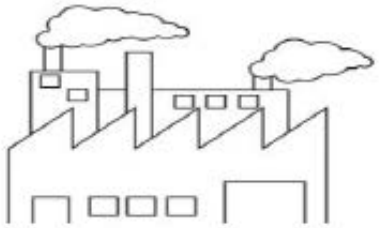
Current issues in ecotoxicology research

Luděk Bláha (blaha@sci.muni.cz)

RECETOX PřF MU

PHARMACEUTICALS



R&D and Manufacturing

Storage Transport

Distribution

Storage Transport

Consumption

Storage Transport

Waste management

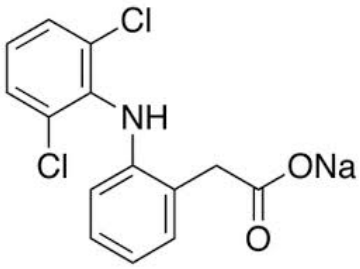
Manufacturing waste

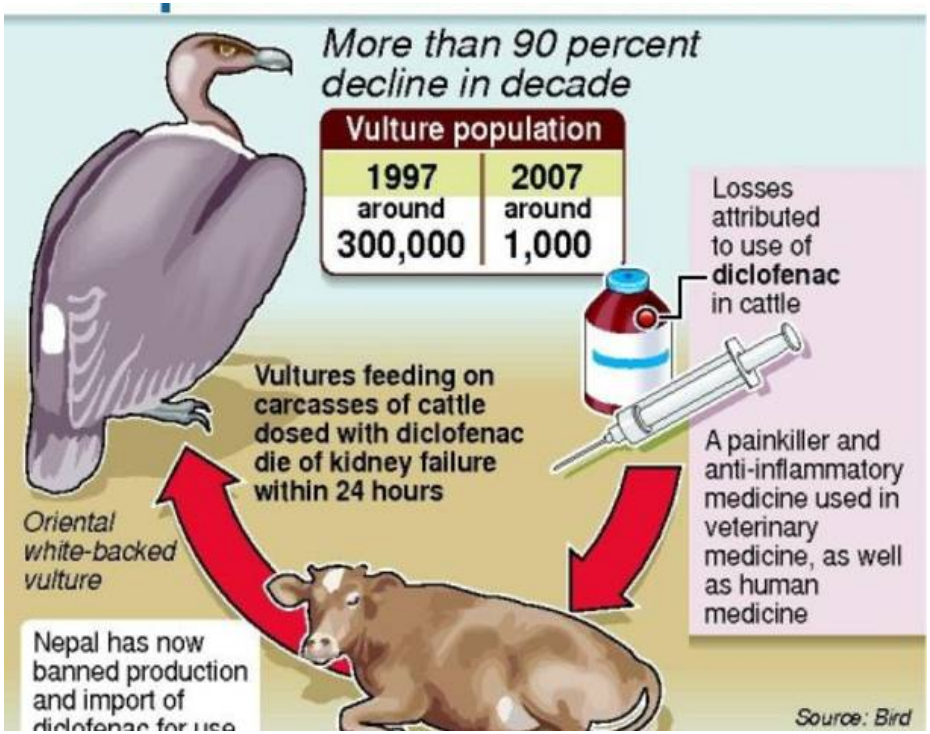
Possible releases to the environment

Example 1 - DICLOFENAC

Unexpected effects at NON-TARGET species

- **nephrotoxicity** at vultures
- Relevant also in EU (ESP, EL,CY)



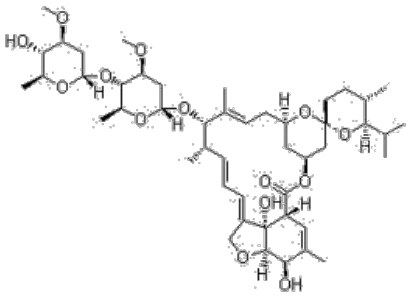


Example 2 – AVERMECTIN-like antiparasitics

Moxidectin – used e.g. in home „spot on" products

Ivermectin – antiparasitics in large herds

- Used **2-times per season** per sheep/cow
- **Kills 100% parasites** in sheep
- Released in dung - **kills 80-90% larvae of dung flies**
- High concentrations in dung (released 2 days post application)
- **Persistent in the soil** (half-life 30 days)
- Can be washed into adjacent streams (highly toxic to water insects)



MIXTURE EFFECTS … VERY LOW CONCENTRATIONS

International ring test (2012-13)

Testing comparability of existing and innovative bioassays for water quality assessment

Main questions:

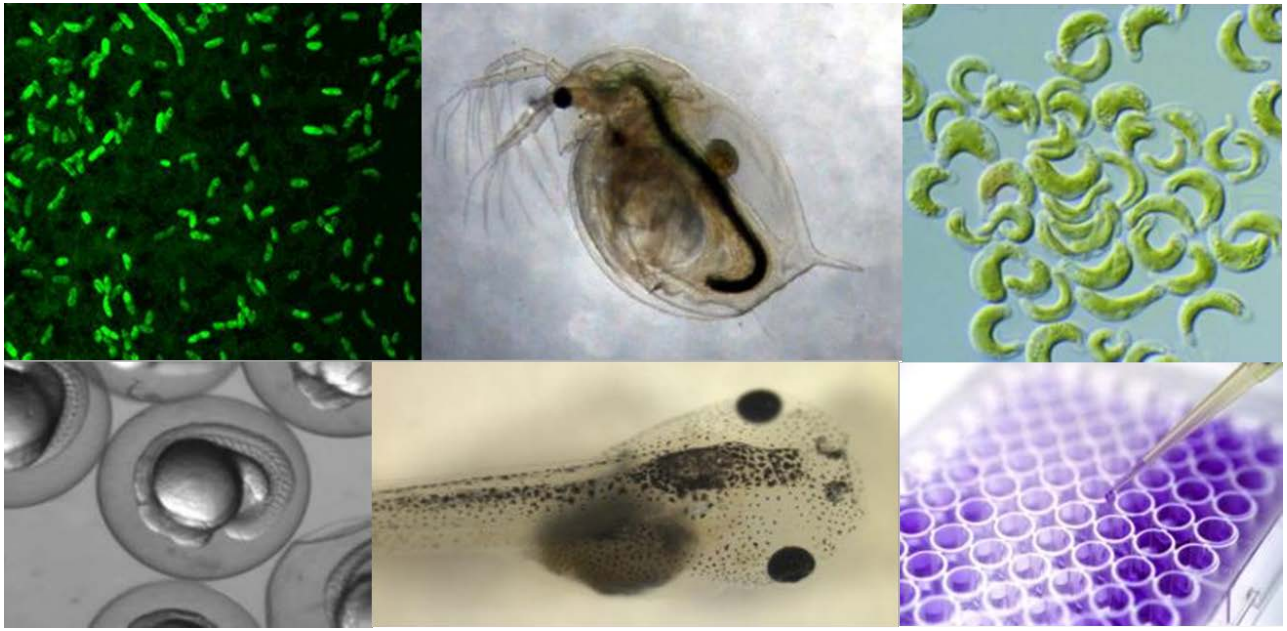
Are current limits (for individual compounds) safe?

Relevance of **"Something from Nothing"** phenomenon ?

3 samples

→ 12 European laboratories – different bioassays

→ ČR – RECETOX: 11 bioassays



Carvalho, R. et al. (2014) Mixtures of chemical pollutants at European legislation safety concentrations: how safe are they? *Toxicol Sci* **141(1): 218-233**

MIXTURE EFFECTS … VERY LOW CONCENTRATIONS

EU WFD priority substances

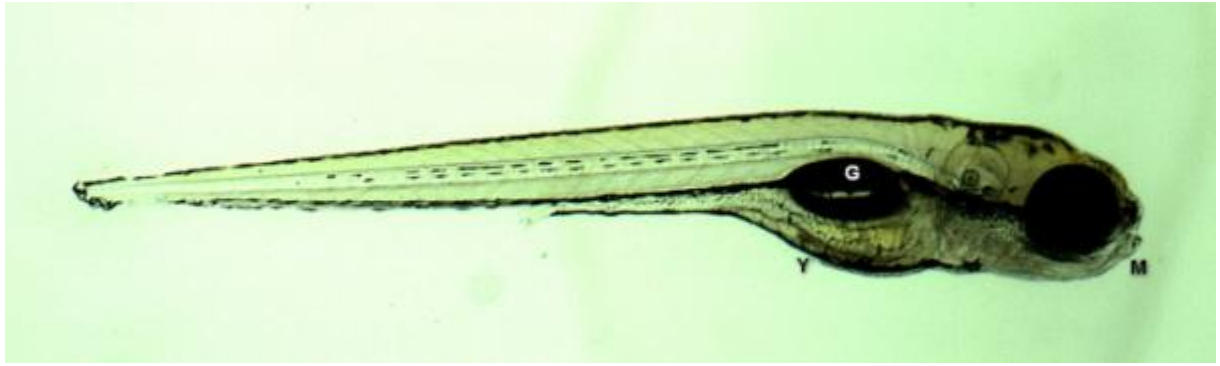
Different concentrations

EQS = limit *(Environmental Quality Standard)*

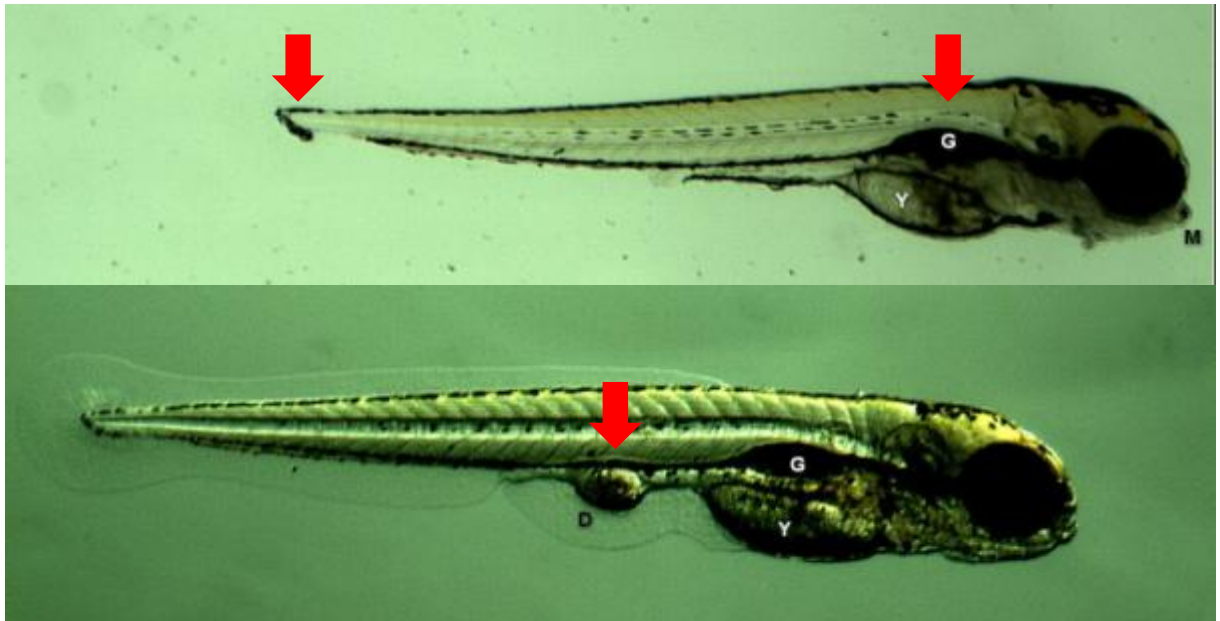
	RM 1[a]	RM 2[a]	RM 3[a]
Priority substances mg/L	around or >EQS	< EQS	< EQS
Atrazine	6	0.6	0.6
BaP	0.0017	0.00017	0.00017
Cadmium[b]	0.8	0.08	0.08
Chlorfenvinphos	1	0.1	0.1
Chlorpyrifos	0.3	0.03	0.03
DEHP (Bis(2-ethylhexyl) phthalate)	13	1.3	1.3
Diclofenac	1	0.1	0.1
diuron	2	0.2	0.2
17beta-estradiol	0.004	0.0004	0.0004
fluoranthene	0.063	0.0063	0.0063
Isoproturon	3	0.3	0.3
Ni[b]	40	4	4
4-Nonylphenol	3	0.3	0.3
Simazine	10	1	1
Carbamazepine	-	-	0.5
Sulfamethoxazole	-	-	0.6
Triclosan (Irgasan)	-	-	0.02
DEET	-	-	41
Bisphenol A	-	-	1.5

MIXTURE EFFECTS … VERY LOW CONCENTRATIONS

Example: Effects of mixtures on *D. rerio* fish embryos



Control

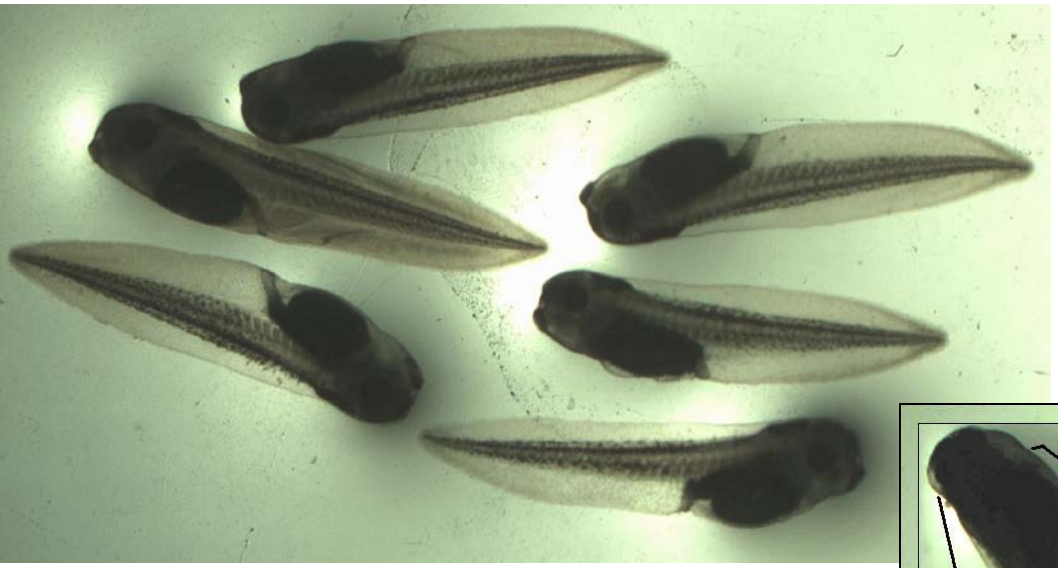


Effects of RM 3 (i.e. safe) mixtures

Carvalho, R. et al. (2014) Mixtures of chemical pollutants at European legislation safety concentrations: how safe are they? *Toxicol Sci* **141(1): 218-233**

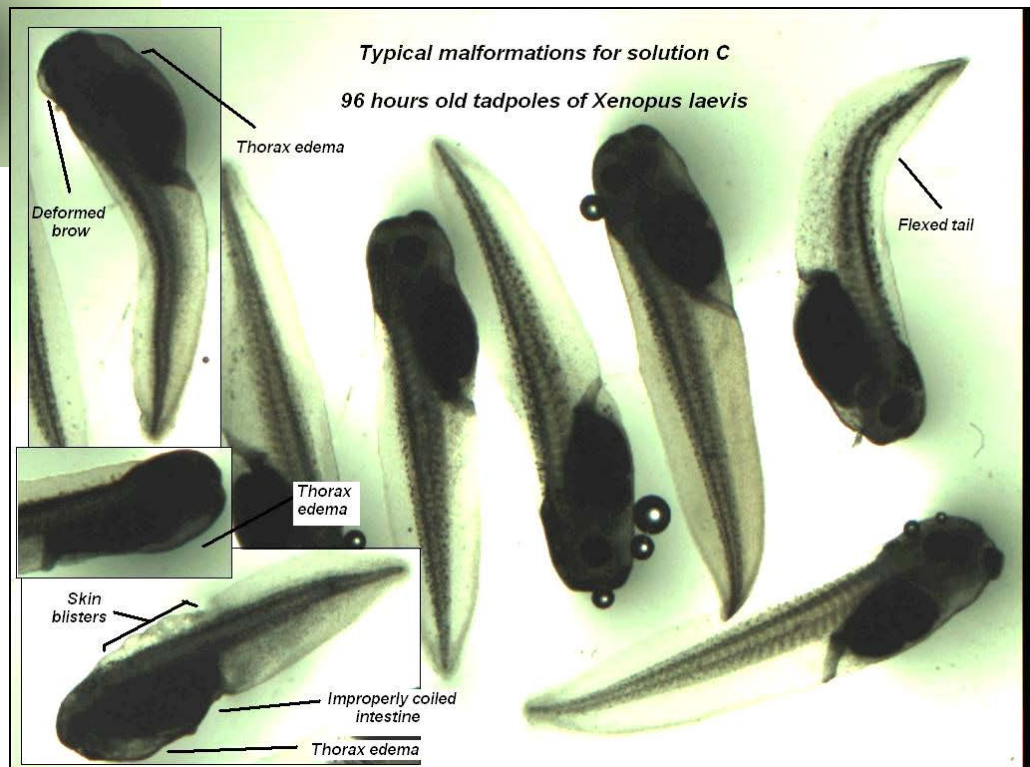
MIXTURE EFFECTS … VERY LOW CONCENTRATIONS

Example: Effects of mixtures on *X. laevis* frog embryos



Controls

Effects of RM 3 (i.e. safe) mixtures



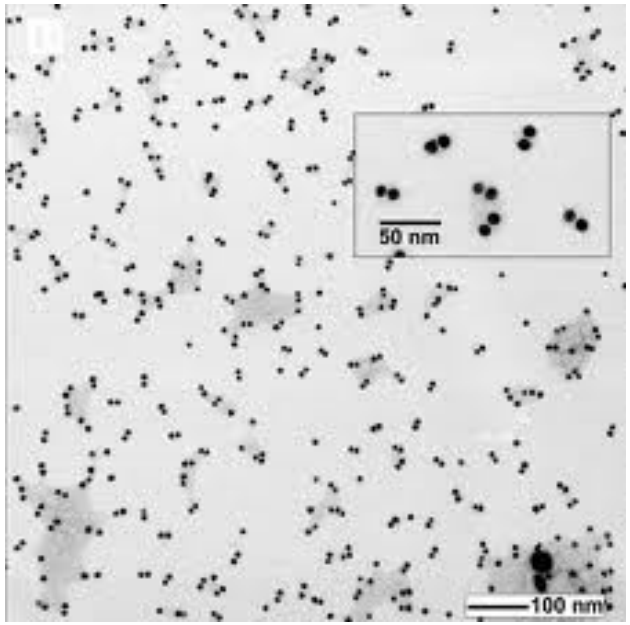
Carvalho, R. et al. (2014) Mixtures of chemical pollutants at European legislation safety concentrations: how safe are they? *Toxicol Sci* **141(1): 218-233**

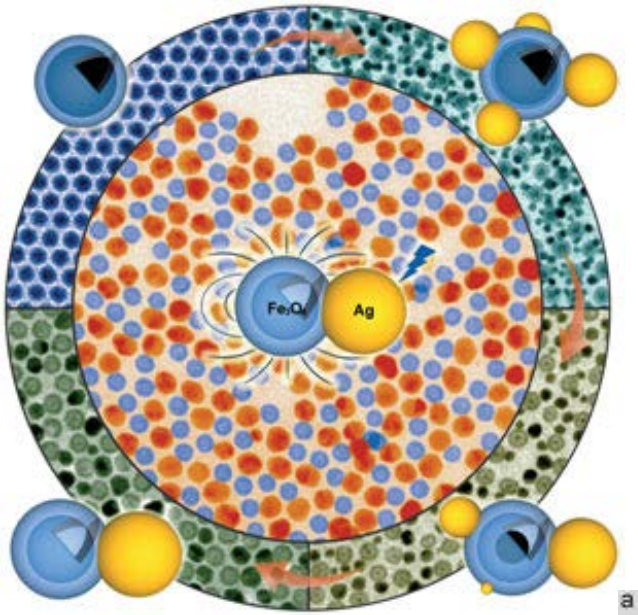
Biotest	A	B	C
Microtox	26 and 36% stimulation of luminescence in 15 and 30 mins of exposure, respectively	18 and 35% stimulation of luminescence in 15 and 30 mins of exposure, respectively	22 and 39% stimulation of luminescence in 15 and 30 mins of exposure, respectively
Algae growth inhibition test 96-h exposure	31% inhibition of growth compared to solvent control	20% inhibition of growth compared to solvent control	16% inhibition of growth compared to solvent control
Acute immobilization test with *D. magna*	90% immobilization after 48 hours of exposure; 25% immobilization occurred in 50% concentration - not statistically significant	no effect observed	no effect observed
Reproduction test with *D. magna* (21-d exposure)	100% mortality after 3 days of the test, no reproduction could be evaluated	31 +/- 37 % inhibition of reproduction, not statistically significant	23 +/- 24 % inhibition of reproduction, not statistically significant
FETAX (96-h exposure)	62 +/- 10 % of malformed embryos; no effect on embryo length observed	43 +/- 12 % of malformed embryos; no effect on embryo length observed	34 +/- 14 % of malformed embryos; no effect on embryo length observed
FET (120-h exposure)	effects observed in number of defected embryos - absence of gas bladder, (head) deformities and underdeveloped embryos were observed the most often.	no significant effects observed	effects observed in number of defected embryos, number of underdeveloped embryos and length
In vitro - cytotoxicity	no effect observed compared to solvent control	no effect observed compared to solvent control	no effect observed compared to solvent control
In vitro - estrogenicity	effect under LOQ	effect under LOQ	effect under LOQ
In vitro - dioxin-like toxicity	effect under LOQ	effect under LOQ	effect under LOQ
In vitro - androgenicity	effect under LOQ	effect under LOQ	effect under LOQ
In vitro - antiandrogenicity	effect under LOQ	effect under LOQ	effect under LOQ

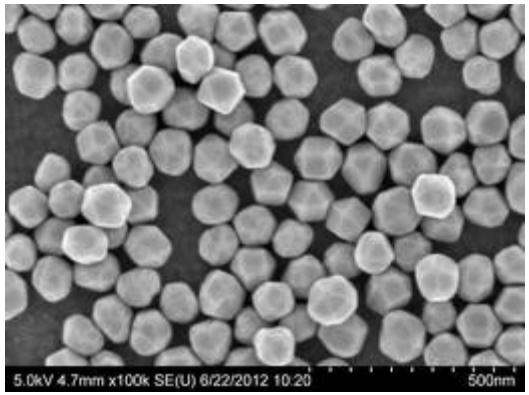
Kde „tradiční“ ekotoxikologie nestačí

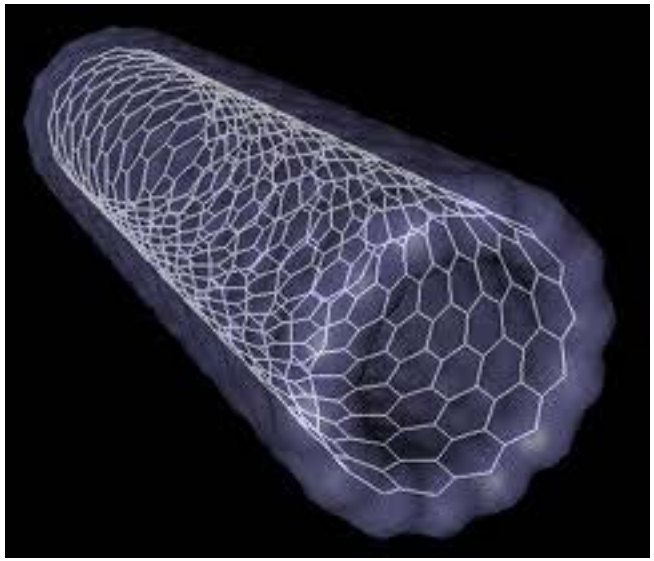
Nano-eco-toxicology

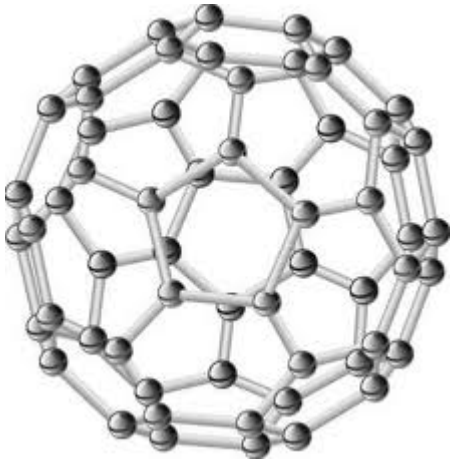
Nanoparticles - examples

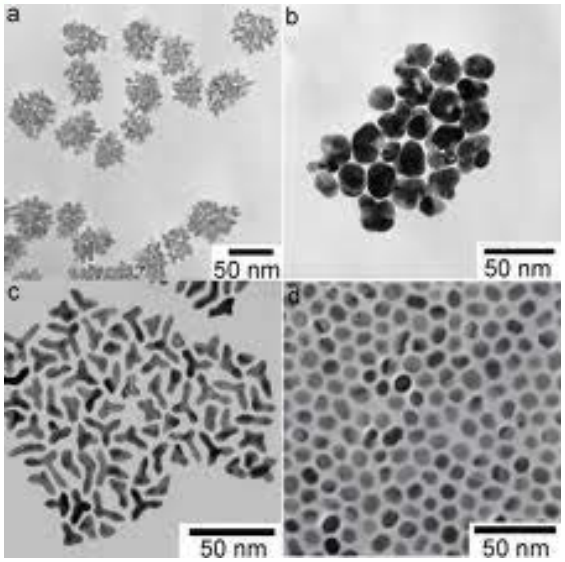












Nanoparticle movement through the environment

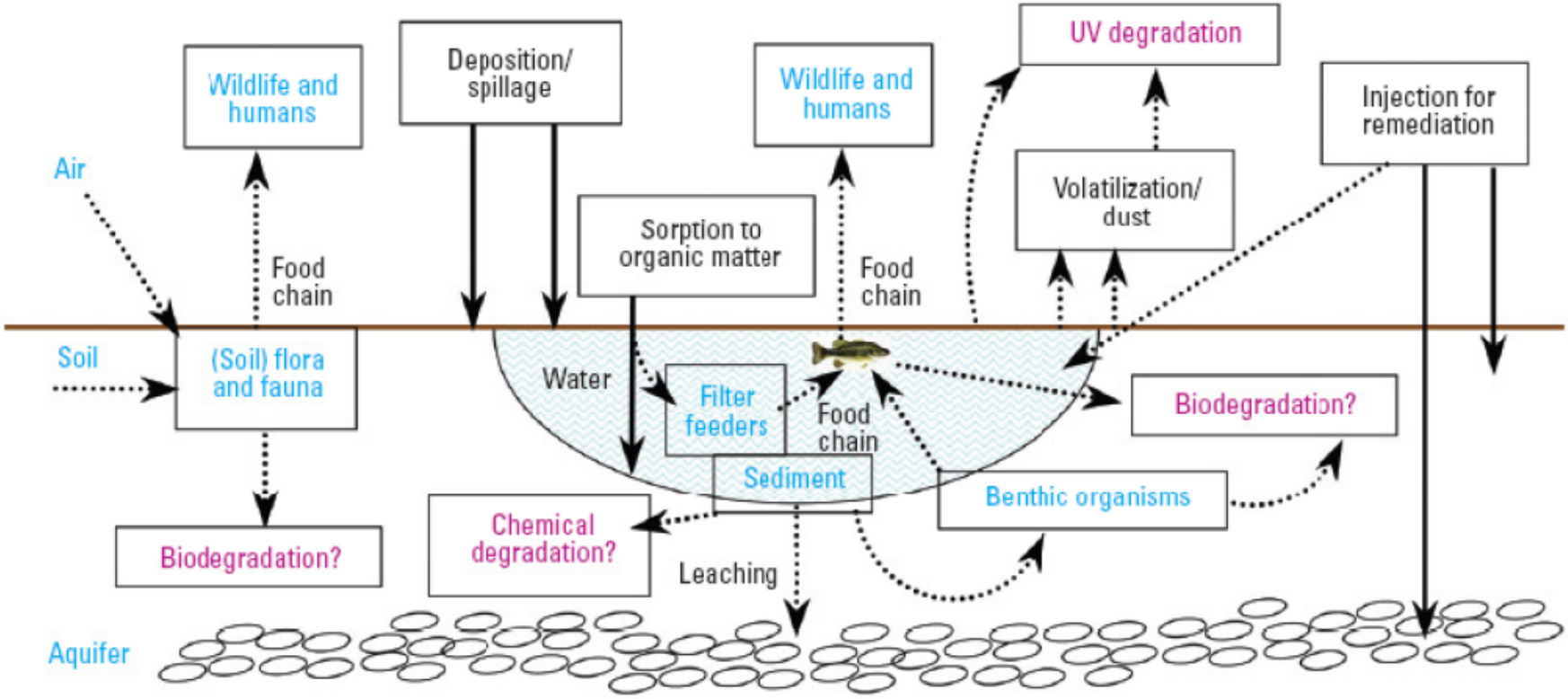
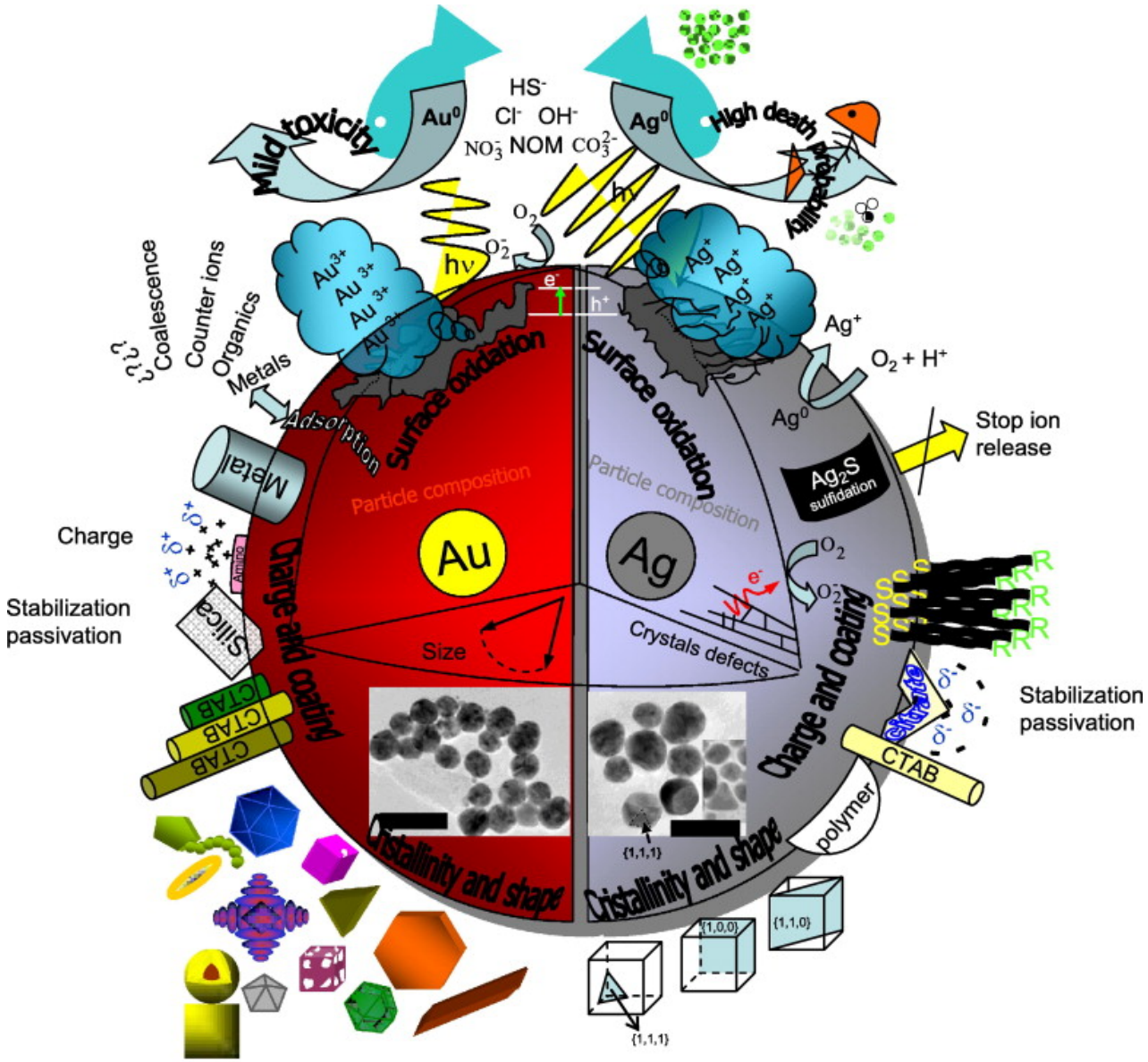


Figure 5. Routes of exposure, uptake, distribution, and degradation of NSPs in the environment. Solid lines indicate routes that have been demonstrated in the laboratory or field or that are currently in use (remediation). Magenta lettering indicates possible degradation routes, and blue lettering indicates possible sinks and sources of NSPs.

Ecotoxicity of nanoparticles …



(Mostly unknown) Parameters may Affect ecotoxicity

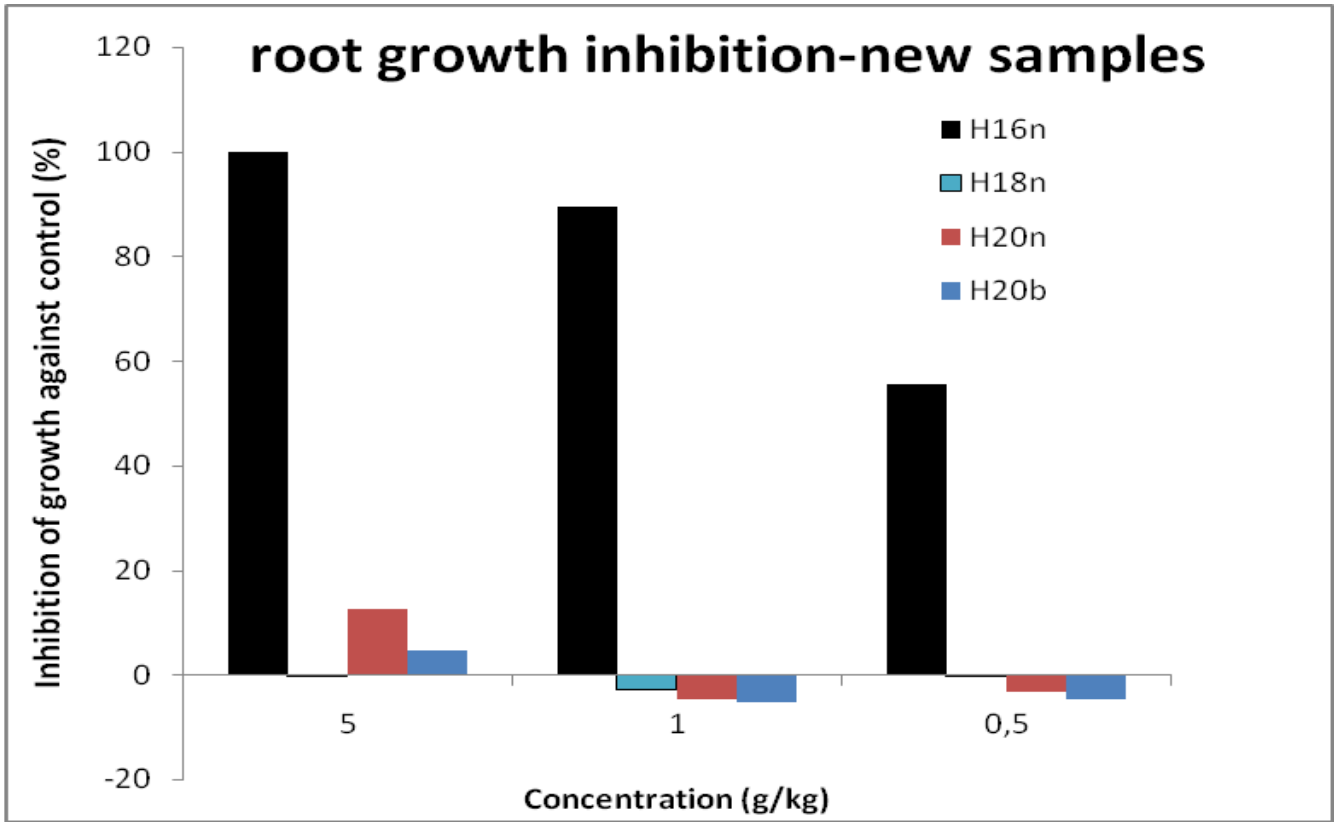
Composition (chemical)
Surface (size, area)
Charge
Reactivity
Interactions with ions, other chemicals…

➔ Effects on environmental Fate and toxicity

Ecotoxicity of nanoparticles – RECETOX example

Comparison of toxicity - 4 „appeared to be the same“ particles
(one producer – 4 different lots)
(zerovalent iron – ZVI – Fe^0)

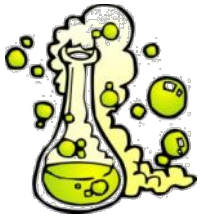
?? Why is H16 so toxic ??



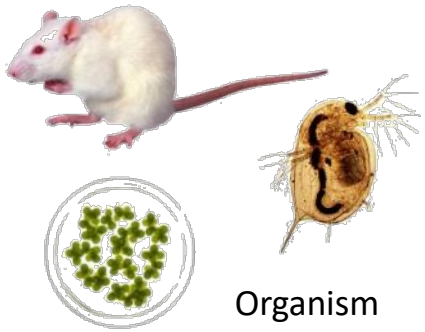
Mechanistic and Computational (ECO)TOXICOLOGY

Hazard assessment

Traditionally – Evaluation of adverse effects using the whole organism models



Chemical

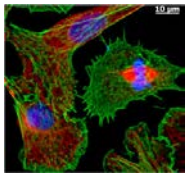


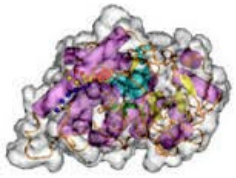
Organism

Adverse Effects
Death
Altered Reproduction
Inhibition of Growth

Tumorigenicity
Skin irritation
…

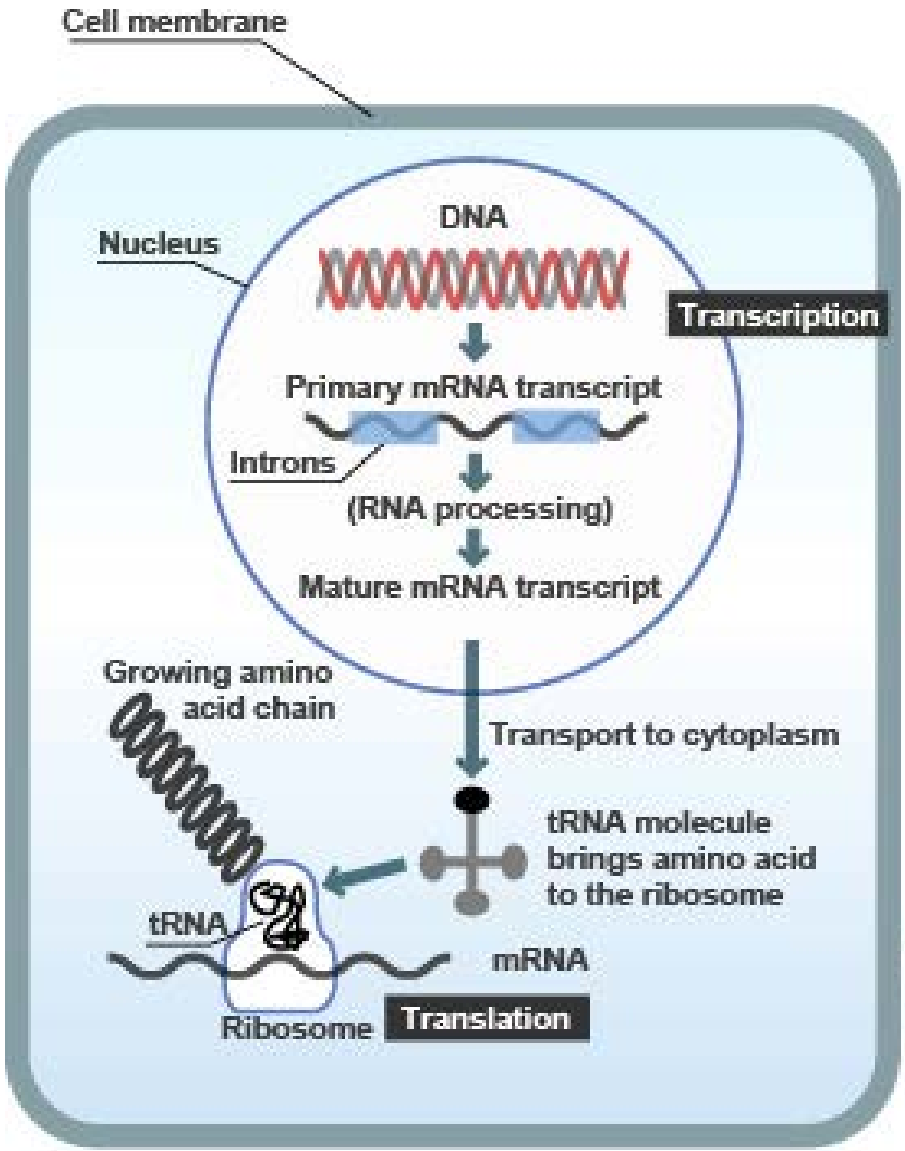
REGULATORY FOCUS
(APICAL ENDPOINTS)

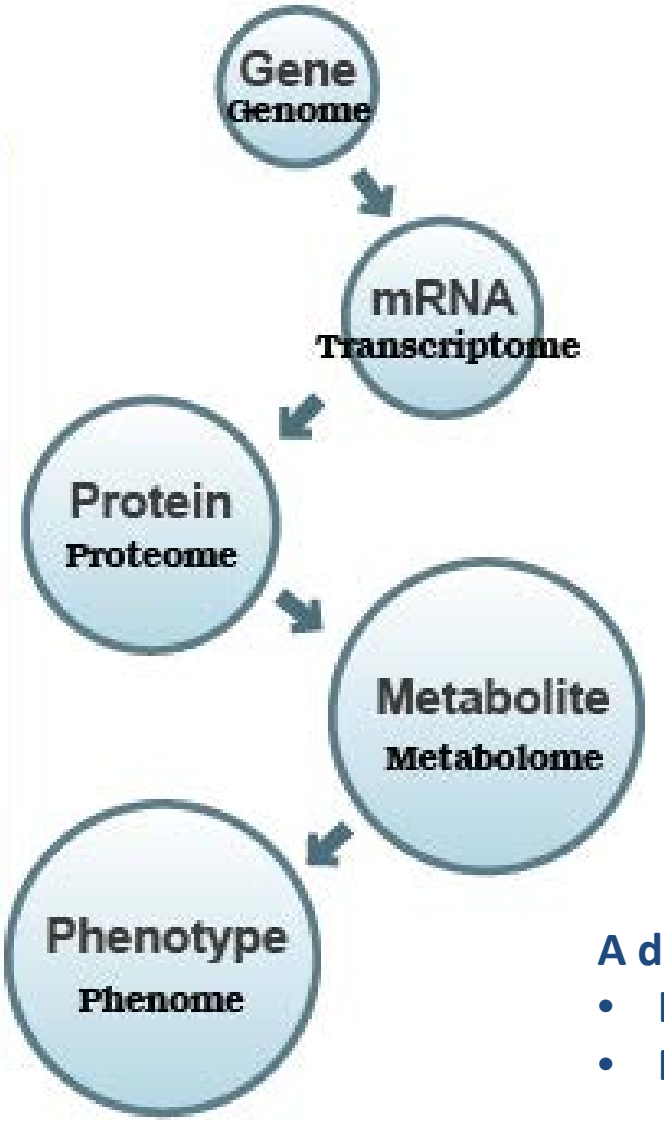




Newly added aspects
What are the mechanisms (MoA – mode of action)?
Can mechanisms serve for predictions?

Extrémní rozvoj analytických technologií → „OMICS“



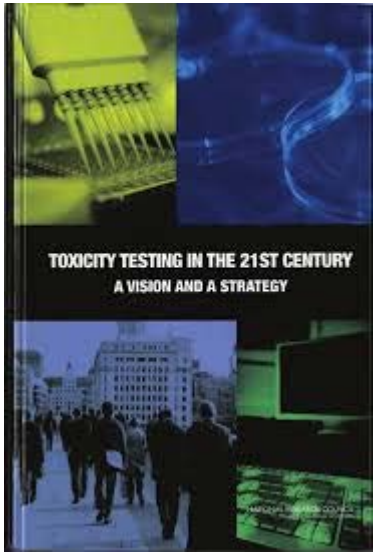


A další „ómy“

- **Lipidóm**
- **Mikrobiom …**

Sběr omics podporují strategické dokumenty & projekty

Toxicity Testing in the 21st Century: A Vision and a Strategy
US National Academies of Sciences
http://www.nap.edu/catalog/11970.html



EPA United States Environmental Protection Agency

LEARN THE ISSUES | SCIENCE & TECHNOLOGY | LAWS & REGULATIONS | ABOUT E

Computational Toxicology Research

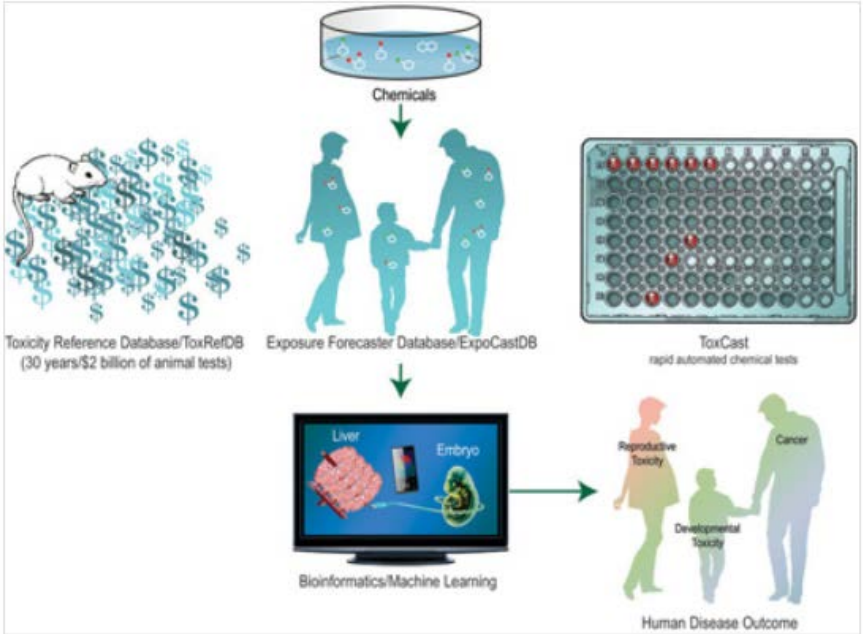
You are here: EPA Home » Research & Development » CompTox » ToxCast™

Key Links

CompTox Home | Research Projects
Basic Information | Chemical Databases
Organization | CompTox Events

ToxCast™

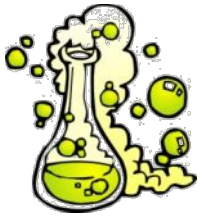
Screening Chemicals to Predict Toxicity Faster and Better



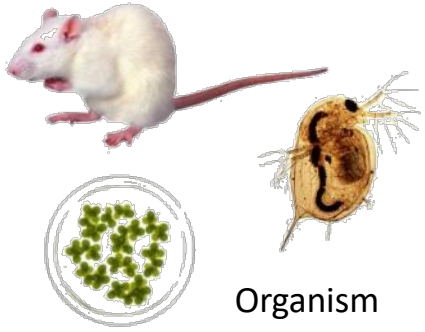
How ToxCast Fits Into CompTox Research

Hazard assessment

Traditionally – Evaluation of adverse effects using the whole organism models



Chemical

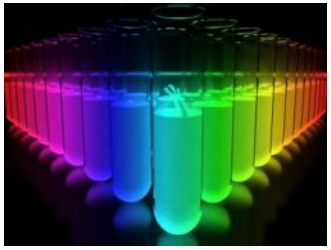


Organism

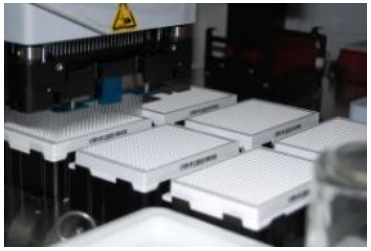
Adverse Effects (EC50)

Death
Inhibition of Growth
Altered Reproduction
Tumor
Skin irritation
.

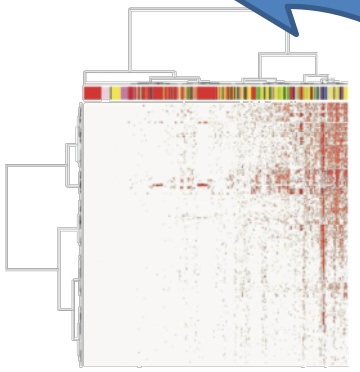
New – Ex vivo / in vitro / In chemico / In silico Methods



10^4 Chemicals



HTS



Chemical-biological interactions, Mechanistic Toxicological Data

Key task/question:

How to link MECHANISTIC INFORMATION with APICAL ENDPOINTS ?

Kvantitativní mechanistické modelování

plos.org create account sign in

PLOS | COMPUTATIONAL BIOLOGY

Browse Publish About Search

advanced search

OPEN ACCESS PEER-REVIEWED

RESEARCH ARTICLE

A Computational Model of the Rainbow Trout Hypothalamus-Pituitary-Ovary-Liver Axis

Kendall Gillies, Stephen M. Krone, James J. Nagler, Irvin R. Schultz

Published: April 20, 2016 • https://doi.org/10.1371/journal.pcbi.1004874

4 Save | 1 Citation | 1,656 View | 4 Share

Article Authors Metrics Comments Related Content

Download PDF Print Share

Abstract
Author Summary
Introduction
Methods

Abstract

Reproduction in fishes and other vertebrates represents the timely coordination of many endocrine factors that culminate in the production of mature, viable gametes. In recent years

Check for updates

Subject Areas

PLoS Comput Biol. 2016 Apr 20;12(4):e1004874.

Kvantitativní mechanistické modelování

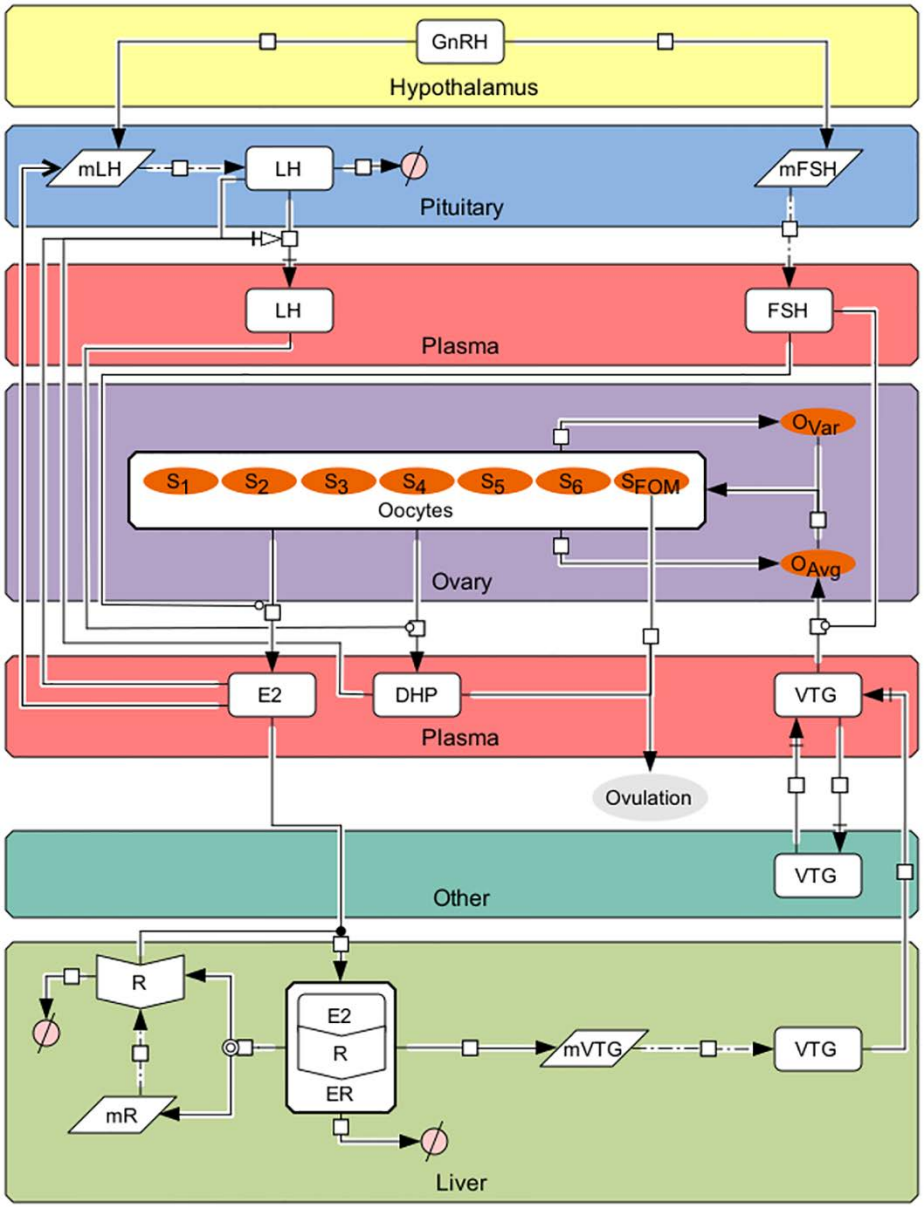


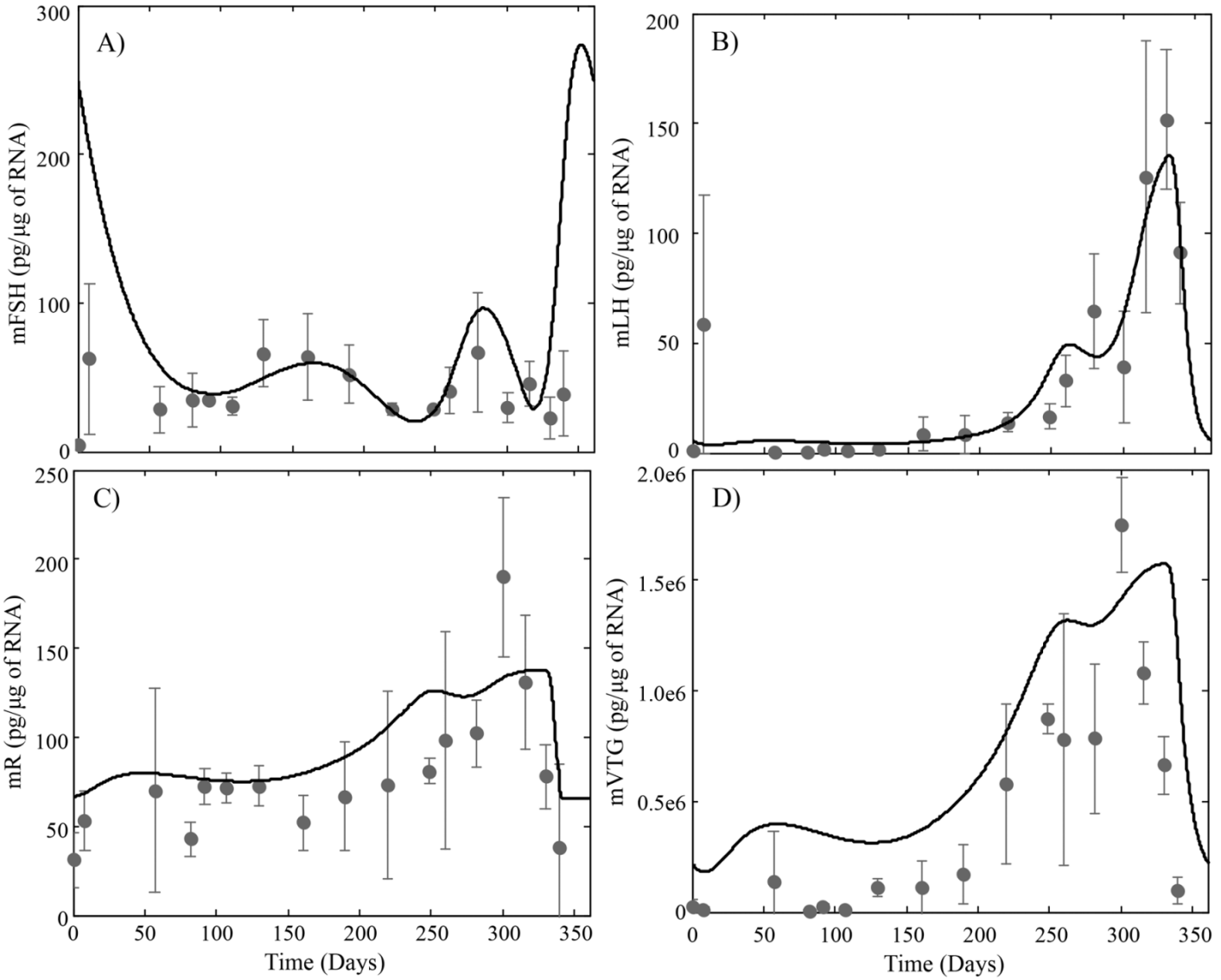
Fig 1. The HPOL signaling network in rainbow trout as formulated in our model.

Arrows and symbols on graph follow CellDesigner vs. 4.4 notation (www.celldesigner.org). GnRH is secreted from the hypothalamus into the pituitary stimulating the production of mFSH and mLH, which then leads to formation of FSH and LH, respectively. FSH, which is being continuously secreted from the pituitary, travels to the ovaries to stimulate production of E2. E2 then travels to the liver to bind with E2 receptors (R; translated from mR) to form ER. ER then stimulates the production of mVTG, which produces VTG_L. Secreted VTG then travels from the liver to the ovaries via the plasma (VTG_P) where it is absorbed by follicles in stages 3 through 6 (the proportion of follicles in these stages are denoted by S_j, j = 3, 4, 5, and 6) during vitellogenesis, the rate of which is affected by FSH_P, to promote oocyte growth (O_{Avg}). Oocyte growth then progresses the oocytes through the stages using a Weibull distribution created from O_{Avg} together with O_{Var}. In the later stages LH_P stimulates the oocytes to produce DHP. Finally, oocytes undergo final maturation (S_{FOM}) and combined with DHP, determine when the fish ovulates

PLoS Comput Biol. 2016 Apr 20;12(4):e1004874.

Kvantitativní mechanistické modelování

Fig 3. HPOL **model predictions** for (A) pituitary levels of FSH_β subunit mRNA, (B) pituitary levels of LH_β subunit mRNA, (C) Hepatic levels of E2 receptor mRNA and (D) Hepatic levels of VTG mRNA
Observed data (dark grey circles; mean ±TG mR*n* = 3)



PLoS Comput Biol. 2016 Apr 20;12(4):e1004874.