Research centre
for toxic compounds
in the environment

Ecotoxicology
New topics and future issues

Ludek Blaha + ecotox colleagues

cetocoen

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2007-13
OP Research and
Development for Innovation

UNIVERSITAS MASARYKIANA BRUNENSIS

Take home messages from this presentation

- Traditional (eco)toxicity testing (based on simple standardized bioassays) and related chemical risk assessment is likely to change in this century
- … towards the use of mechanistic data (omics), that is translated this into mechanistic knowledge (Adverse Outcome Pathways, AOPs) and mathematical models
  - The paradigm shift is strongly promoted by fluential players – OECD, US EPA, European Commission (example shown – OECD AOPWiki)
  - Also in line with minimizing use of animals and implementation of „3R“ policies (examples shown)
  - Toxicological predictions = computational (AI) models are becoming more and more advanced

Current approaches

(black box of apical endoints)

vs

Future

(mechanistic understanding & AOPs)

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)

Hazard assessment

Traditionally – Evaluation of adverse effects using the whole organism models

Chemical

Organism

Adverse Effects

Death

Inhibition of Growth

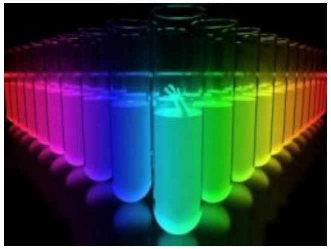
Altered Reproduction

Tumor

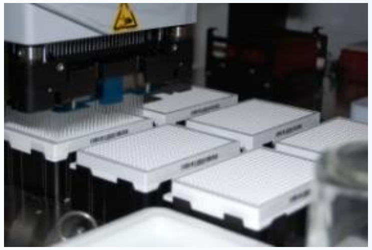
Skin irritation

…

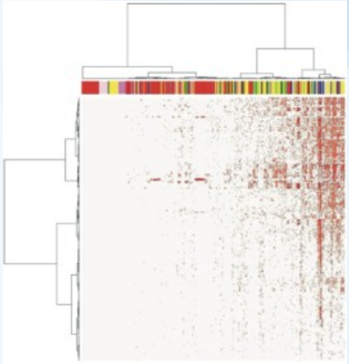
New – Ex vivo / in vitro / In chemico / In silico Methods



10^4 Chemicals



HTS
High-Throughput-Screening



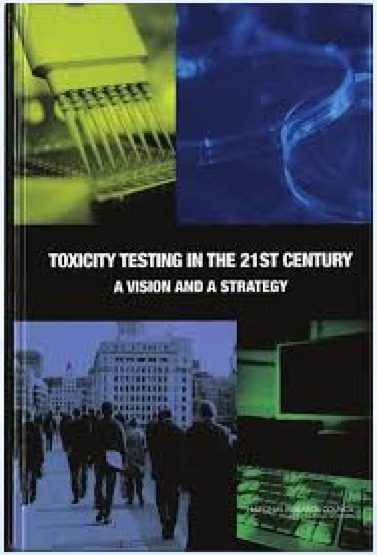
Chemical-biological interactions, Mechanistic Toxicological Data

Key task/question:

How to link MECHANISTIC INFORMATION with APICAL ENDPOINTS ?

MoA and omics are supported by strategic documents

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


TOXICITY TESTING IN THE 21ST CENTURY
A VISION AND A STRATEGY
NATIONAL RESEARCH COUNCIL

EPA United States Environmental Protection Agency

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Computational Toxicology Research

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

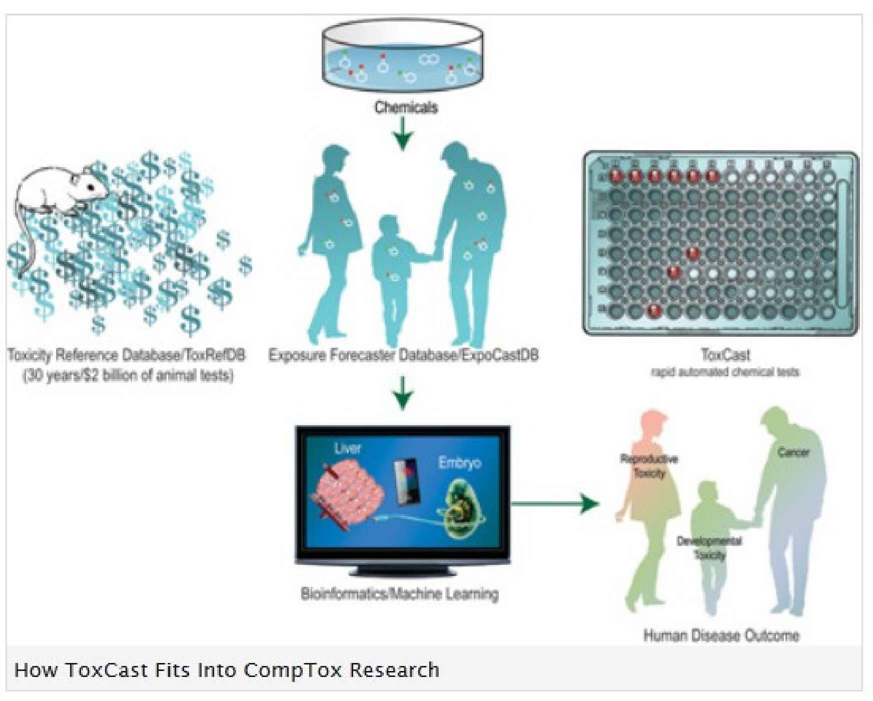
Key Links

CompTox Home
Basic Information
Organization

Research Projects
Chemical Databases
CompTox Events

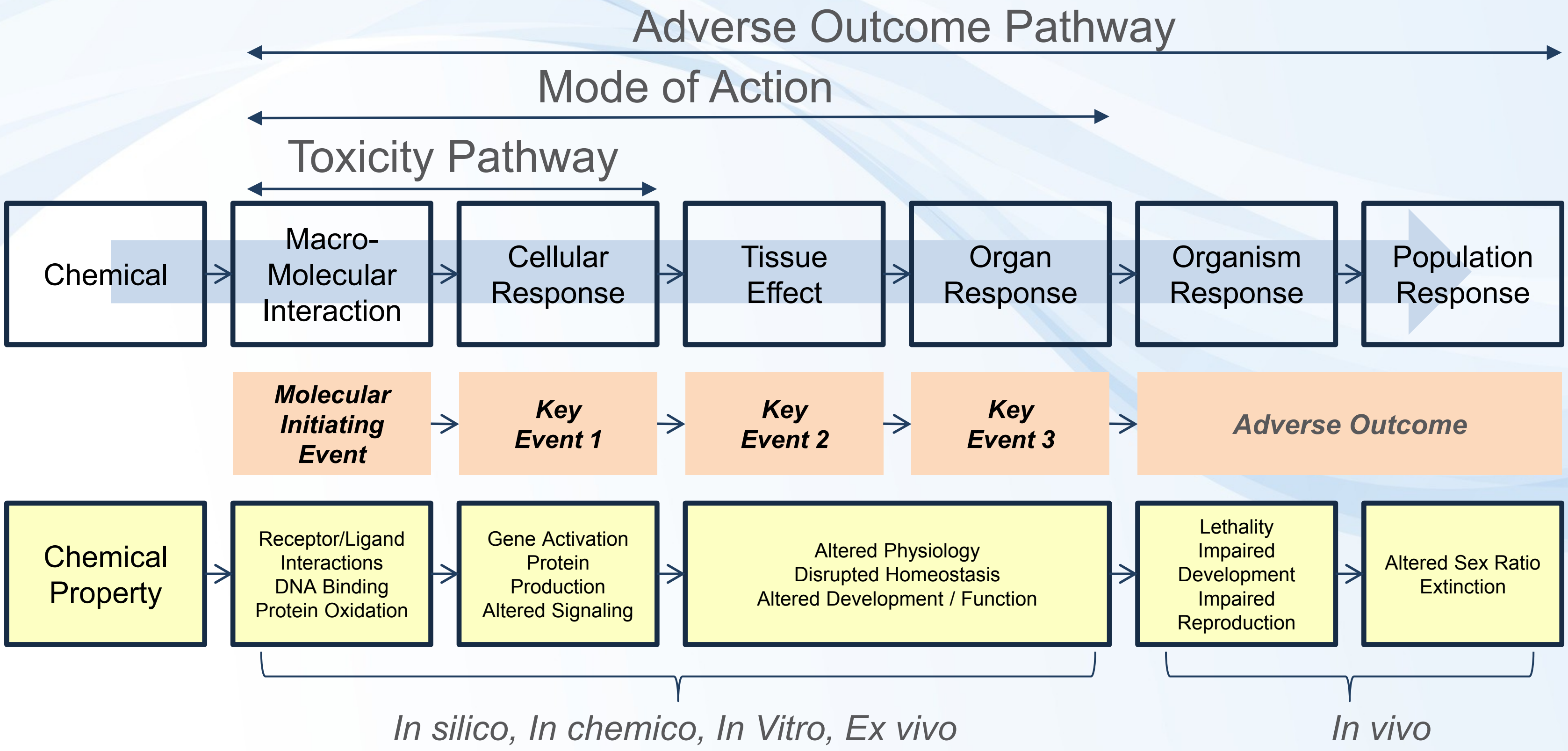
ToxCast™

Screening Chemicals to Predict Toxicity Faster and Better


Chemicals
Toxicity Reference Database/ToxRefDB
(30 years/$2 billion of animal tests)
Exposure Forecaster Database/ExpoCastDB
ToxCast
rapid automated chemical tests
Liver
Embryo
Bioinformatics/Machine Learning
Reproductive Toxicity
Developmental Toxicity
Cancer
Human Disease Outcome

How ToxCast Fits Into CompTox Research

Adverse Outcome Pathways



Adverse Outcome Pathway

Mode of Action

Toxicity Pathway

Chemical → Macro-Molecular Interaction → Cellular Response → Tissue Effect → Organ Response → Organism Response → Population Response

Molecular Initiating Event → ***Key Event 1*** → ***Key Event 2*** → ***Key Event 3*** → ***Adverse Outcome***

Chemical Property → Receptor/Ligand Interactions, DNA Binding, Protein Oxidation → Gene Activation, Protein Production, Altered Signaling → Altered Physiology, Disrupted Homeostasis, Altered Development / Function → Lethality, Impaired Development, Impaired Reproduction → Altered Sex Ratio, Extinction

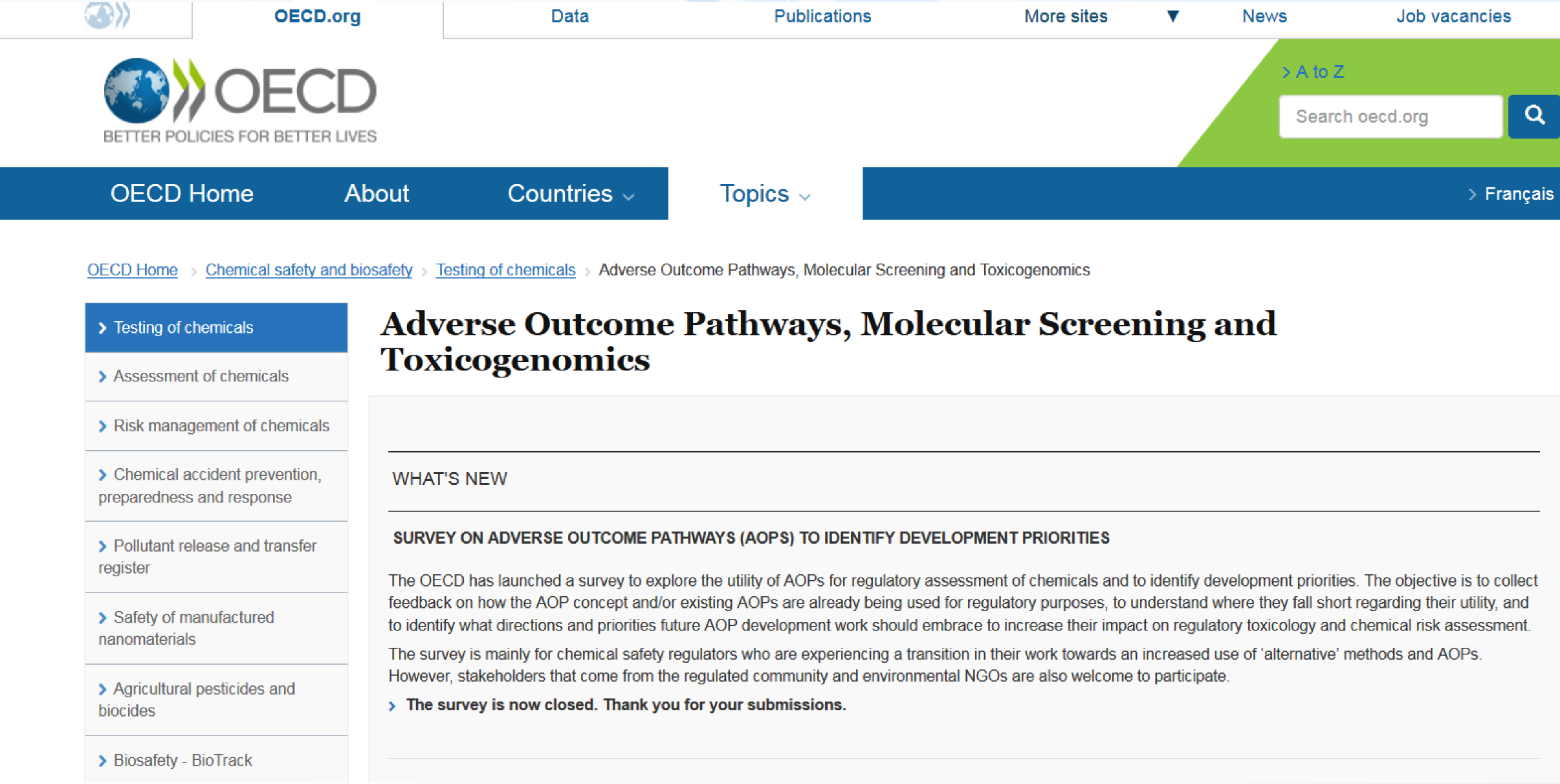
In silico, In chemico, In Vitro, Ex vivo

In vivo

The **EXISTING KNOWLEDGE** is used **to link the** two anchor points: **Molecular Initiating Event** (MIE) and **Adverse Outcome** (AO) **via a series** of intermediate steps: **Key Events**

Ankley, G. T., R. S. Bennett, et al. (2010). "Adverse outcome pathways: a conceptual framework to support ecotoxicology research and risk assessment." Environmental Toxicology and Chemistry **29**(3): 730-741.

AOP = Global strategy with support from OECD, EU, USA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OECD Home › Chemical safety and biosafety › Testing of chemicals › Adverse Outcome Pathways, Molecular Screening and Toxicogenomics
Testing of chemicals
Assessment of chemicals
Risk management of chemicals
Chemical accident prevention, preparedness and response
Pollutant release and transfer register
Safety of manufactured nanomaterials
Agricultural pesticides and biocides
Biosafety - BioTrack

Adverse Outcome Pathways, Molecular Screening and Toxicogenomics

WHAT'S NEW

SURVEY ON ADVERSE OUTCOME PATHWAYS (AOPS) TO IDENTIFY DEVELOPMENT PRIORITIES

The OECD has launched a survey to explore the utility of AOPs for regulatory assessment of chemicals and to identify development priorities. The objective is to collect feedback on how the AOP concept and/or existing AOPs are already being used for regulatory purposes, to understand where they fall short regarding their utility, and to identify what directions and priorities future AOP development work should embrace to increase their impact on regulatory toxicology and chemical risk assessment.

The survey is mainly for chemical safety regulators who are experiencing a transition in their work towards an increased use of 'alternative' methods and AOPs. However, stakeholders that come from the regulated community and environmental NGOs are also welcome to participate.

› **The survey is now closed. Thank you for your submissions.**

http://www.oecd.org/chemicalsafety/testing/projects-adverse-outcome-pathways.htm

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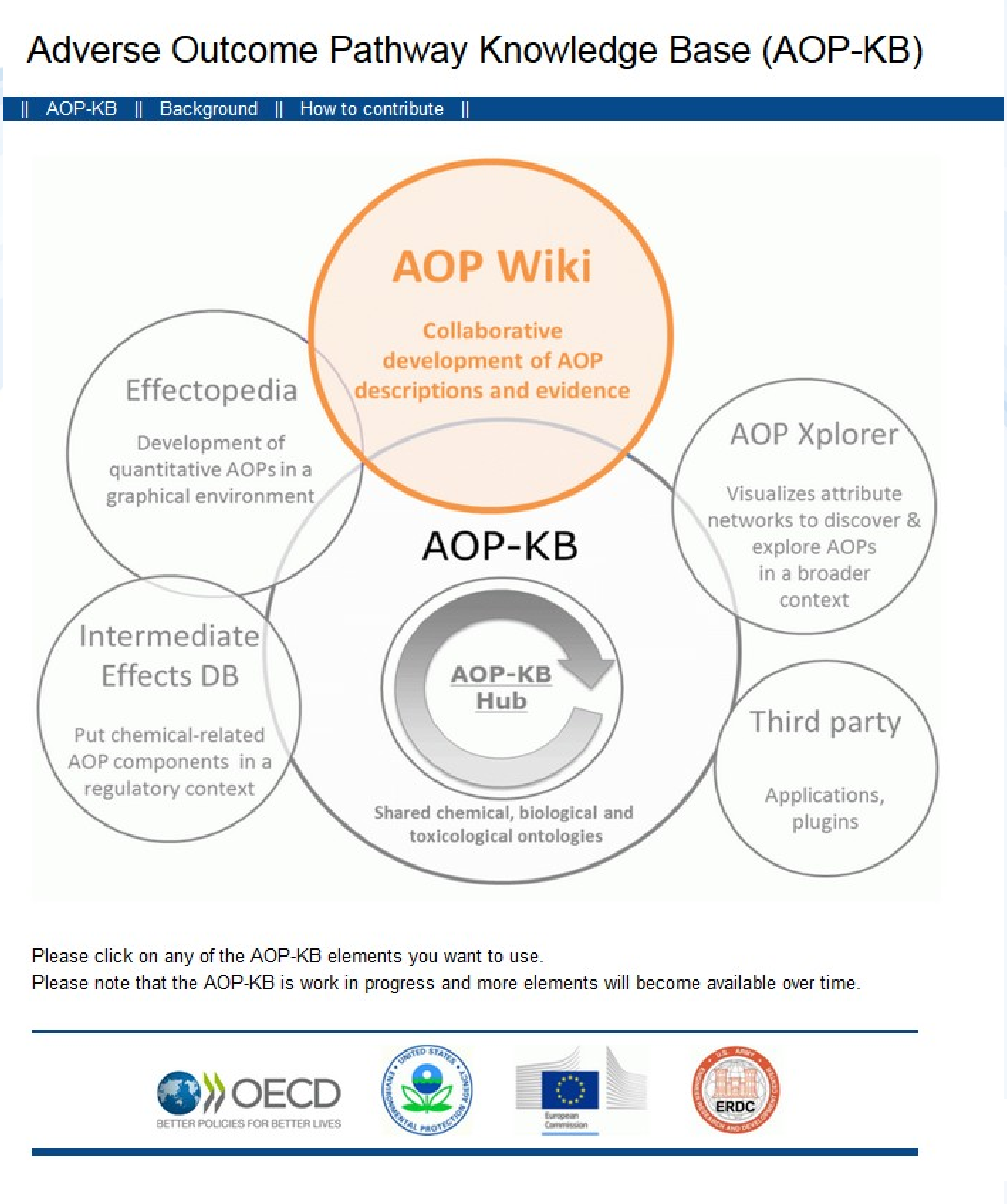

Adverse Outcome Pathway Knowledge Base (AOP-KB)

|| AOP-KB || Background || How to contribute ||

AOP Wiki

Collaborative development of AOP descriptions and evidence

Effectopedia

Development of quantitative AOPs in a graphical environment

AOP Xplorer

Visualizes attribute networks to discover & explore AOPs in a broader context

AOP-KB

AOP-KB Hub

Shared chemical, biological and toxicological ontologies

Intermediate Effects DB

Put chemical-related AOP components in a regulatory context

Third party

Applications, plugins

Please click on any of the AOP-KB elements you want to use.
Please note that the AOP-KB is work in progress and more elements will become available over time.

http://aopkb.org/

Key documents

OECD Guidance document and a template for developing and assessing adverse outcome pathways (Series No. 184, Series on Testing and Assessment)

Handbook for AOP developers

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AOP Wiki

- https://aopkb.org/aopwiki/index.php/Main_Page
- Wiki-based platform for development of AOPs
- Only members of an OECD AOP development project can create / edit AOPs

What AOPs are now in AOP Wiki (spring 2019)

OECD Endorsed (WNT and TFHA)	7	1x ecotoxicology: Aromatase inhibition leading to reproductive dysfunction (in fish)
EAGMST Approved	3	1x Ecotox - Androgen receptor agonism leading to reproductive dysfunction
Other OECD status	40	
Under Development	241	

Check online: https://aopwiki.org/aops

- OECD Extended Advisory Group on Molecular Screening and Toxicogenomics (EAG MST)
- The Working Group of the National Coordinators of the Test Guidelines Programme (WNT)

AOP Example: MIE aromatase inhibition

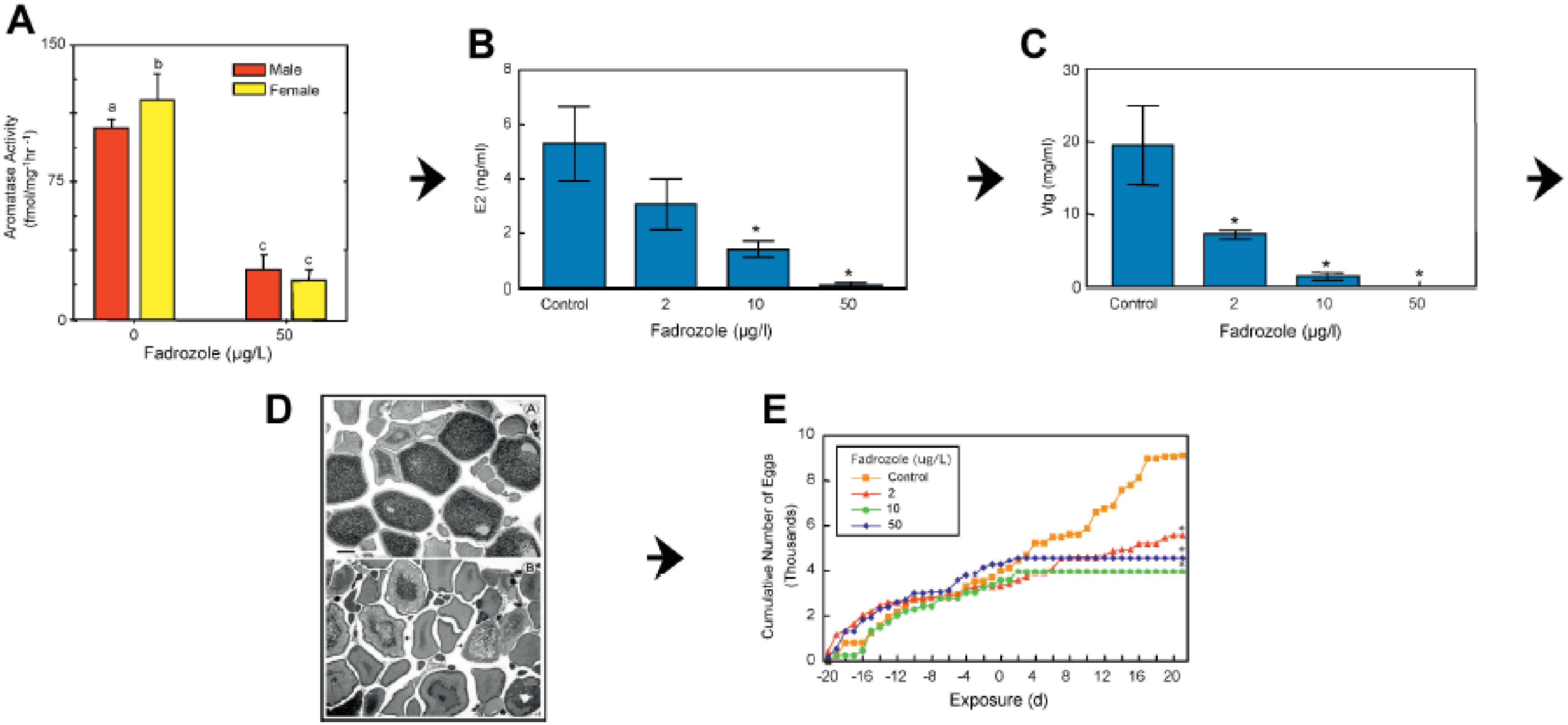
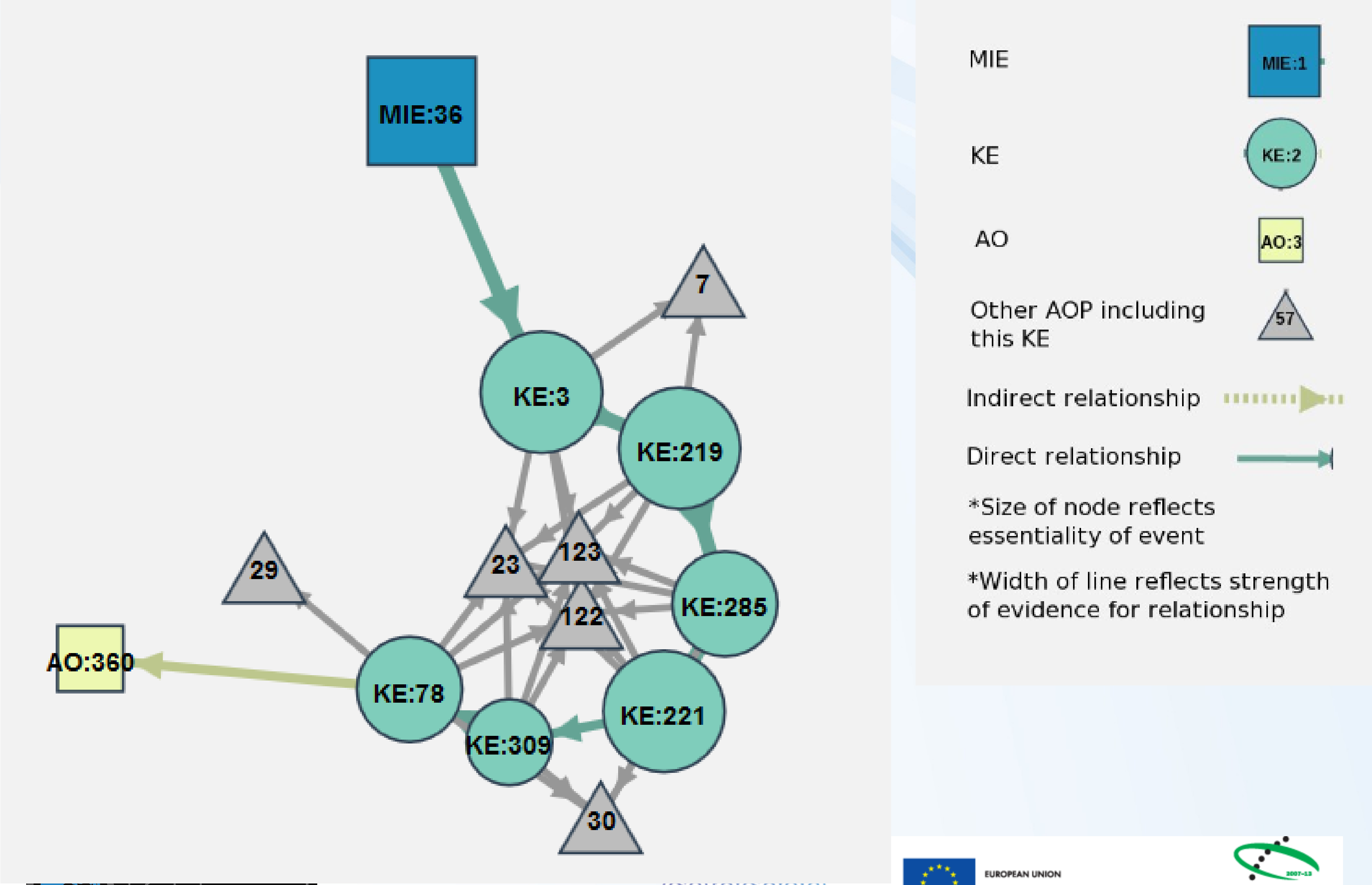


Fig. 3. An adverse outcome pathway in fish [2,50]. Aromatase inhibitor example. (**A**) Aromatase inhibition by fadrozole; (**B**) Reduction in circulating estradiol; (**C**) Reduction in circulating vitellogenin (Vtg); (**D**) Histopathology of ovarian tissue, top panel normal ovary, bottom panel fadrozole treated; note oocyte atresia; (**E**) Adverse outcome on egg production–fecundity (© Elsevier, Used with permission,)

Environmental Toxicology and Chemistry, Vol. 30, No. 1, pp. 64–76, 2011

Aromatase inhibition leading to reproductive dysfunction (in fish)

https://aopwiki.org/wiki/index.php/Aop:25


MIE:36
7
KE:3
KE:219
29
23
123
122
KE:285
AO:360
KE:78
KE:309
KE:221
30
MIE:1
KE:2
AO:3
57

MIE

KE

AO

Other AOP including this KE

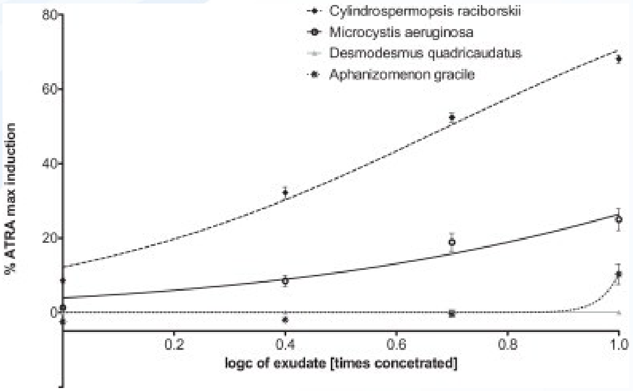
Indirect relationship

Direct relationship

*Size of node reflects essentiality of event

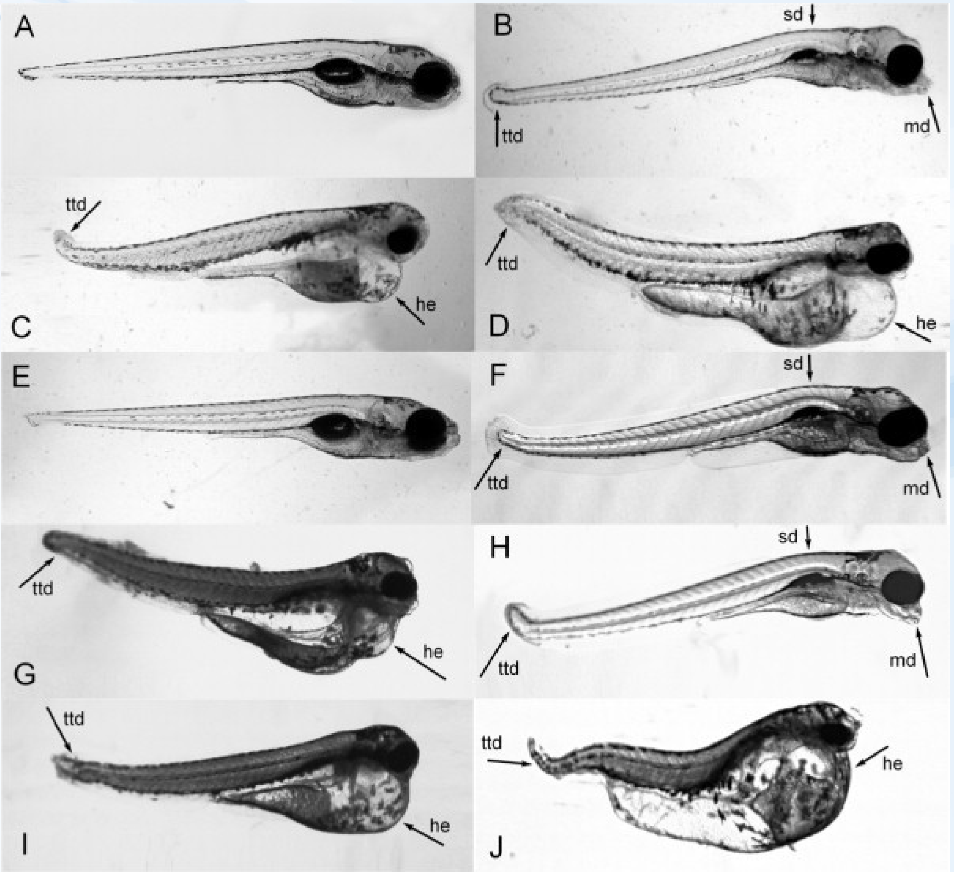
*Width of line reflects strength of evidence for relationship

AOP Example from RECETOX: Modulation of RAR/RXR → developmental toxicity in fish



Activation of RAR/RXR

in P19/A15 cells by atRA and cyanobacterial metabolites



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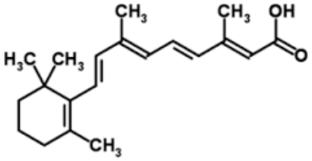
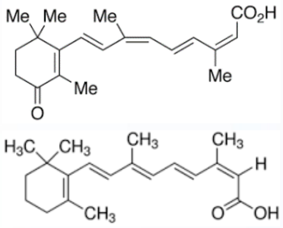
ZF exposed to ATRA and cyanobacterial (120 hpf) - Control (A), exudates of *C. raciborskii* 3.3 (B) and 10 (C), *M. aeruginosa* 10 (D) and *D. quadricaudatus* 17 (E). ATRA 4 μg/L (13.3 nM) (F), 12 μg/L (40 nM) ((G) and (H)), 36 μg/L (I) and 108 μg/L (J).



CH3
CH3
OH
H3C
CH3
O
CH3

atRA



Me
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CO2H
Me
Me
O
H3C
CH3
CH3
CH3
H
CH3
O
OH

other RAs in cyanos

Jonáš et al. 2014 Aquatic Toxicology
http://dx.doi.org/10.1016/j.aquatox.2014.06.022

International QSAR Foundation

Effectopedia

The Online Encyclopedia of Adverse Effect Pathways

- http://www.effectopedia.org/ -> link to program download
- Visually Expresses AOPs in their **biological context**:
  - Life-stage, Taxonomy, Gender, Time-to-effect..
- **Quantitative Relationships**
- **ADME** (Absorption, Distribution, Metabolism, Excretion)
- Open-knowledge, crowd-sourcing
- Formal approval not required to enter / modify
- Credit to authors / reviewers
- Even fragments of information are welcome (any contribution)
- Export<->Import from/to AOP Wiki & others

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Related Projects & Studies & Databases

- **TOXNET - http://toxnet.nlm.nih.gov/**
  - searching databases on toxicology, hazardous chemicals, environmental health, and toxic releases
- **Tox21 - http://www.epa.gov/ncct/Tox21/**
  - 10,000 chemicals
  - 14 concentrations, 4 logs, 3 replicates
  - 1536 well plates, 2-8 uL volumes
  - 50+ assays

- **ToxCast - http://www.epa.gov/ncct/toxcast/**
  - App. 2000 chemicals
  - 700+ assay, 300 signaling pathways
  - DATA AVAILABLE iCSS Dashboard
    - http://actor.epa.gov/dashboard
    - http://ww.epa.gov/ncct/toxcast/data.html

Related Projects & Studies & Databases

- **ToxRefDB** (Toxicity Reference Database)
  - *in vivo* toxicological data
  - http://actor.epa.gov/toxrefdb/faces/Home.jsp
- **ExpoCast**
  - information on human exposures
  - http://www.epa.gov/ncct/expocast/
- **Human Toxome Project**
  - information on human exposures
  - http://www.ewg.org/sites/humantoxome/
- **Agriculture Health Study**
  - Occupational Exposure to Pesticides – a cohort study
  - http://aghealth.nih.gov/

Summary

ALTERIVS NON SIT QVI SVVS ESSE POTEST
LAVS DEO, PAX VIVIS, REQVIES AETERNA SEPVLTIS
OMNE DONVM PERFECTVM A DEO, IMPERFECTVM A DIABOLO
AVREOLVS PHILIPPVS THEOPHRASTVS

- **Toxicology is about doses**
  - The goal is LD(LC)50 or NOAEL/NOEC
- **Legislation defines**

  … what assays and how to do them
  - About 30 assays
  - The most widely used standard - OECD Guidelines for Testing of Chemicals

OECD

- **Replacing „black box“ in traditional testing**
  - Synthesis of mechanistic and omics data
  - Adverse Outcome Pathways
  - Strategically supported by OECD, EU, USA

ERDC
saop
Adverse Outcome Pathway WIKI
OECD

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Do we need testing with animals?

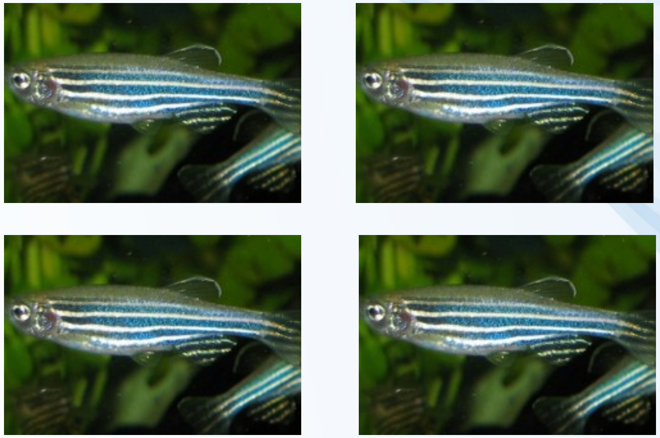
Are there alternatives ?

„Alternatives“ to toxicity testing … 3R rules

3Rs

REPLACEMENT

Online Computer Simulations and Applications



REDUCTION

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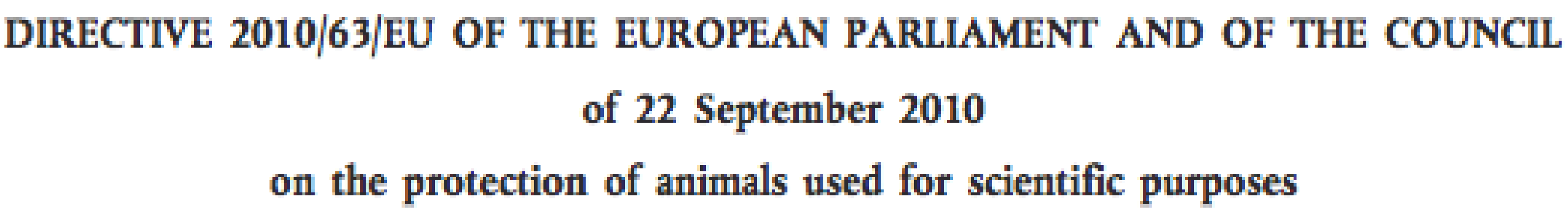
REFINEMENT

European Policies on 3Rs

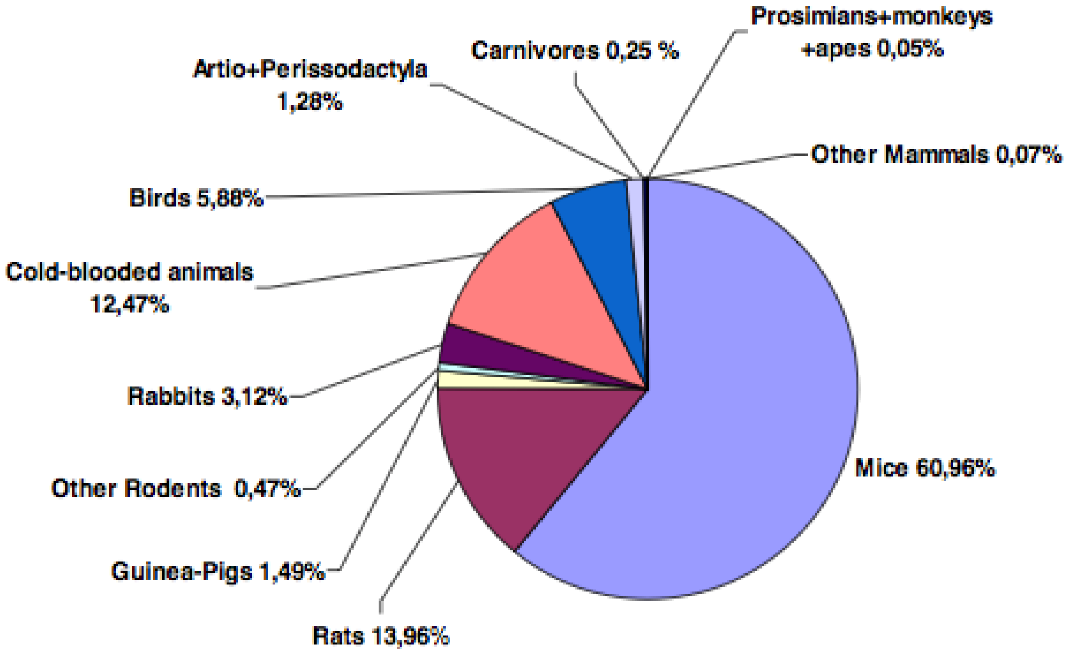


DIRECTIVE 2010/63/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 22 September 2010

on the protection of animals used for scientific purposes

Figure 1.1
Percentages of animals used by classes in the Member States



Use of animals in EU (2011)

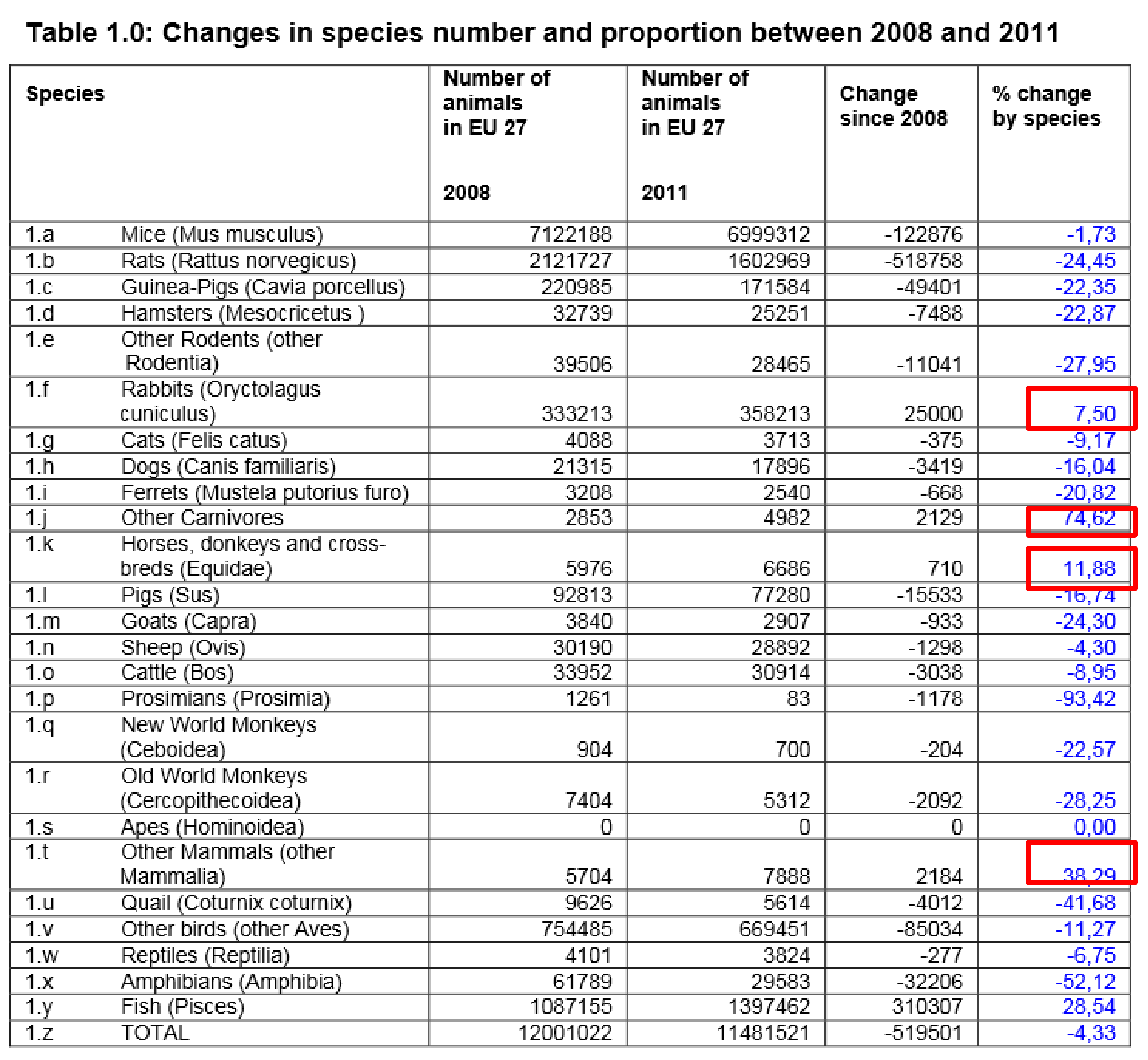
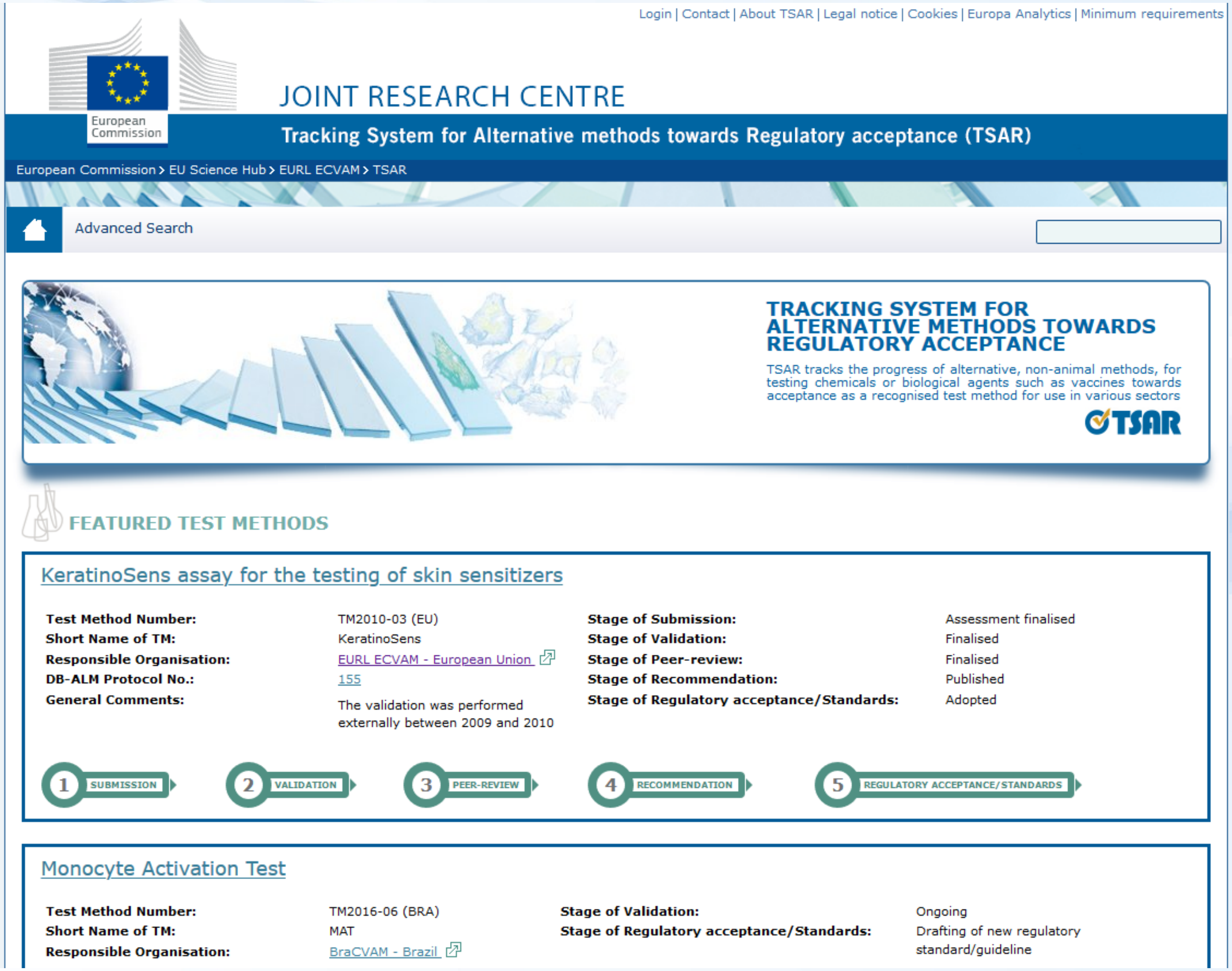


Table 1.0: Changes in species number and proportion between 2008 and 2011

Species		Number of animals in EU 27 2008	Number of animals in EU 27 2011	Change since 2008	% change by species
1.a	Mice (Mus musculus)	7122188	6999312	-122876	-1,73
1.b	Rats (Rattus norvegicus)	2121727	1602969	-518758	-24,45
1.c	Guinea-Pigs (Cavia porcellus)	220985	171584	-49401	-22,35
1.d	Hamsters (Mesocricetus)	32739	25251	-7488	-22,87
1.e	Other Rodents (other Rodentia)	39506	28465	-11041	-27,95
1.f	Rabbits (Oryctolagus cuniculus)	333213	358213	25000	7,50
1.g	Cats (Felis catus)	4088	3713	-375	-9,17
1.h	Dogs (Canis familiaris)	21315	17896	-3419	-16,04
1.i	Ferrets (Mustela putorius furo)	3208	2540	-668	-20,82
1.j	Other Carnivores	2853	4982	2129	74,62
1.k	Horses, donkeys and cross-breds (Equidae)	5976	6686	710	11,88
1.l	Pigs (Sus)	92813	77280	-15533	-16,74
1.m	Goats (Capra)	3840	2907	-933	-24,30
1.n	Sheep (Ovis)	30190	28892	-1298	-4,30
1.o	Cattle (Bos)	33952	30914	-3038	-8,95
1.p	Prosimians (Prosimia)	1261	83	-1178	-93,42
1.q	New World Monkeys (Ceboidea)	904	700	-204	-22,57
1.r	Old World Monkeys (Cercopithecoidea)	7404	5312	-2092	-28,25
1.s	Apes (Hominoidea)	0	0	0	0,00
1.t	Other Mammals (other Mammalia)	5704	7888	2184	38,29
1.u	Quail (Coturnix coturnix)	9626	5614	-4012	-41,68
1.v	Other birds (other Aves)	754485	669451	-85034	-11,27
1.w	Reptiles (Reptilia)	4101	3824	-277	-6,75
1.x	Amphibians (Amphibia)	61789	29583	-32206	-52,12
1.y	Fish (Pisces)	1087155	1397462	310307	28,54
1.z	TOTAL	12001022	11481521	-519501	-4,33

https://tsar.jrc.ec.europa.eu/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JOINT RESEARCH CENTRE
Tracking System for Alternative methods towards Regulatory acceptance (TSAR)
European Commission > EU Science Hub > EURL ECVAM > TSAR
Advanced Search
TSAR
FEATURED TEST METHODS
1 SUBMISSION
2 VALIDATION
3 PEER-REVIEW
4 RECOMMENDATION
5 REGULATORY ACCEPTANCE/STANDARDS

TRACKING SYSTEM FOR ALTERNATIVE METHODS TOWARDS REGULATORY ACCEPTANCE

TSAR tracks the progress of alternative, non-animal methods, for testing chemicals or biological agents such as vaccines towards acceptance as a recognised test method for use in various sectors

KeratinoSens assay for the testing of skin sensitizers

Test Method Number: TM2010-03 (EU)
Short Name of TM: KeratinoSens
Responsible Organisation: EURL ECVAM - European Union
DB-ALM Protocol No.: 155
General Comments: The validation was performed externally between 2009 and 2010
Stage of Submission: Assessment finalised
Stage of Validation: Finalised
Stage of Peer-review: Finalised
Stage of Recommendation: Published
Stage of Regulatory acceptance/Standards: Adopted

Monocyte Activation Test

Test Method Number: TM2016-06 (BRA)
Short Name of TM: MAT
Responsible Organisation: BraCVAM - Brazil
Stage of Validation: Ongoing
Stage of Regulatory acceptance/Standards: Drafting of new regulatory standard/guideline

- >60 3Rs Tests submitted to ECVAM since 2008 (update 01/2015)
- 10 validated or ongoing validation => Prioritisation!

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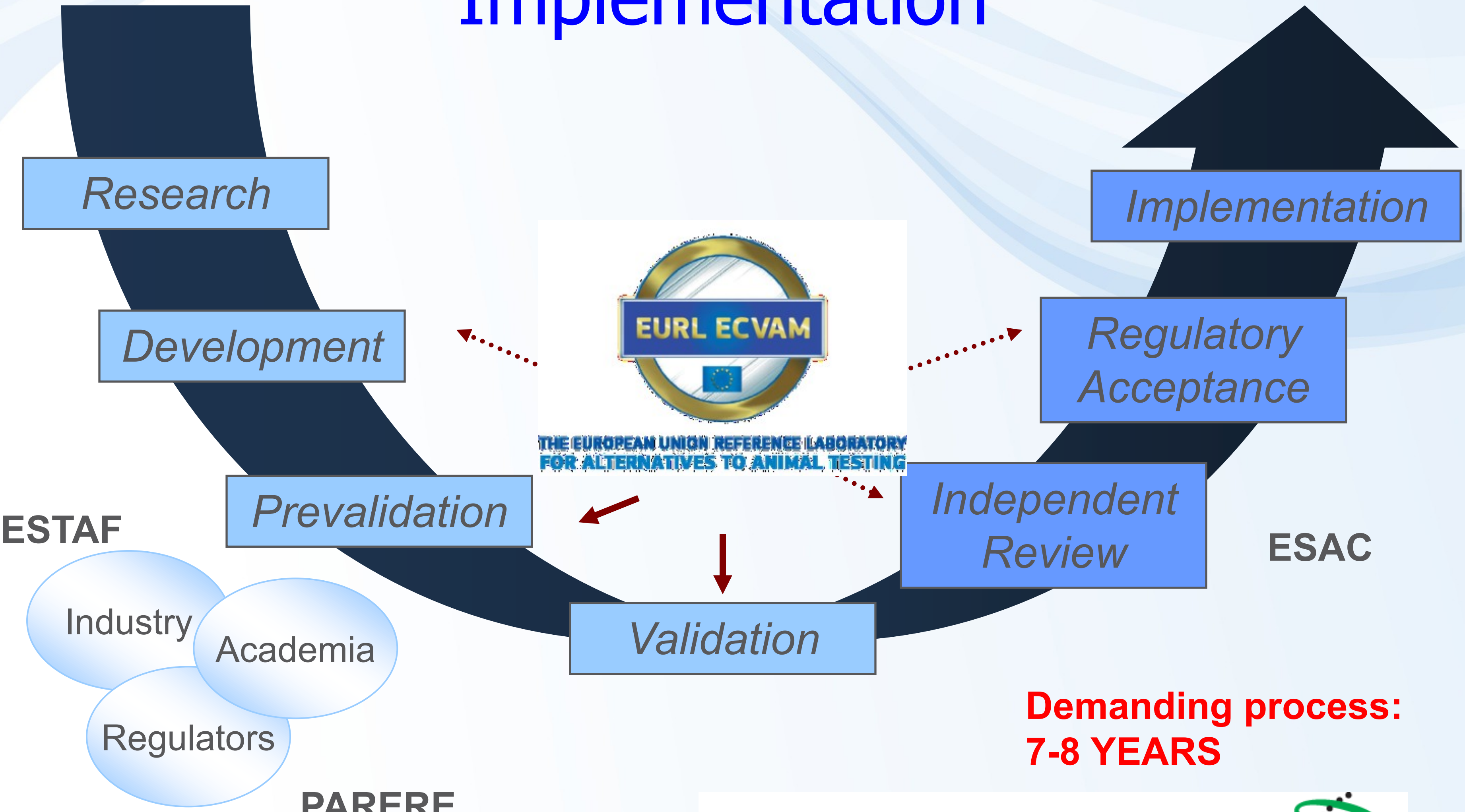
Alternative Methods – R&D to Implementation



Research

Development

Prevalidation

Validation

Independent Review

Regulatory Acceptance

Implementation

EURL ECVAM

THE EUROPEAN UNION REFERENCE LABORATORY FOR ALTERNATIVES TO ANIMAL TESTING

ESTAF

Industry

Academia

Regulators

PARERE

ESAC

Demanding process:
7-8 YEARS

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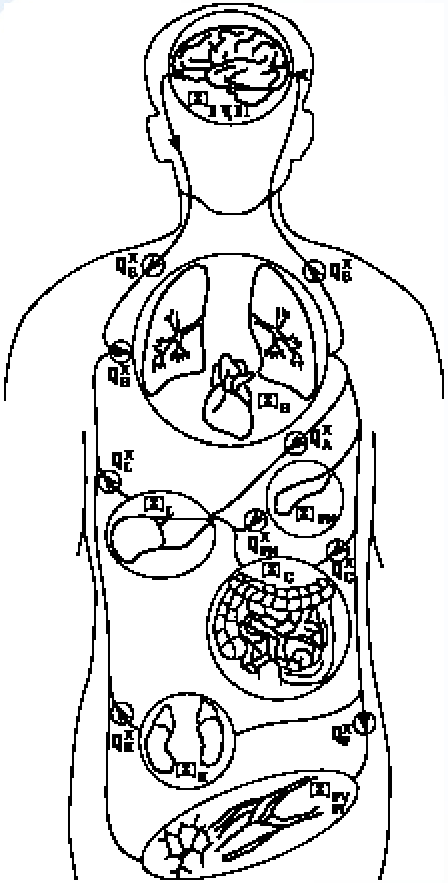
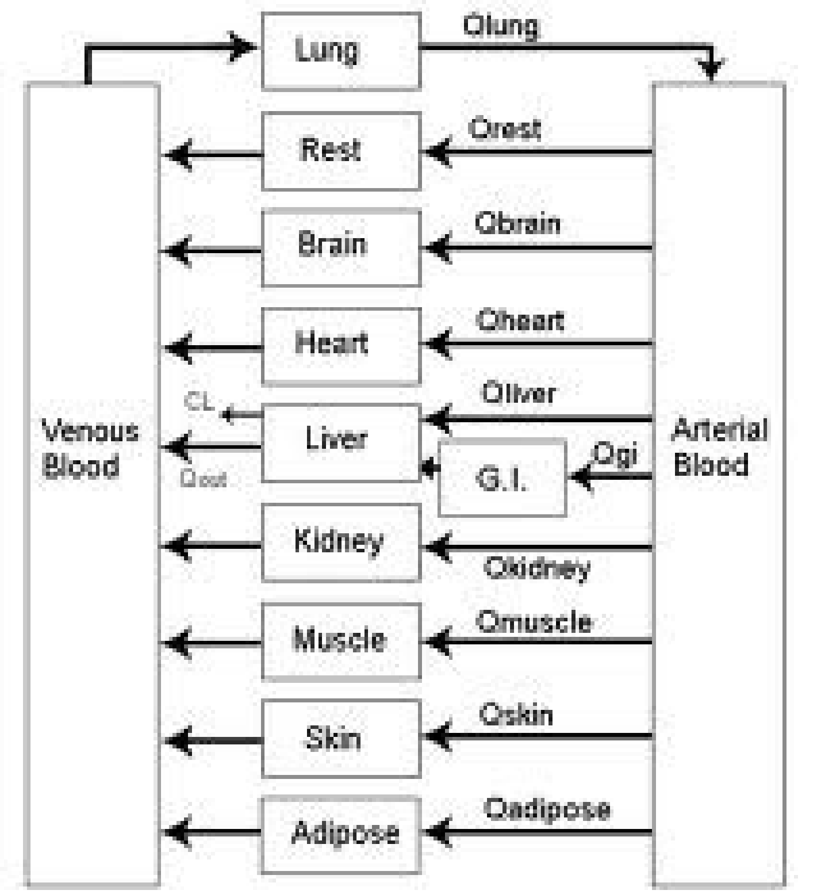
COMPUTATIONAL (ECO)TOXICOLOGY

?

PBPK models

PBPK (PBTK)
Physiologically based pharmacokinetic (toxicokinetic) models




Lung
Qlung
Rest
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Brain
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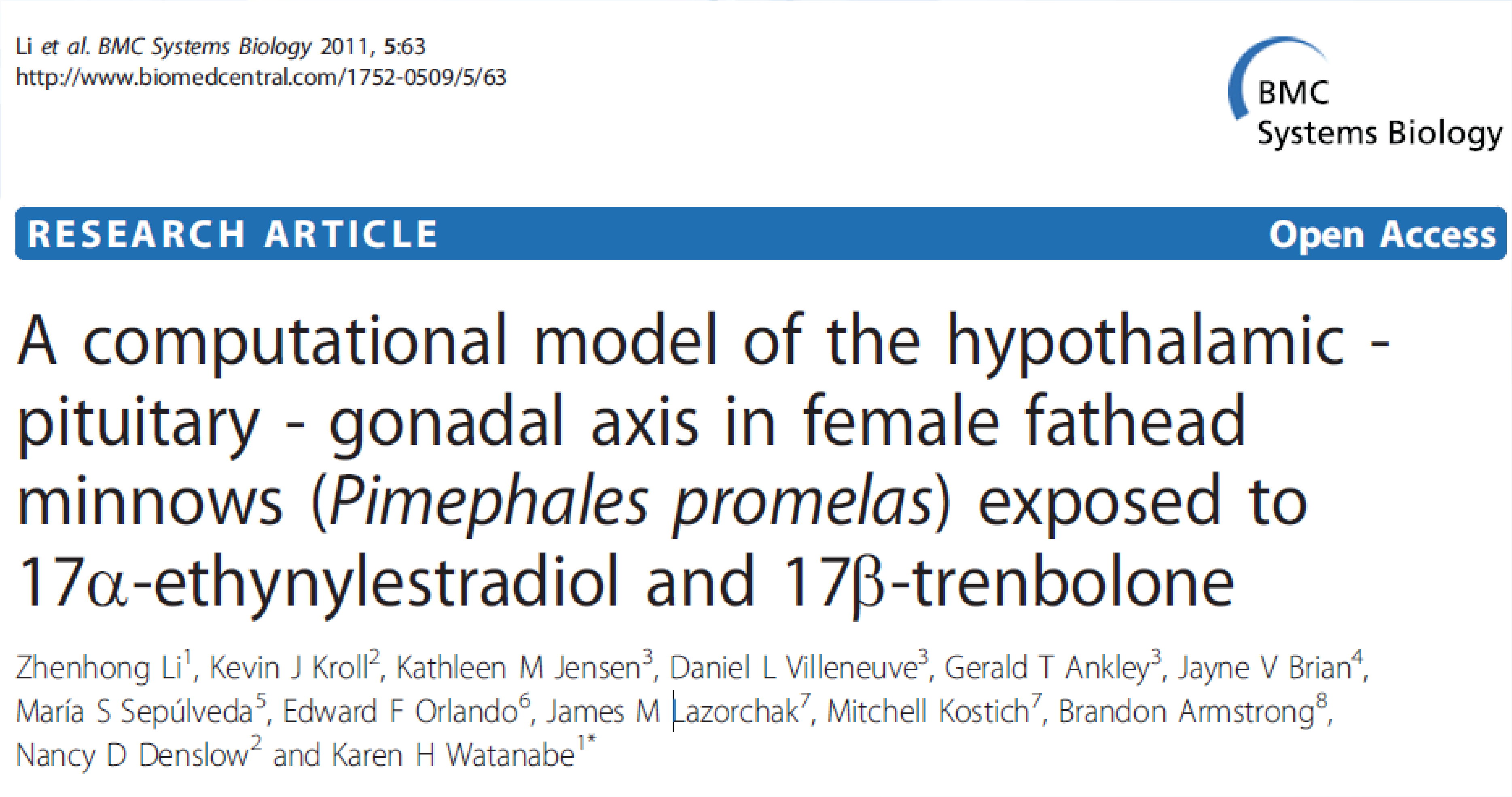
Heart
Qheart
Venous Blood
CL
Liver
Qout
Qliver
G.I.
Qgi
Arterial Blood
Kidney
Qkidney
Muscle
Qmuscle
Skin
Qskin
Adipose
Qadipose

Fragmentation of a complex systém to „boxes“

→ All Processes described by arrows (mathematical equations)

Example – computational toxicology for EDCs



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

BMC Systems Biology

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*]

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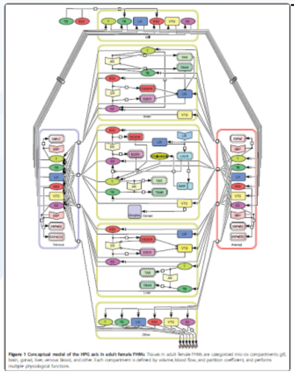
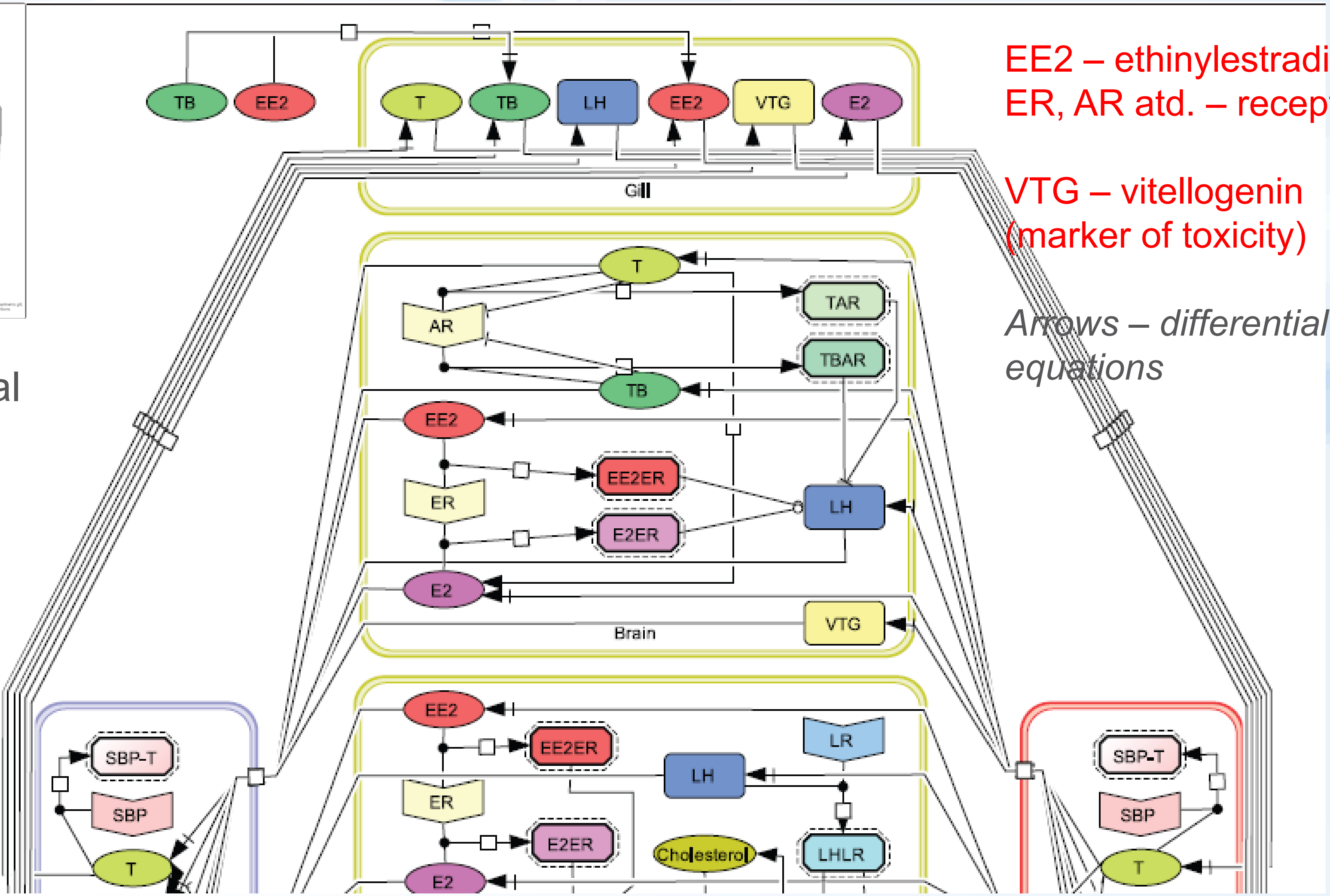


Conceptual model


TB
EE2
T
TB
LH
EE2
VTG
E2
Gill
T
TAR
AR
TBAR
TB
EE2
EE2ER
ER
LH
E2ER
E2
VTG
Brain
EE2
EE2ER
LR
LH
ER
E2ER
Cholesterol
LHLR
E2
SBP-T
SBP
T
SBP-T
SBP
T

EE2 – ethinylestradiol
ER, AR atd. – receptors

VTG – vitellogenin (marker of toxicity)

Arrows – differential equations

Research centre for toxic compounds in the environment

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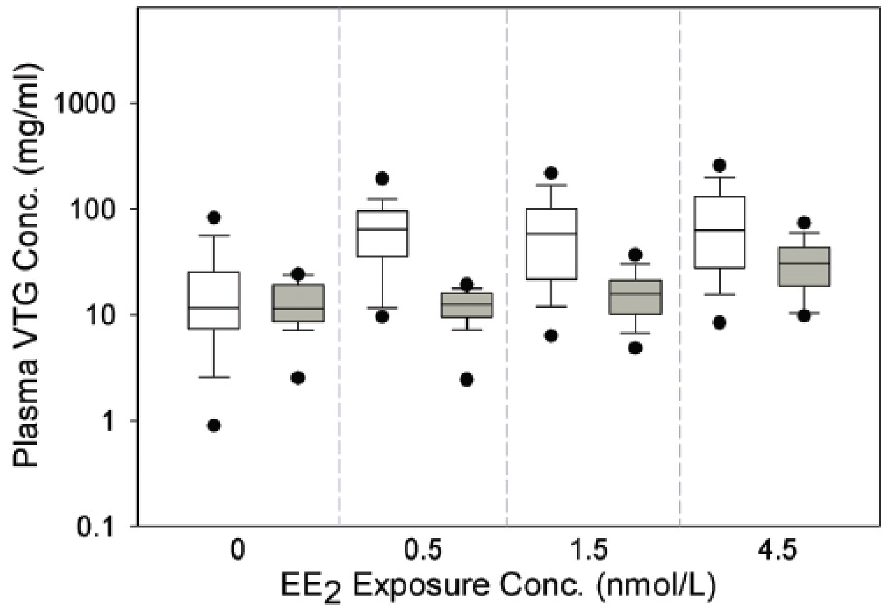


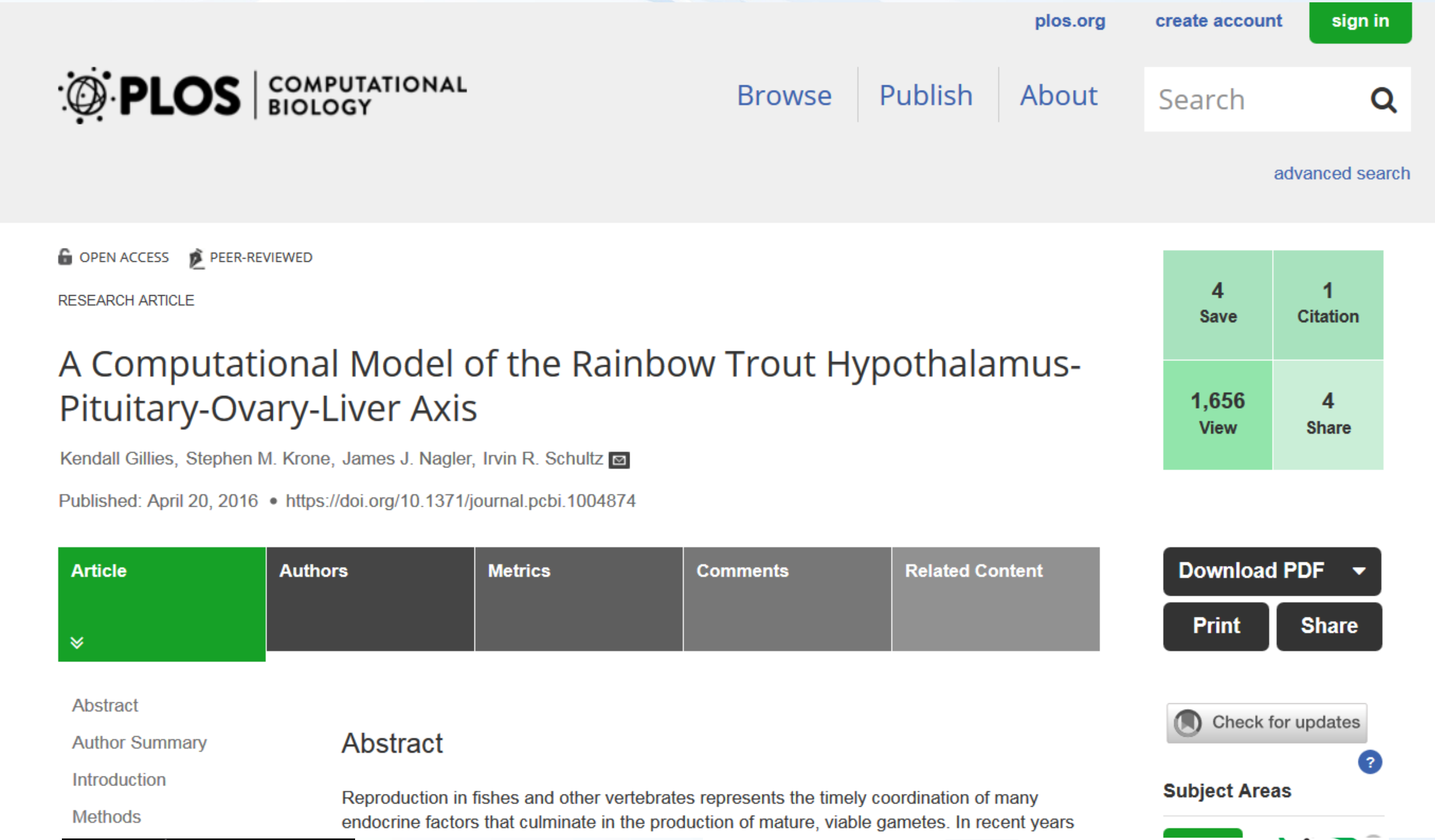
Figure 6 Comparison of model predictions with measured data in female FHMs exposed to EE_2. $n = 28$ at each sampling time. White boxes represent model predictions, and grey boxes represent measured data [42]. The x-axis represents EE_2 concentrations in ng/L. The solid line within the box marks the 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

Update – quantitative mechanistic/computational toxicology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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

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

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

Update – quantitative mechanistic/computational toxicology

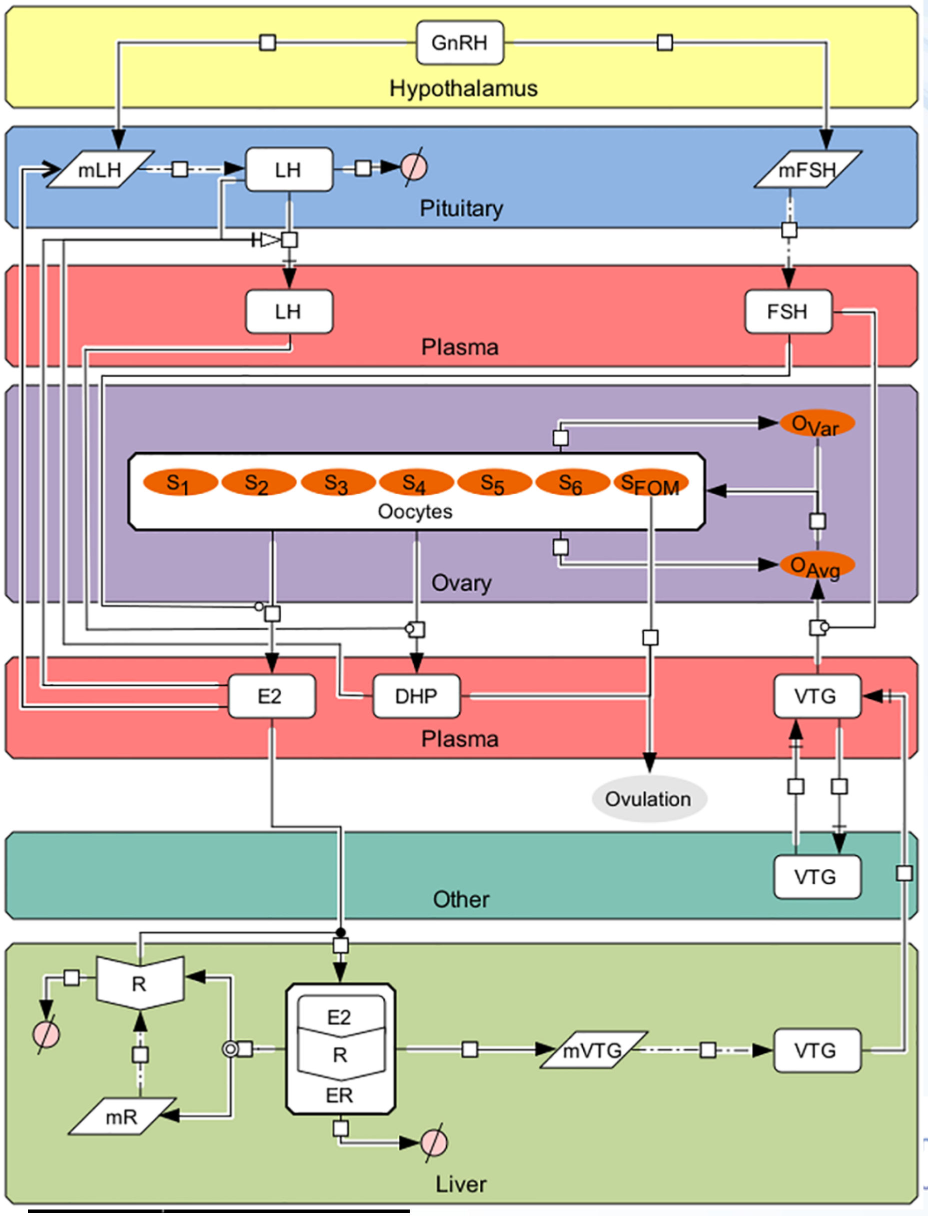
GnRH
Hypothalamus
mLH
LH
mFSH
Pituitary
LH
FSH
Plasma
O_{Var}
S_1
S_2
S_3
S_4
S_5
S_6
S_{FOM}
Oocytes
O_{Avg}
Ovary
E2
DHP
VTG
Plasma
Ovulation
VTG
Other
R
E2
R
ER
mVTG
VTG
mR
Liver

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.

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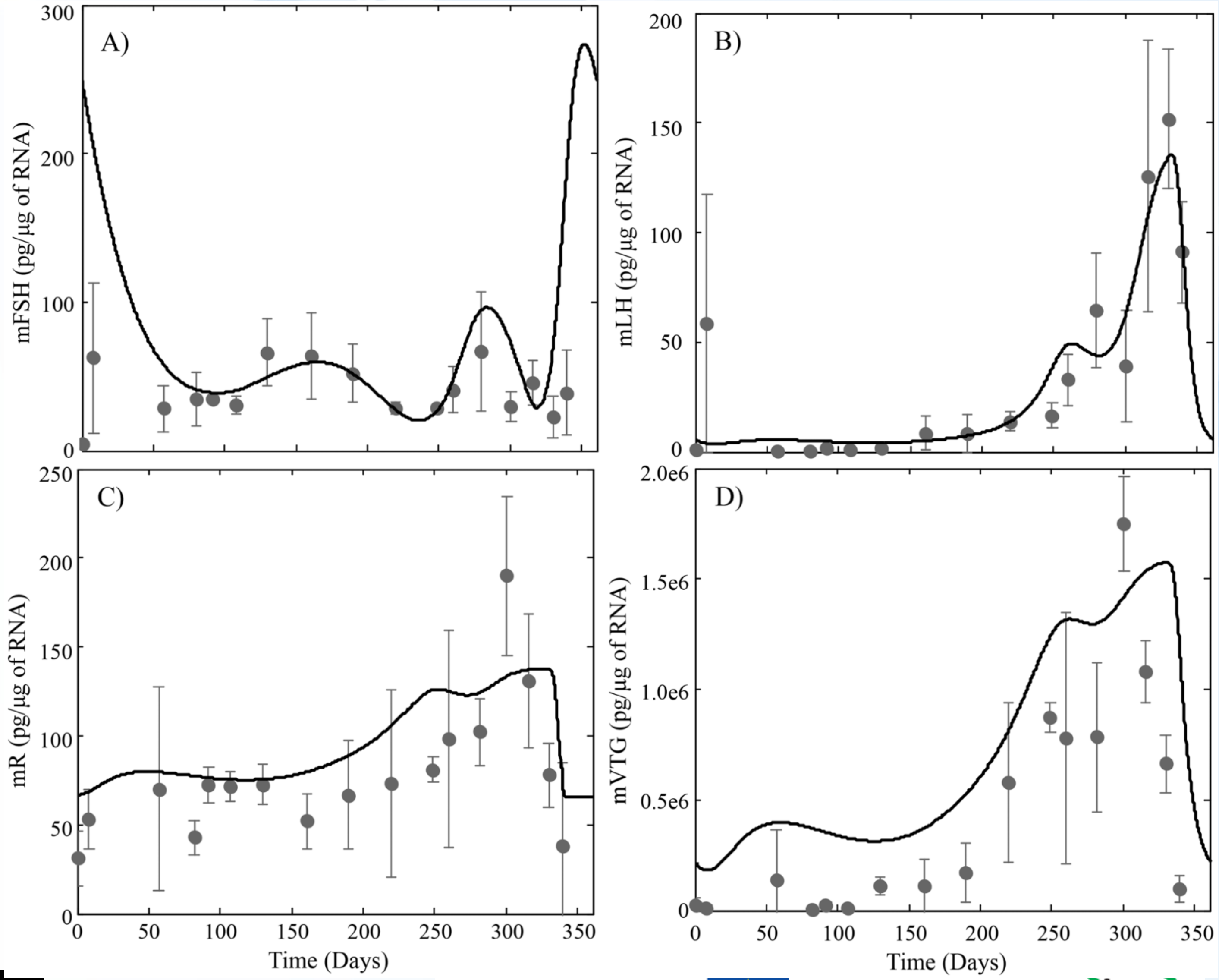
Fig 3. HPOL **model predictions** for (A) pituitary levels of FSH_β subunit mRNA, (B) pituitary levels of LH_β subunit mRNA, (C) Hepatic levels of E2 receptor mRNA and (D) Hepatic levels of VTG mRNA **Observed data** (dark grey circles; mean TG mR*n* = 3)



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Global Climate Change

INTERACTIONS BETWEEN CHEMICAL AND CLIMATE STRESSORS: A ROLE FOR MECHANISTIC TOXICOLOGY IN ASSESSING CLIMATE CHANGE RISKS

Michael J. Hooper,*† Gerald T. Ankley,‡ Daniel A. Cristol,§ Lindley A. Maryoung,||
Pamela D. Noyes,# and Kent E. Pinkerton††
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‡U.S. Environmental Protection Agency, Office of Research and Development, National Health and Environmental Effects Research Laboratory,
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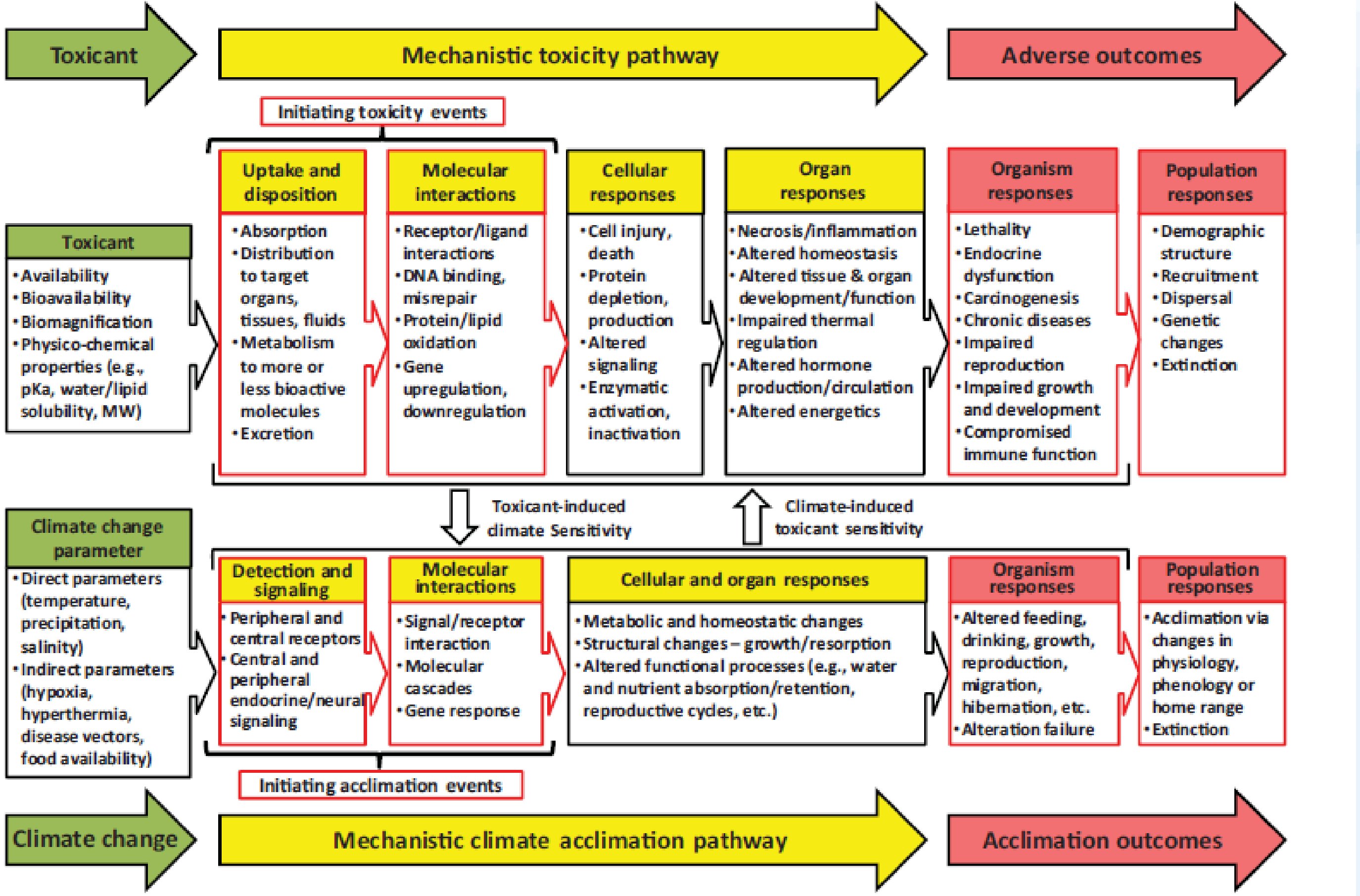
||Department of
#Nicholas Sc
††Center for Health



Toxicant → **Mechanistic toxicity pathway** → **Adverse outcomes**

Initiating toxicity events

Toxicant
- Availability
- Bioavailability
- Biomagnification
- Physico-chemical properties (e.g., pKa, water/lipid solubility, MW)

Uptake and disposition
- Absorption
- Distribution to target organs, tissues, fluids
- Metabolism to more or less bioactive molecules
- Excretion

Molecular interactions
- Receptor/ligand interactions
- DNA binding, misrepair
- Protein/lipid oxidation
- Gene upregulation, downregulation

Cellular responses
- Cell injury, death
- Protein depletion, production
- Altered signaling
- Enzymatic activation, inactivation

Organ responses
- Necrosis/inflammation
- Altered homeostasis
- Altered tissue & organ development/function
- Impaired thermal regulation
- Altered hormone production/circulation
- Altered energetics

Organism responses
- Lethality
- Endocrine dysfunction
- Carcinogenesis
- Chronic diseases
- Impaired reproduction
- Impaired growth and development
- Compromised immune function

Population responses
- Demographic structure
- Recruitment
- Dispersal
- Genetic changes
- Extinction

Toxicant-induced climate Sensitivity

Climate-induced toxicant sensitivity

Climate change parameter
- Direct parameters (temperature, precipitation, salinity)
- Indirect parameters (hypoxia, hyperthermia, disease vectors, food availability)

Detection and signaling
- Peripheral and central receptors
- Central and peripheral endocrine/neural signaling

Molecular interactions
- Signal/receptor interaction
- Molecular cascades
- Gene response

Cellular and organ responses
- Metabolic and homeostatic changes
- Structural changes – growth/resorption
- Altered functional processes (e.g., water and nutrient absorption/retention, reproductive cycles, etc.)

Organism responses
- Altered feeding, drinking, growth, reproduction, migration, hibernation, etc.
- Alteration failure

Population responses
- Acclimation via changes in physiology, phenology or home range
- Extinction

Initiating acclimation events

Climate change → **Mechanistic climate acclimation pathway** → **Acclimation outcomes**

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‡U.S. Environmental Protection Agency, Office of Research and Development, National Health and Environmental Effects Research Laboratory, Mid-Continent Ecology Division, Duluth, Minnesota
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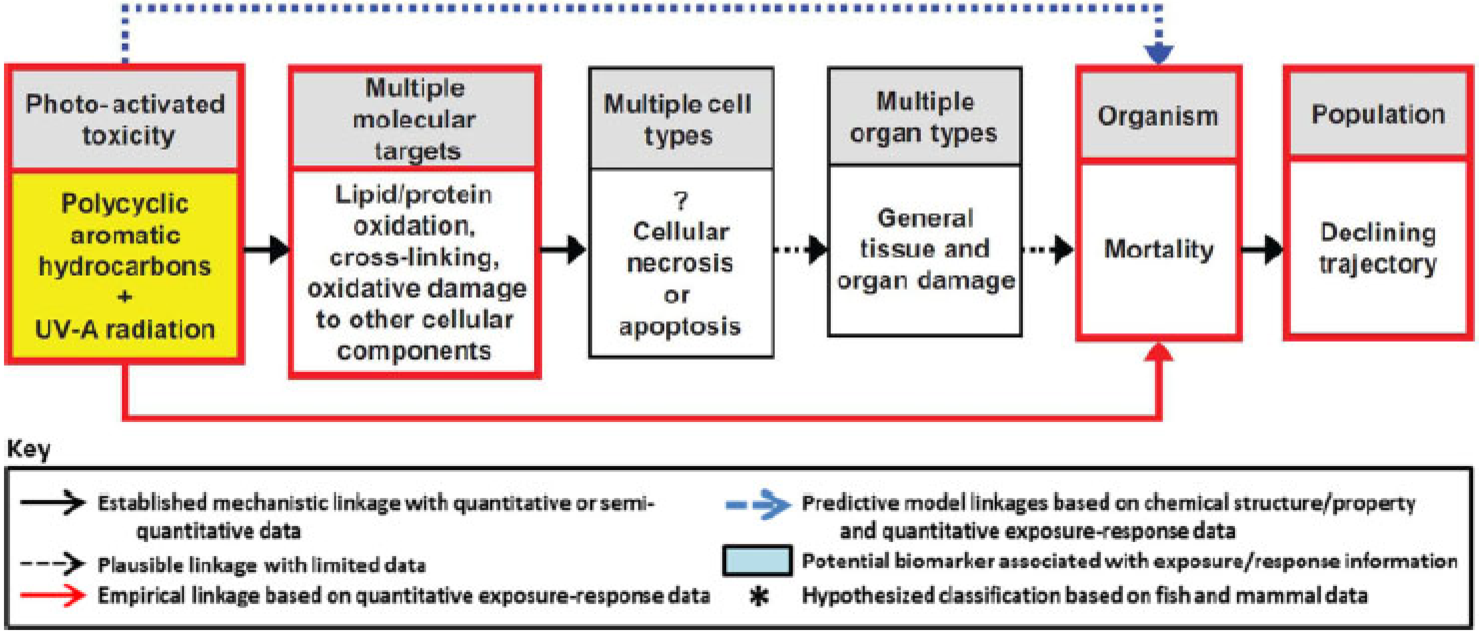
Photo-activated toxicity
Polycyclic aromatic hydrocarbons + UV-A radiation
Multiple molecular targets
Lipid/protein oxidation, cross-linking, oxidative damage to other cellular components
Multiple cell types
? Cellular necrosis or apoptosis
Multiple organ types
General tissue and organ damage
Organism
Mortality
Population
Declining trajectory
Key
Established mechanistic linkage with quantitative or semi-quantitative data
Plausible linkage with limited data
Empirical linkage based on quantitative exposure-response data
Predictive model linkages based on chemical structure/property and quantitative exposure-response data
Potential biomarker associated with exposure/response information
Hypothesized classification based on fish and mammal data

Fig. 2. Adverse outcome pathway of the interaction of ultraviolet radiation with polycyclic aromatic hydrocarbons. With permission from Ankley et al. [14]. [Color figure can be seen in the online version of this article, available at wileyonlinelibrary.com.]

Closing remarks

- Ecotoxicology is exciting **science**!
- **Interface**: science and society
- Many **opportunities**
- Sometimes **hard work**

  10% inspiration and 90% „perspiration“

- Be creative: move frontiers
- Keep the purpose in mind
- Be critical: do not accept perceptions as facts
- Speak up: you have something to say!