Centrum pro výzkum toxických látek v prostředí

Ecotoxic effects

- Cellular and organisms levels -

Luděk Bláha, PřF MU

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

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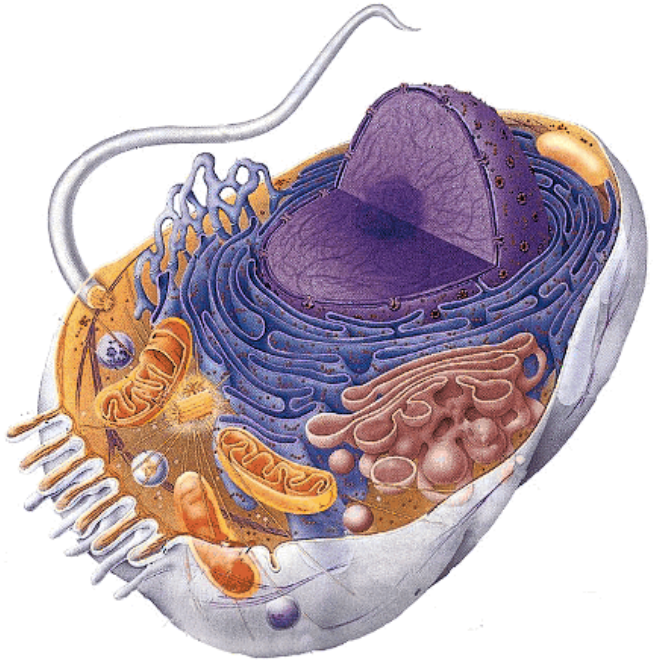
OP Vzdělávání pro konkurenceschopnost

UNIVERSITAS MASARYKIANA BRUNENSIS

INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

Toxicity at cellular level

Molecular mechanisms
(effects on proteins, membranes, DNA) **manifest at cellular level**



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Life trajectories of the cell

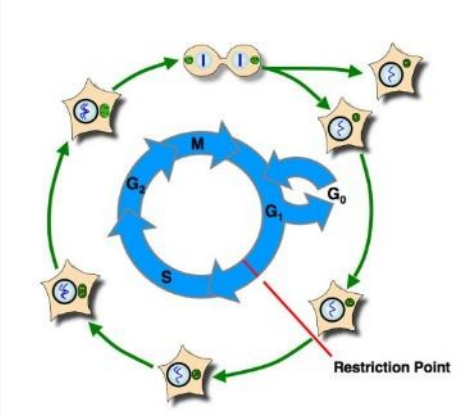
Regular pathways of cell life

1) **Cycling** (cell cycle, proliferation)
2) Due to limited proliferation → **senescence or**
   or terminal **differentiation**
   or cell death (controlled) – **apoptosis**

Homeostasis assured through careful check of key processes, i.e.

Cell membrane integrity
Aerobic respiration (mitochondria)
Proteosynthesis (ribozomes)
DNA integrity

…. Effects on these processes → toxicity



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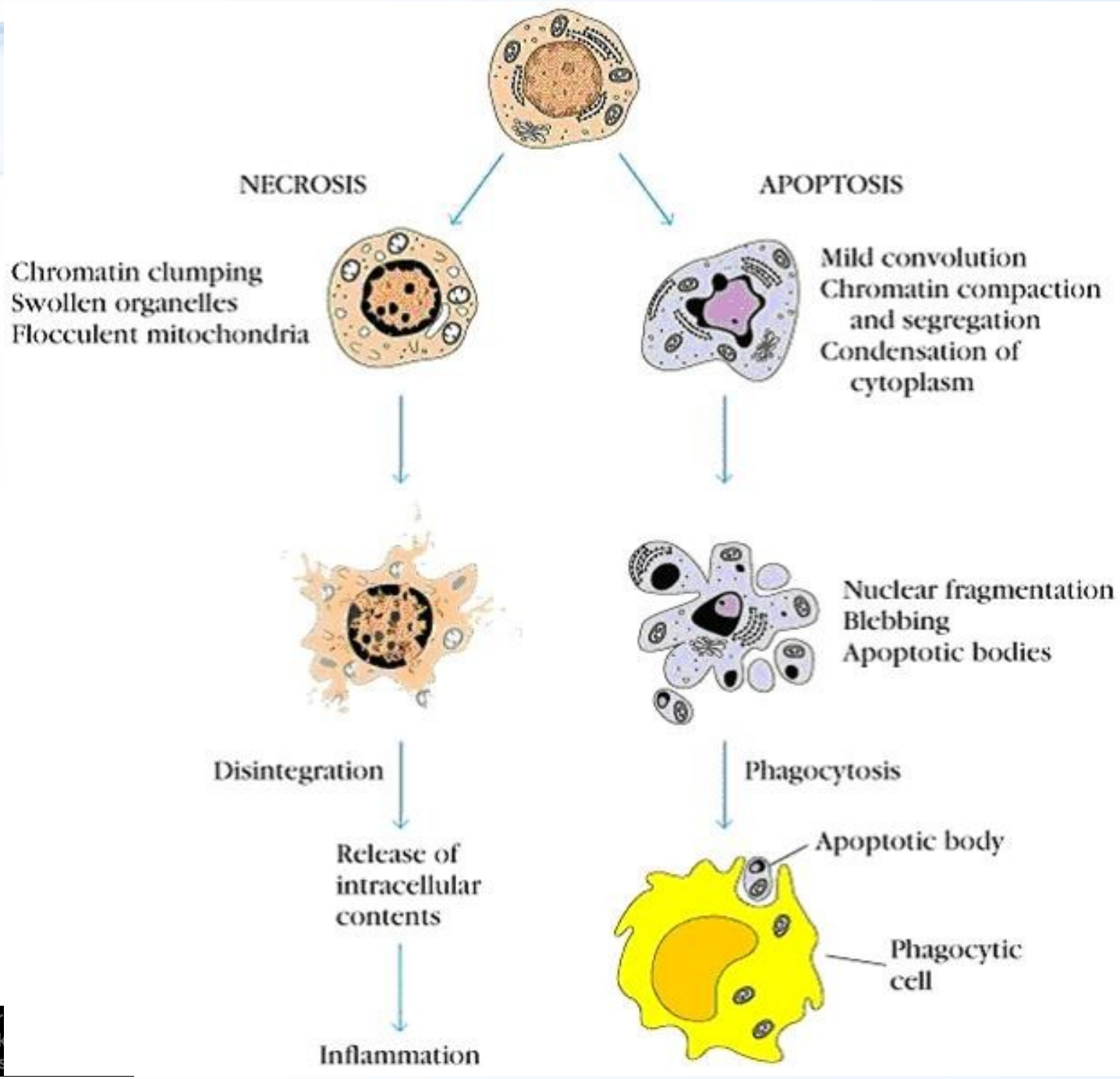

NECROSIS
APOPTOSIS
Chromatin clumping
Swollen organelles
Flocculent mitochondria
Mild convolution
Chromatin compaction
and segregation
Condensation of
cytoplasm
Nuclear fragmentation
Blebbing
Apoptotic bodies
Disintegration
Phagocytosis
Release of
intracellular
contents
Apoptotic body
Phagocytic
cell
Inflammation

IMPACTS and manifestation of toxicity at cell level

Disruption of cell proliferation

- Tumors, cancer
- Immune system disruption (proliferation in many processes)

Disruptions of differentiation

- Important for early development (embryotoxicity, teratogenicity)
- Tumors (cells often NOT differentiated)
- Immune systém

Disruptions of apoptosis

- Tumors (cells escape apoptosis)
- Effects on immune system
  - (TCDD induced activation of AhR → apoptosis in thymus → loss of functional immune reactions

The cellular effects further propate
→ **level of the ORGANISM**

Acute lethal toxicity (fish) & relevant toxicity mechanisms

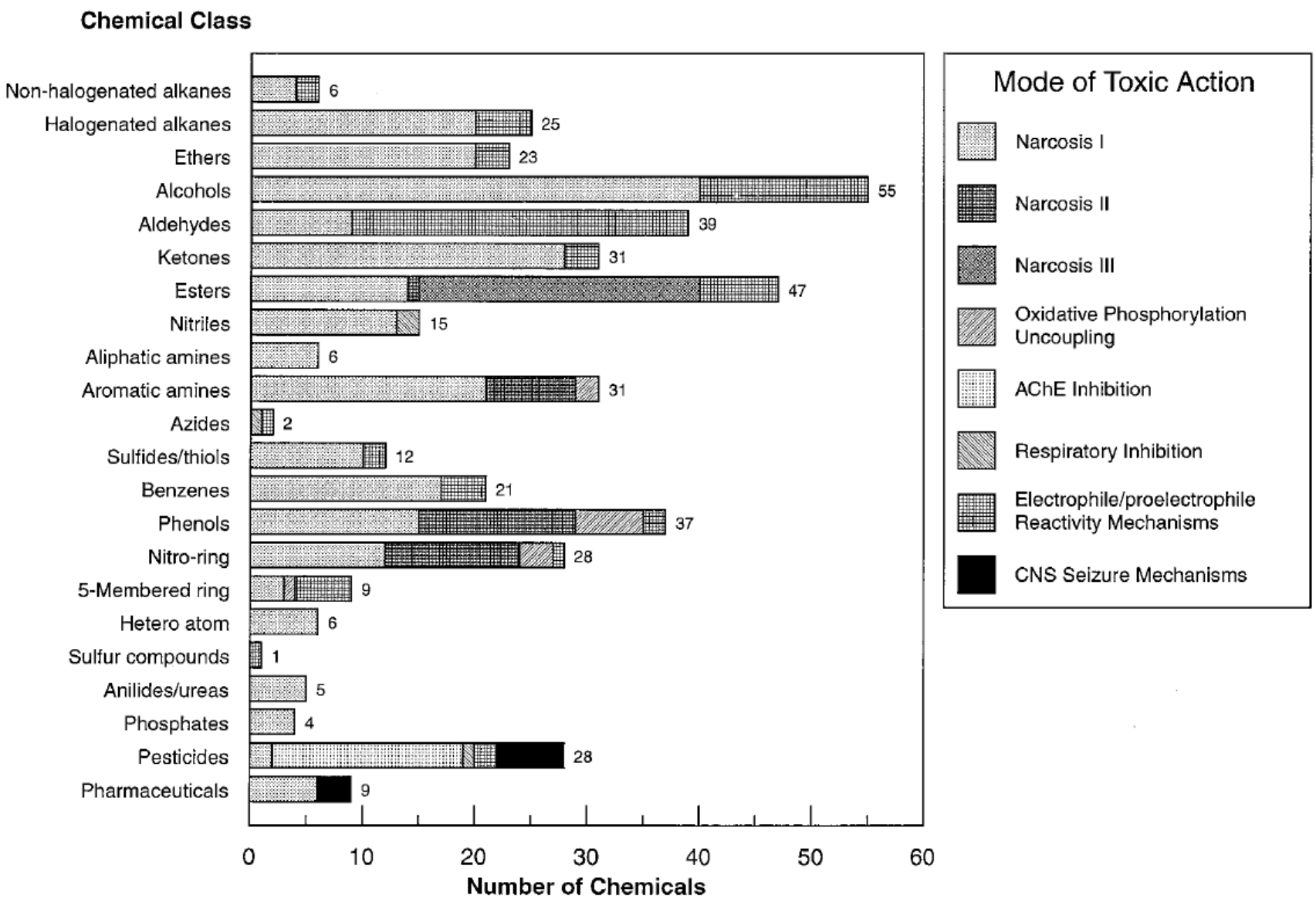


Fig. 4. Observed modes of toxic action associated with fathead minnow 96-h LC50 values (see Appendix 2) as a function of chemical classes.

Russom et al. Environmental Toxicology and Chemistry, Vol. 16, No. 5, pp. 948–967, 199

CHRONIC and DELAYED TOXICITY

„Chronic“ mechanisms less explored

Usually not tested in ecotoxicity assays

Slow manifestation and effects in ecosystems

Various effects:

- → growth inhibition (~ lower food uptake)
- → diseases such as carcinogenicity
- → teratogenicity and embryotoxicity, developmental toxicity
- → Reproduction toxicity

„Systemic“ effects

→ **Organ-specific** types of toxicity

- → Imunotoxicity
- → Neurotoxicity
- → Nefrotoxicity etc.

Effects at different levels - ORGANISM

- **Organism level –** important in ecotoxicology (see Bioassays)
  - Effects on structure
  - Effects on metabolism (maintenance)
  - Effects on regulation

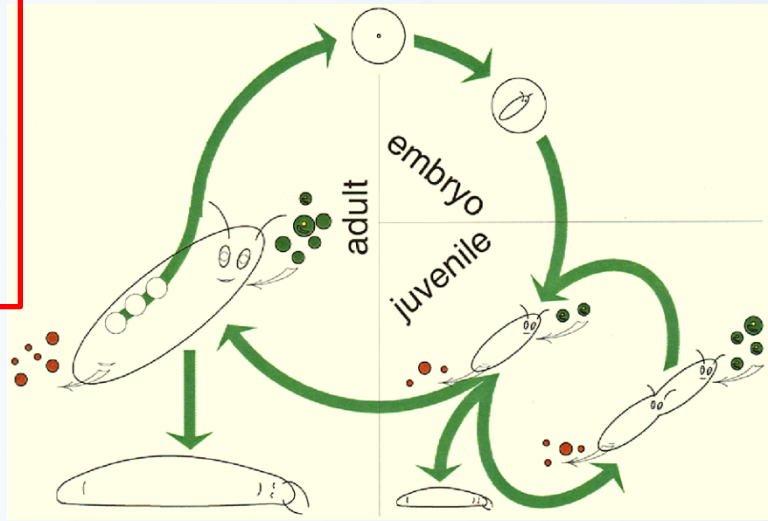
→Changes in functions (e.g. Ethinylestradiol)

→Repair, survival, **growth**

→**Death (lethality)**

→Proliferation = **Reproduction**

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



Energy
hv
food

Losses
heat
faeces

Life
(*maintenance*)

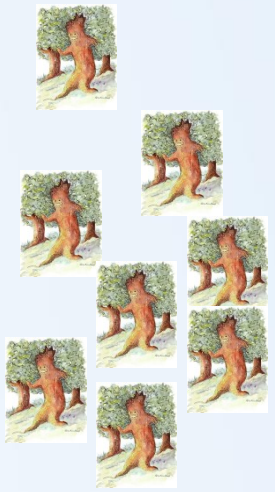
Metabolism

Control,
Interactions
with environment

Defence
against pathogens
predators …

Growth
to sexual
maturity

Reproduction



Defence against
toxicants

Chemical
stress

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v prostředí

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

Energy
hv
food

Losses
heat
faeces

Life
(*maintenance*)

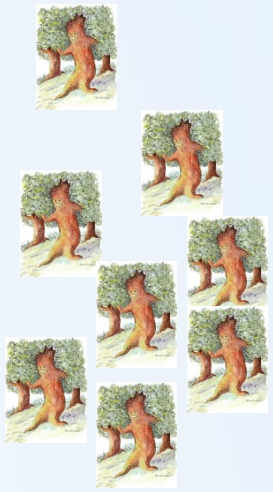
Metabolism

Control,
Interactions
with environment

Defence
against pathogens
predators …

Growth
to sexual
maturity

Reproduction



Defence against
toxicants

Chemical
stress

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v prostředí

Chemical stress

+ ... another stress (food scarcity)

Energy
hv
food

Losses
heat
faeces

Life (*maintenance*)

Metabolism

Control, Interactions with environment

Defence against pathogens predators …

Growth to sexual maturity

Reproduction

Defence against toxicants

Chemical stress

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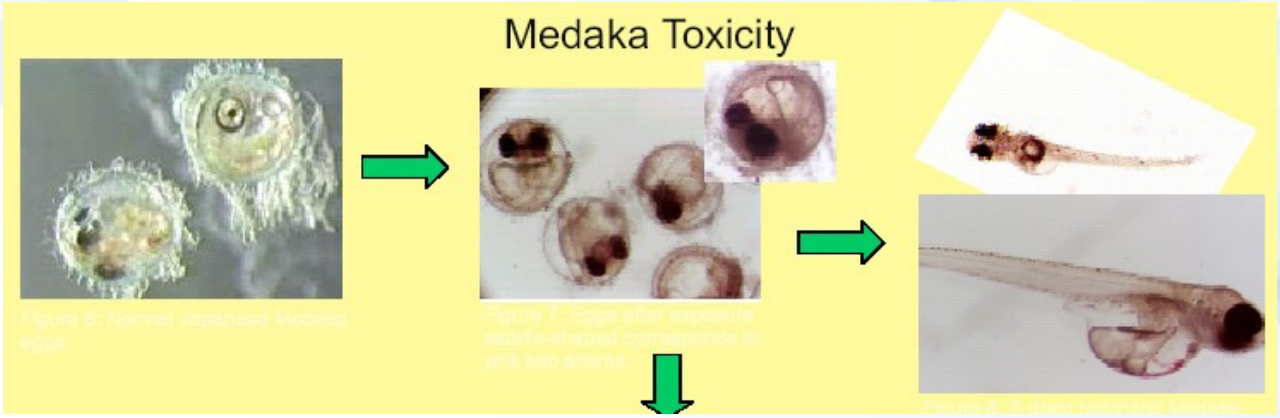
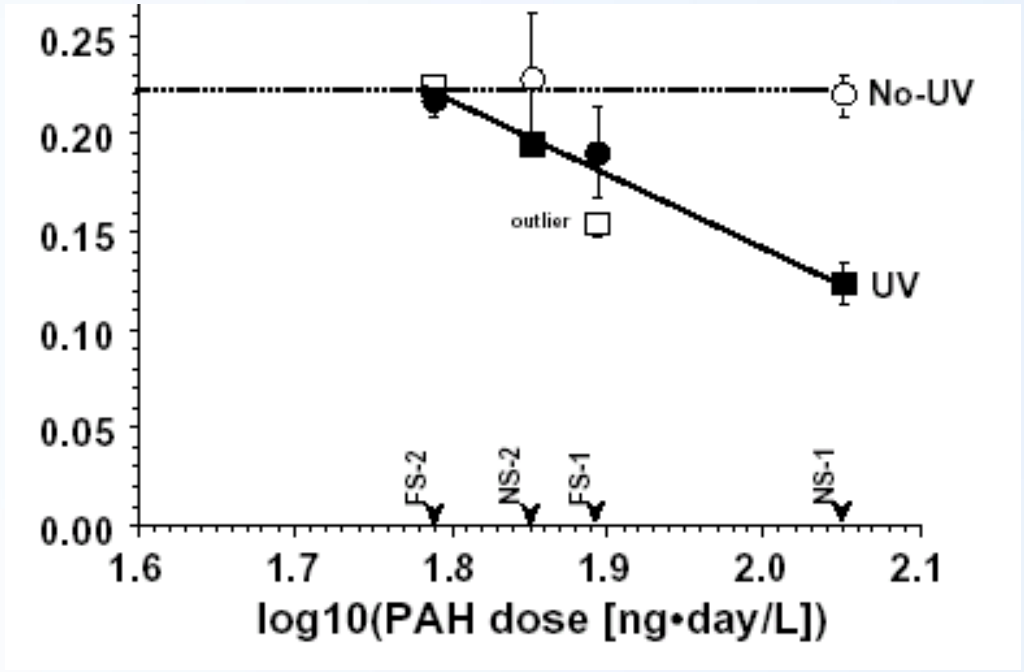
Example - GROWTH inhibition in fish

Exposures to PAHs +/- UV (phototoxicity)

Model fish = Japanese medaka



Growth is proportional to food/feed consumption (measuring of food consumption answers how toxicant affects the growth)



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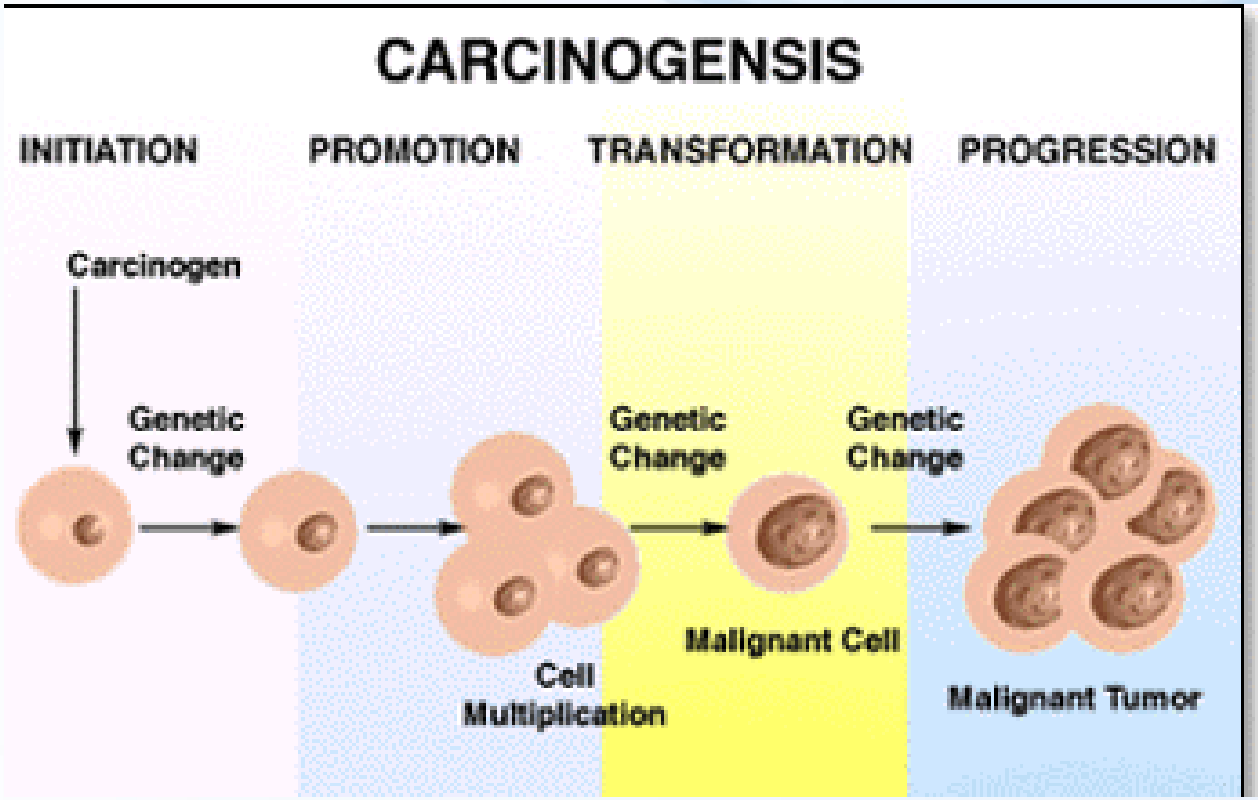
Carcinogenicity

Complex process with four main phases/steps:

- initiation (*DNA changes*) = mutagenesis
- promotion (*changes fixed in genome, cell proliferation etc)*
- transformation (*formation of malignant cells)*
- progression (*neoplasia, metastasing)*

RELEVANT mostly for HUMAN toxicology but tumors observed also in wild biota



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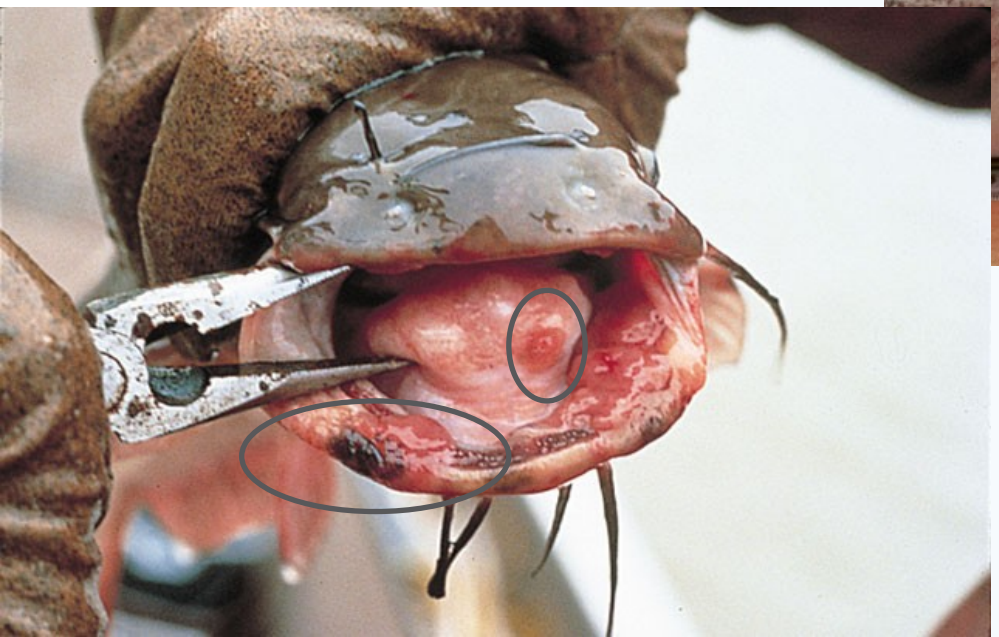
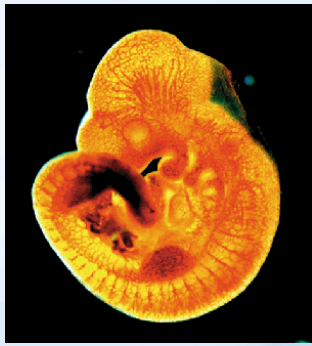


Endocrine disruption

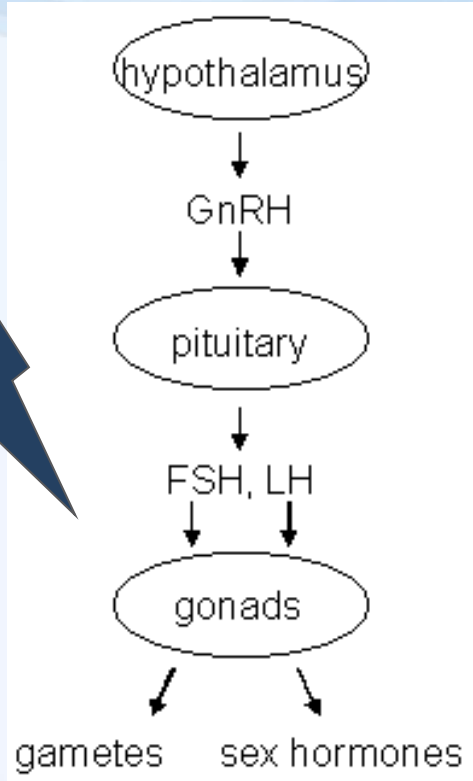
- **Interference of xenobiotics with normal functioning of hormonal system**



Known consequences

→ Disruption of homeostasis, reproduction, development, and/or behavior (and other hormone-controlled processes), such as

- Shift in sex ratio, defective sexual development
- Low fecundity/fertility
- Hypo-immunity, carcinogenesis
- Developmental processes - malformations
- etc.



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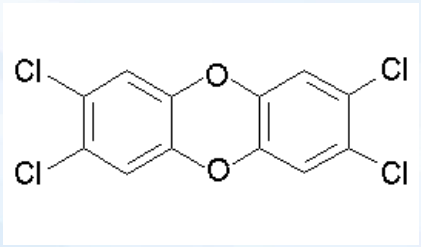
Endocrine disrupters in the environment?

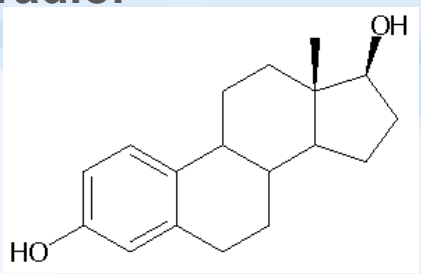
EDCs…

- Persistent Organic Compounds (POPs and their metabolites)
- steroid hormones and their derivatives from contraception pills
- alkylphenols
- organometallics (butyltins)
- pharmaceuticals
- Pesticides
- + number of unknowns …

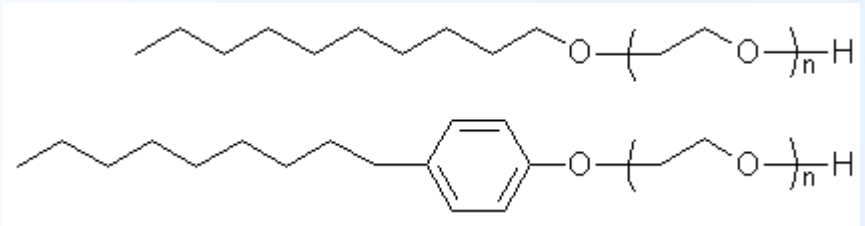
2,3,7,8-TCDD



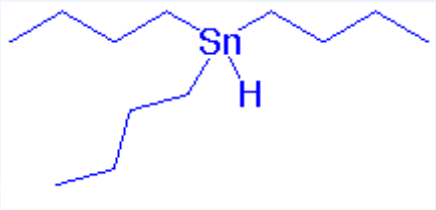
estradiol



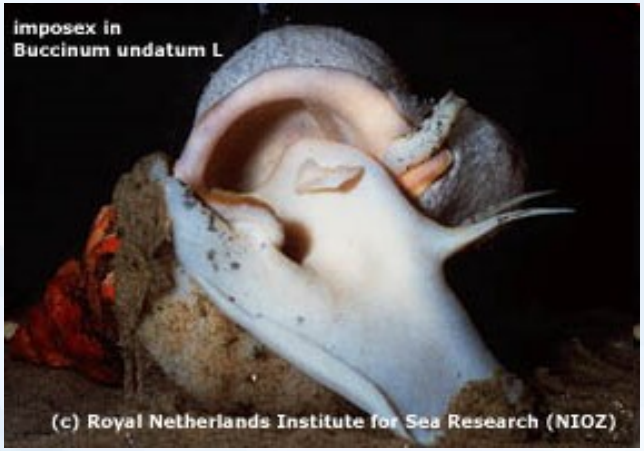
alkylphenols



Tributyl-tin



Effects of EDs in invertebrates (molluscs)



One of the first EDC effects: = imposex

- Development of male sexual characteristic in females
- Effects of alkyltins (e.g. **Tributyl tin**) – anti-fouling agents

BIOFOULING

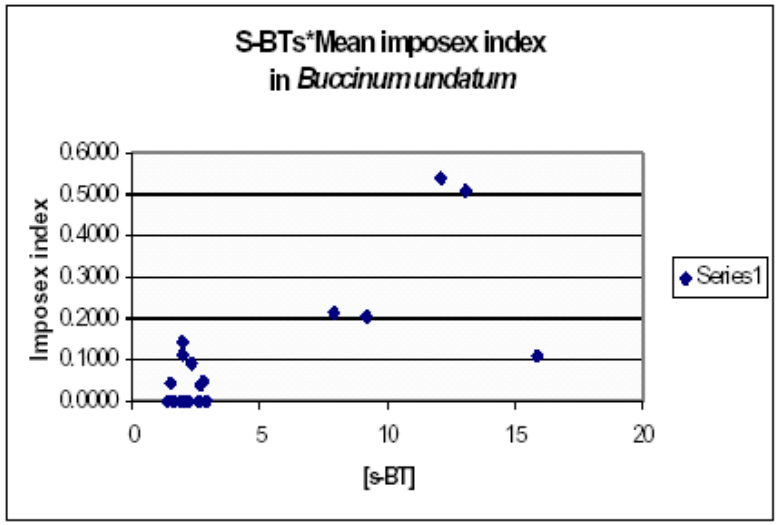
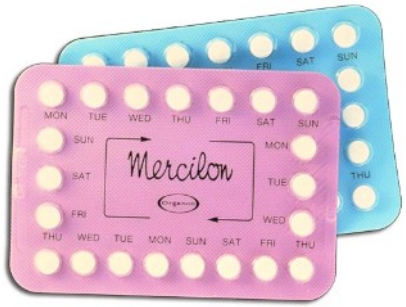
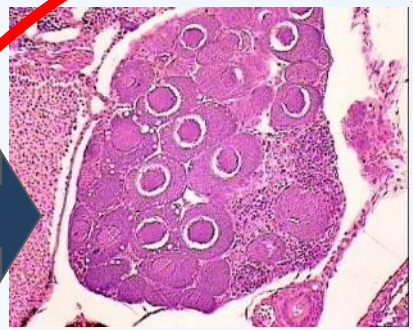


Figure 5. Relationship of Imposex index and total organotins in *Buccinum undatum*.

Female estrogens and contraception pills





Feminization
Intersex
Female eggs (oocytes) formed in male testes

Reproduction disruption
Decline in fish populations

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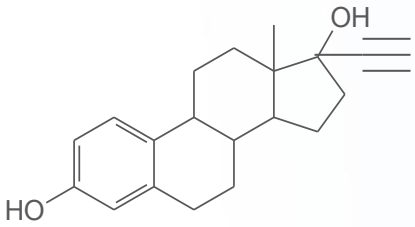
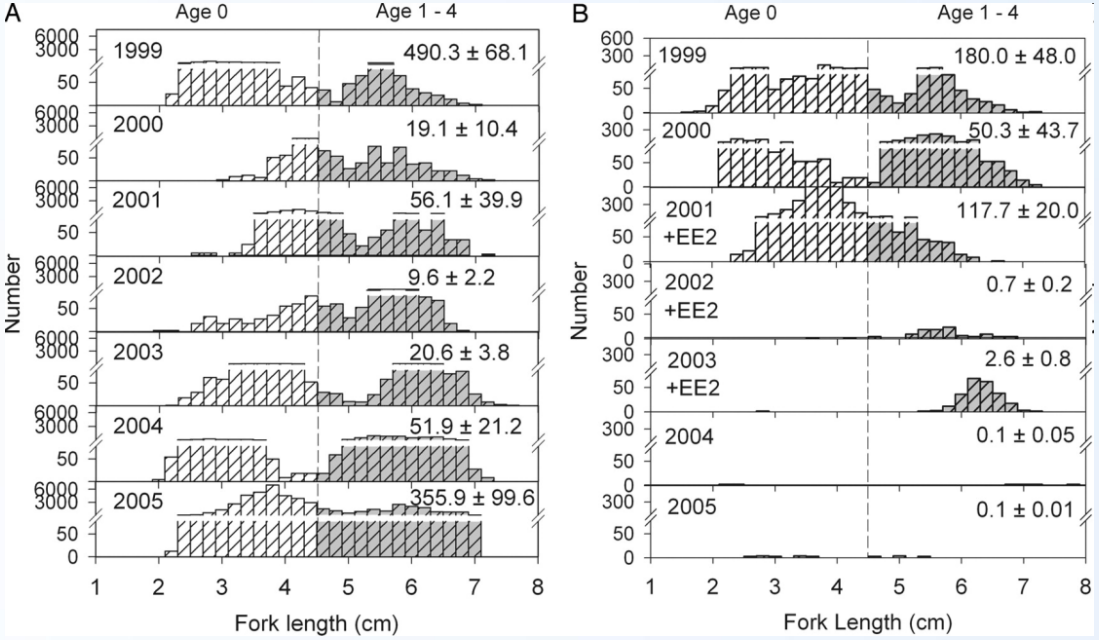
Kidd, K.A. et al. 2007. Collapse of a fish population following exposure to a synthetic estrogen. PNAS 104(21):8897-8901

EE2 - 5 ng/L (!)



Control lake **lake with EE2**



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Reproduction toxicity, developmental toxicity, embryotoxicity and teratogenicity

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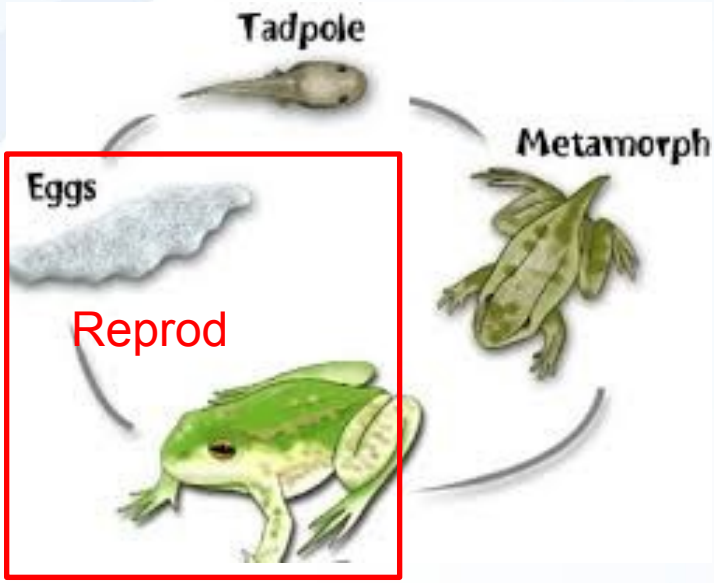
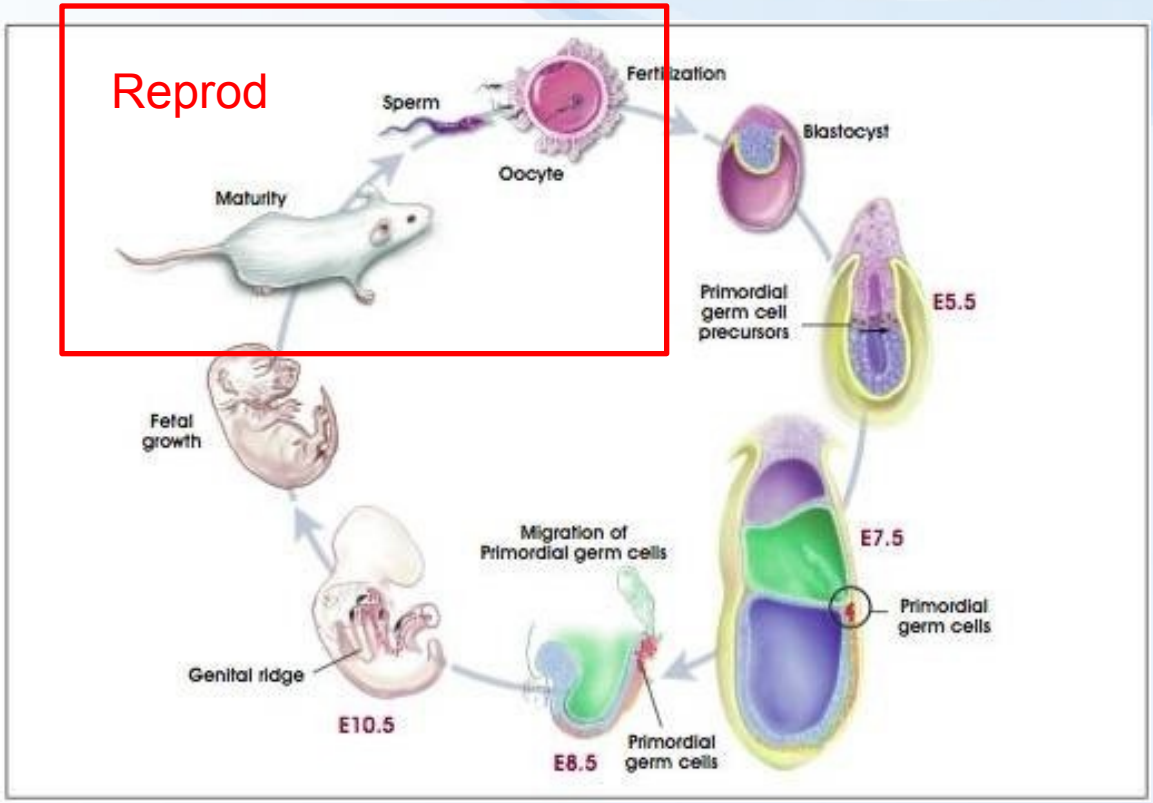
toxických látek
v prostředí

Reproduction and development are closely related





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DEVELOPMENTAL TOXICITY

Embryotoxicity

= general term – toxicity to embryo

Teratogenicity

= morphological developmental effects

Malformations, missing organs etc.

- well characterized in aquatic vertebrates

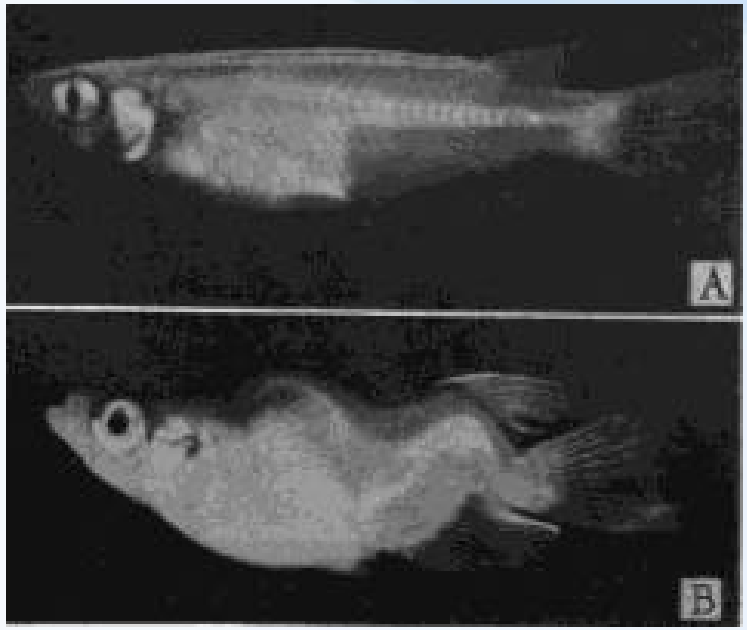
-ecotoxicity tests - Danio rerio, Xenopus laevis

Teratogenicity effects

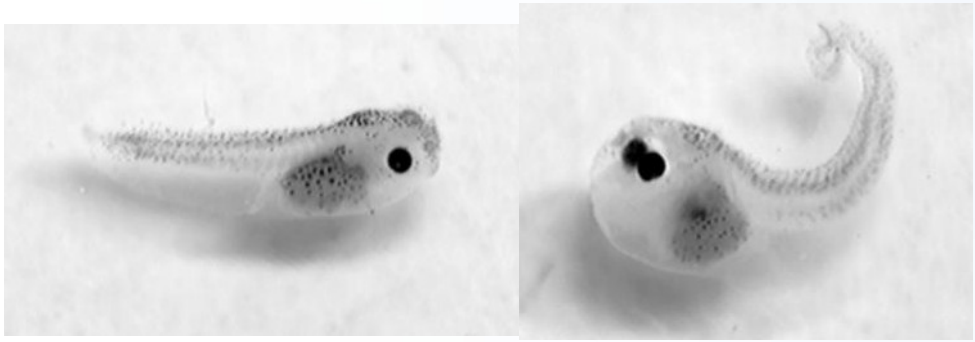
Examples of teratogens

- *organochlorine compounds (**DDT, DDE**)*
- *new types of pesticides **ATRAZIN***
- ***PCBs** and compounds with dioxin-like mechanims*
- ***toxic metals***
- *natural toxins (e.g. From cyanobacteria)*

Japanese medaka
teratogenicity of **PCBs**



Embryos of frogs *X. laevis*
Controls exposure to cyanotoxins



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IMMUNOTOXIC EFFECTS OF ECOTOXICANTS

Environmental Pollution
Volume 152, Issue 2, March 2008, Pages 431-442

doi:10.1016/j.envpol.2007.06.075 | How to Cite or Link Using DOI

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Cited By in Scopus (3)

Persistent organic pollutants (POPs) in Caspian seals of unusual mortality event during 2000 and 2001

Natsuko Kajiwara[a], [1], Mafumi Watanabe[a], [1], Susan Wilson[b], Tariel Eybatov[c], Igor V. Mitrofanov[d], David G. Aubrey[e], Lev S. Khuraskin[f], Nobuyuki Miyazaki[g] and Shinsuke Tanabe[a]

Examples

- **Mortalities of seals, dolfins – morbillivirus infections /** PCBs, PCDDs
- Elevated **skin lesions (fungi, bacteria) in fish from contaminated sites**
- **Arsenic → direct toxicity to natural killer cells in immune system (responsible for removal of tumors → increased carcinogenicity)**
- Prenatal exposures to DIOXINS → complete „apoptosis“ (convolusion) of thymus → not immune system in offsprings (no T-cells)

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NEUROTOXIC EFFECTS (e.g. Insecticides)

1] Acute toxicity

- spasms, effects on CNS, suffocation, death

2] Chronic effects

→ effects on behaviour, learning etc..

Behavioral changes – critical for **survival of individuals and populations**

- male-female attraction / reproduction, foraging, hiding from predators

-Loss of synchronization in release of gametes

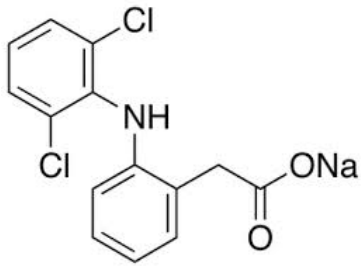
(aquatic invertebrates and vertebrates)

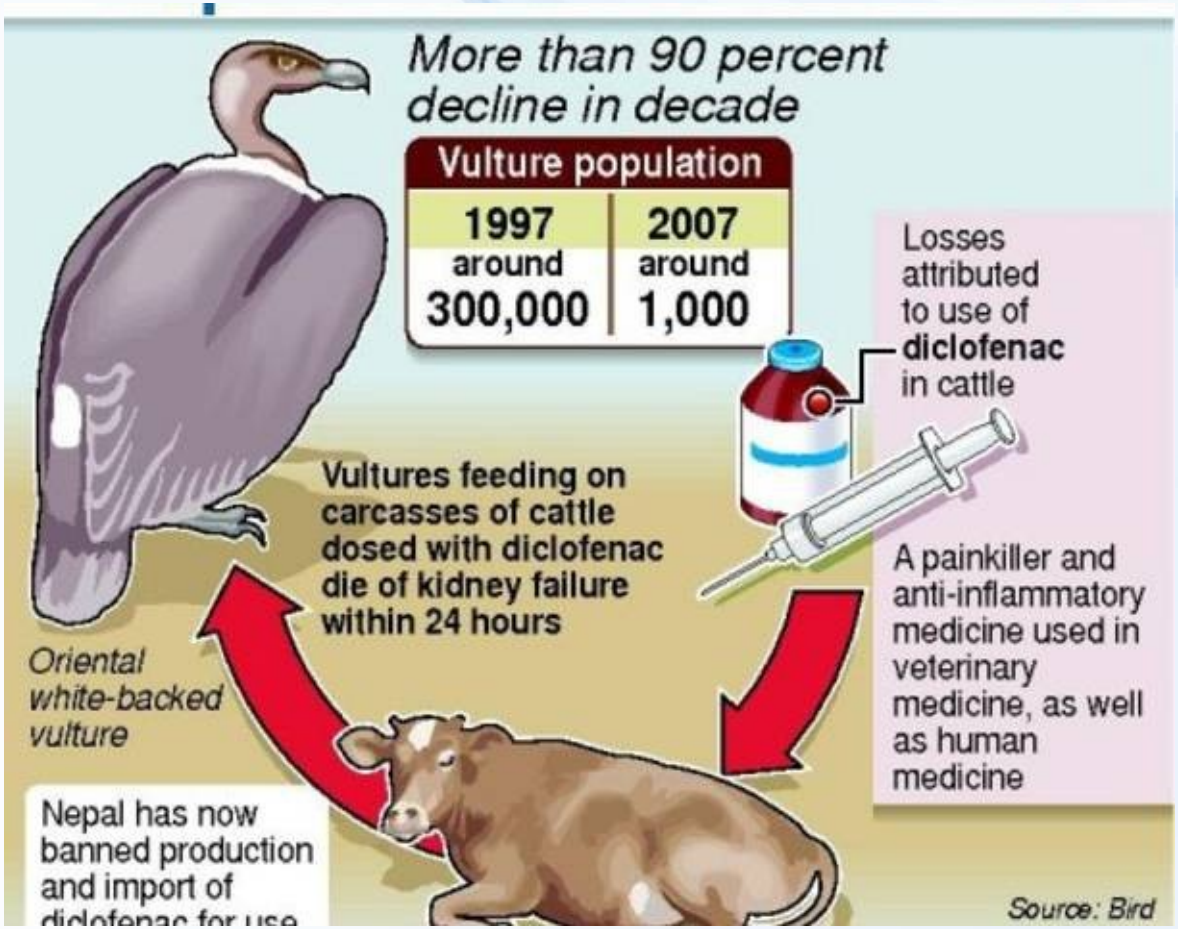
- C**omplex reproduction behaviour** *(birds and mammals)*
- Slower burrying of molluscs into sediments ← fast predation

→ lower fitness and lower reproduction success

NEFROTOXICITY IN VULTURES

- **Damaging effects of veterinary pharmaceuticals on vulture populations**
  - primary effect → kidney in vultures = **nephrotoxicity**

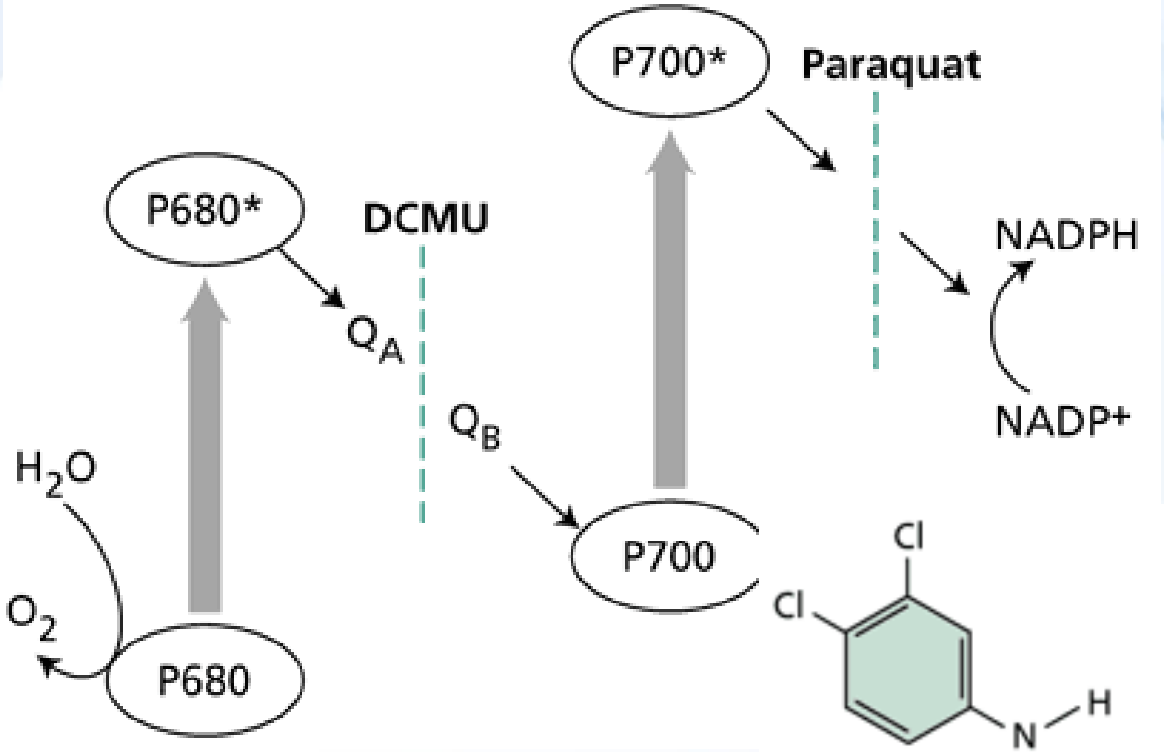




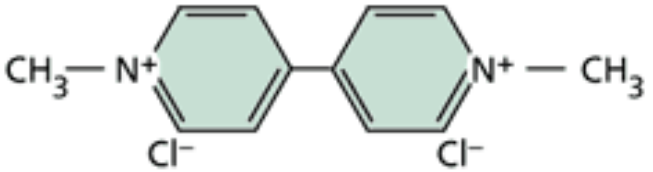
TOXIC EFFECTS TO PRODUCERS (plants, algae)

Unique process of PHOTOSYNTHESIS

Target to many herbicidies – e.g. Diuron (DCMU) and Paraquat



DCMU (diuron)
(Dichlorophenyl-dimethylurea)



Paraquat
(methyl viologen)

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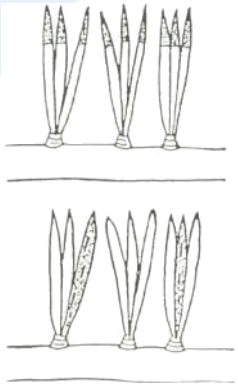
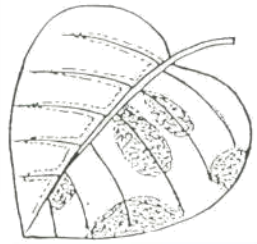
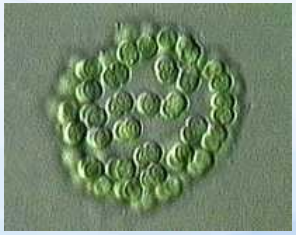
Acute effects in producers

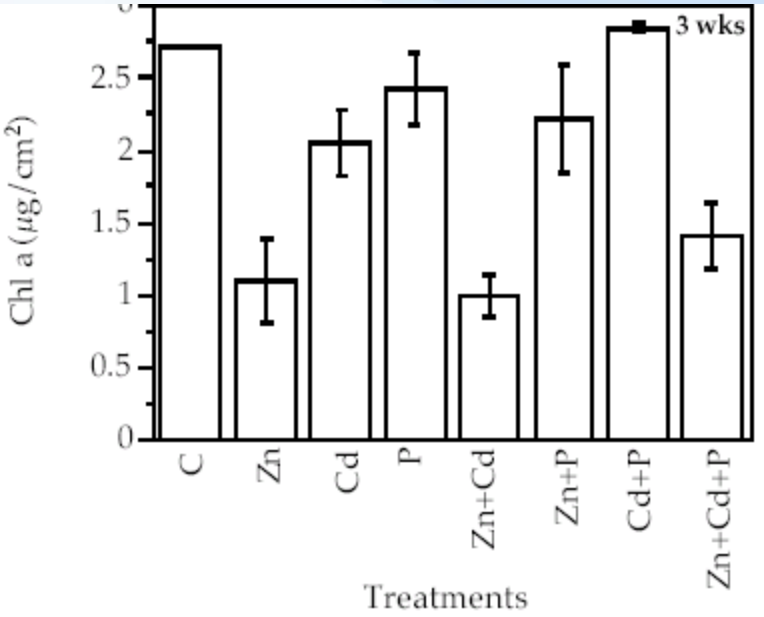
Damage to photosynthetic pigments cell and plant death





Example:
Effects of metals on chlorophyll-a content in algae





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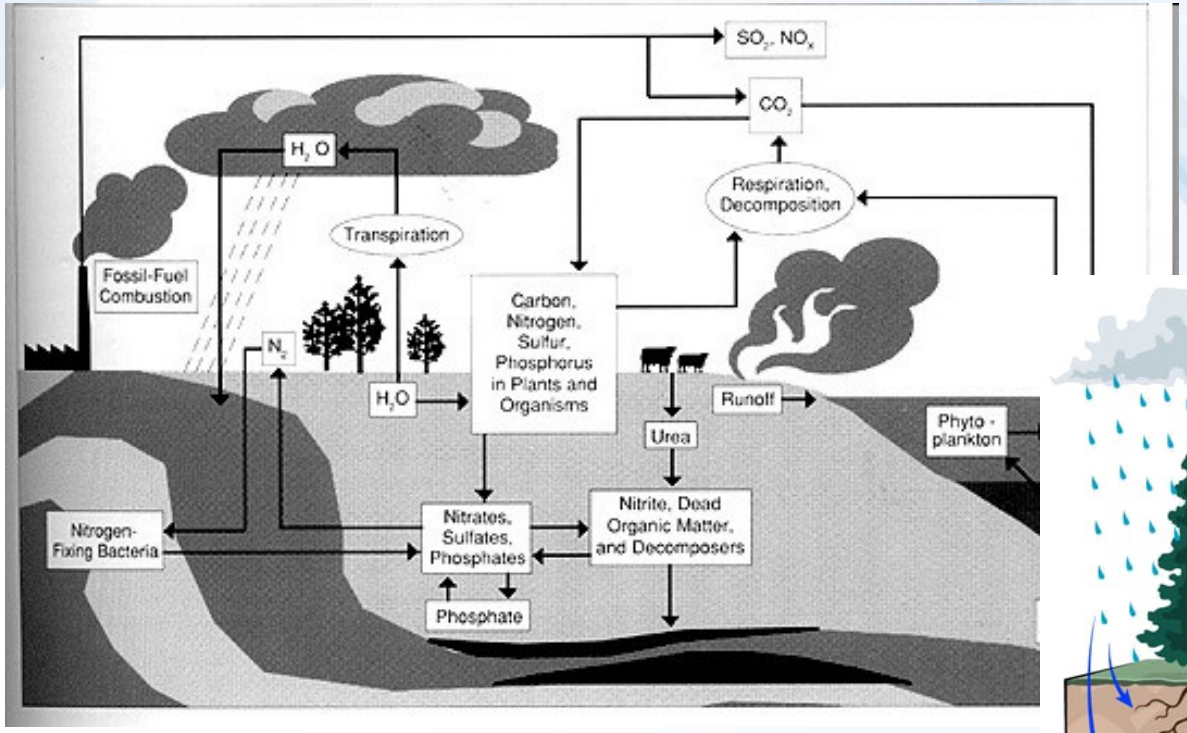
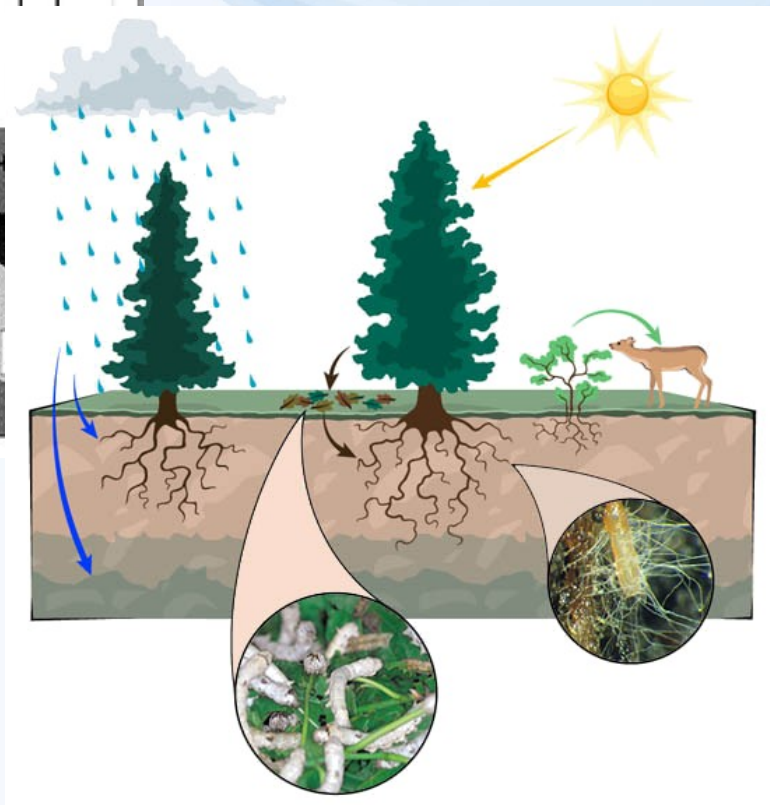
EFFECTS on DECOMPOSERS
bacteria, microorganisms
Key component for global GEO-BIO-CHEMICAL CYCLES





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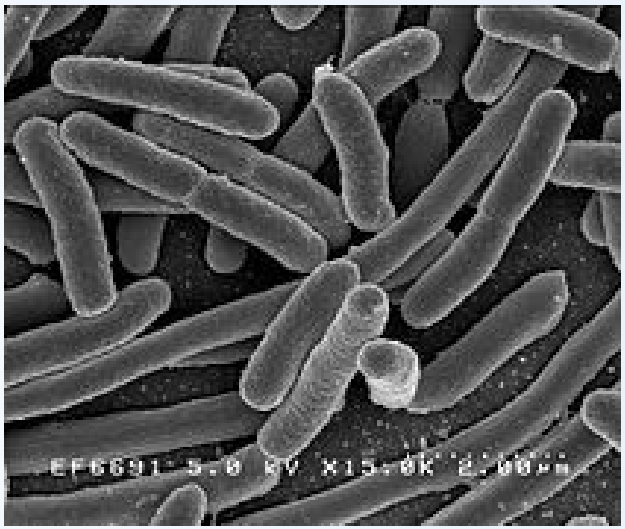
Specific notes on ecotoxicity to microorganisms

1) Unicellular (or small in general)
   large specific surface – easy uptake of chemicals

2) Relativelly good protection (**cell wall**)

3) **Fast division and proliferation**
   - generally good ADAPTATION of populations
   (antimicrobial resistencies)



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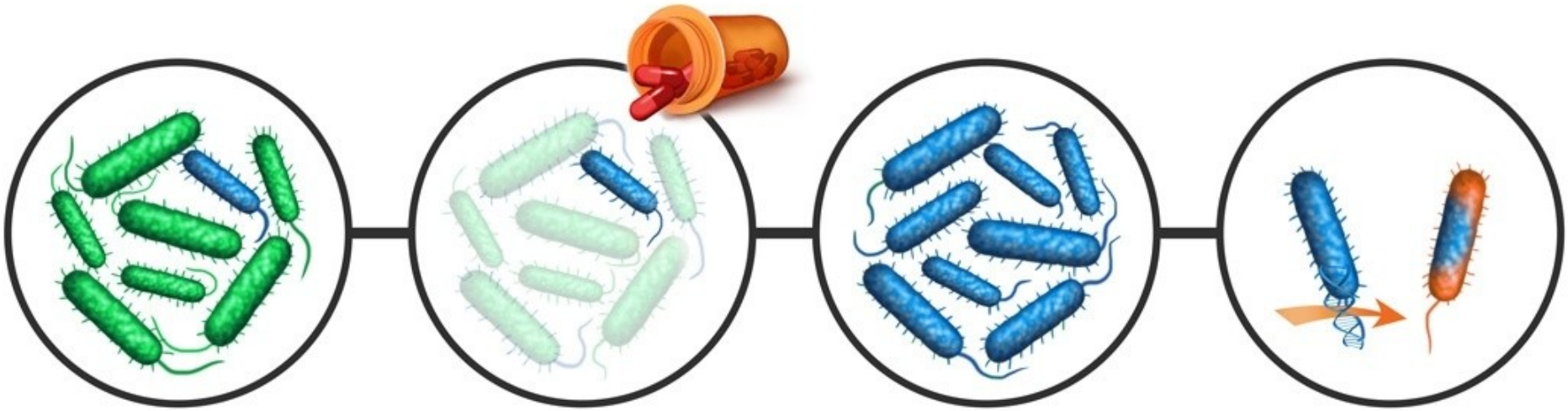
Antibiotic Resistance in Bacteria



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.

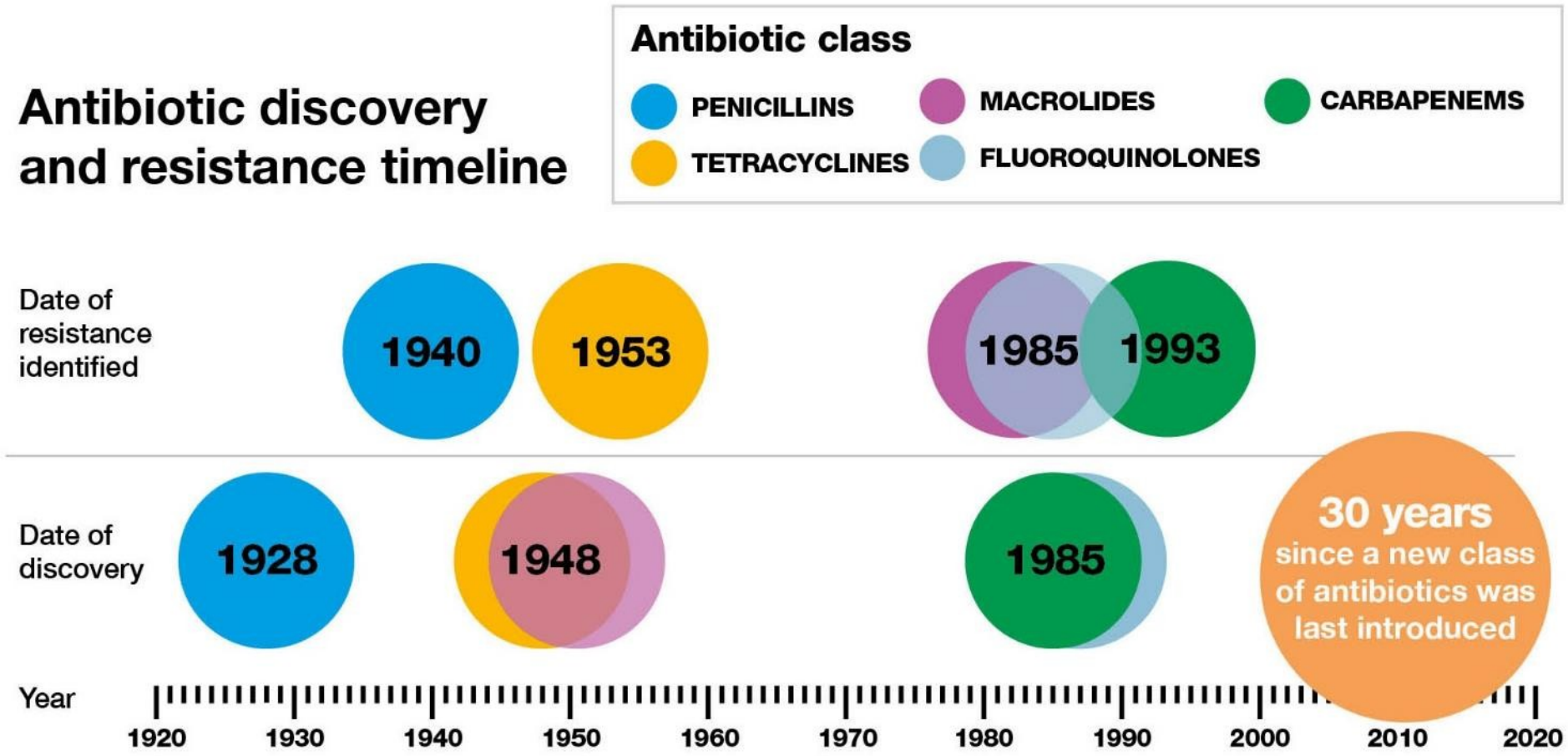
Step 3

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

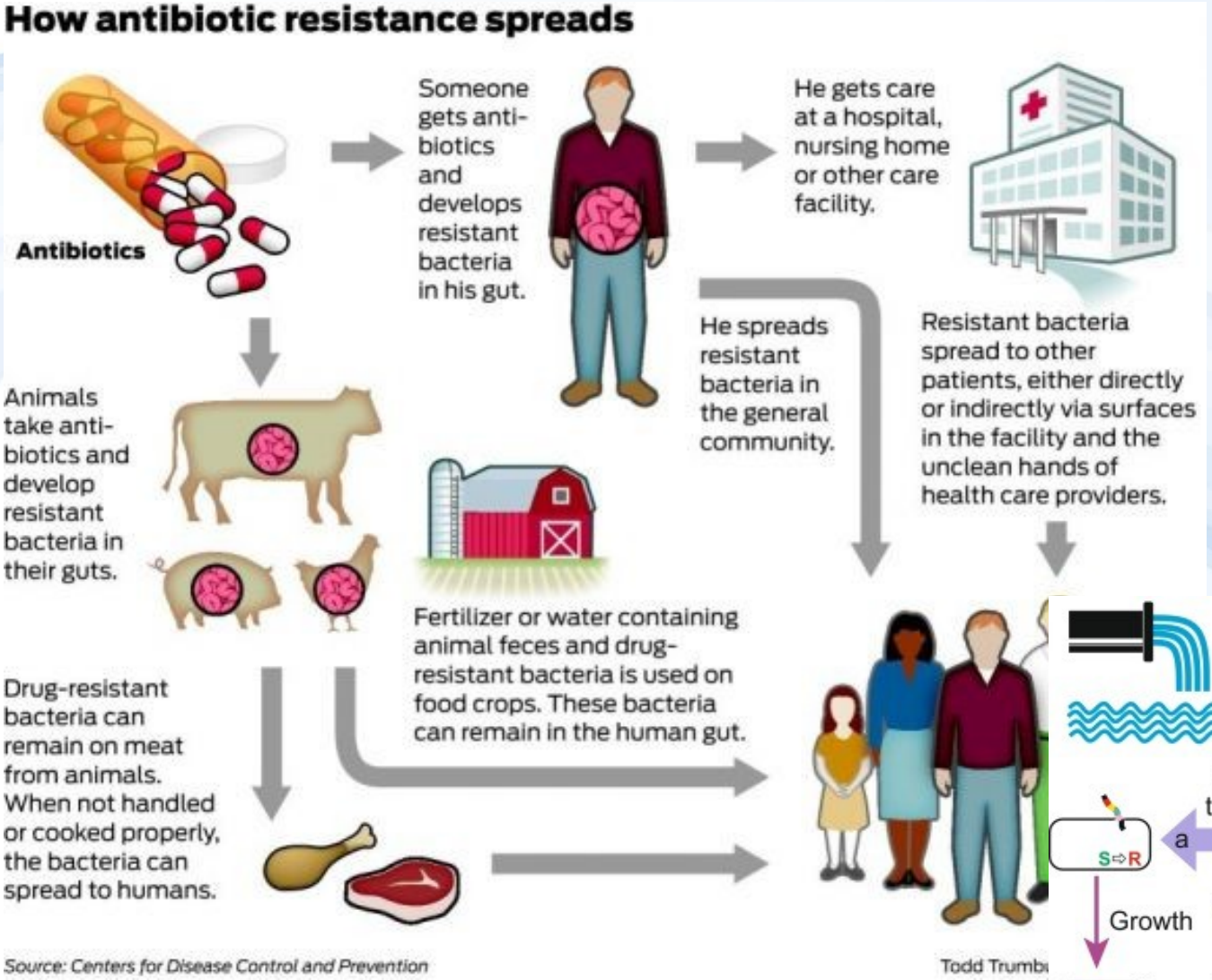
Step 4

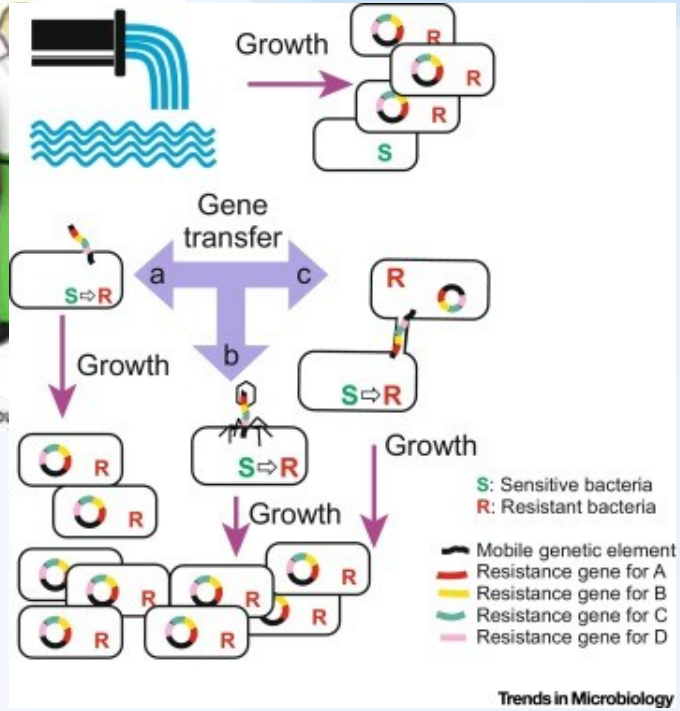
Antibiotic resistant bacteria can transfer their mutation to other bacteria.

Therapeutic antibiotics … and resistance



Centrum pro výzkum toxických látek v prostředí





Spread of ARG *(antibiotic resistence genes)* … also at waste water treatment plants

Centrum pro výzkum toxických látek v prostředí

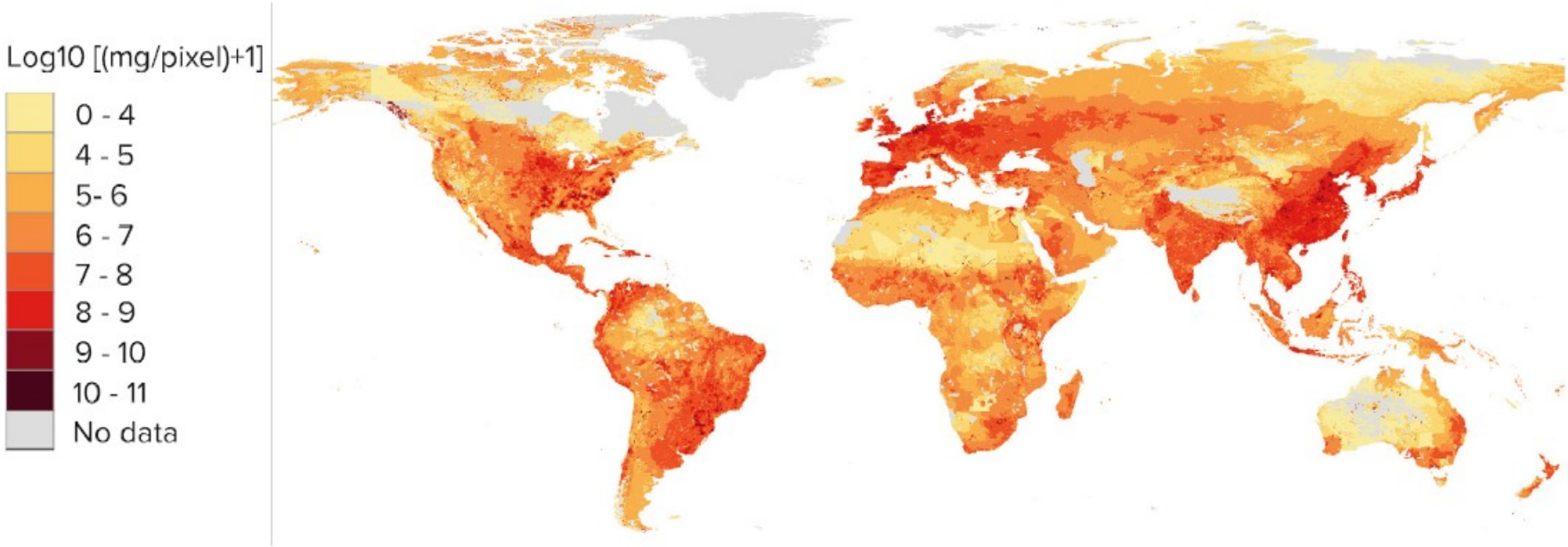
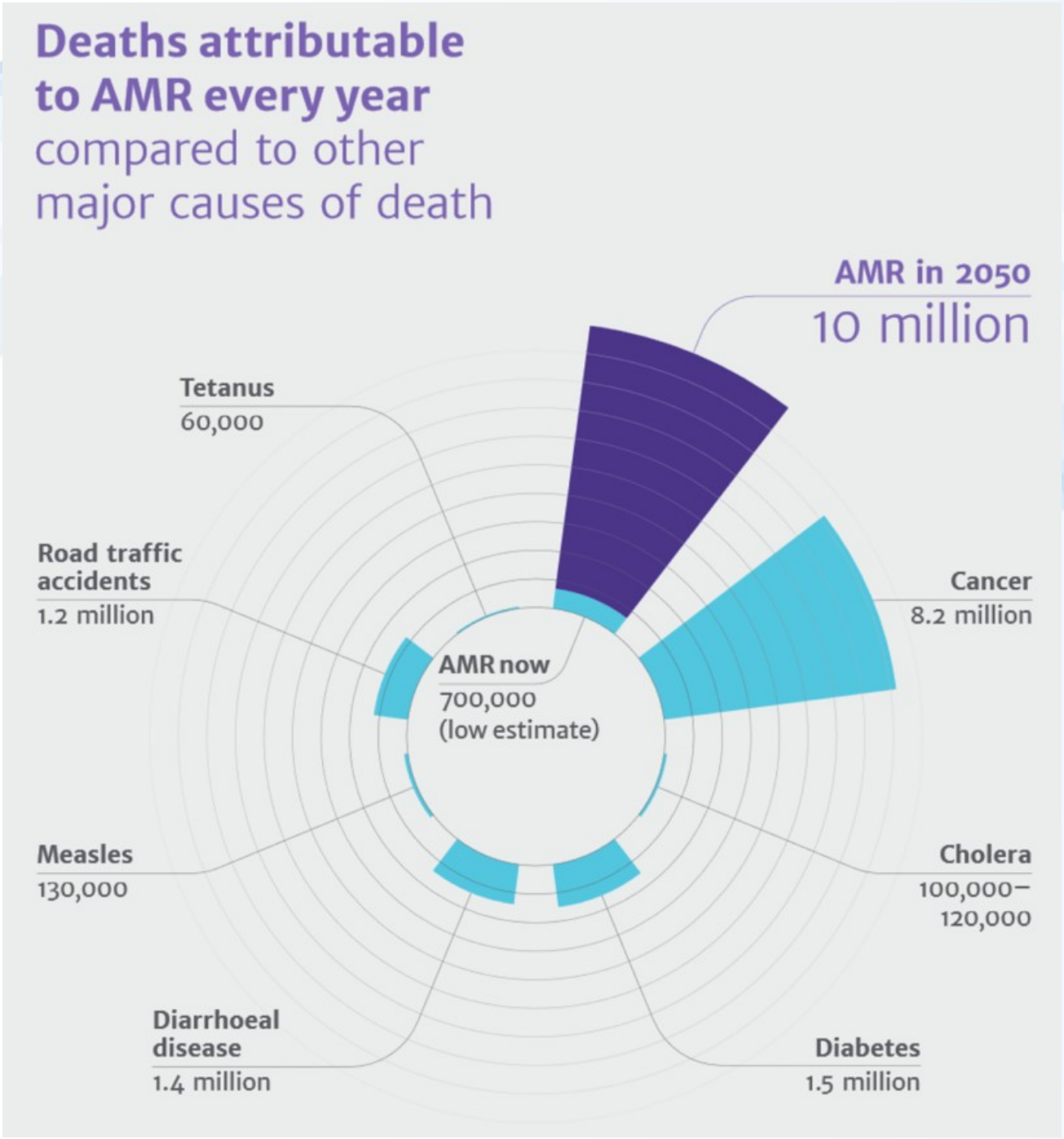


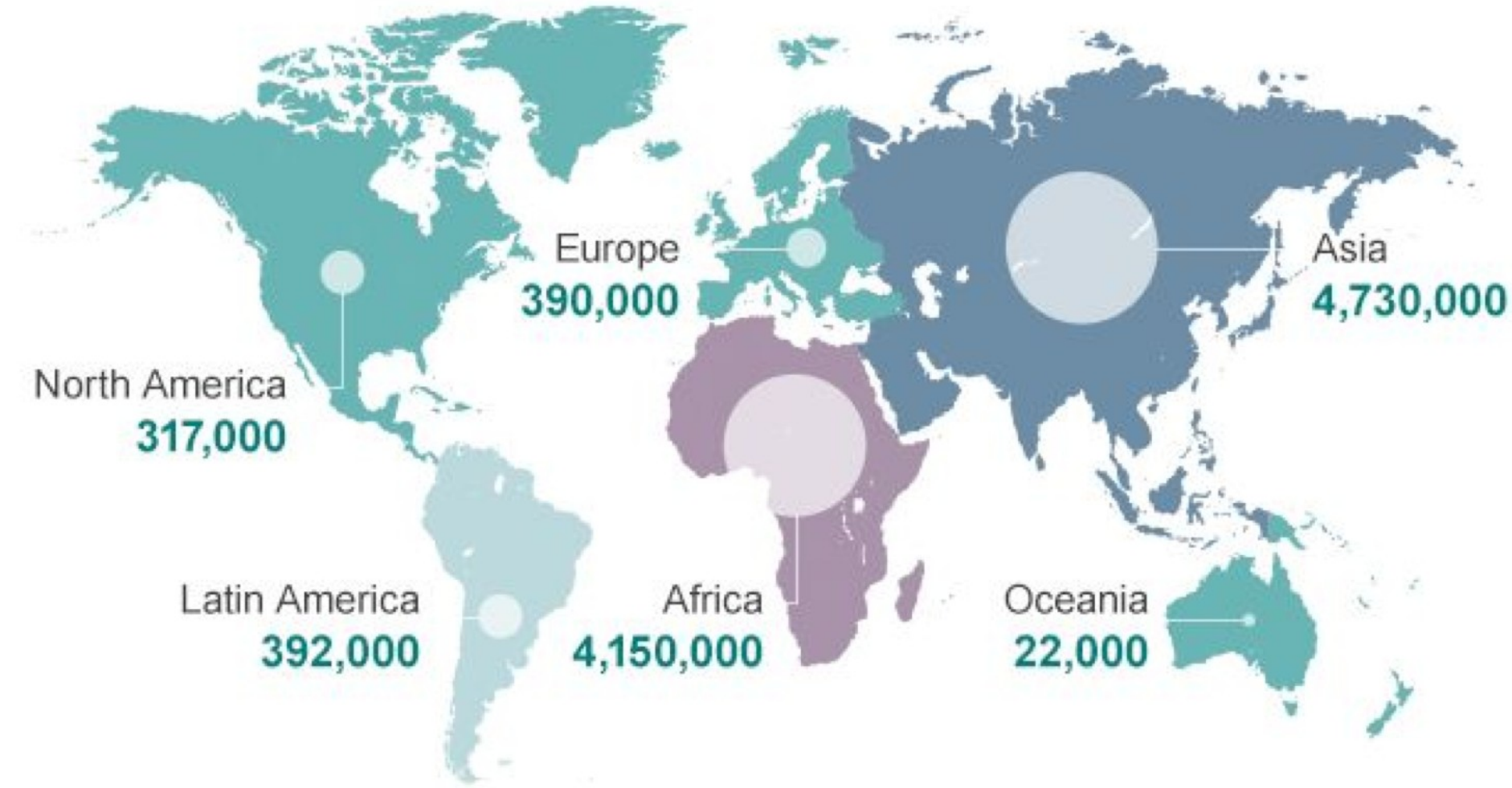
FIGURE 1: Global antibiotic consumption in livestock (milligrams per 10 km² pixels) 2010

Source: Van Boeckel et al. 2015



WHO Report: The Review of Antimicrobial Resistance, Chaired by Jim O'Neil, UK, 2014

Deaths attributable to antimicrobial resistance every year by 2050



Total 10 million deaths per year

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