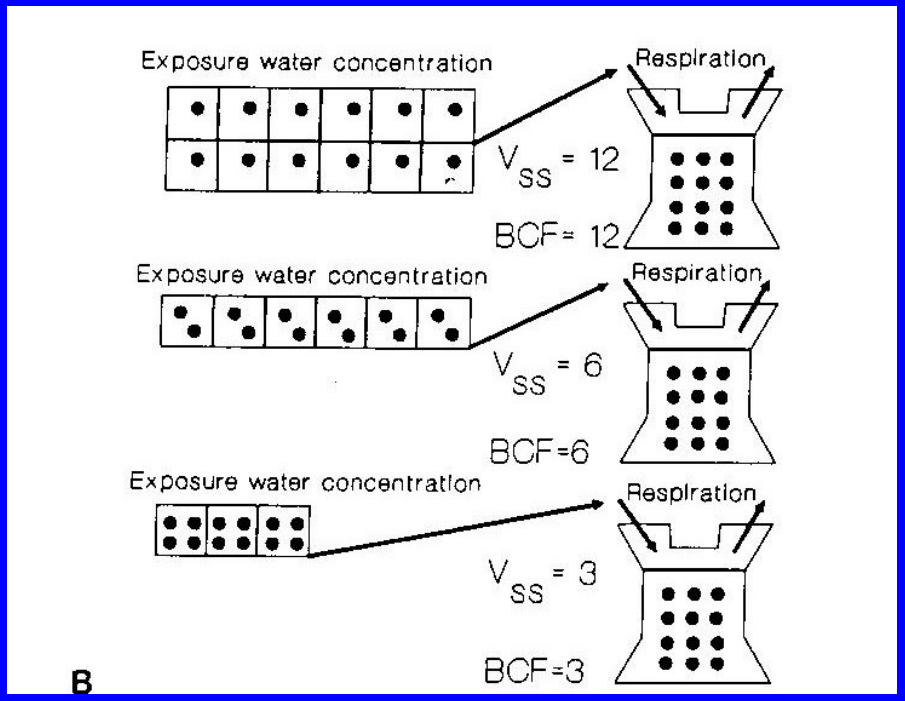
- Related to lipophilicity (logP, Kow): tendency of compounds to accumulate in body lipids (incl. membranes)

  Narcotic toxicity to fish: ***log (1/LC50) = 0.907 . log Kow - 4.94***

- The toxic effects occur at the same "molar volume" of all narcotic compounds (***volume of distribution principle***)

Volume of distribution principle

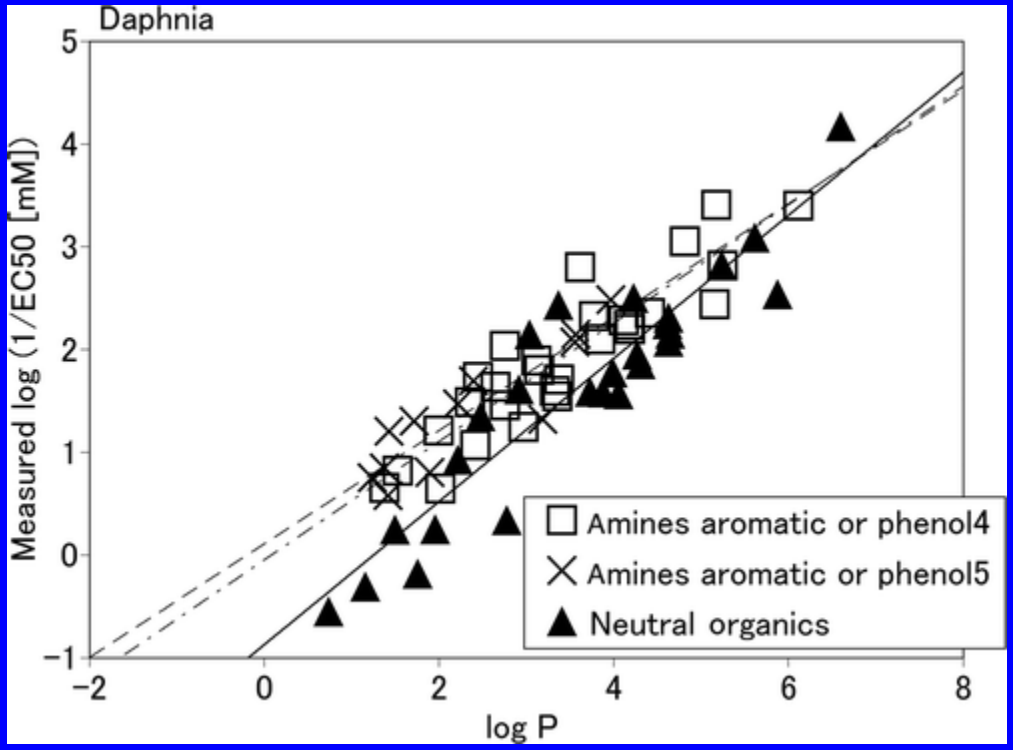




Narcotic toxicity in ecotoxicology

Acute basal toxicity

Direct correlation logP vs EC50 at aquatic organisms (*Daphnia, fish)*



Example:

Neutral organics

→ Nonpolar narcosis

Amines, phenols

→ Polar narcosis

(similar logP → higher toxicity, i.e. higher Values of 1/EC50 in comparison to neutral organics)

Enzyme inhibition as a toxicity mechanism

Enzyme inhibition - toxicity mechanism

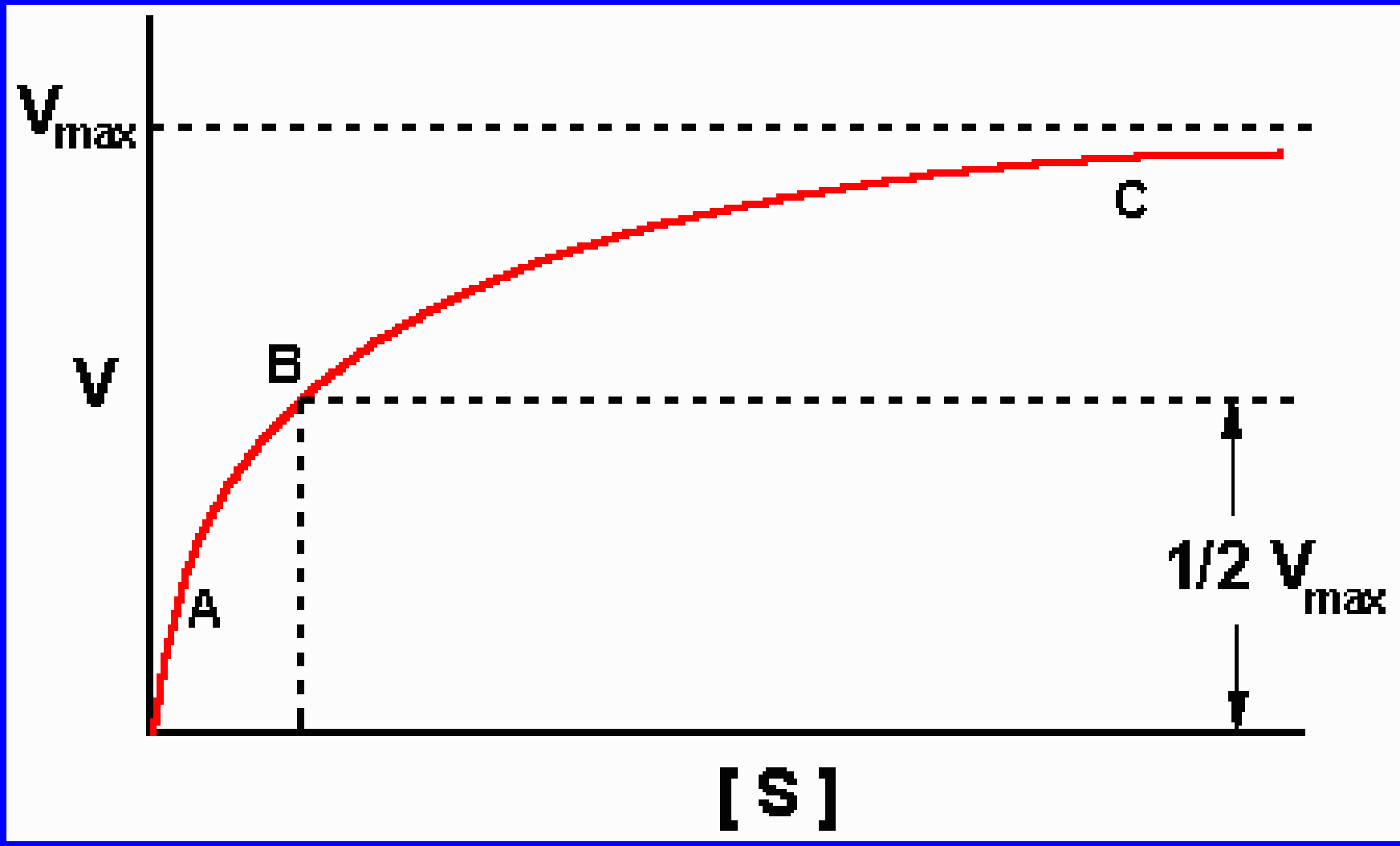
- **Millions of enzymes** *(vs. millions of compounds)*
  : body fluids, membranes, cytoplasm, organels

- **Compound - an enzyme inhibitor ?**
  - Enzymology: interaction of xenobiotics with enzymes
  - Competitive vs. non-competitive:
    active site vs. side domains
  - Specific affinity – inhibition (effective) concentration

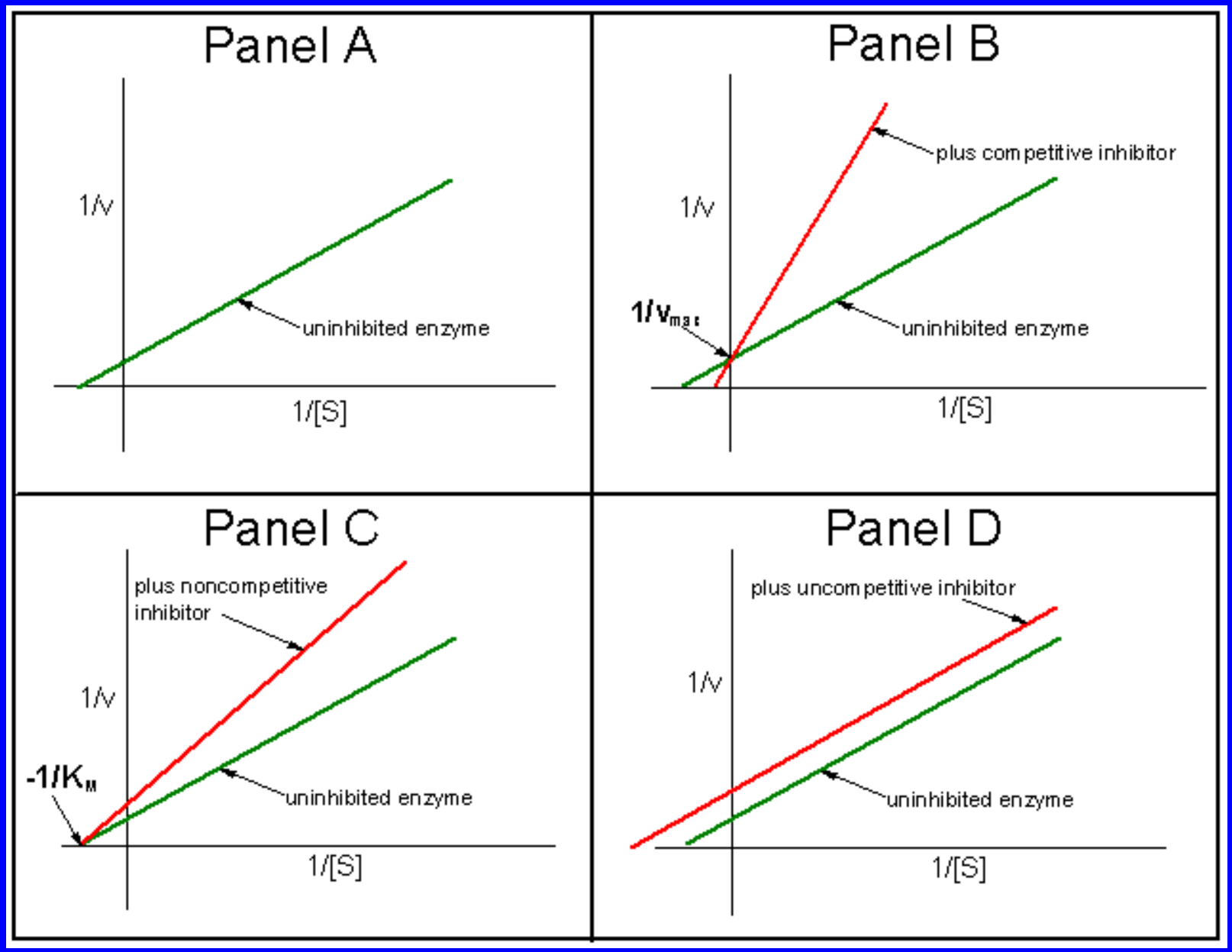
- What enzymes are known to be selectively affected ?

- **Nonspecific** inhibitions (!)
  Compound affects high osmomolarity or pH …

Enzyme inhibition - toxicity mechanism



Enzyme inhibition - toxicity mechanism



Enzyme inhibition – few examples

Acetylcholinesterase (organophosphate pesticides)

Microsomal Ca^{2+}-ATPase (DDE)

Inhibition of hemes – respiratory chains (cyanides)

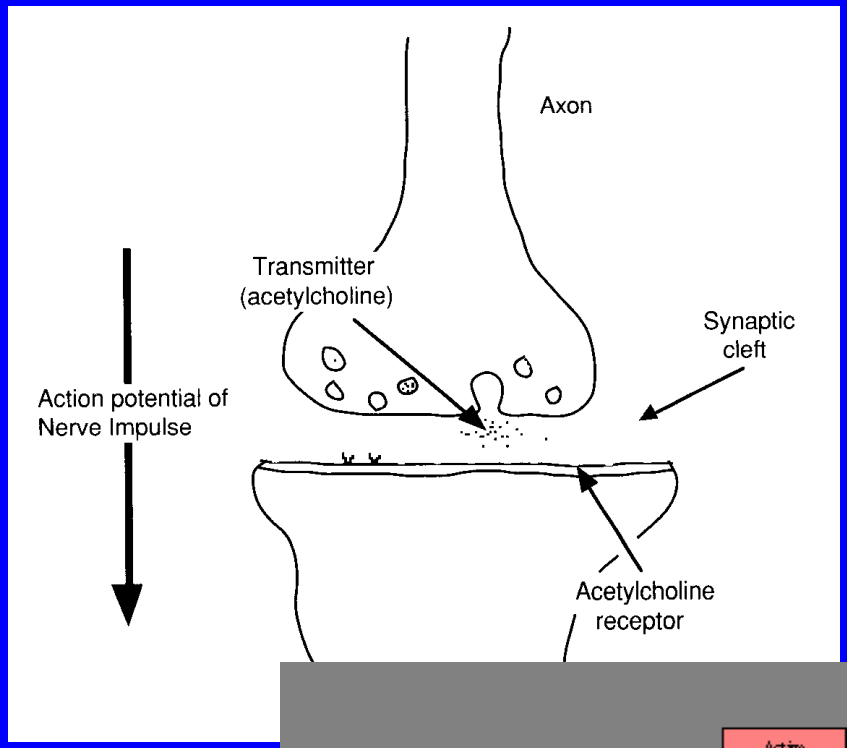
d-Aminolevulinic Acid Dehydratase (ALAD) inhibition
(lead - Pb)

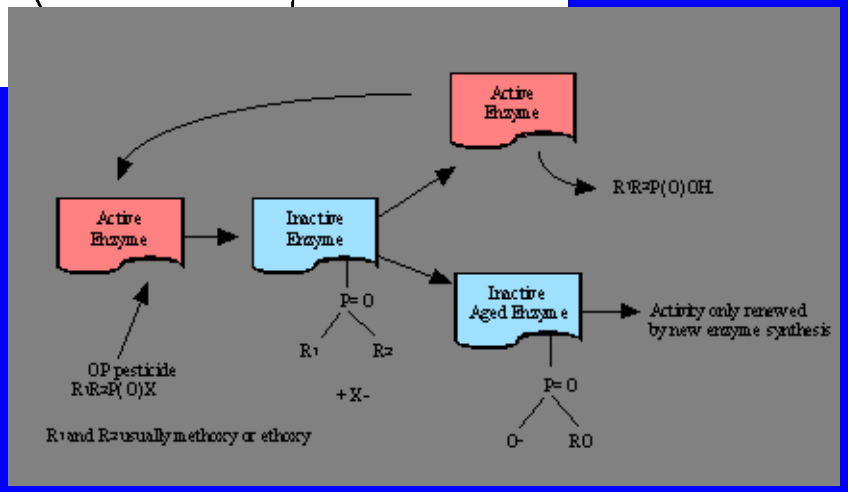
Inhibition of proteinphosphatases *(microcystins)*

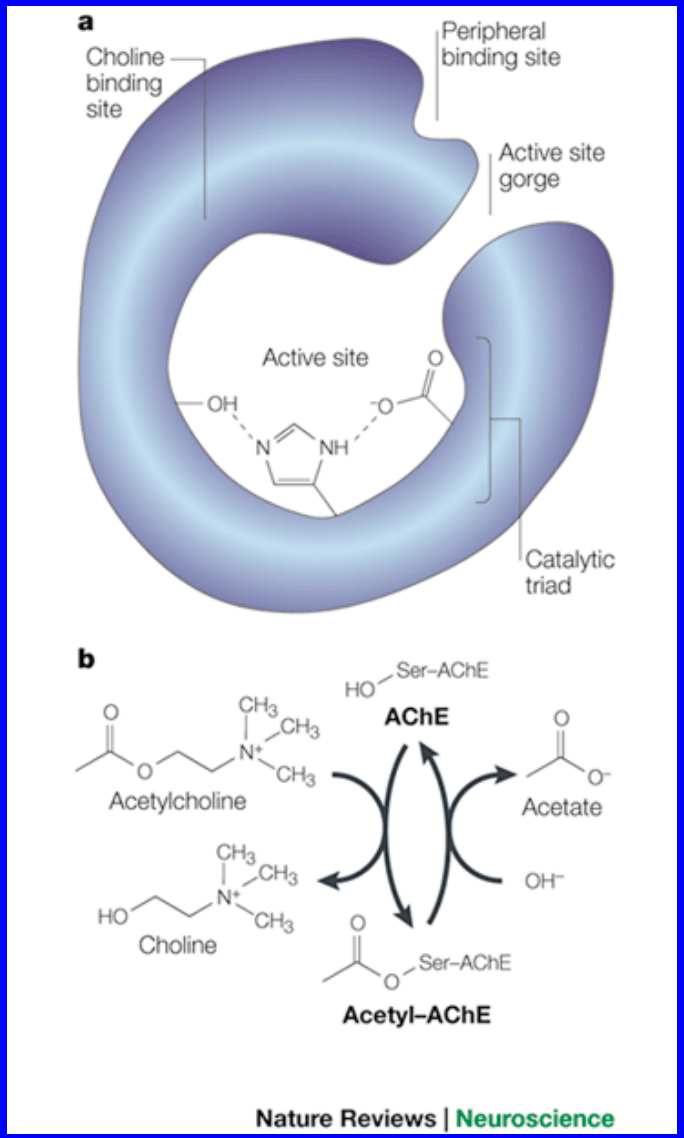
Glyphosate (roundup) action

(Enzyme inhibitions are beyond many others → see e.g. REGULATIONS etc.)

Acetylcholinesterase inhibition by organophosphate pesticides







Inhibition of Ca^{2+}-ATPase by DDE

Ca2+:

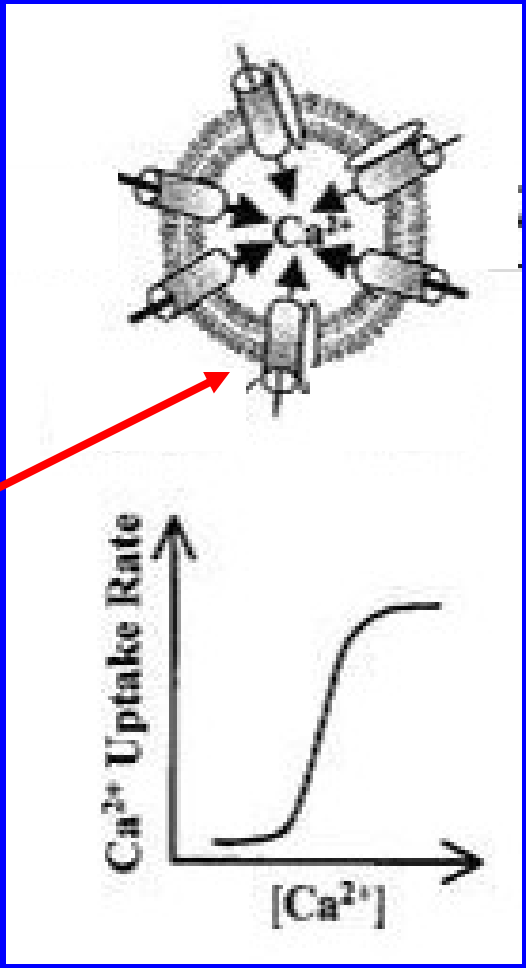
general regulatory molecule

contractility of muscles

calcium metabolism in bird eggs

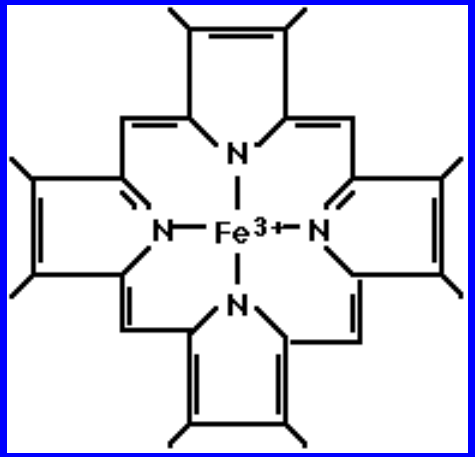
stored in ER
(endo-/sarcoplasmatic reticulum)

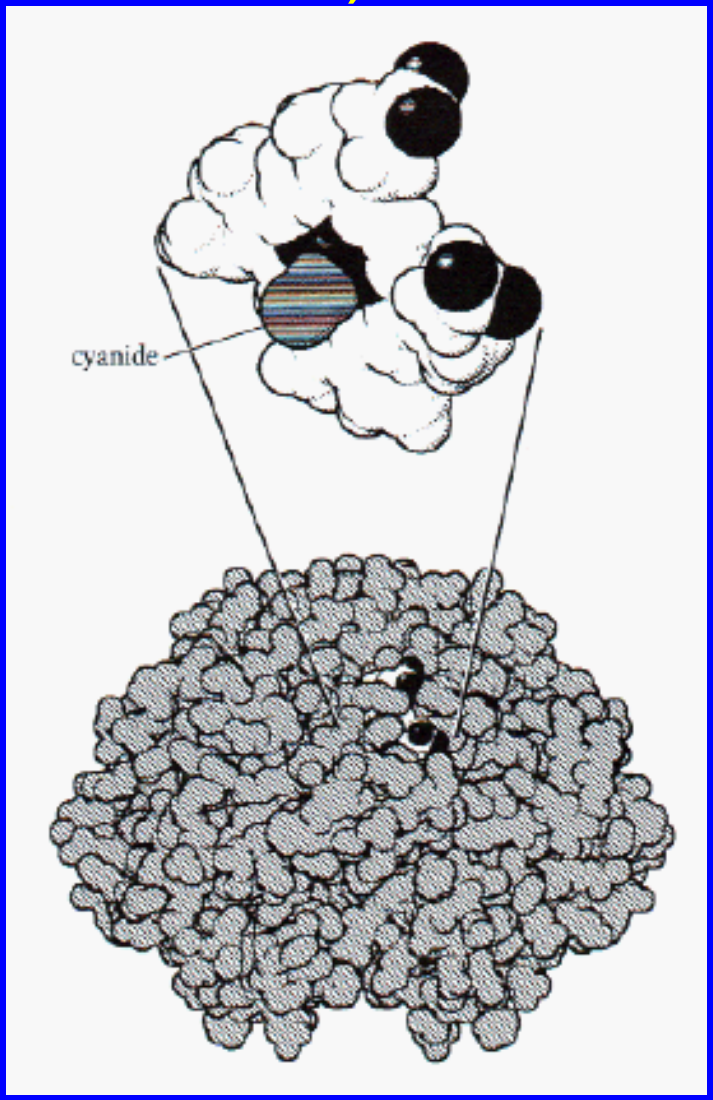
concentrations regulated by
Ca^{2+}-ATPase



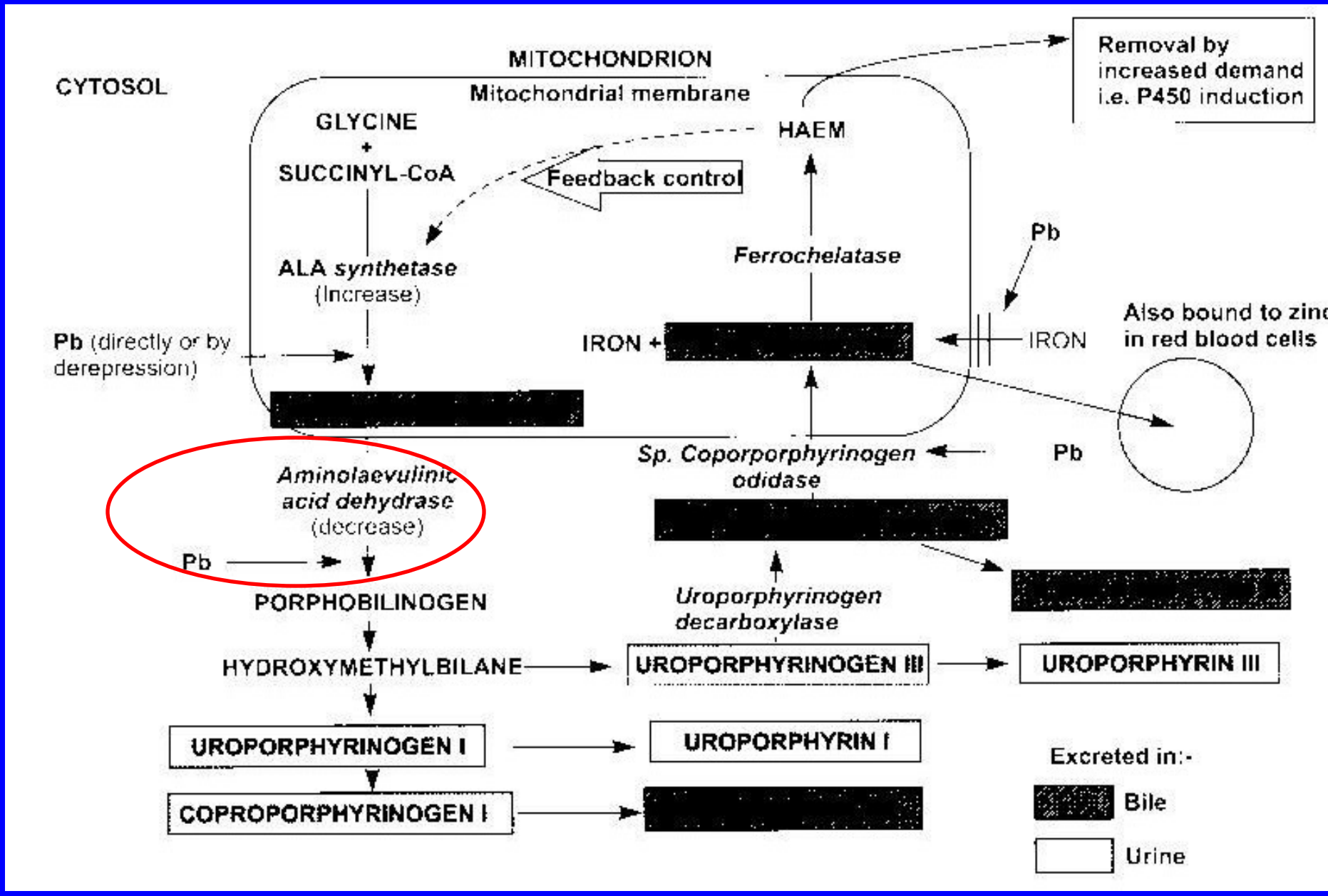
Inhibition of hemes by **cyanide**

oxidations in respiratory chains; Hemoglobin (also CYP450)



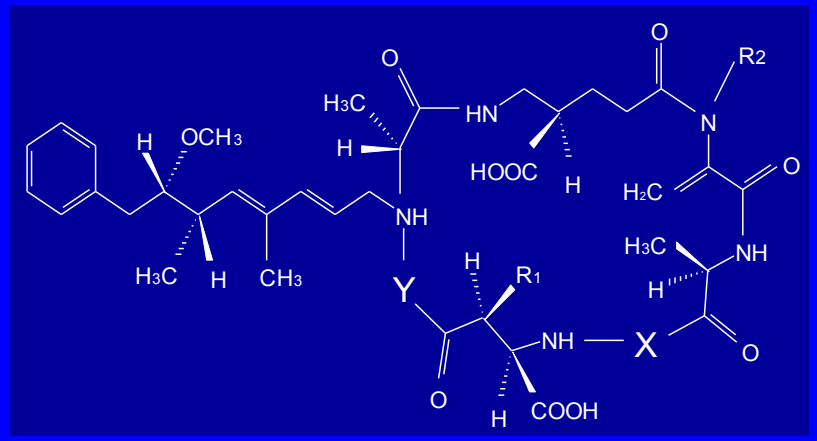


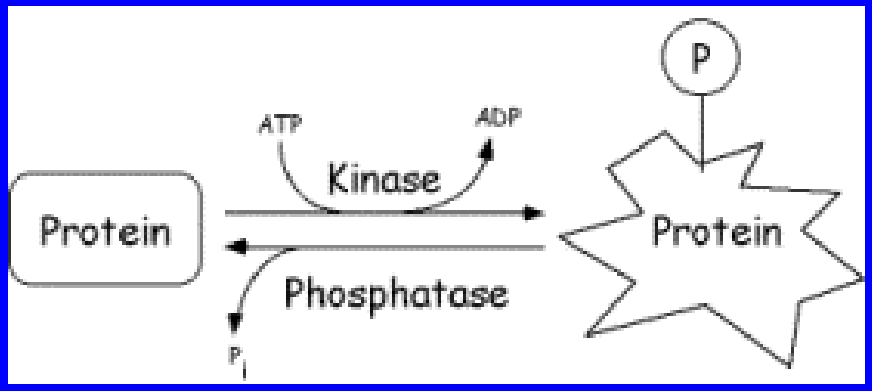
ALAD inhibition by lead (Pb)

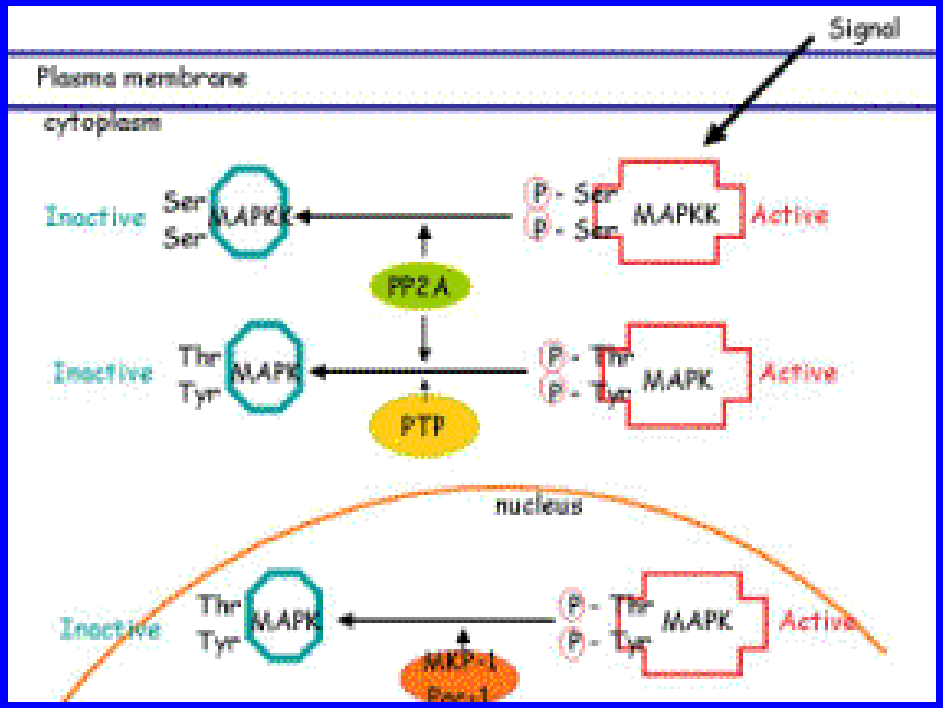


PPase inhibitions by microcystins (liver !)

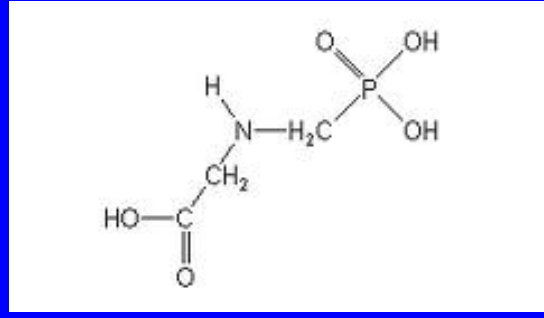
Microcystins – produced in eutrophied waters by cyanobacteria; kg – tons / reservoir







Glyphosate



N-(phosphonomethyl)glycine

Broad-spectrum herbicide („RoundUp“)

Selective inhibition of ESPs 5-*enol*pyruvylshikimate-3-phosphate synthase;

(synthesis of aromatic aa – Tyr, Trp, Phe)

Uptake via leafs - only to growing plants

„Non-toxic“ to other organisms

(no ESPs in animals, aa-like chemical - rapid degradation)