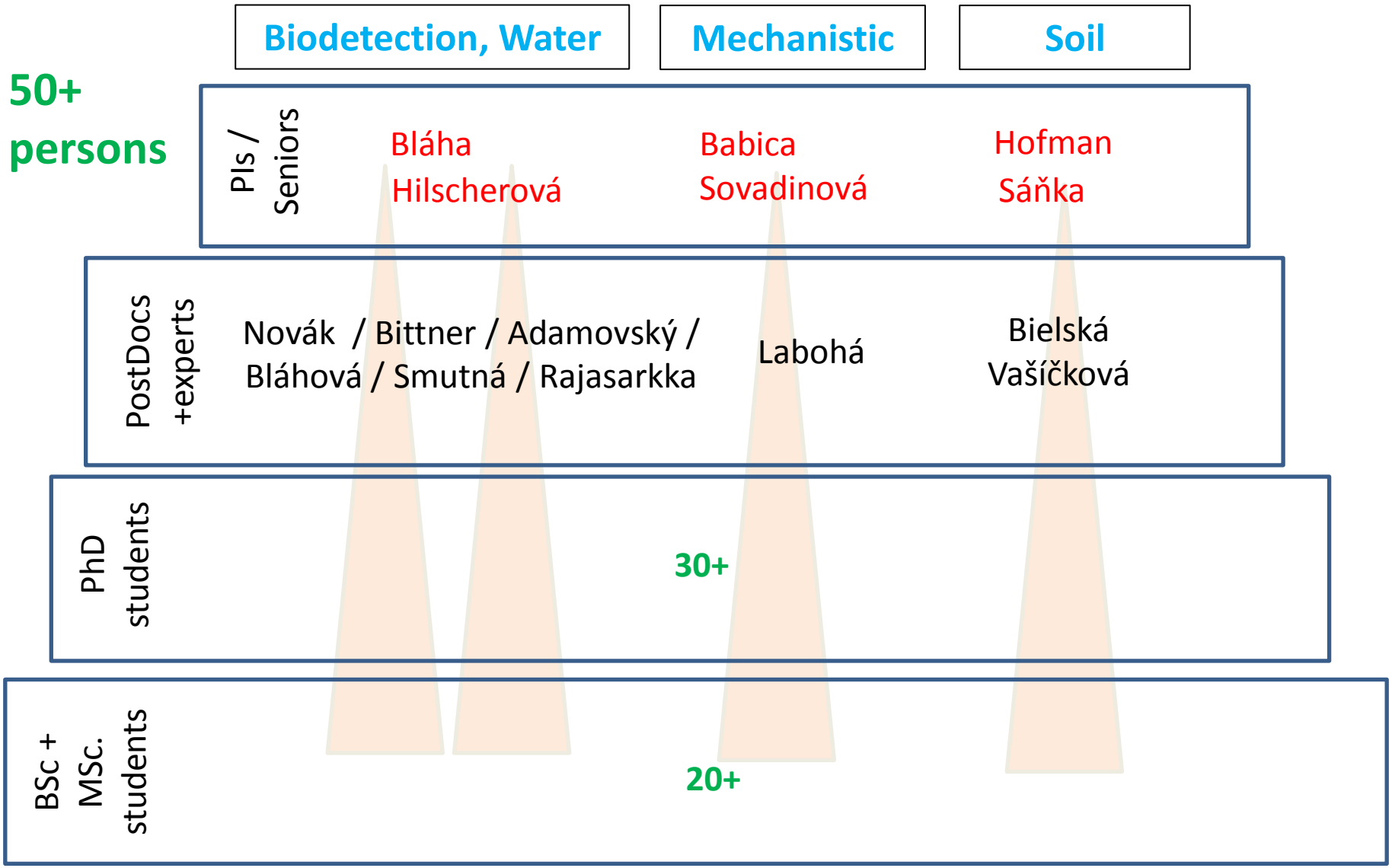
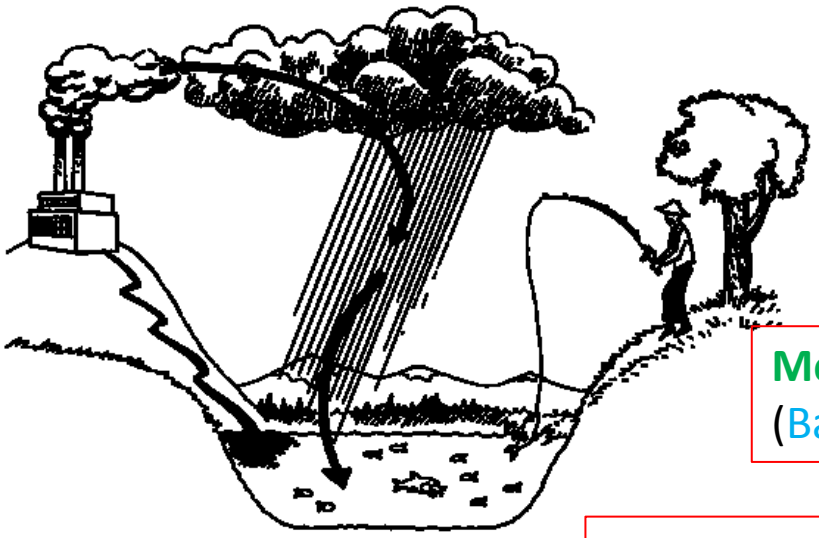
RESEARCH CENTRE
FOR TOXIC COMPOUNDS
IN THE ENVIRONMENT (RECETOX)

Ecotoxicology at MUNI RECETOX



Ecotoxicology - areas and research questions



Effect-based tools
in vitro and in vivo
(Hilscherová, Bláha)

Mechanistic toxicology
(Babica, Sovadinova)

Biomarkers *in vivo*
(Hilscherová, Bláha)

Cyanobacterial blooms and their envi- and health risks
(Hilscherová, Bláha, Babica)

Focus today 2016-11-03

Envi technologies and risk assessment
(Bittner, Bláha, Babica)

Soil ecotoxicology and environmental chemistry (Hofman et al)

Effect-based tools (EBTs) (KH, LB)

Funding: FP7 Solutions, GACR KH, GACR MS, TACR JK, NPU (proposals GACR GL, GACR JK)

- **AOP (MoA)-based set of assays** (**bioanalytical detectors *in vitro***) - toxic potencies of complex samples and individual compounds
- **In vivo battery of aquatic models** (bacteria, algae, invertebrates, fish embryo, frog embryo)

- Effect-directed analysis (**EDA**) and targeted **mixture** effect investigations
- Linked to detailed advanced chemical analyses – target indicated by bioassay, non-target for identification of unknowns (RECETOX, cooperation UFZ, EAWAG)

- Ready-to use assays (immobilized cells/biosensors) fast ready-to-use versions with high long-term stability and fast response

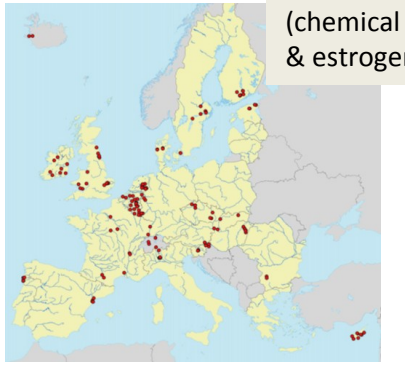
Aquatic environment

- Mixture effects (contributions of natural and anthropogenic chems), emerging pollutants
- **AOPs -** Relation of *in vitro* to *in vivo* effects – mechanistic studies
  - e.g. retinoids in early development and neurotoxicity (fish and frog embryos)
- EBTs applications with passive sampling (dosing)

Assessment of mixtures relevant for human exposure

- Outdoor air and indoor samples
  – focus on emerging pollutants
- Mixtures from food exposure

Pan-EU monitoring (chemical & estrogenicity)



Biomarkers *in vivo* (KH, LB)

Funding: NPU, RMU, HBM4EU

HPLC/MS/MS and biochemical techniques

– optimized towards minimal sample consumption

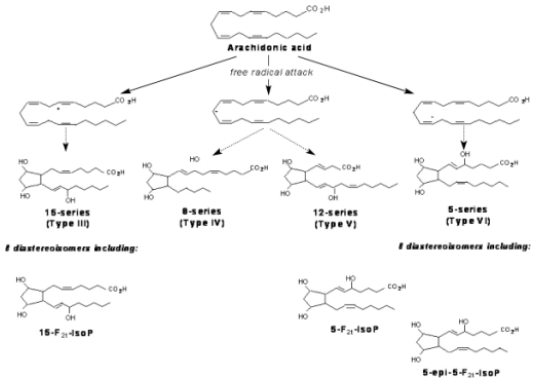
- e.g. GSH/GSSG, OH-dG, lipids (isoprostanes, MDA)

Previous studies

– cyanobacterial and multistressor exposure to aquatic organisms

(sublethal endpoints in in vivo studies – collaborations with Veterinary U)

- collaboration – effects of **inhalation exposure to nanoparticles**

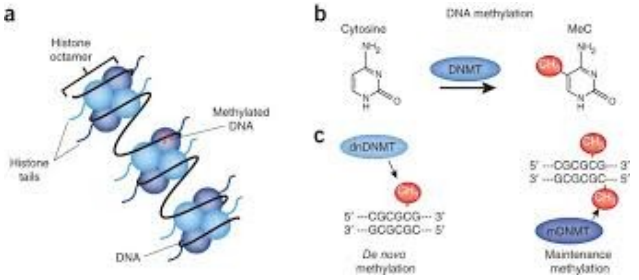


Gene expressions –effects on specific pathways (towards **AOP** key events)

- e.g thyroid-related genes, estrogen-related genes, retinoid-related genes
- **moving towards *omics* profiling**

Epigenetics

- Cellomics - phenotype/functional responses
- DNA-methylations of specific target genes
- Applications – in vivo: human cohort study, ecotox models
  - in vitro: mechanistic investigations



Cyanobacterial blooms
and their envi- and health risks (KH, LB, PB)

Funding: GACR KH, GACR MS, GACR LB/PB, GACR OA

One point of view:

Focus on environment, character of pollution in reservoirs and ponds

- Toxicity/sublethal effects of the individual bioactive metabolites produced by organisms from water blooms and their mixtures to affected organisms
- Co-occurrence with other contaminants – possible interactions in effects

Another point of view:

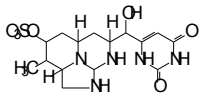
Identification of new bioactive molecules

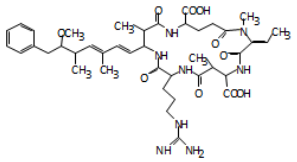
- Production of bioactive secondary metabolites by different species
- Identification through EDA

In Vitro MoA Toxicology

- New targets and mechanisms of well-recognized toxins (MCs, CYN, cyanoLPS)
  - Immunotoxicity
    - Effects on **MΦ**
    - 1x postdoc, 1x PhD, GACR postdoc, collab. w/ IBP ASCR
  - Effects on **TLR & Intestinal cells**
    - 1x postdoc, collab. w/ IBP ASCR, GACR proposal pending
  - Effects on **neuronal cells**
    - human iNSC, collab. w/ Prof. Kang, Seoul Natl U
    - MCSA proposal in preparation
- Understudied but relevant organs & tissues
  - Testicular cells, lung cells, kidney (future projects)

Environmental occurrence & fate, biotransformation





Mechanistic toxicology (PB, IS)

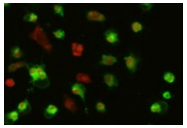
- **Increasing relevance of in vitro models**
  - •Non-cancer cell lines (**stem cells**) –> GJIC capable
  - •Microenvironment –> **3D cultures**, co-cultures
- **Effects of chemicals on tissue homeostasis**
  - •Proliferation, Cell survival (Apoptosis/Necrosis), Differentiation, In Vitro Neoplastic Transformation
  - • Gap junctional intercellular communication, nongenomic signaling
  - • The role of progenitor and stem cells in (toxico)pathologies

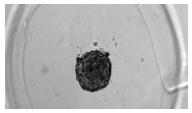
New methods & endpoints

- (Semi-) **High Content Imaging/Analysis**
- GJIC evaluation
- 3D cultures - hepatospheroids
- apoptosis/necrosis, cell cycle, genotox
-

Metabolic markers

- **In Vitro Toxicokinetics & IVIVE**



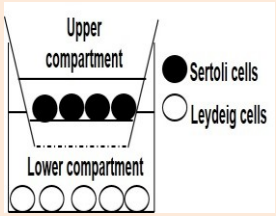


Liver progenitor and adult stem cells

- Collab. w/ Prof. Trosko, Upham, MSU
- Connexin/pannexin (hemi)channels (collab. w/ Prof. Vinken, VUB)
- Cyanotoxins – GACR project

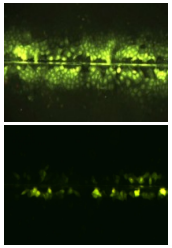
Somatic testicular cells – Leydig/Sertoli

- Effects of contaminants on male fertility?



Bronchial/lung cells

- Chronic respiratory diseases, inflammation
- Indoor/Outdoor Air Contaminants

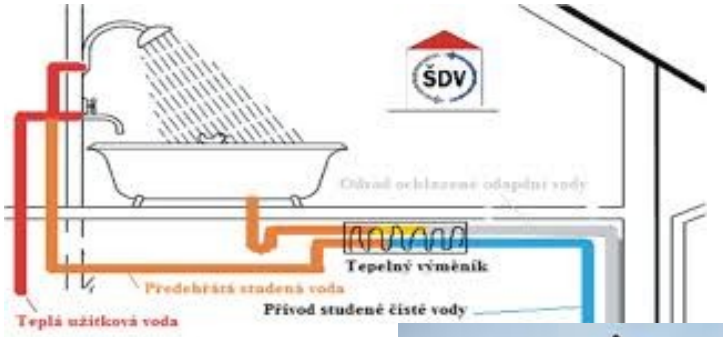


Target in cancer prevention / therapy?

- •(Dietary) chemopreventive agents
- • Anticancer metabolites from cyanobacteria (collab. w/ Dr. Hrouzek, Algatech)
- • nsPEF (collab. w/ Prof. Kolb, INP Greifswald)

Envi technologies (MB, PB, LB)

COMBATING **BIOFOULING**



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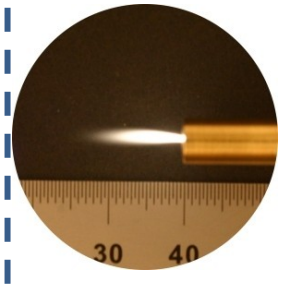
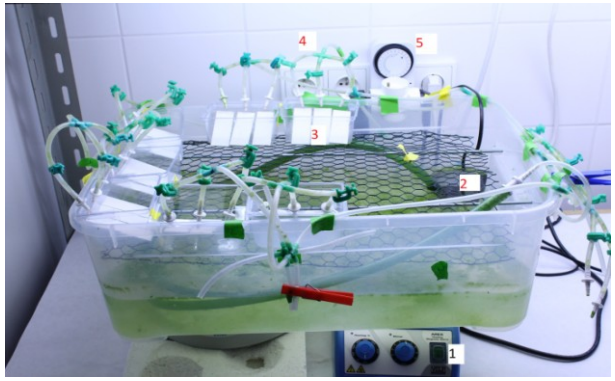


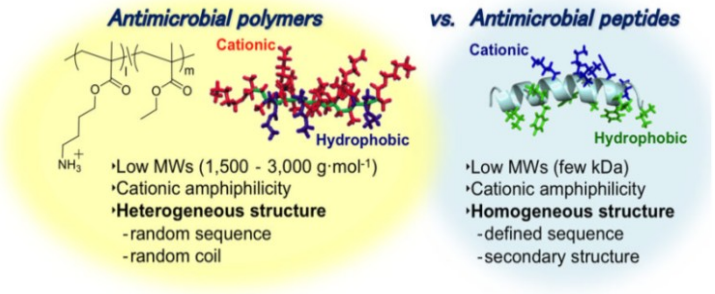
Anti-biofouling:
surface plasma modifications
coop with MUNI Physics dept



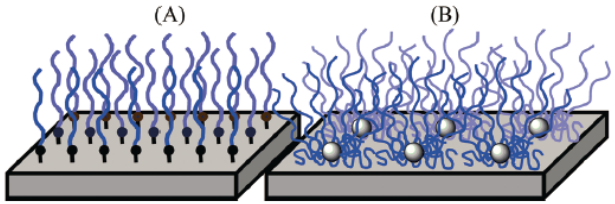
New polymer materials for control of aquatic microorganisms

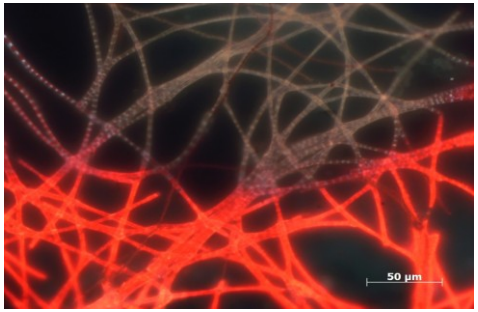
- biomedical => environmental applications?
- solutions/suspensions, antifouling
- Prof. Kuroda, UMICH, Prof. Ando, NAIST

Biomimetic polymers



Star-shaped polymers

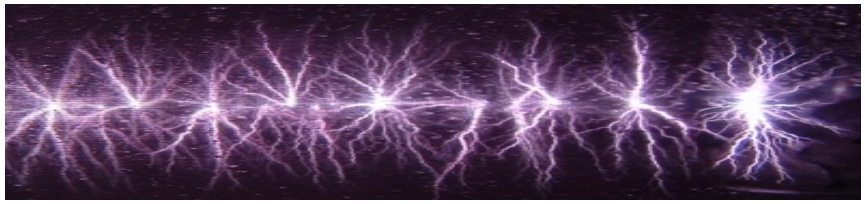


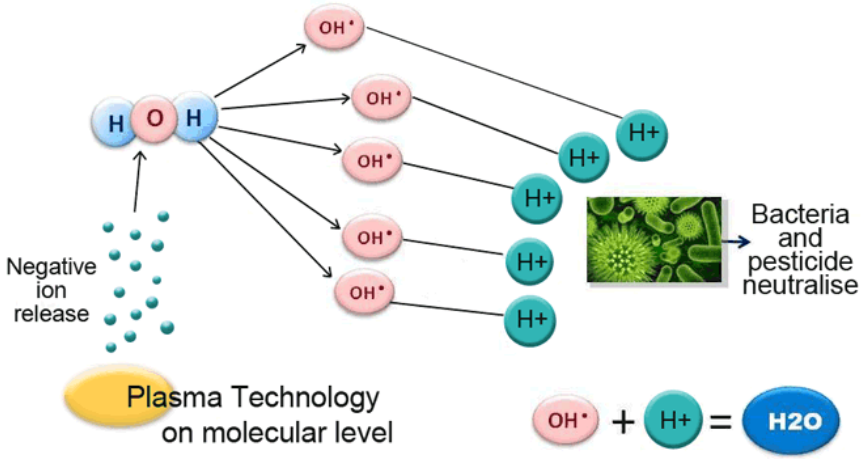


Envi technologies (MB, PB, LB)

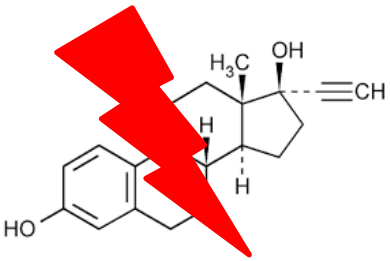
Plasma treatment for water purification (INP Greifswald, DE)

* ITN NaToxAq



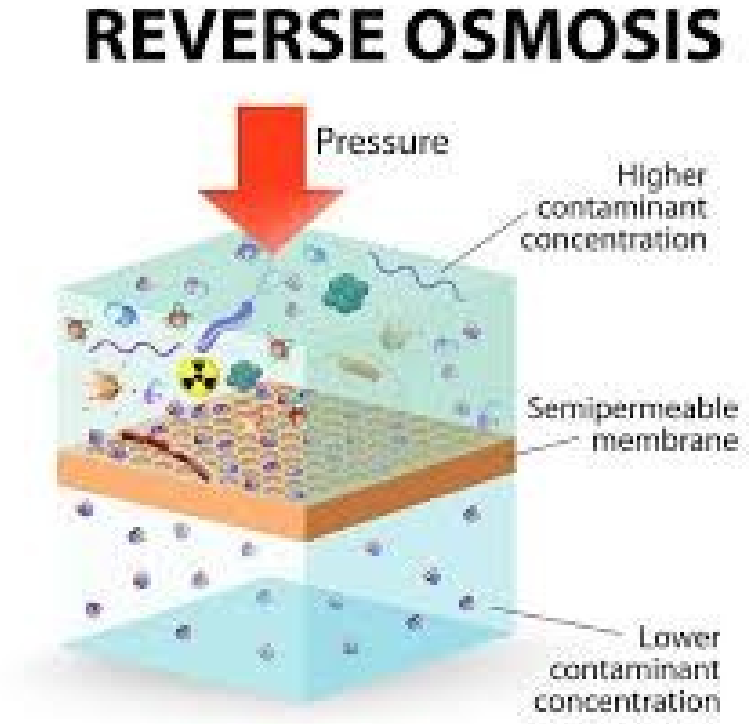


REMOVAL OF ENDOCRINE DISRUPTERS



Reverse osmosis applications

- Industry (ASIO Ltd) cooperation
- **Toxicant preconcentrations** for instrumental and bioassay applications



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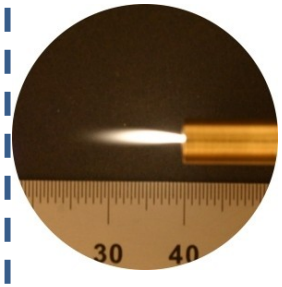

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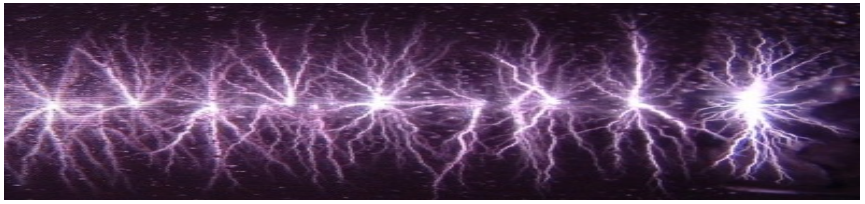

Occupational risks
antineoplastics and their management
- contracted research w/hospitals
- CP, 5PU/FBAL, cisPt, oxalyPt, total Pt

New polymer materials for control of aquatic microorganisms
- biomedical => environmental applications?
- solutions/suspensions, antifouling
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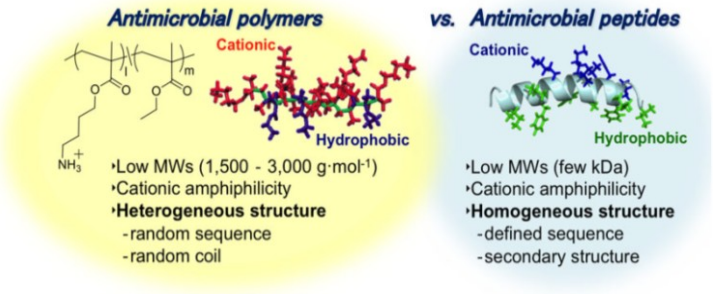

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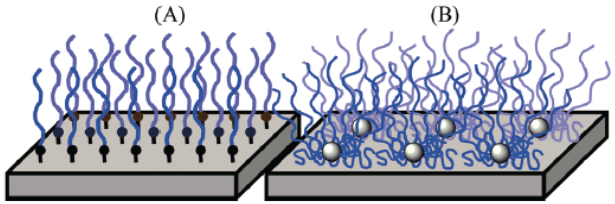

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www.recetox.cz

MASARYKŮV ONKOLOGICKÝ ÚSTAV

www.mou.cz

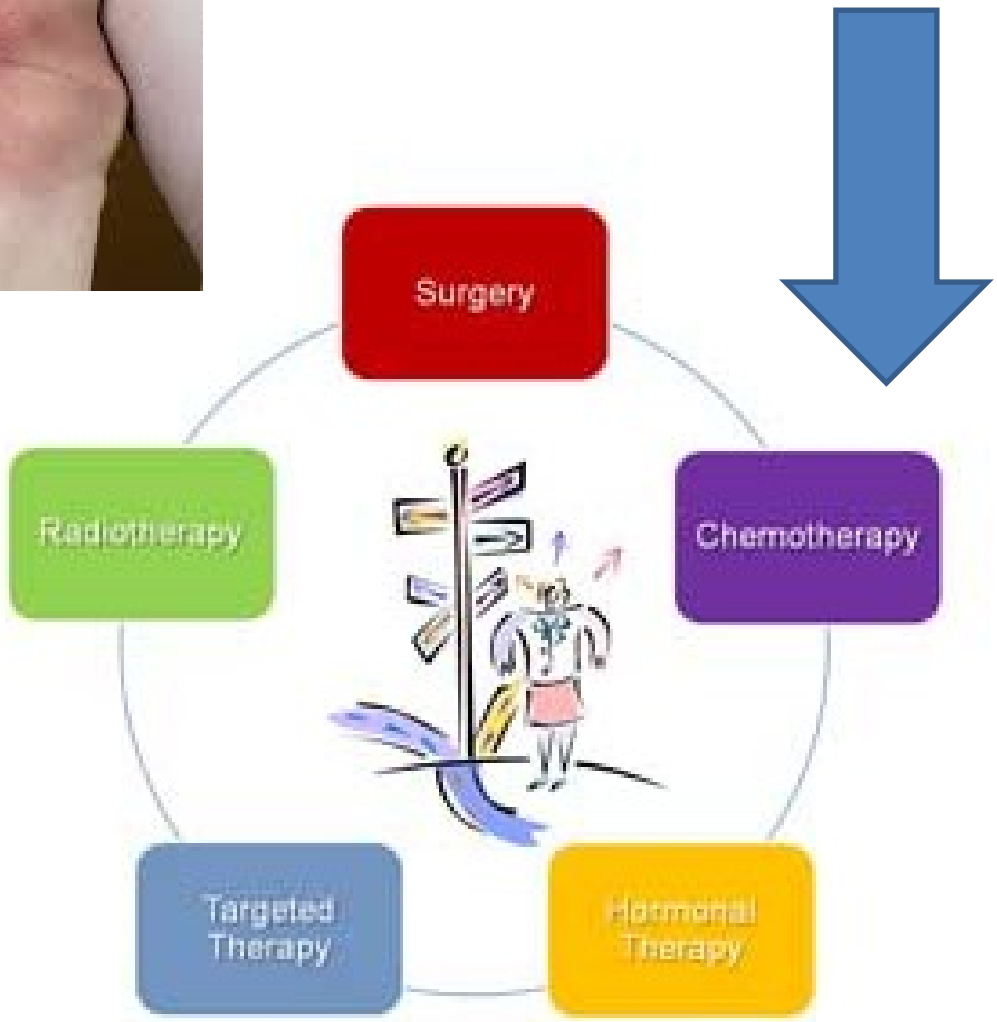
Expozice a zdravotní rizika cytostatik pro pracovníky nemocnic

Luděk Bláha, Lenka Doležalová, Šárka Kozáková,
Jan Kuta, Lucie Bláhová, Pavel Odráška

RECETOX, Přírodovědecká fakulta MU, Brno
Masarykův onkologický ústav, Brno

CYTO

www.cytostatika.cz


Surgery
Radiotherapy
Chemotherapy
Targeted Therapy
Hormonal Therapy

Proč studovat rizika protinádových léčiv?

- **Stále rostoucí spotřeba**
  - Více pacientů s nádory, časnější diagnostika
  - Více protokolů / kombinací
    - Příklad – MOÚ počty příprav 2010:23000 vs 2015:38000

- **Primární cíl – bezpečnost pacienta**
  - (pre-)klinické testy / nežádoucí účinky
  - QA/QC v přípravě a podávání léčiv, mikrobiologická bezpečnost atd.

- **Bezpečnost pracovníků … ?**
  - lékárníci, sestry, lékaři, sanitářky, uklízečky
  - menší priorita a pozornost

Nebezpečnost – **karcinogenita** (13 terapií = IARC 1)

IARC – WHO INTERNATIONAL AGENCY FOR RESEARCH ON CANCER
www.iarc.fr

Group 1 („Carcinogenic to humans“)	**Group 2A („Probably carcinogenic“)**
Arsenic trioxide	Azacitidine
Azothioprin	BCNU
Chlorambucil	CCNU
Chlomaphazine	Chlorozolocin
Cyclophosphamide	Cisplatin
Myleran	Doxorubicin HCL
Melphalan	N-Ethyl-N-Nitrosourea
Semustine	Etopside
Tamoxifen	Mechlorethamine HCL
Thiotepa	N-Methyl-nitrosourea
Treosulfan	Procarbazine HCL
Mustargen-Oncovin-Procarbazine-Prednisone (MOPP)	Teniposide
Etopside-Cisplatin-Bleomycin (ECB)	

Zdravotní účinky při vysokých (terapeutických) dávkách

REPRODUKČNÍ toxicita
VÝVOJOVÁ toxicita (embryotoxicita, teratogenita)

US Food & Drug Administration (FDA)

kategorizace nebezpečnosti léčiv pro těhotenství

United States FDA Pharmaceutical Pregnancy Categories	
Pregnancy Category A	Adequate and well-controlled human studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
Pregnancy Category B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.
Pregnancy Category C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Pregnancy Category D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
Pregnancy Category X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

US FDA

45 léčiv

kategorie „D“

Drug	Pregnancy Category	Drug	Pregnancy Category
Arsenic trioxide	D	Imatinib mesylate	D
Azathioprine	D	Interferon alfa-2b	X
Bleomycin	D	Irinotecan HCL	D
Capecitabine	D	Leflunomide	X
Carboplatin	D	Lomustine	D
Carmustine	D	Mechlorethamine HCL	D
Chlorambucil	D	Melphalan	D
Cisplatin	D	Mercaptopurine	D
Cladribine	D	Methotrexate	X
Cyclophosphamide	D	Mitoxantrone HCL	D
Cytarabine	D	Oxaliplatin	D
Dactinomycin	D	Paclitaxel	D
Daunorubicin HCL	D	Pipobroman	D
Docetaxel	D	Procarbazine	D
Doxorubicin HCL	D	Tamoxilin	D
Epirubicin	D	Temozolomide	D
Etopside	D	Teniposide	D
Floxuridine	D	Thalidomide	X
Fludarabine	D	Thioguanine	D
Fluorouracil	D	Thiotepa	D
Gemcitabine	D	Topotecan	D
Hydroxyurea	D	Tositumomab	X
Ibritumomab tiuxetan	D	Vinblastine sulfate	D
Idarubicin	D	Vincristine sulfate	D
Ifosfamide	D	Vinorelbine tertrate	D

Rizika pro pracovníky ?

Desítky různých studií … ne vždy konzistentní výsledky

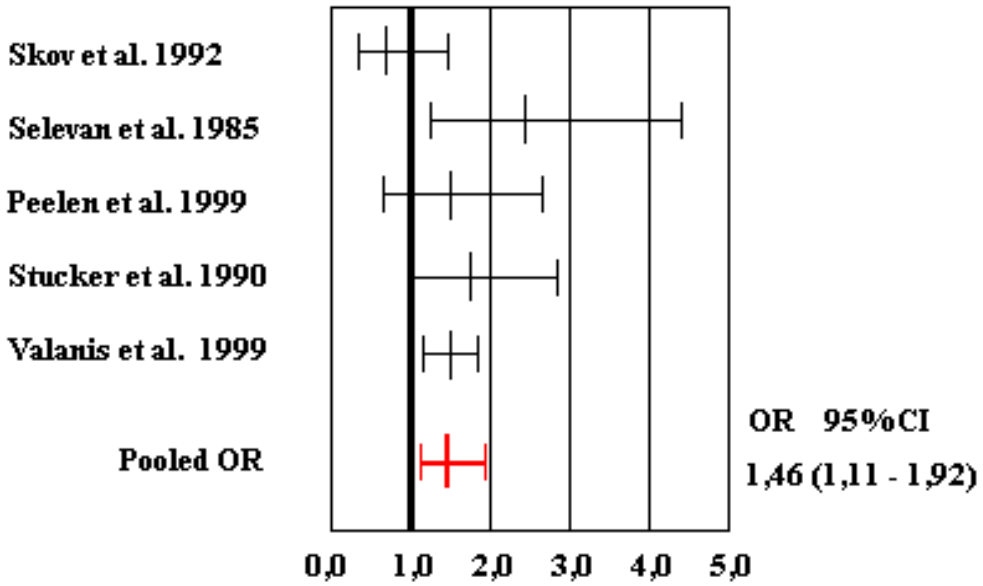
METAANALYTICKÁ STUDIE - Dranitsaris et al. Are health care providers who work with cancer drugs at an increased risk for toxic events? Systematic review and metaanalysis of the literature. J Oncol Pharm Practice 2005; 11: 69-78

- Rizika **NEVÝZNAMNÁ**
  - Vývojové malformace
  - Mrtví novorozenci
  - Akutní účinky
  - Přímé riziko karcinogenity

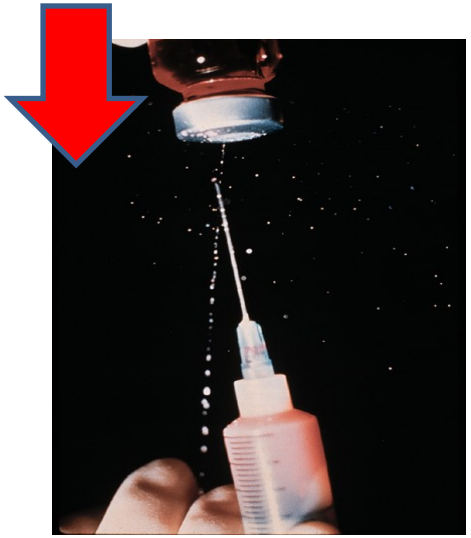
- **VYSOCE VÝZNAMNÉ RIZIKO**

  Spontánní potraty

  RR = 1,46 95% CI = (1,11 – 1,92)



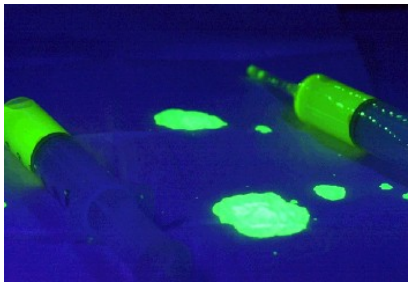
Zdroje expozice cytostatikům



Expoziční cesty a monitoring

- **Vzduch:**
  - **Aspirace léčiv –** plynná fáze, vázány na částice/aerosoly
  - **Výsledky projektu CYTO:** malý význam

- **Povrchy – kontaminace rukou**
  - Přímý vstup přes kůži
  - Přenos na potraviny (Hands → Mouth)



Design monitoringu: POVRCHY

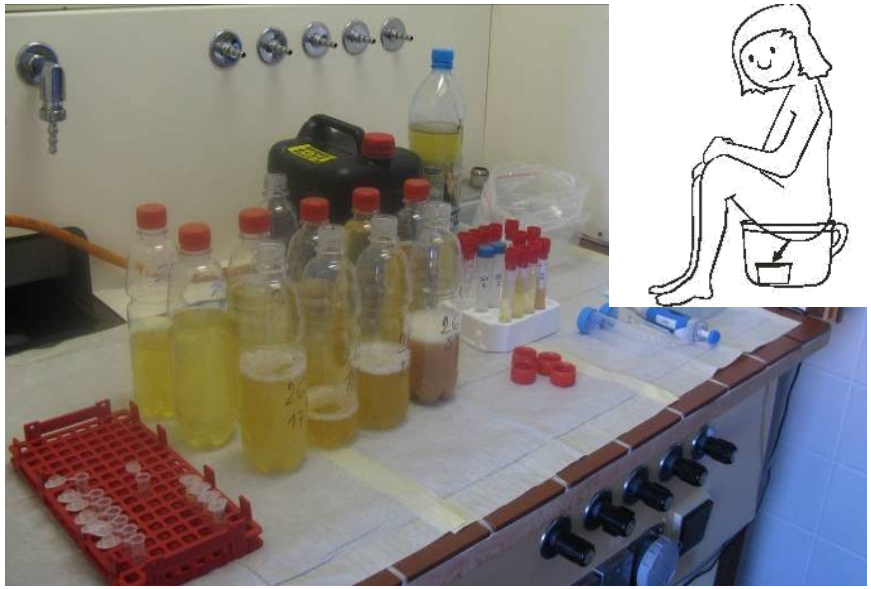
- Lékárny (přípravna, sklady, kanceláře atd.)
- Nemocniční prostory (stacionáře, lůžková odd.)

  - „Stoly“ (= stoly + židle + police)
  - „Podlahy“
  - „Další“ (telefony, klávesnice, madla u lednice…)

BIOMONITORING

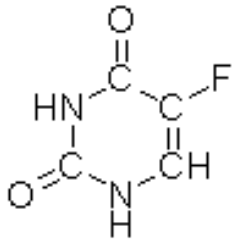
Biomonitoring

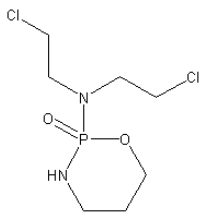
- oplachy rukou
- směsné vzorky moče reprezentující 24-hod exkreci

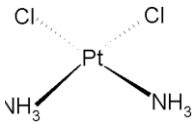


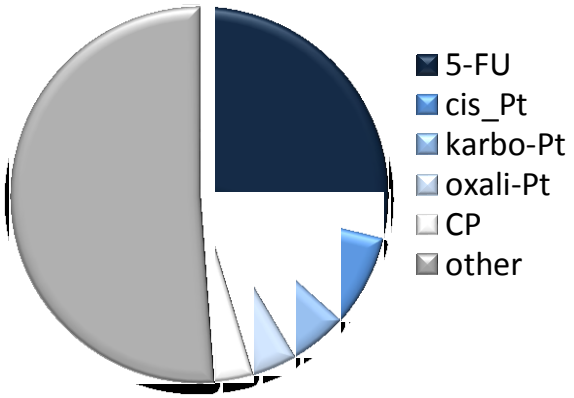
Metody

- **Standardizované protokoly**
  - Video / Zaškolování pracovníků v nemocnicích
  - www.cytostatika.cz
- **Vzorkování –** povrchové stěry
- **Extrakce a analýzy**
  - LC-MS/MS
    - Cyklofosfamid (CP)
    - 5-Fluorouracil (FU) **nově od 2015**
  - ICP-MS
    - Pt (platinová cytostatika)
- **Standardní protokoly, databáze**

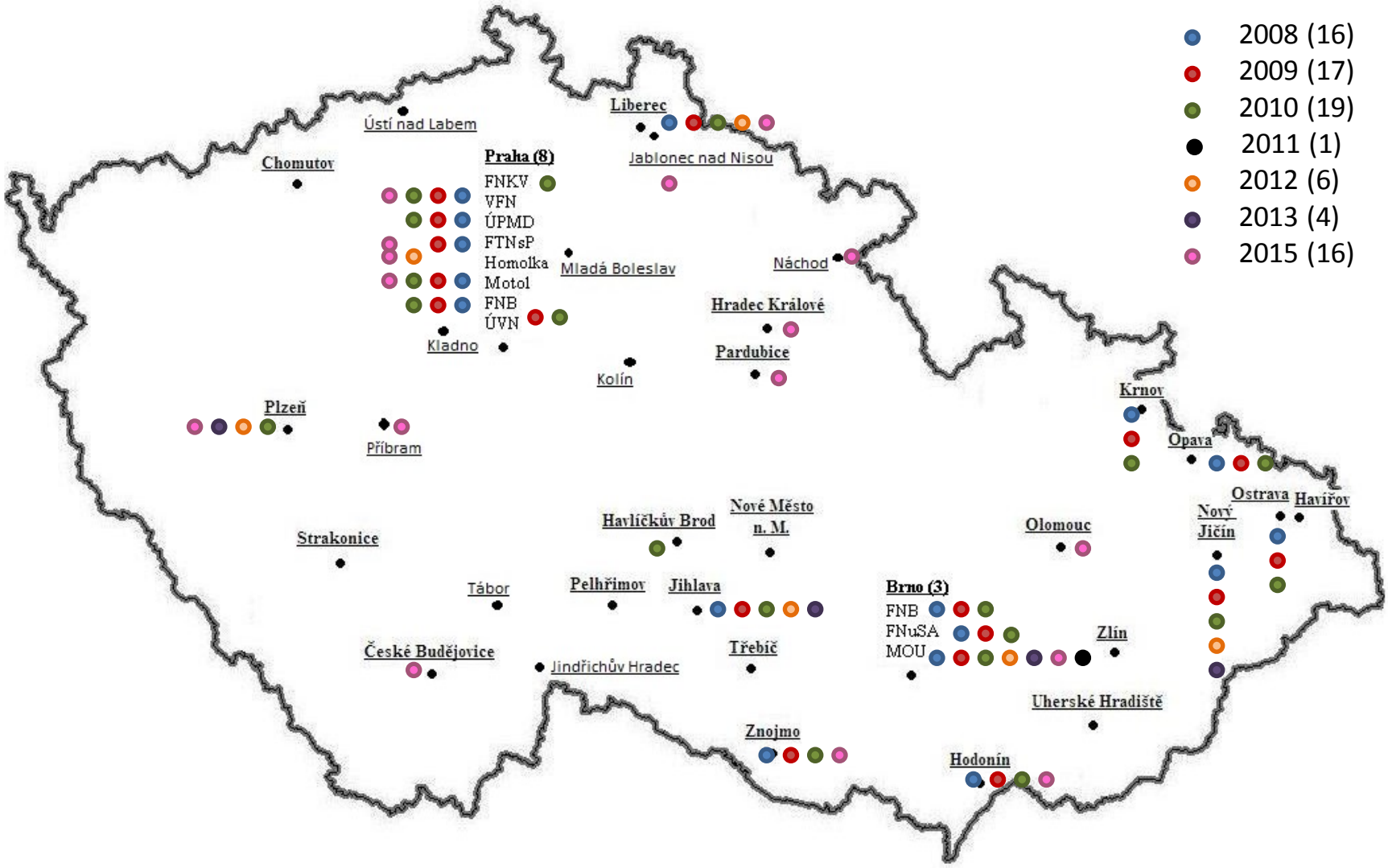








Zapojené nemocnice v ČR



Výsledky – kontaminace povrchů 2008-2015

	Cyklofosfamid pg/cm²			Platina pg/cm²			5-Fluorouracil pg/cm²		
	N/Npos.	Median	Min/Max	N/Npos.	Median	Min/Max	N/Npos.	Median	Min/Max
N=840	644 / 321	<1	<1 / 33853	663 / 413	1.1	<0.2 / 7343	96 / 53	13.4	<7 / 234905
Lékárny									
Přípravna									
Stůl	135 / 83	7.1	<1 / **33853**	144 / 97	1.3	<0.2 / 5333	29 / 20	16.1	<7 / **234905**
Podlaha	89 / 57	5.8	<1 / 638	72 / 47	0.9	<0.2 / 84	10 / 5	3.6	<7 / 564
Kliky, telefony, klávesnice	89 / 39	2.2	<1 / 4656	63 / 43	1.5	<0.2 / 450	3 / 1	<7	<7 / 61
Sklad léčiv									
Stůl	105 / 29	<1	<1 / 1466	95 / 40	<0.2	<0.2 / **7343**	3 / 0	<7	<7 / <7
Podlaha	79 / 23	<1	<1 / 235	61 / 28	<0.2	<0.2 / 57	3 / 1	<7	<7 / 25
Kliky, telefony, klávesnice	35 / 11	<1	<1 / 1184	38 / 22	0.8	<0.2 / 23	3 / 1	<7	<7 / 15
Nemocniční prostory									
Denní stacionář									
Stůl	16 / 12	15.5	<1 / 1324	9 / 9	2.6	1.1 / 96	4 / 3	**135.7**	<7 / 262
Podlaha	34 / 32	**101.9**	<1 / 3244	62 / 59	**47.0**	<0.2 / 5390	9 / 8	**189.7**	<7 / 775
WC	13 / 12	4.5	<1 / 144	13 / 13	**673.7**	0.5 / 4220	6 / 3	6.7	<7 / 220
Sesterny									
Stůl	29 / 16	2.2	<1 / 221	55 / 23	<0.2	<0.2 / 227	14 / 11	**119.2**	<7 / 49510
Kancelářské prostory									
Kliky, telefony, klávesnice	29 / 6	<1	<1 / 142	20 / 4	<0.2	<0.2 / 3.7	11 / 1	<7	<7 / 38

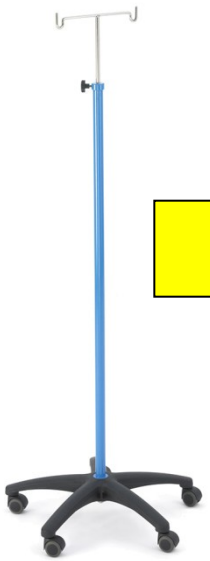
Výsledky – podzim 2016

Tabulka 3: Kontaminace zdravotnických zařízení s vyšším počtem příprav CL (více než 1500 příprav za měsíc) v ČR - **kampaň podzim 2016**. Sumární statistiky pro Pt, CP a FU - analýzy stěrů pracovního prostředí (přípravny, administrativní část a nemocniční prostory) u celkem **8 zúčastněných zdravotnických zařízení**.
*- hodnota pod limitem detekce metody

	Platina pg/cm^2	Cyklofosfamid pg/cm^2	5-fluorouracil pg/cm^2
Lékárna - Přípravna (Izolátor, Materiálová propusť, Přípravna CL, Balení)			
Analyzované vzorky (počet, N)	18	32	32
Median (pg/cm2)	0.81	18.2	12.5
Průměr (pg/cm2)	2.79	138.6	89.5
Maximum (pg/cm2)	18.9	1521	983
Administrativní část			
Analyzované vzorky (počet, N)	8	11	11
Median (pg/cm2)	<0.17*	<1.1*	<6.9*
Průměr (pg/cm2)	<0.17	1.11	<6.9
Maximum (pg/cm2)	<0.17	8.63	<6.9
Nemocnice - (Stacionář, Lůžková část, WC, Pracovní prostory - Sesterny)			
Analyzované vzorky (počet, N)	30	31	31
Median (pg/cm2)	0.88	7.73	18.7
Průměr (pg/cm2)	153.6	1335	145.1
Maximum (pg/cm2)	2825	29695	1681

Příklad – řízení rizik

www.mou.cz



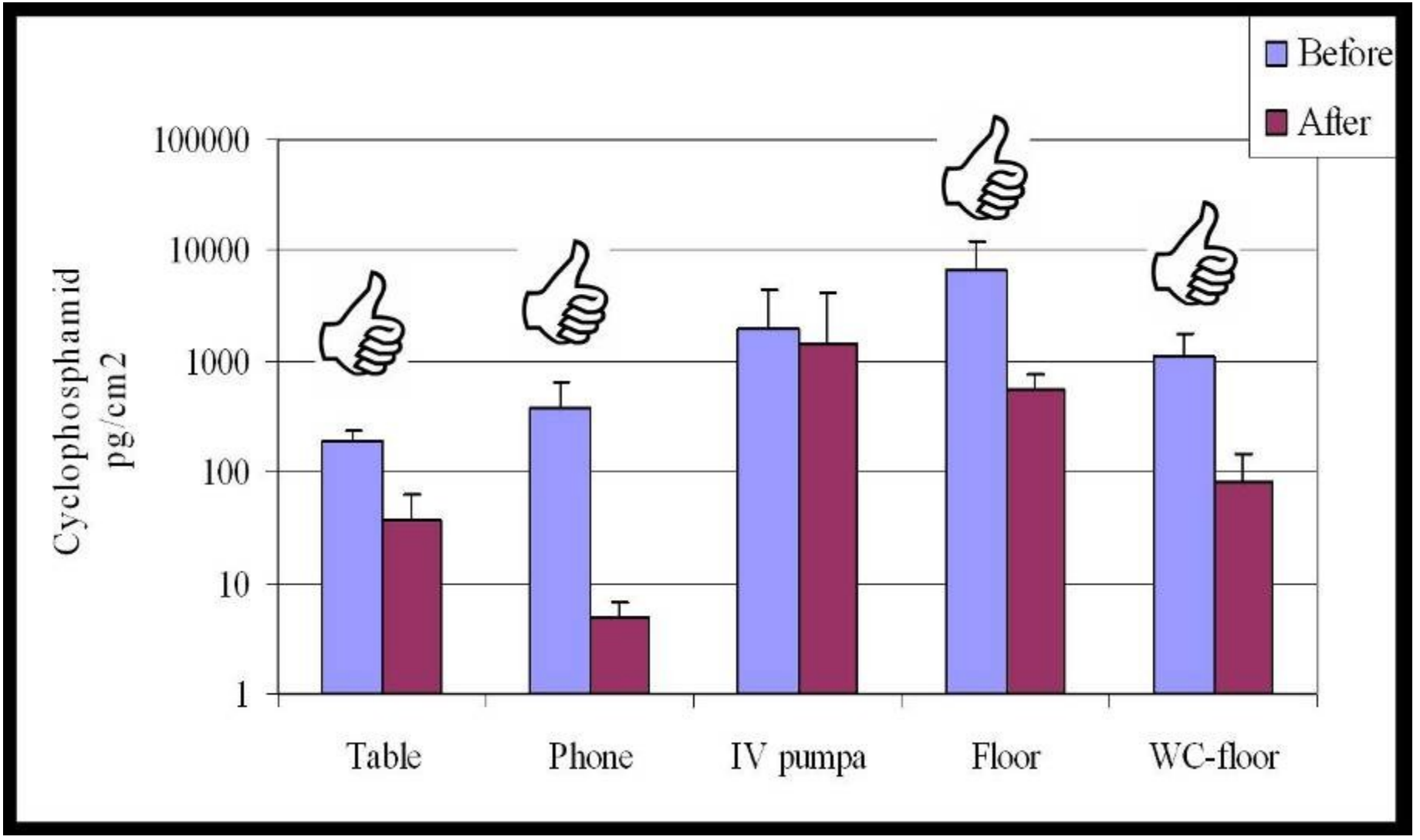
Držáky na zdi

Více kanálové sety

Toalety se samočistícím sedátkem

Příklad – cyklofosfamid

(**before / after –** před / po zavedení nových postupů)



Doporučené limity (Treshold Guidance Values)

Bouwman-Boer et al. „Occupational Safety and Health“ in *Practical Pharmaceutics* 2015

TGV (percentile)	**5-fluorouracil** pg/cm^2	**Platinum** pg/cm^2	**Cyclophosphamide** pg/cm^2	References
75th	30	4		Schierl et al. 2009
90th	100		100	Kiffmeyer et al. 2013
90th			100	Sessink 2011
75th	**38** (provisional) **(27%>TGV; N=96; 2015)**	**12** **(8%>TGV;N=663)**	**67** **(20%>TGV; N=644)**	**CYTO 2006-2010 MONITORING 2008-2015**

Dr. Paul Sessink (Exposure Control B.V., NL) www.exposurecontrol.nl

Health based (cancer) surface contamination limits for cyclophosphamide in hospitals

POVRCHY

	Strive risk level			Prohibitory risk level
Urine CP (ug/24 hr)	< 0.02	0.02 – 0.2	0.2 - 2	> 2
Contamination CP (ng/cm^2)	< 0.1	0.1 – 1	1.0 – 10	> 10
Action	No	Yes At short notice	Yes Immediately	Yes Stop working
Monitoring	Now and then	Yes	Yes	Yes

Shrnutí

- Dlouhodobě běžící výzkum expozice cytostatikům v lékárnách a nemocničních prostorách od roku 2008
  - Analýzy nejběžnějších a široce používaných cytostatik: CP, Pt, FU
- Samotná realizace monitoringu vede ke zlepšení situace a snížení expozic na sledovaných pracovištích – pokles 2008-2015
  - Specifická opatření a změny režimu – další zlepšení situace
- Doporučené limity (Technical Guidance Values) byly odvozeny s využitím statistických metod a umožňují řídícím pracovníkům v nemocnicích sledovat kvalitu práce a úroveň kontaminace
- **Hlavní otevřené otázky**
  - Lékárny (s dobrým povědomím o problematice a rizicích) jsou méně kontaminovány než další místa v nemocnicích
  - Sestry na denních stacionářích – více exponovaná skupina
  - Sanitářky, údržba, úklid - často s horším proškolením a menším povědomím o rizicích - jsou nejvíce exponovanou skupinou (např. velmi vysoké koncentrace v prostorách WC).

Current issues in ECOTOXICOLOGY

Examples

PHARMACEUTICALS

R&D and Manufacturing

Storage Transport

Distribution

Storage Transport

Consumption

Storage Transport

Waste management

Manufacturing waste

Possible releases to the environment

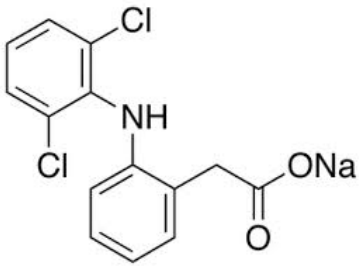
Environmental Life-Cycle of Pharmaceuticals
created by CG Daughton
US EPA, Las Vegas
2 December 2006
transformation/degradation
M mineralization
stewardship opportunities
Manufacturer
Commerce distribution
Wholesalers Distributors
Agriculture (e.g., orchards)
runoff
excrement
pets
euthanized carcasses
potential for acute/chronic poisoning of wildlife scavengers
carcasses of medicated animals
airborne dusts (e.g., medicated feed)
occupational human pulmonary exposure
physician samples
Physicians
Feedstores
Vet use
domestic animals
CAFOs
Aquaculture
prescribing
unsold product
Reverse distributors
dispensing pharmacies Rx & OTC
waste residuals pretreatment
humanitarian donations: excess or unusable leftovers
atmospheric release (e.g., anaesthetics)
sloughing of antibiotic-resistant bacteria/genes
Waste Treatment (e.g., lagoons)
manure solids
Soil amendment/ disposal
Take-Backs, Mail-Backs, Collection events
Human consumer use
Gene Exchange multi-drug resistance
exposure to resistant bacteria
naturally occurring bacteria
Incineration
unused/expired leftovers
LTCFs Hospitals Hospice
acute poisonings: accidental & purposeful
Diversion Abuse (e.g., pharming)
diversion by gleaners
Landfill
trash
RCRA Hazardous Waste
release of dermal products from bathing
Leftover medications
Stored awaiting disposal
Disposal by consumer
Incineration
excretion from oral & parenteral use
Disposal by Coroner's
research of Ruhoy 2006
optional
Law enforcement (controlled substances)
Waste Treatment
toilet
groundwater (artificial recharge, colloidal transport)
Aquatic exposure
sediments (sorption)
toilet or sewerage
straightpiping & overflow events
Wildlife exposure (scavengers)
runoff
leachates
Plant-Made Pharmaceuticals (PMPs)
finished drinking water treatment
receiving waters
Waste Treatment
Sludge Biosolids
landfill
Molecular Pharming
"toilet-to-tap"
drug residues & transformation by-products
Recreation
Advanced Treatment (recycling)
aqueous effluent
Soil Amendment
groundwater
PMPs cross-contaminating food supply
irrigation
Wildlife exposure from grazing/ foraging
Chronic, Low-Level, Incidental Human Exposure
Oral & Dermal
uptake by plants & crops
uptake by soil-dwelling organisms

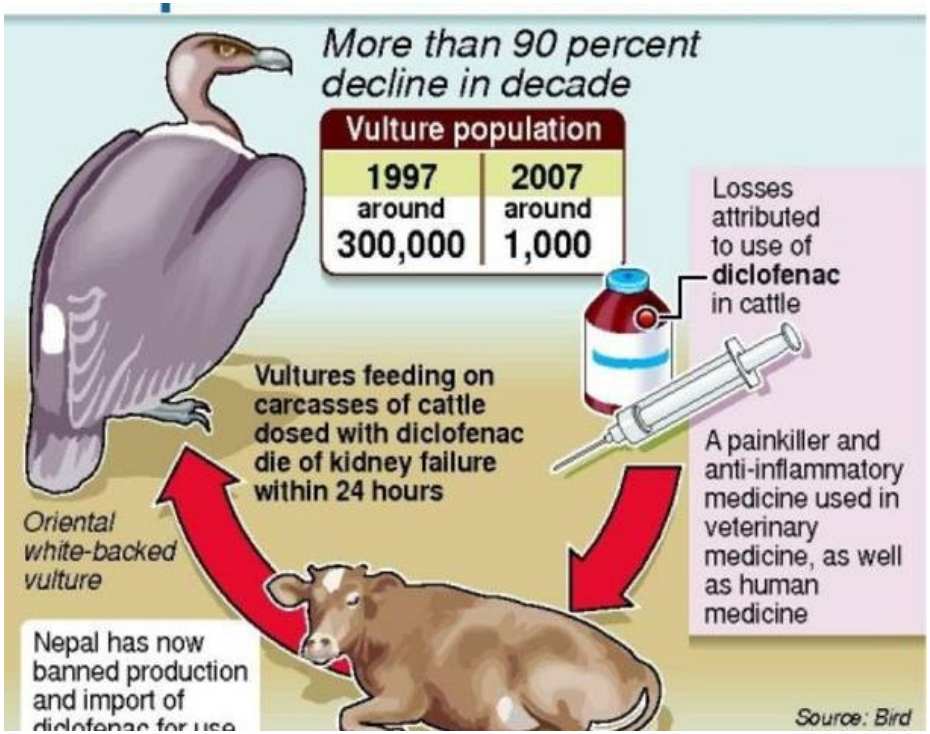
Example 1 - DICLOFENAC

Unexpected effects at NON-TARGET species

- **nephrotoxicity** at vultures
- Relevant also in EU

(ESP, EL,CY)



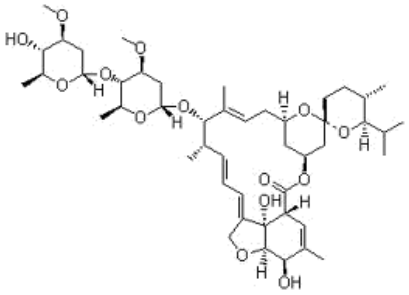


Example 2 – AVERMECTIN-like antiparasitics

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)

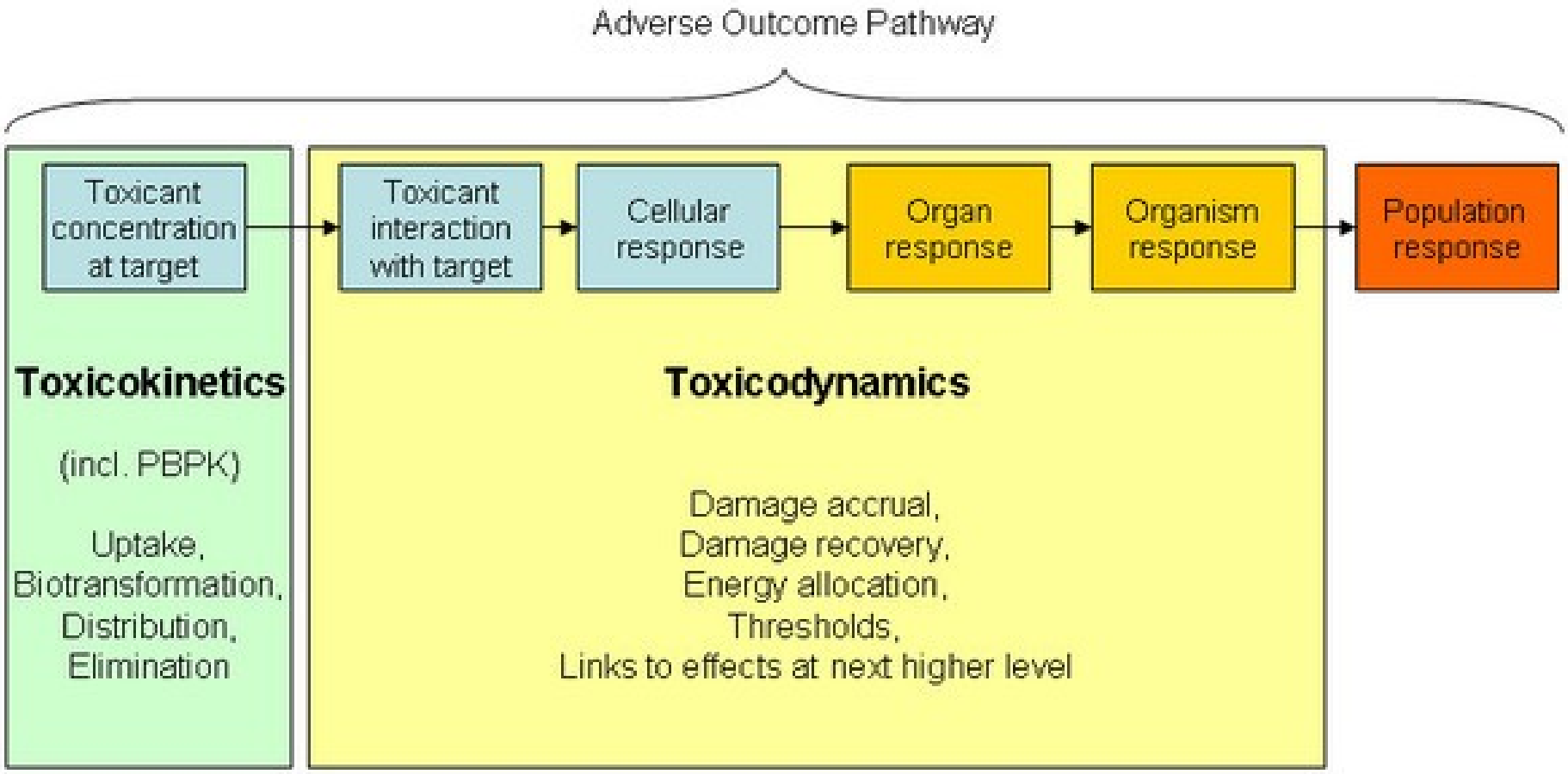


COMPUTATIONAL (ECO)TOXICOLOGY

Adverse outcome pathways

… and its modelling

Key is to understand the mechanisms at low levels of organization



Computational Toxicology Research

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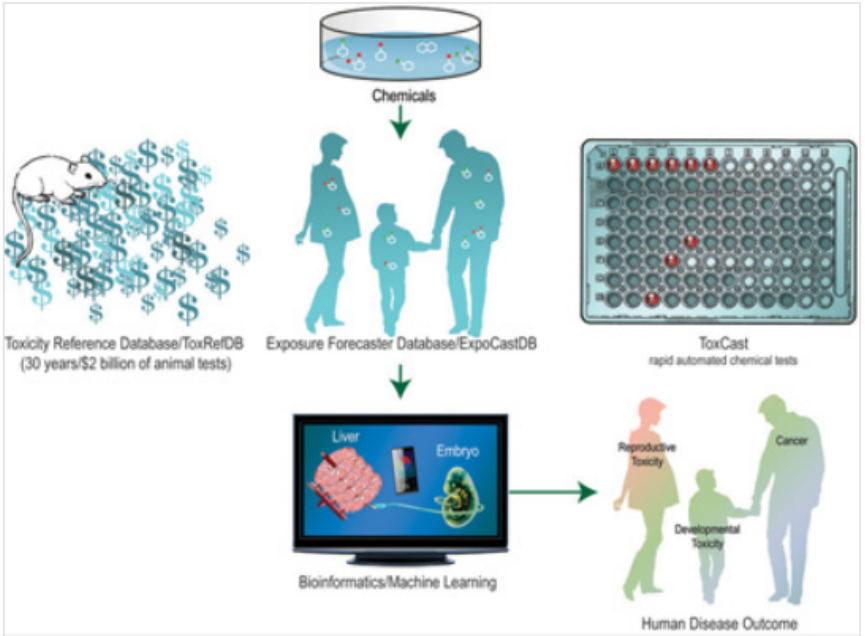
ToxCast™

Screening Chemicals to Predict Toxicity Faster and Better

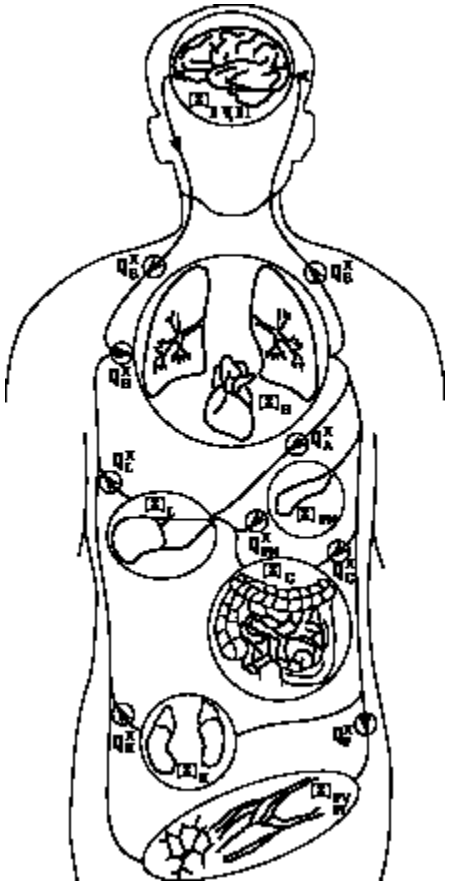


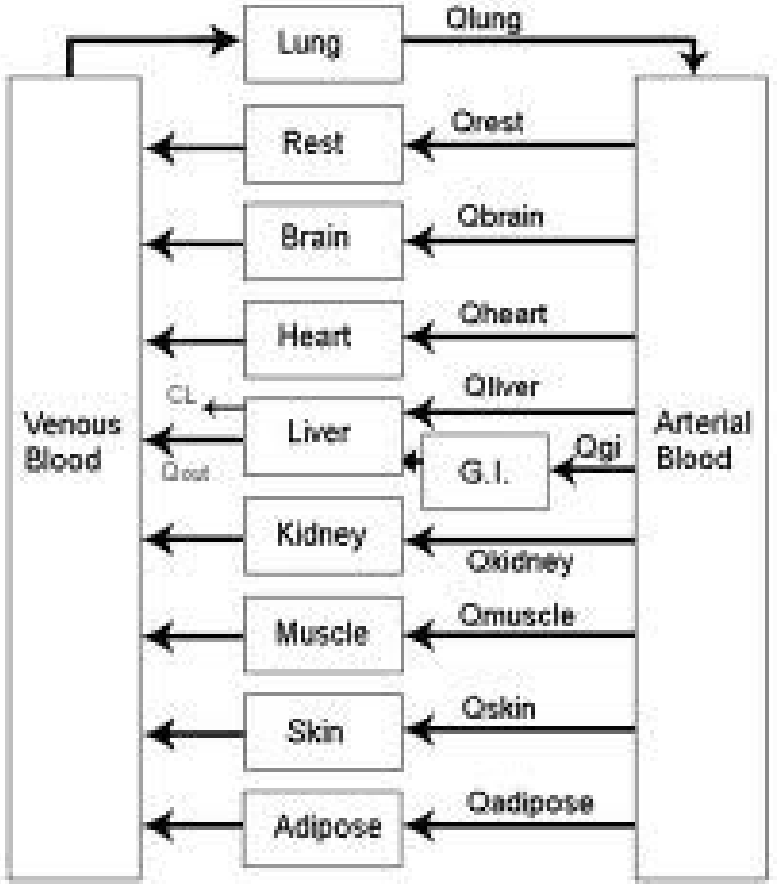
How ToxCast Fits Into CompTox Research

ToxCast Resources

PBPK models

PBPK (PBTK)
Physiologically based pharmacokinetic (toxicokinetic) models





Fragmentation of a complex systém to „boxes“

→ All Processes described by arrows (mathematical equations)

Example

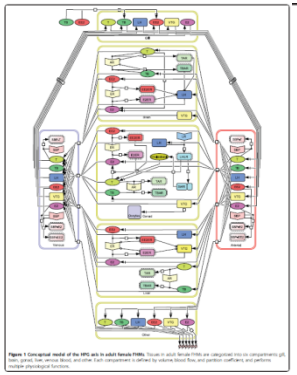
Li *et al. BMC Systems Biology* 2011, **5**:63
http://www.biomedcentral.com/1752-0509/5/63

RESEARCH ARTICLE Open Access

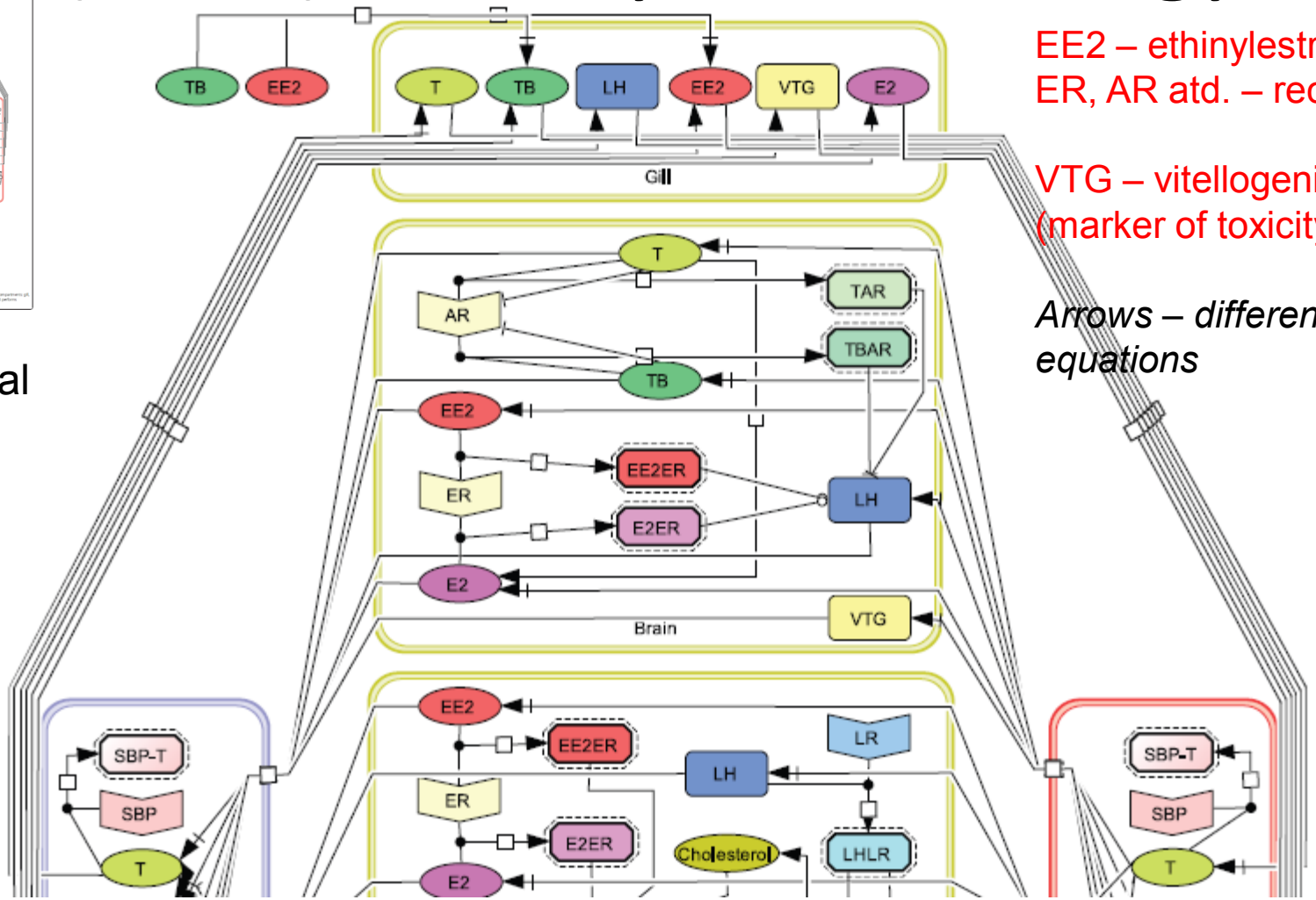
A computational model of the hypothalamic - pituitary - gonadal axis in female fathead minnows (*Pimephales promelas*) exposed to 17α-ethynylestradiol and 17β-trenbolone

Zhenhong Li[1], Kevin J Kroll[2], Kathleen M Jensen[3], Daniel L Villeneuve[3], Gerald T Ankley[3], Jayne V Brian[4], María S Sepúlveda[5], Edward F Orlando[6], James M Lazorchak[7], Mitchell Kostich[7], Brandon Armstrong[8], Nancy D Denslow[2] and Karen H Watanabe[1*]

Li (2011) BMC Systems Biology



Conceptual model



EE2 – ethinylestradiol
ER, AR atd. – receptors

VTG – vitellogenin (marker of toxicity)

Arrows – differential equations

Li (2011) BMC Systems Biology

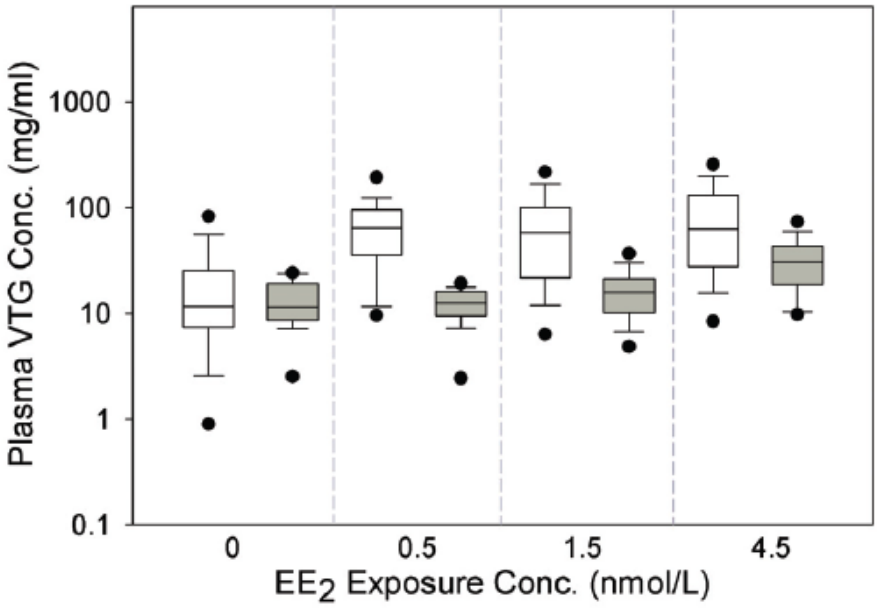


Figure 6 Comparison of model predictions with measured data in female FHMs exposed to EE_2. $n = 28$ at each sampling time. White boxes represent model predictions, and grey boxes represent measured data [42]. The x-axis represents EE_2 concentrations in ng/L. The solid line within the box marks the median; the boundary of the box farthest from zero indicates the 75th percentile; the boundary of the box closest to zero indicates the 25th percentile; the whisker (error bar) farthest from zero marks the 90th percentile; whisker (error bar) closest to zero marks the 10th percentile; the circle farthest from zero marks the 95th percentile; and the circle closest to zero marks the 5th percentile.

Results:

MODELLED (white)
Vs
MEASURED (grey)

…good comparable