Why does interdisciplinary matter within the field of ecotoxicology?

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IWS - TU2 - September 6, 2023

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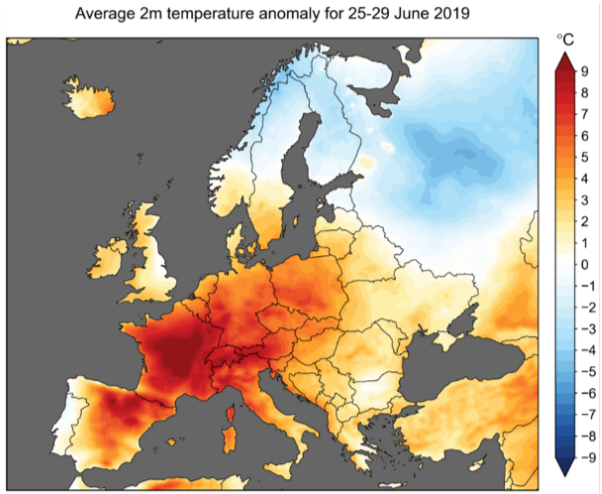
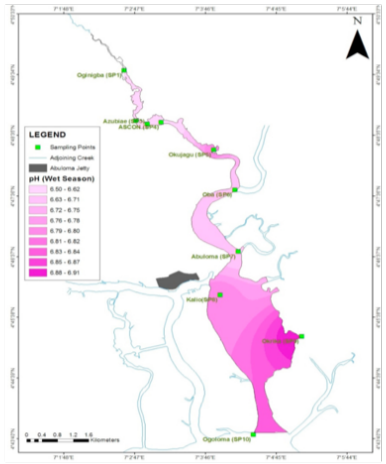
Detailed content

Ecosystems are under...

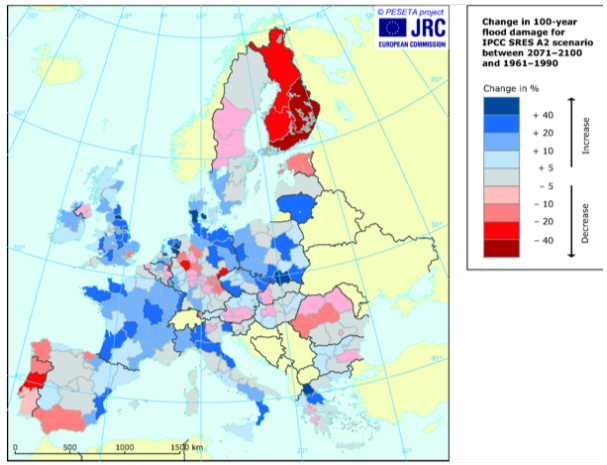
...environmental pressure
due to variations in temperature, flow, conductivity...



https://climate.copernicus.eu/record-breaking-temperatures-june



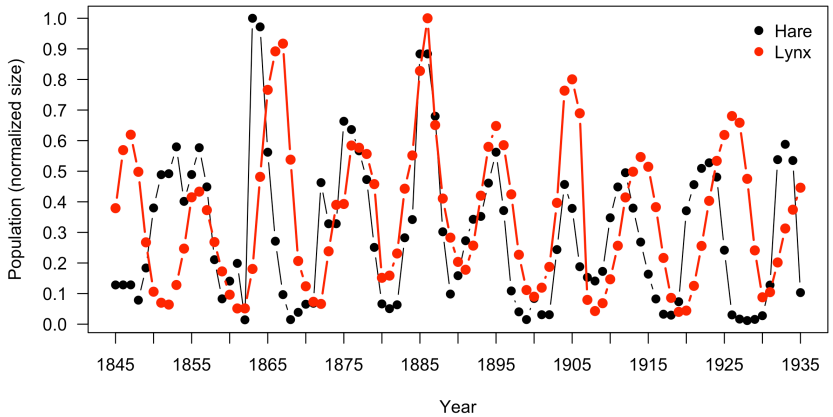
L.B. Ibanga, J.A. Nkwoji, A.I. Usese, I.C. Onyema, L.O. Chukwu. 2019. Hydrochemistry and heavy metals concentrations in sediment of Woji creek and Bonny estuary, Niger Delta, Nigeria. *Regional Studies in Marine Science*, 25, 10043.



https://www.eea.europa.eu/data-and-maps/figures/projected-change-in-damage-of-river-floods-with-a-100-year-return-period-between-2071-2100-and-1961-1990

Ecosystems are under...

...ecological pressure
due to competition, predation, resource availability...



Ecosystems are under...

...chemical pressure
due to massive rejection of xenobiotics in air, soil and water

http://www.univers-nature.com/actualite/le-reste/plus-dune-commune-sur-deux-concernees-par-la-pollution-aux-nitrates-57979.html

https://www.paperblog.fr/3707710/environnement-la-nature-est-a-80-detruite-par-les-industries/

https://www.thehindu.com

Ecotoxicology

- A scientific field at the bridge of chemistry, toxicology and ecology

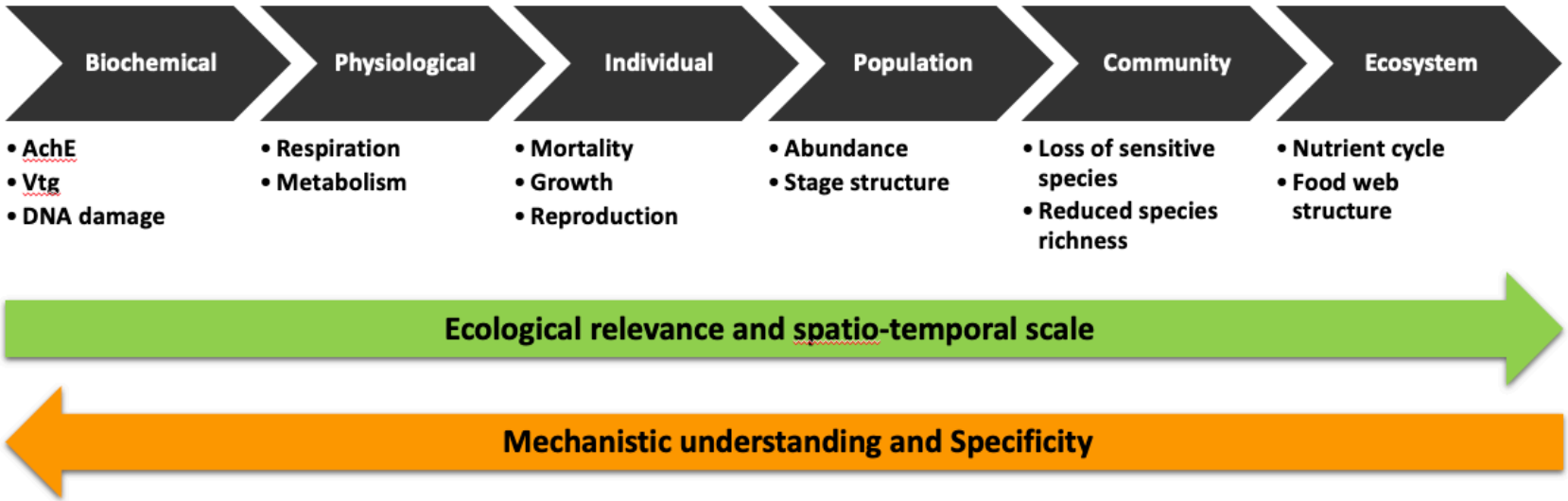
  The branch of toxicology concerned with the study of toxic effects, caused by natural or synthetic pollutants, to the constituents of ecosystems, animals (including humans), vegetables and microorganisms, in an integrated context [Truhaut, 1977]

  Ecology in the presence of toxicants [Chapman, 2002]

- In ecotoxicology, the answer of the ecosystem to environmental perturbations (physical, chemical and/or biological) is studied in all compartments of the biosphere (air, soil and water) and at all levels of biological organization [Walker et al., 2006]

From one level of organization to the next

Depending on the level of biological organization, answers to chemical pressure may strongly differ [Clements, 2000]



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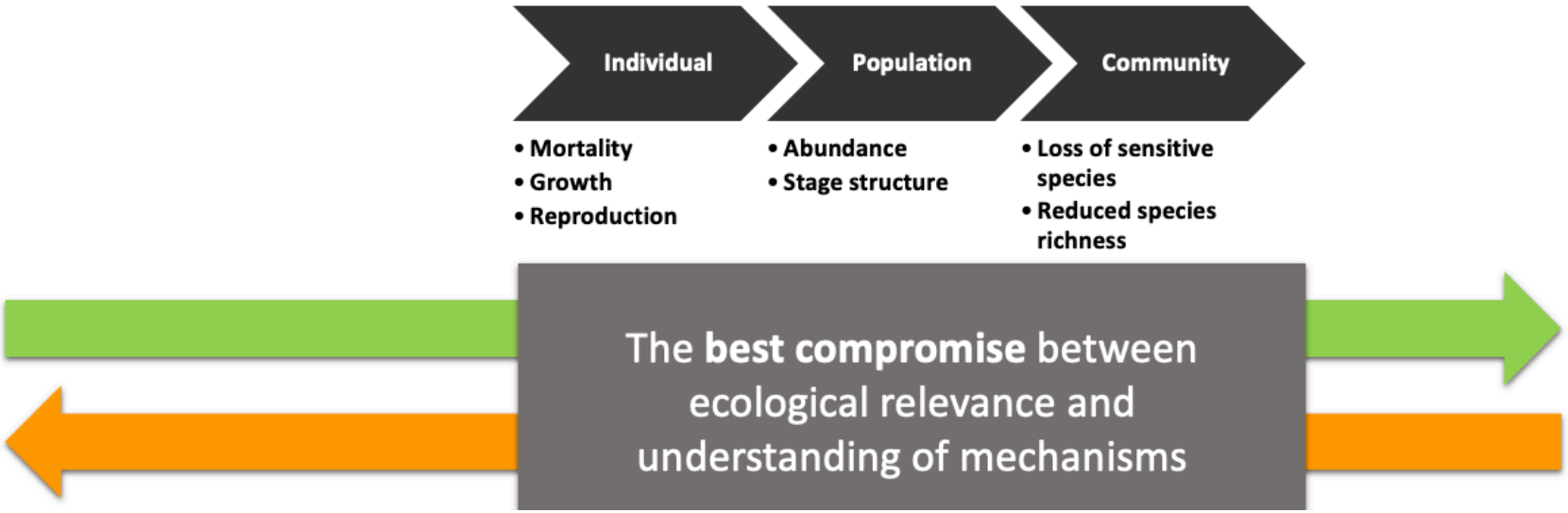
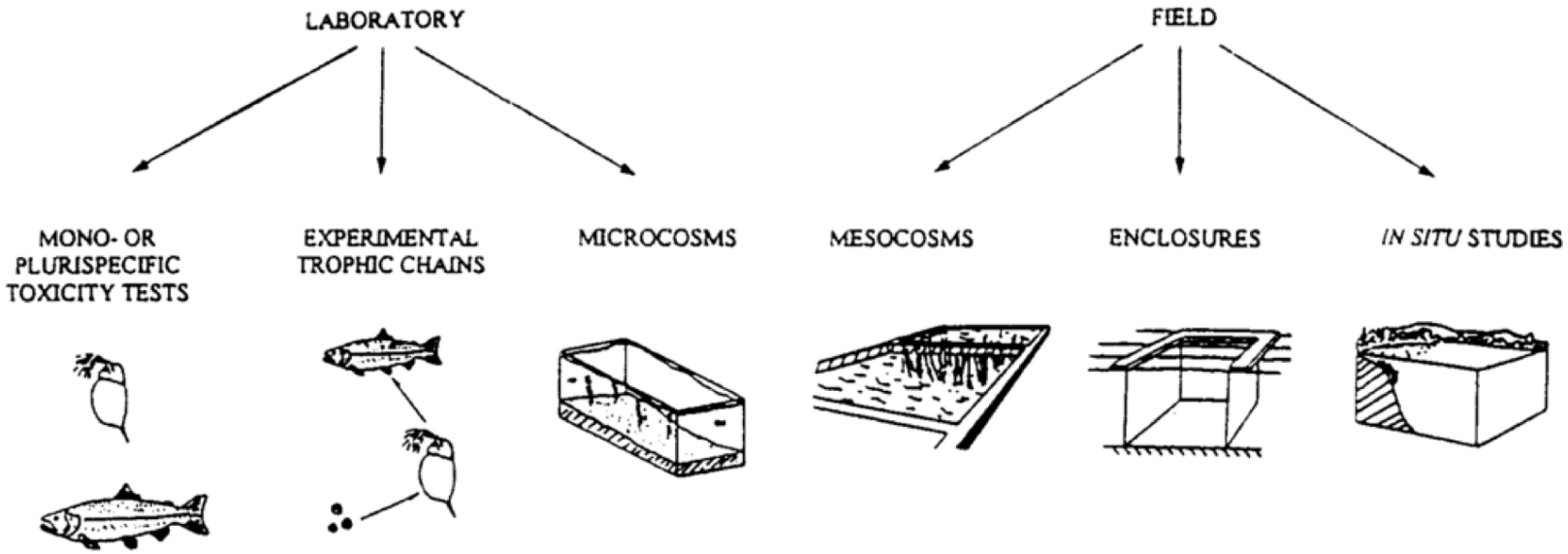
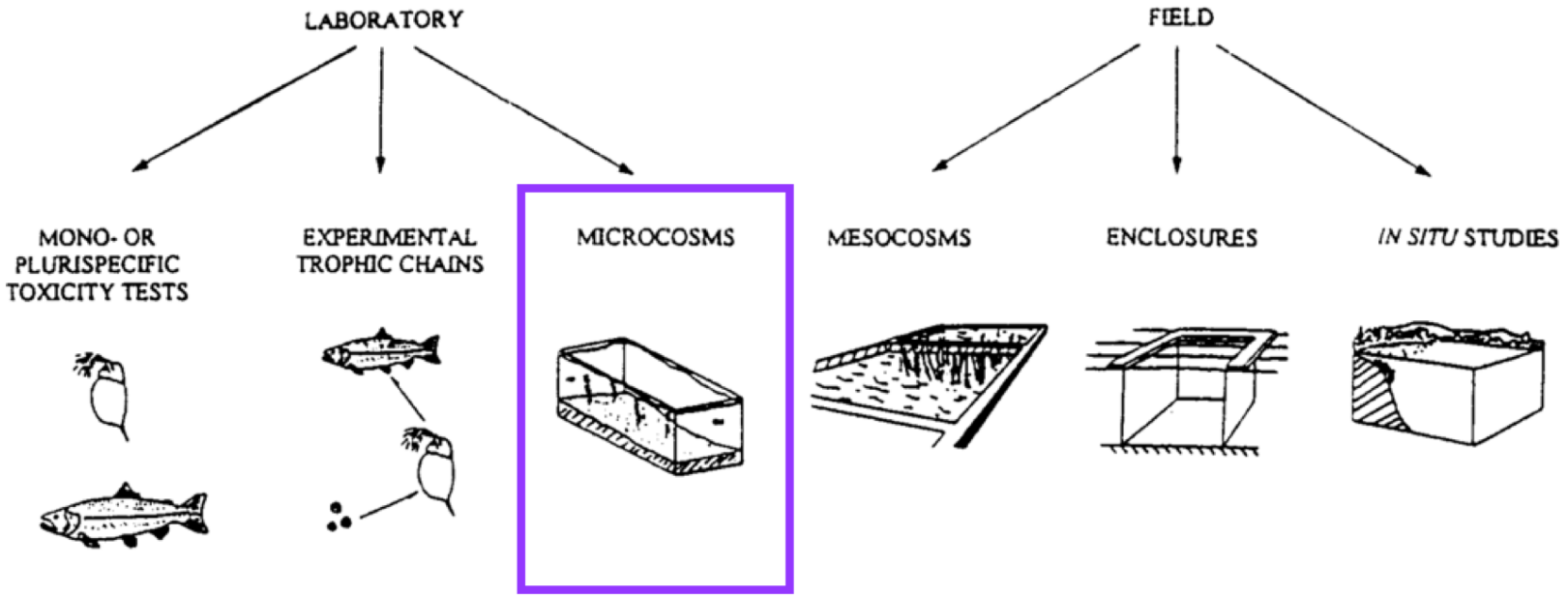


A variety of experimental devices



[Caquet et al., 1996]

A variety of experimental devices



[Caquet et al., 1996]

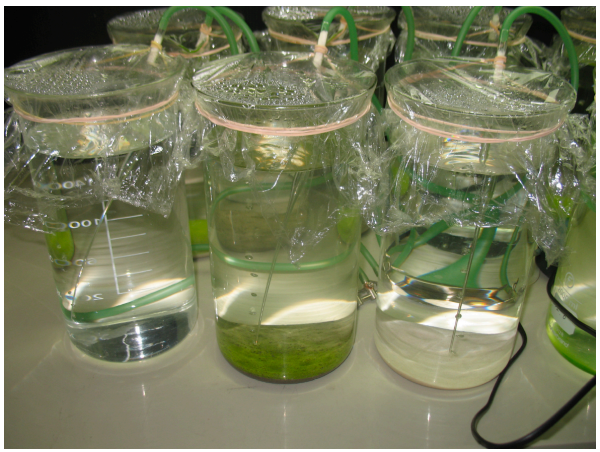
Bernard CLÉMENT

Associate professor, ENTPE

Research theme

Use of lab aquatic microcosms for the environmental risk assessment

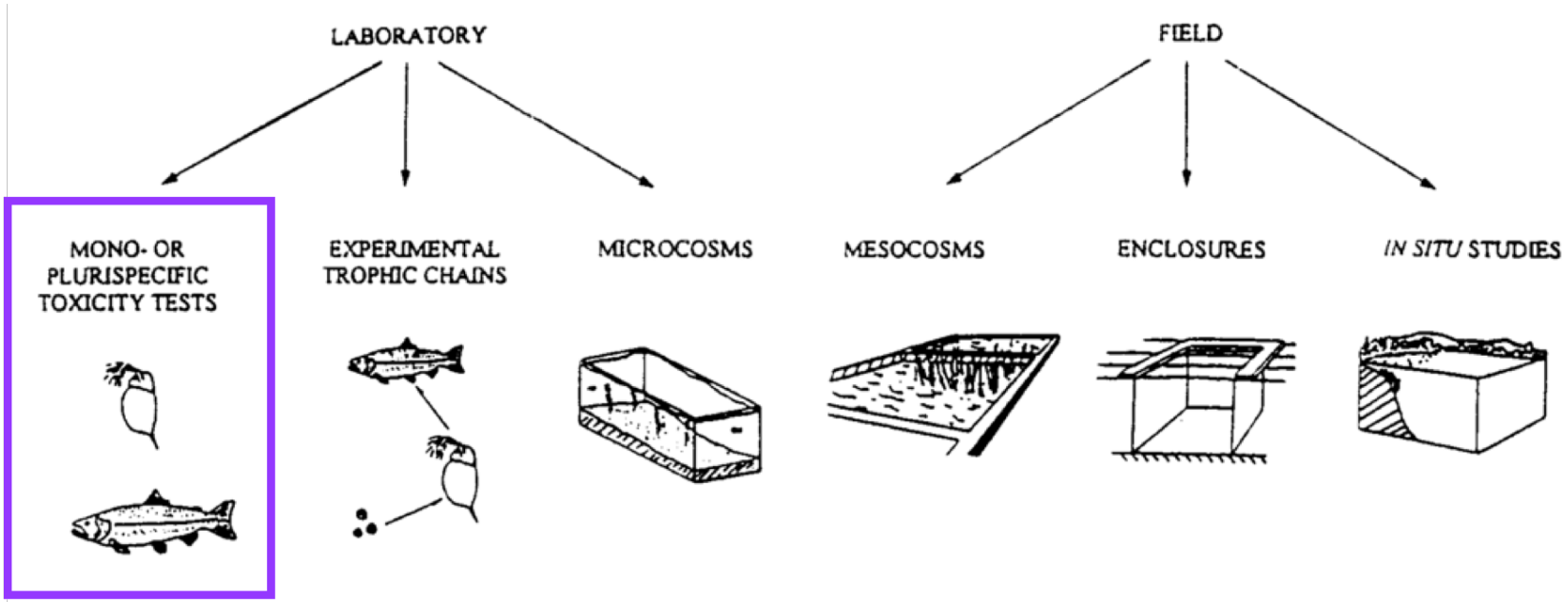




https://umr5023.univ-lyon1.fr/annuaire/details/1/99-clement-bernard

[Clément et Cadier, 1998]

A variety of experimental devices



[Caquet et al., 1996]

A key challenge in ecotoxicology:

Extrapolating from one level to the next

- From the individual level...
  - Account for the time-dependency of effects
  - Identify critical life history traits
  - Identify chemical modes of action
- ... to the population level...
  - Decipher Population dynamic including individual effects
  - Identify critical demographic parameters
- ... to the community level
  - Species sensitivity distributions
  - Community functioning accounting for ecological interactions

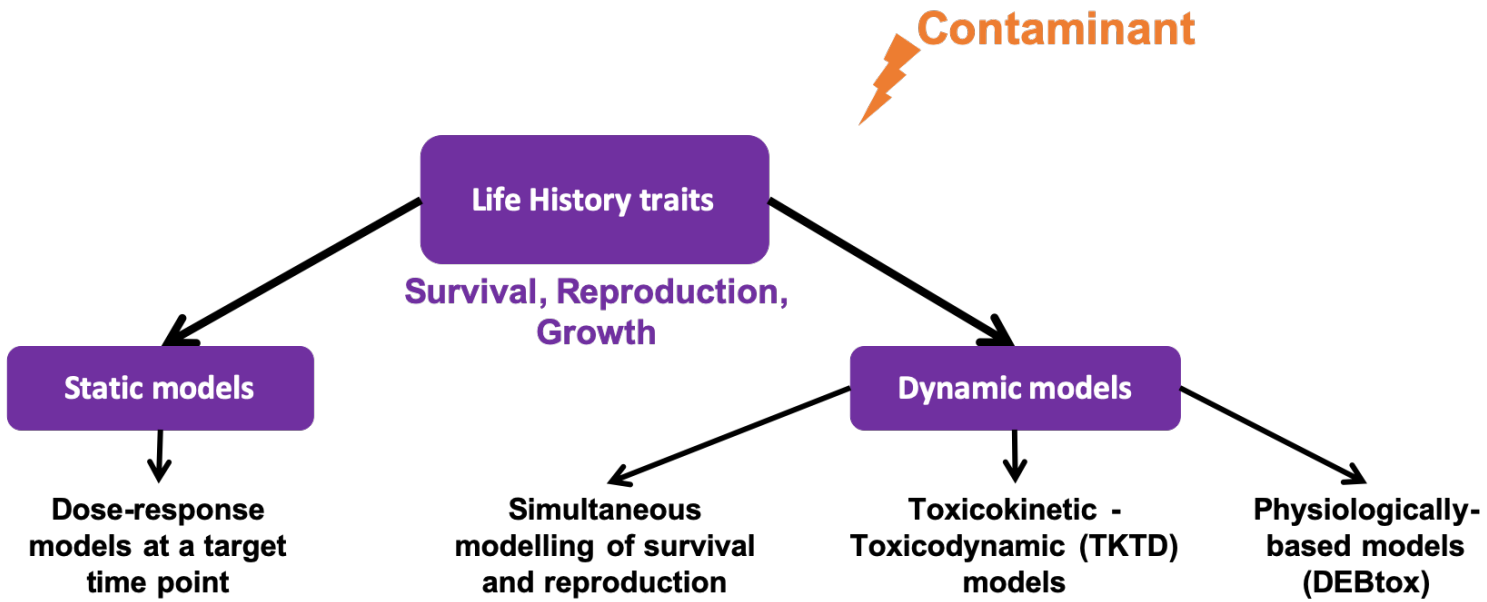
How do we face up to such challenges?

Here does interdisciplinary matter a lot!

- At the individual level
  - Dose-response models
  - Toxicokinetic models
  - Toxicokinetic-toxicodynamic models
- At the population level
  - Matrix population models
  - Space-state variable models
  - Individual-based models
- At the community level
  - Probability distribution models
  - Dynamical systems
  - Bayesian networks

Modelling at the individual level

- Estimating individual toxicity indices;
- Accounting for the individual variability.



Modelling at the individual level

- Estimating individual toxicity indices;
- Accounting for the individual variability.

- Choose the appropriate model according to the data **and** to the research question;
- Choose an inference method for estimating model parameters.

Detailed content

Definition of toxicity tests or bioassays

- Bioassay is a word commonly used instead of **biological assay** or **toxicity tests**. It's a particular type of scientific experiment.
- Bioassays are typically conducted to measure the effects of potentially toxic substances on living organisms.
- Bioassays can be
  - **qualitative**: dedicated to assess physical effects of a substance that cannot be quantified (*e.g.*, abnormality or deformity).
  - **quantitative**: dedicated to estimate the potency of a substance by measurement of the biological response/effect it produces; quantitative bioassays are typically analyzed using **statistical methods**.

Definition of toxicity tests (*continued*)

Several kind of substances can be studied, for example:

- Pesticides, pharmaceutical, cosmetic substances
- Effluents (industrial discharges, outputs from water plants)
- Polluted soils, waste, sediments.

According to the substance, different kinds of experiments can be conducted:

- A control versus one treatment;
- A control and several treatments.

A treatment can be a fixed concentration of a substance (C_1, C_2...) or a time-variable concentration $C(t)$.

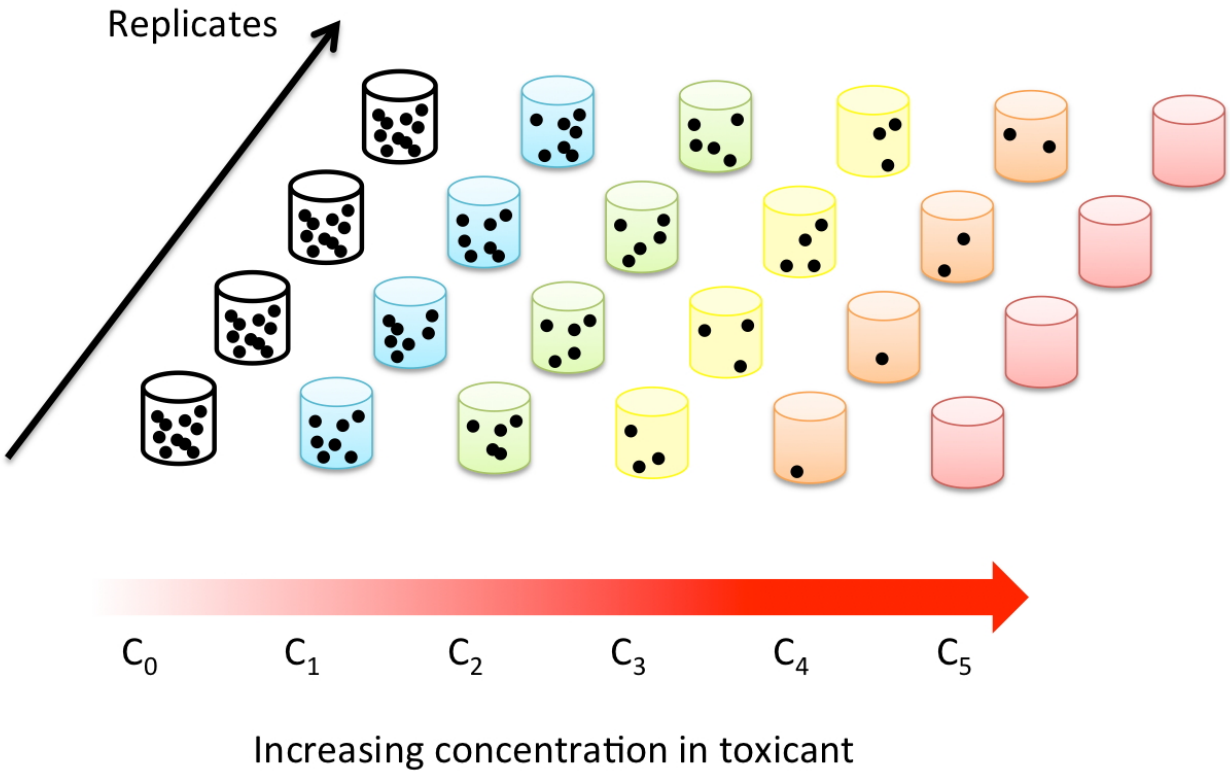
Acute vs. chronic quantitative bioassays

- **Acute toxicity**: from some hours to some days (*e.g.*, survival or mobility inhibition)
  $\rightarrow$ short-time exposure at high concentrations;
  $\rightarrow$ rapid impact on organisms.
- **Chronic toxicity**: from some days to some weeks (*e.g.*, growth or reproduction inhibition, sub-individual biomarkers)
  $\rightarrow$ long-time exposure at low concentrations.

Standard experimental design

Under standardized protocols, individuals are counted **over time**, that is at regular time points

Endpoints can be survival, growth and/or reproduction for example.



Who define standard protocols?

Organisation for Economic Cooperation and Development

$\longrightarrow$ Free of charges

International Organization for Standardization

$\longrightarrow$ Not free

Other institutions:

- **US EPA** (US Environmental Protection Agency)
- **ASTM** (American Society for Testing and Materials)
- **DIN** (Deutsches Institut für Normung)
- **MITI** (Ministry of International Trade and Industry in Japan)

Example of a toxicity test

Daphnia magna, acute immobilisation test (OECD 202, 1984) and chronic reproduction test (OECD 211, 2012)

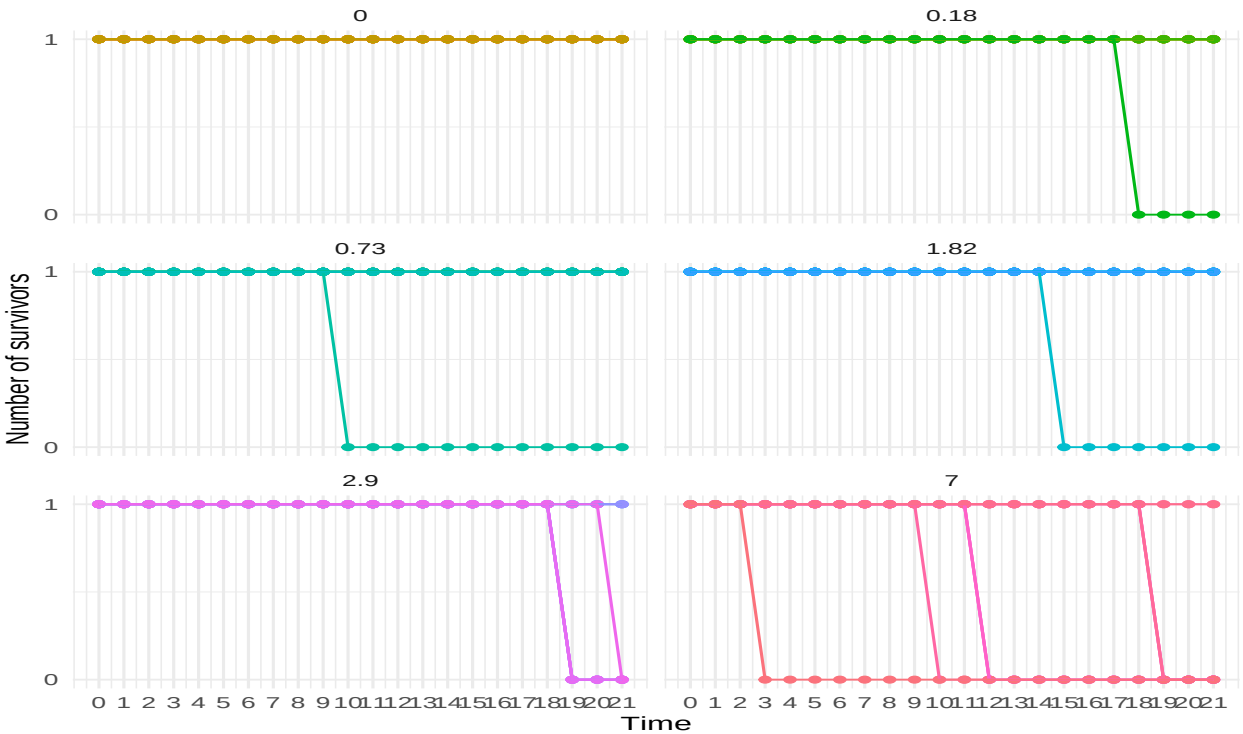
Daphnia magna

Acute test: the number of immobile daphnids is determined for each concentration at 24 and 48 hours.

Chronic test: offspring are daily counted during 21 days.

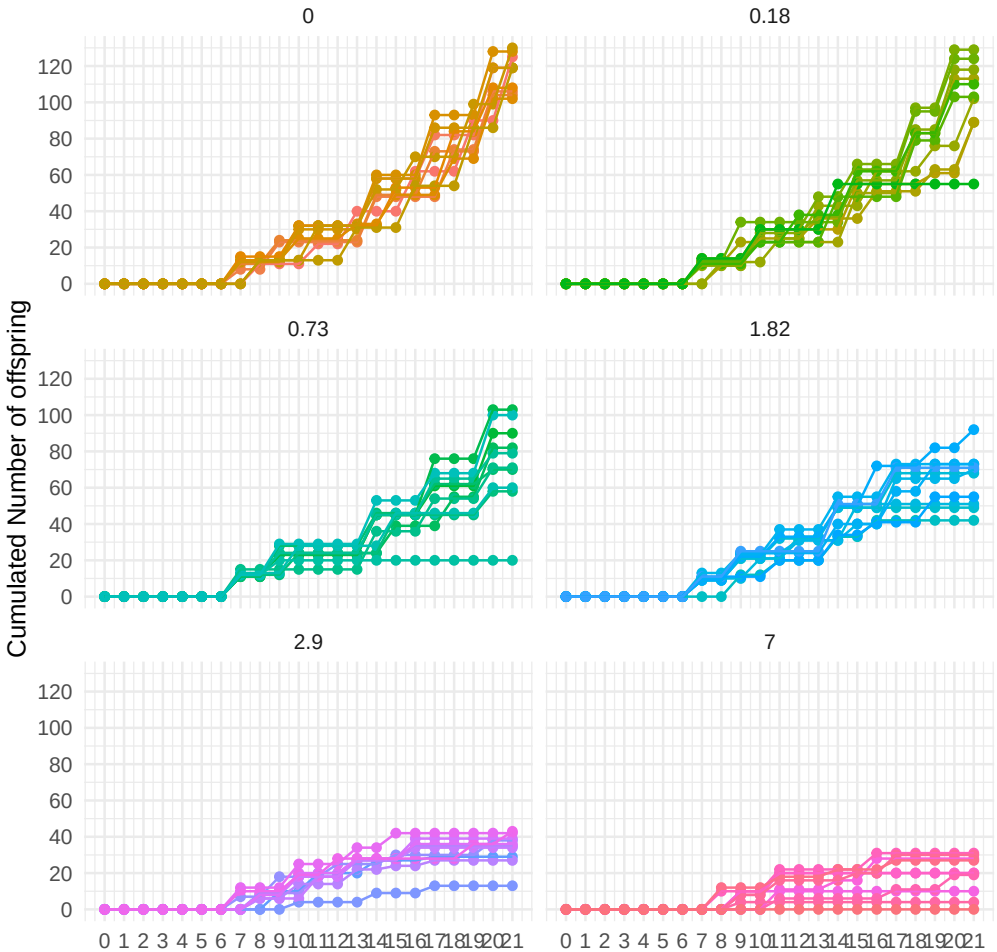
Example of survival data

Effect of chlordane on *D. magna* survival during 21 days (10 replicates of 1 individual):



Example of reproduction data

Effect of chlordane on *D. magna* reproduction during 21 days (10 replicates of 1 individual):



Detailed content

Standard analyses of toxicity test data

Derive Critical Effect Concentrations

also called "summary statistics of toxicity" or "thresholds".

$\rightarrow$ Most common indicators to quantitatively assess risks for single species exposed to single contaminants.

$\rightarrow$ Estimation of the exposure level (*e.g.*, concentration) above which adverse effects can occur on organisms, and below which adverse effects are unlikely, *i.e.*, which can not be distinguished from background noise [OECD, 2006].

OECD (2006). *Current approaches in the statistical analysis of ecotoxicity data: a guidance to application*. Technical report ENV/JM/MONO(2006)18.

x% effective or lethal concentrations

$\rightarrow$ obtained by fitting a dose-response model to toxicity test data at a chosen target time point, then deriving the dose which corresponds to a given effect level (usually 10, 20 or 50%).

Advantages of EC_x or LC_x

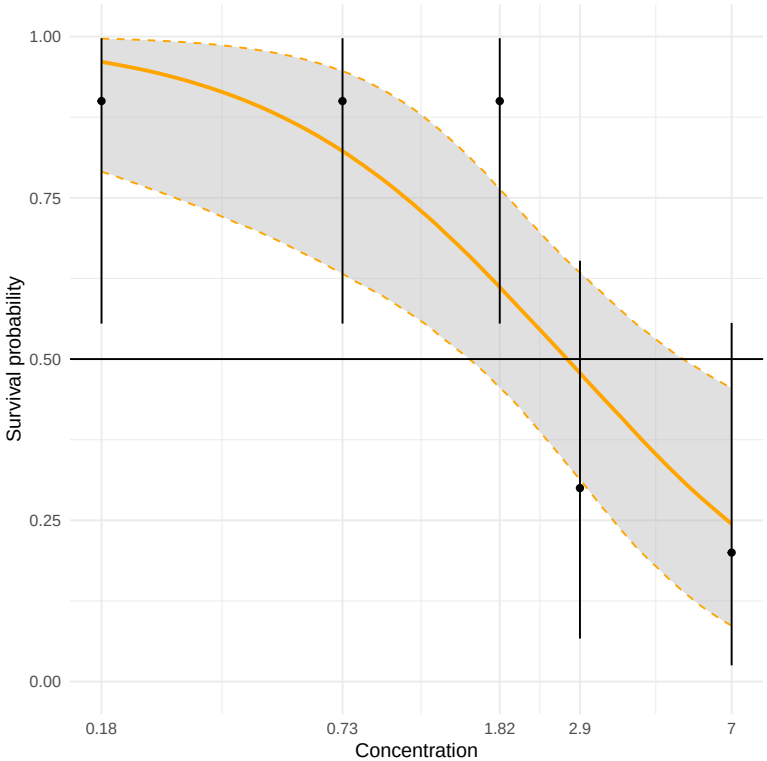
- capture and account for the whole dose-response curve;
- slightly dependent on the experimental design;
- may be associated to uncertainty limits.

Shortcomings of EC_x or LC_x

- sometimes technical difficulties when fitting;
- choice of a mathematical model;
- choice of an effect level x and the exposure duration.

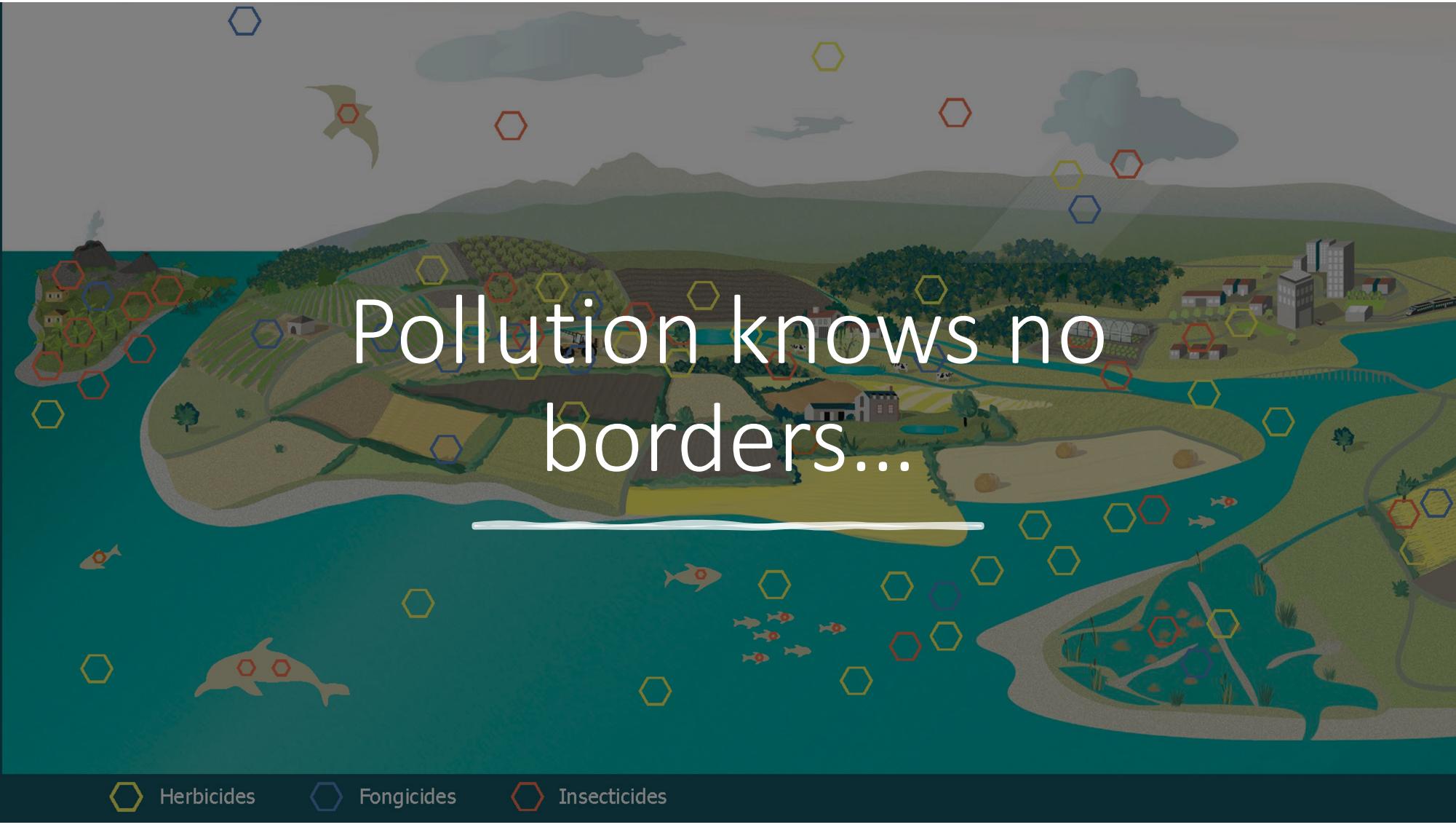
Example of LC_x estimation

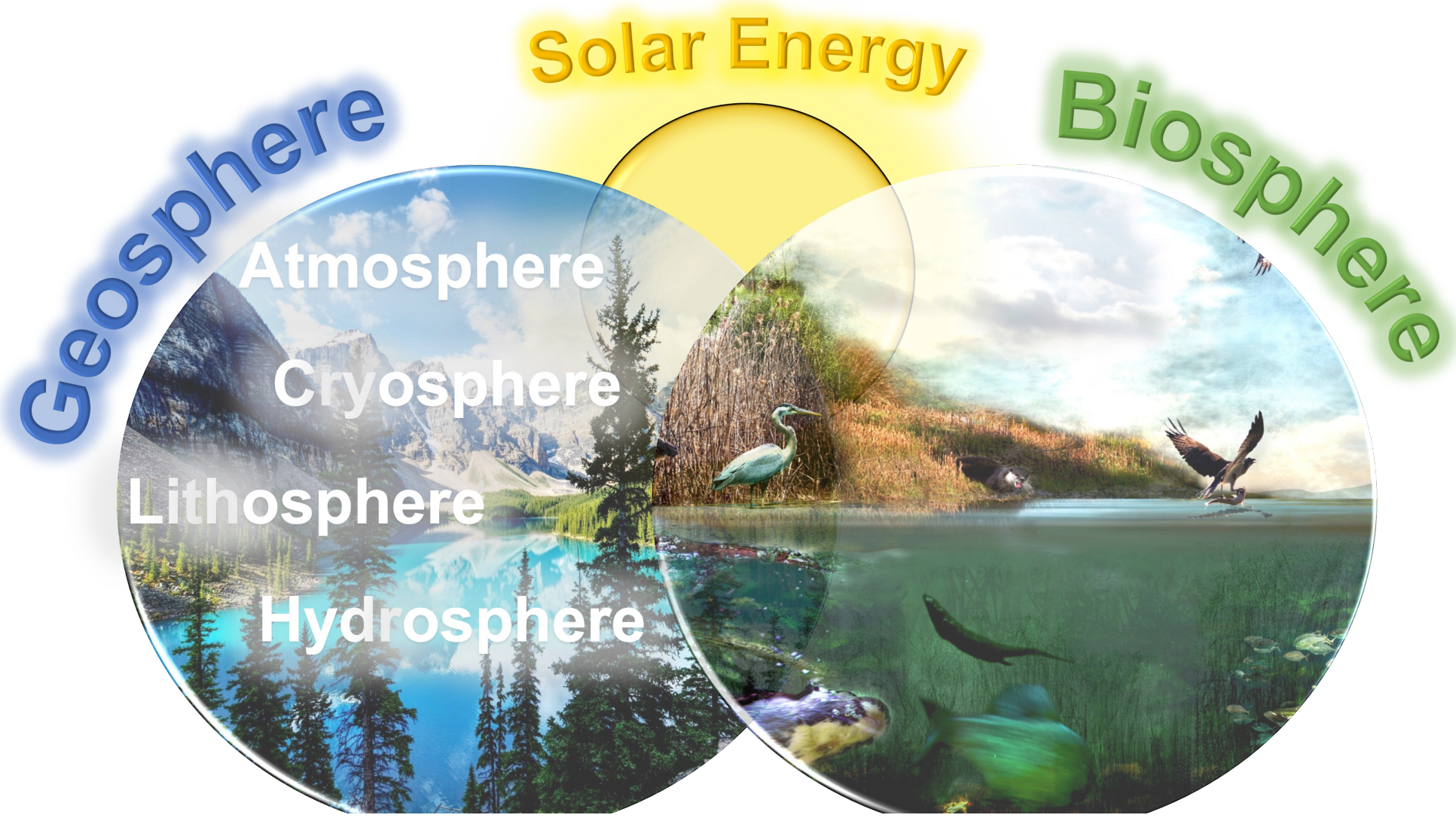
Use of survival data at the end of the experiment (day 21)



	median	2.5%	97.5%
LC50	**2.67**	**1.50**	**5.3**

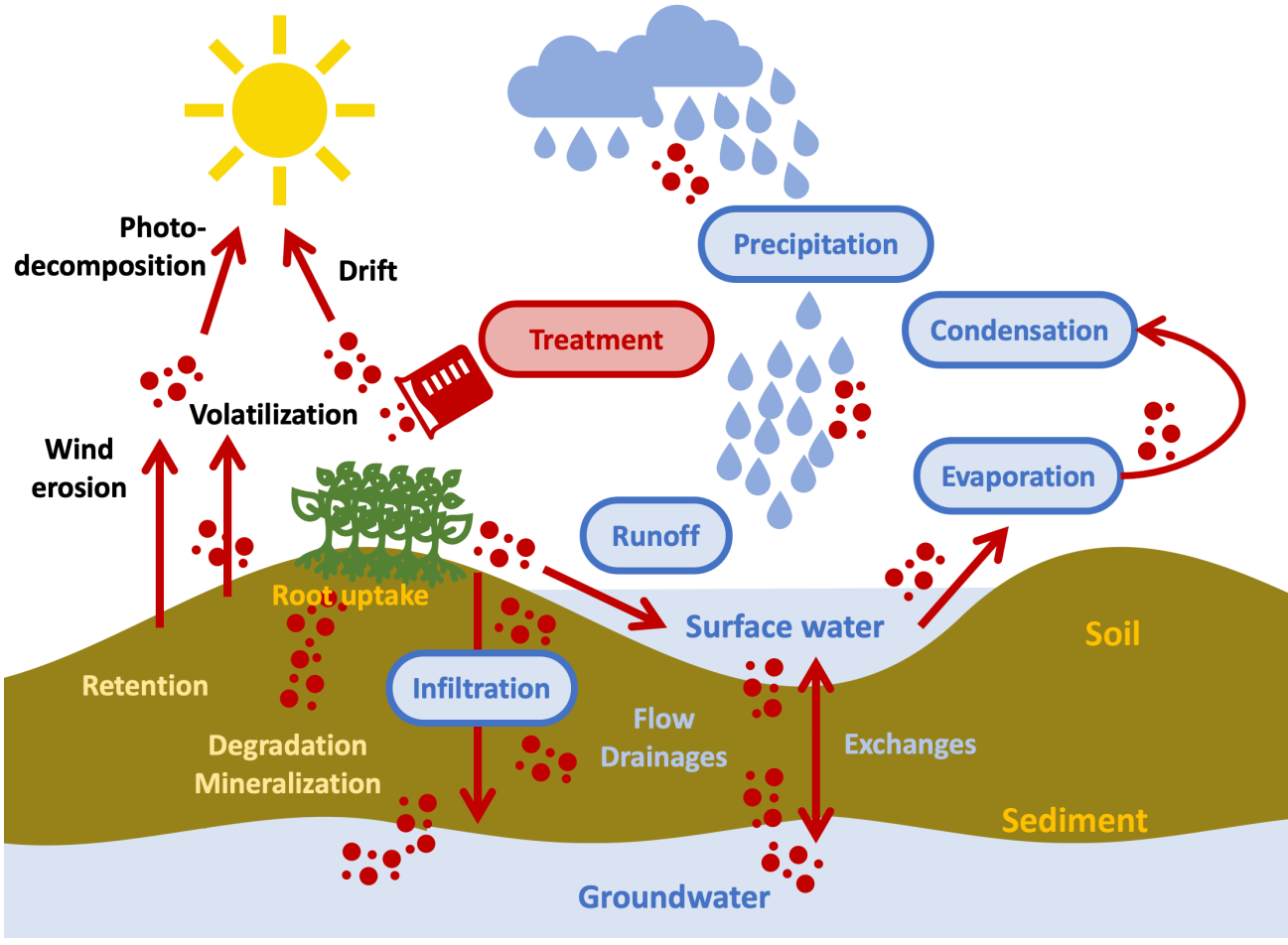
Table of content


Pollution knows no borders…
Herbicides
Fongicides
Insecticides

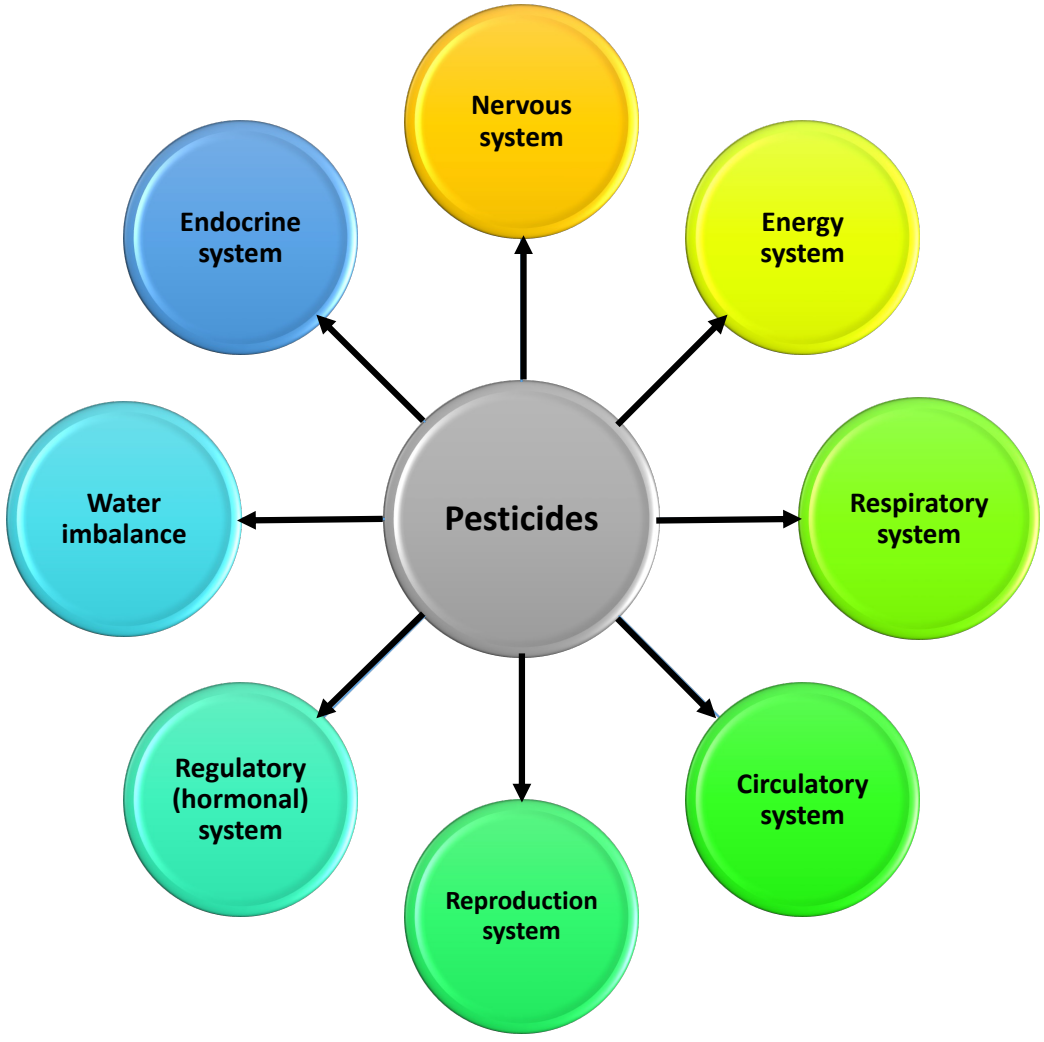

Solar Energy
Geosphere
Biosphere
Atmosphere
Cryosphere
Lithosphere
Hydrosphere

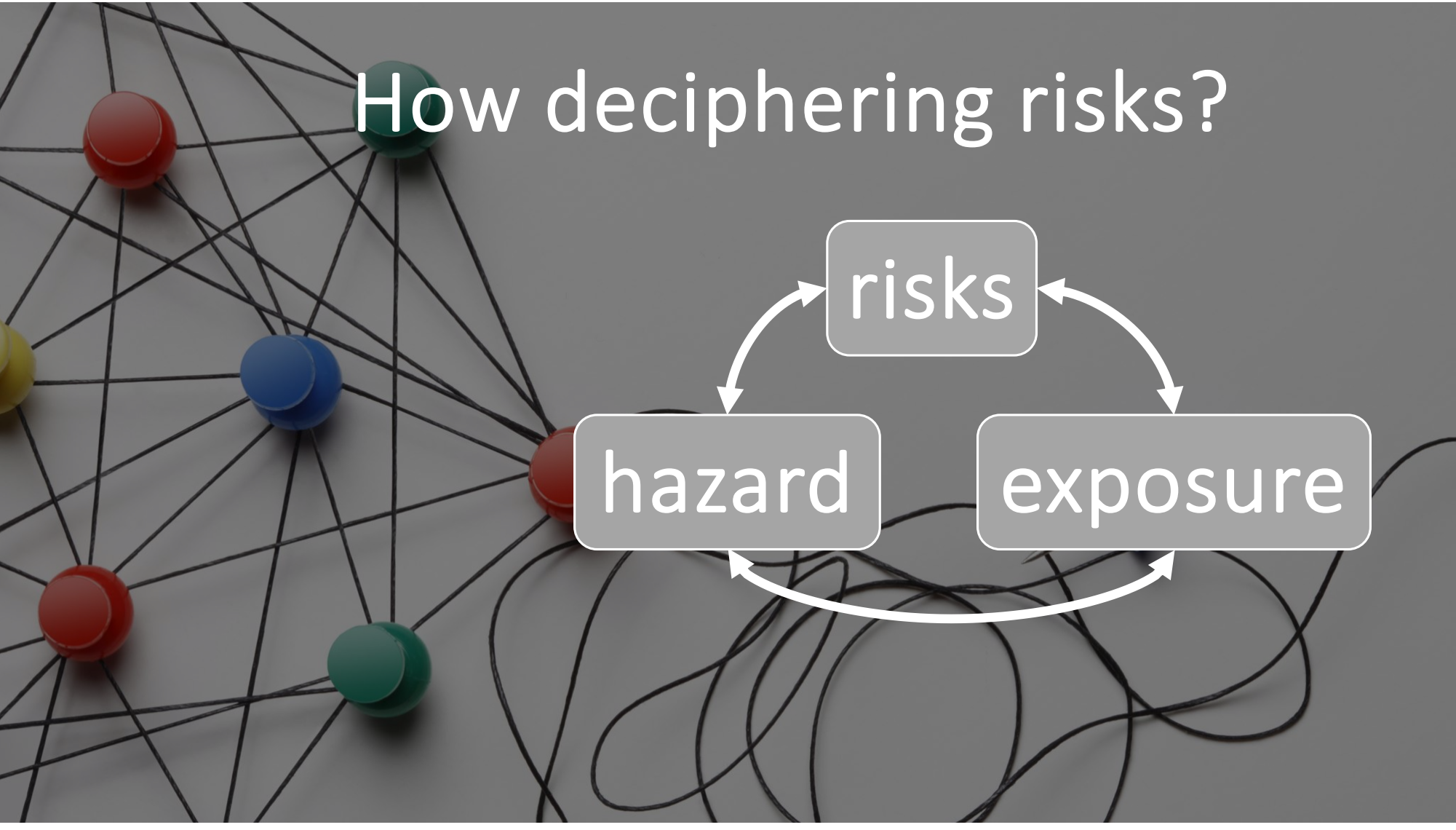
Pesticides

A threat that knocks at the door

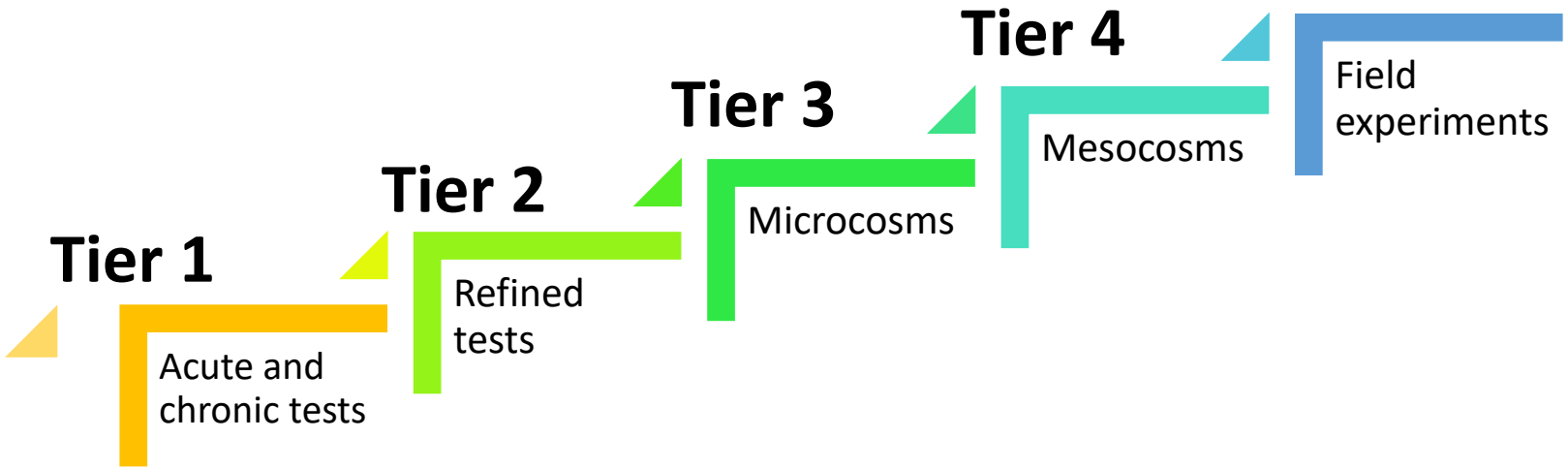


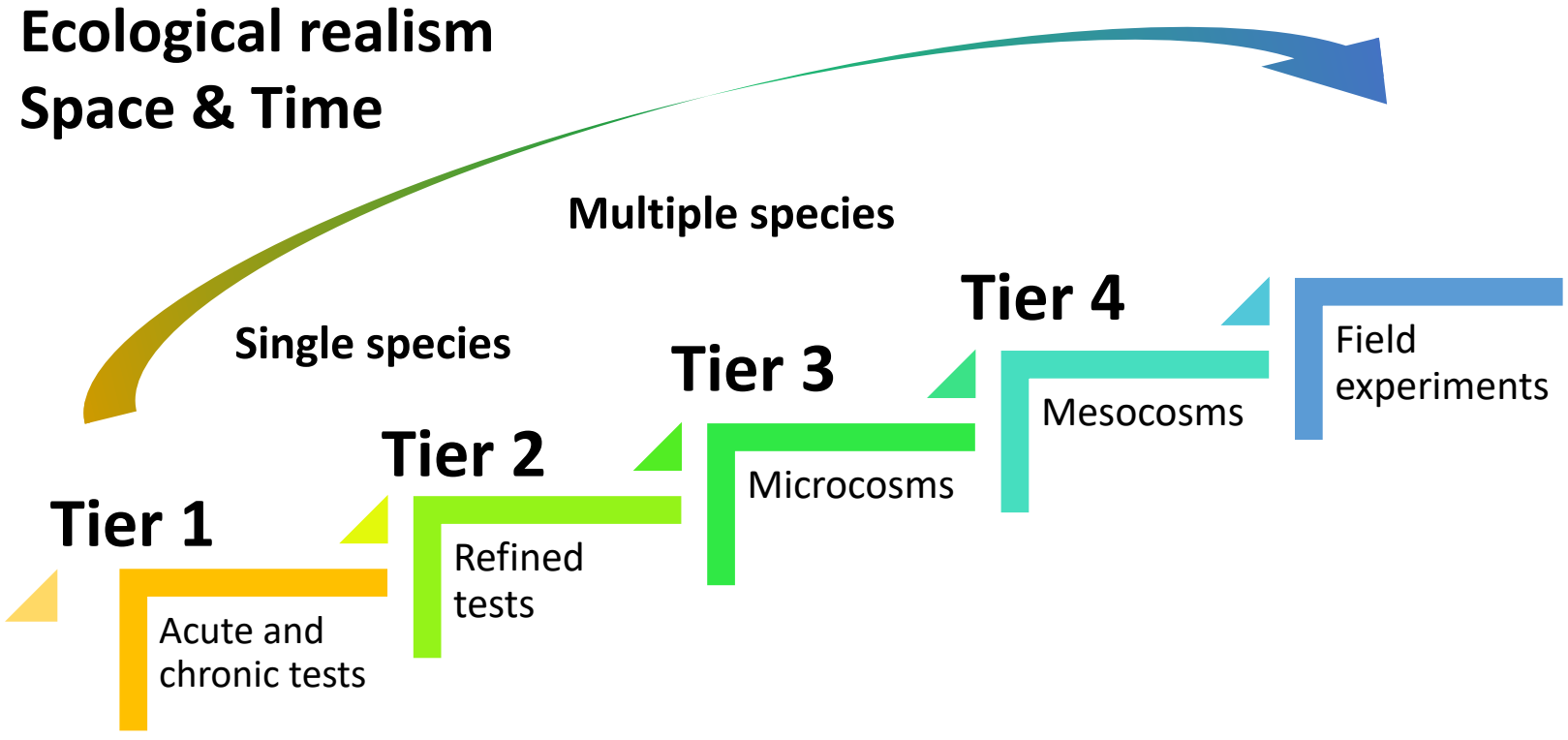
Adverse effects on human health

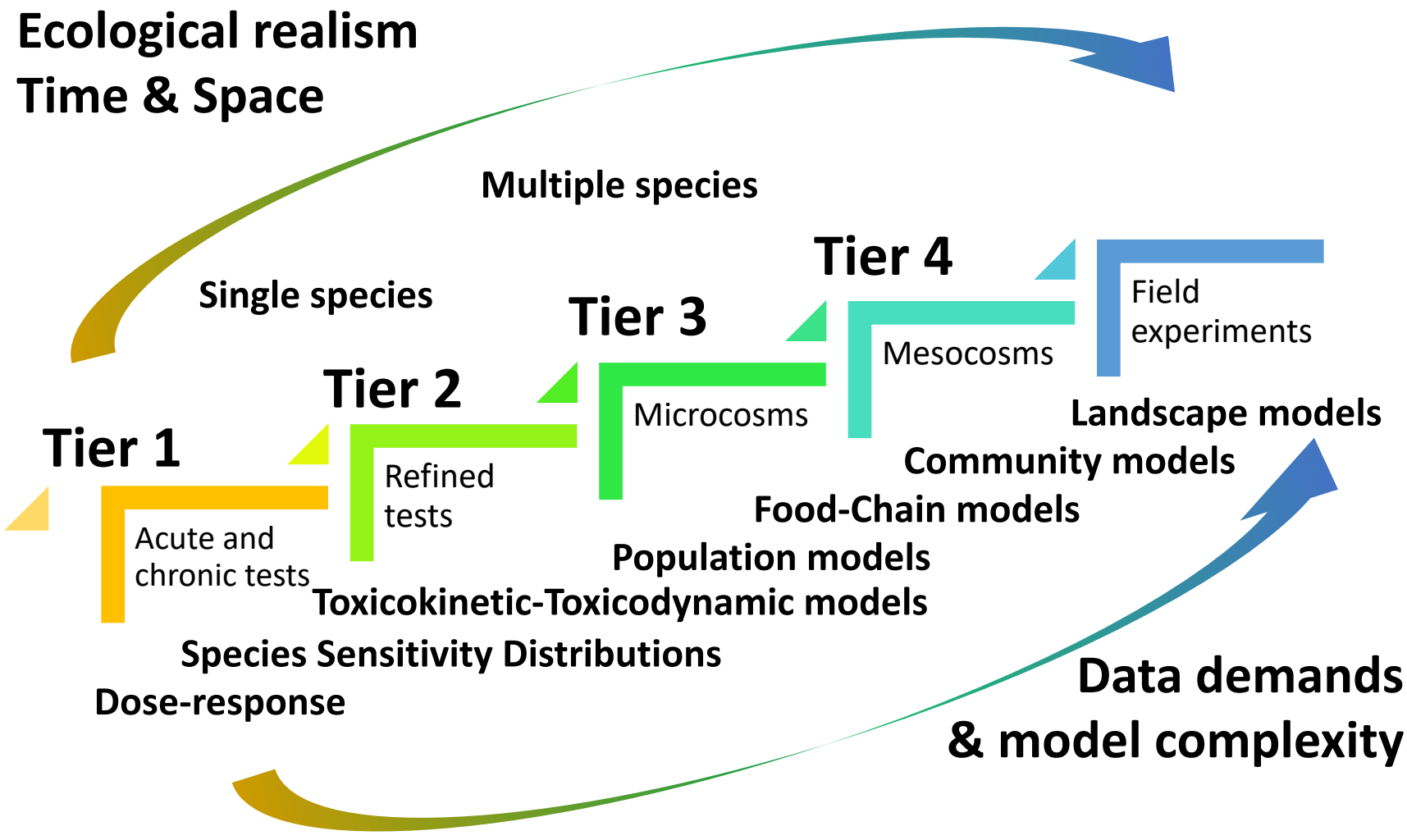



How deciphering risks?
risks
hazard
exposure

Regulatory risk assessment

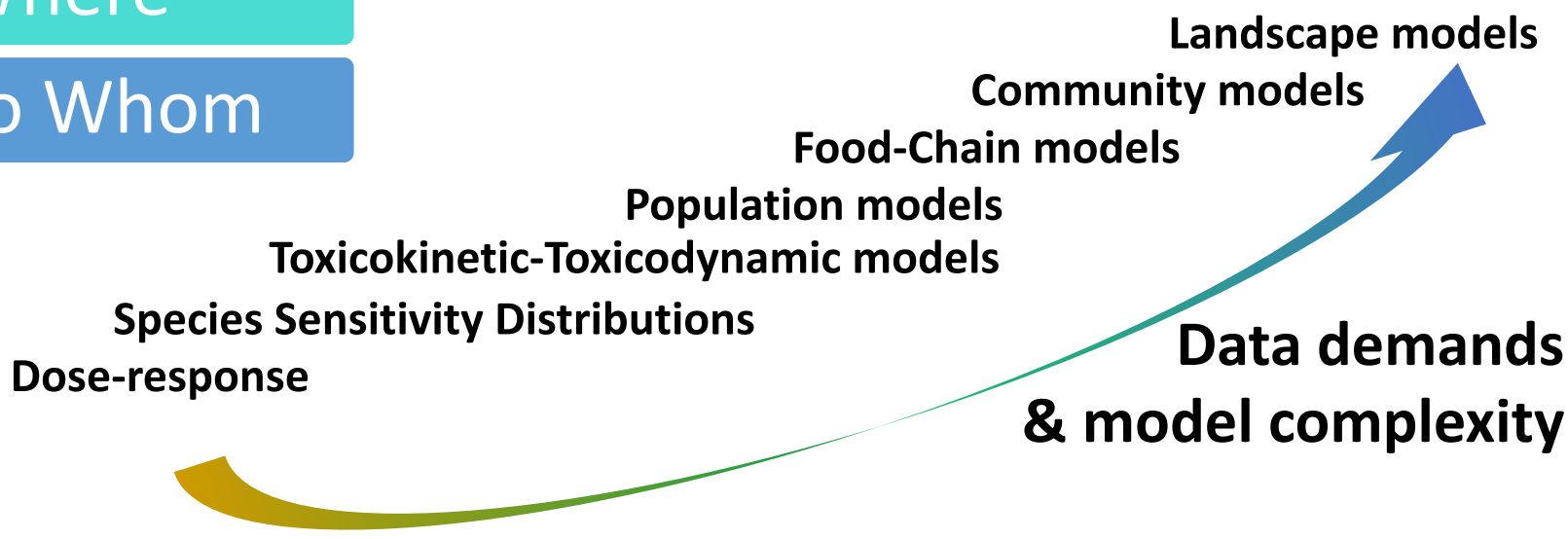



Ecological realism
Space & Time
Multiple species
Single species
Tier 1
Acute and chronic tests
Tier 2
Refined tests
Tier 3
Microcosms
Tier 4
Mesocosms
Field experiments


Ecological realism
Time & Space
Multiple species
Single species
Tier 1
Acute and chronic tests
Dose-response
Tier 2
Refined tests
Species Sensitivity Distributions
Tier 3
Microcosms
Toxicokinetic-Toxicodynamic models
Population models
Tier 4
Mesocosms
Food-Chain models
Community models
Field experiments
Landscape models
Data demands
& model complexity

6W-rule

- Who
- What
- Why
- When
- Where
- To Whom



 Who	Who needs the model?
 What	What is the context of use of the model?
 Why	Why is the model needed?
 When	When will is the model be used?
 Where	Where will is the model be used?
 To Whom	Who are the model results intended for?

MOSAIC

MOdeling and StAtistical tools for ecotoxlCology

Does the dose make the poison ?

Illustration by Sergio Aquindo

MOSAIC is a turnkey decision-making tool for ecotoxicologists and regulators. Without wasting time on extensive mathematical and statistical technicalities, users are given advanced and innovative methods for a valuable quantitative environmental risk assessment.

Get LC_x / NEC estimates!

Get EC_x estimates!

Get HC_p estimates!

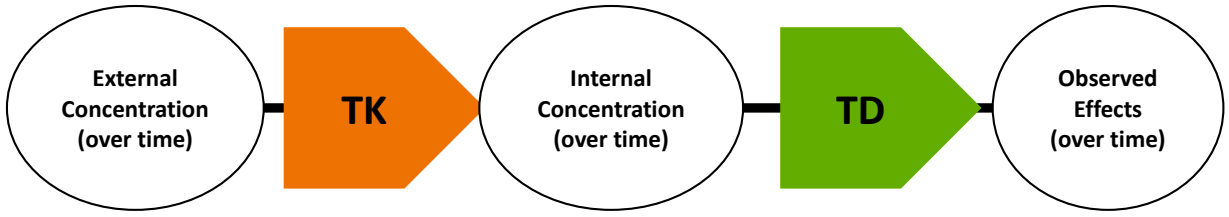
Need some help?

Dose-response

$$f[C] = \frac{d}{1 + \left(\frac{[C]}{EC_{50}}\right)^b}$$

repro surv standard

growth



$$\begin{cases} \frac{d[C(t)]}{dt} = k_u[C_{exp}] - k_e[C(t)] \\ BCF = \frac{k_u}{k_e} \end{cases}$$

bioacc

surv guts-fit

GUTS - predict

$$D_w(t) = e^{-k_d t} k_d \int^t e^{k_d \tau} C_w(\tau)\, d\tau$$

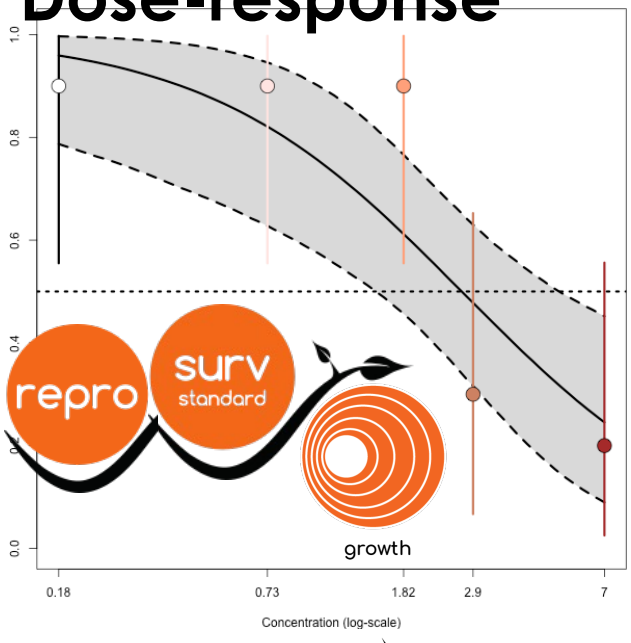
$$S_{IT}(t) = \exp(-h_b t)\left(1 - 1/\left(1 + \left(\frac{\max_{0 \le \tau \le t}(D_w(\tau))}{m_w}\right)^{-\beta}\right)\right)$$

MOSAIC

modeling and statistical tools for ecotoxicology

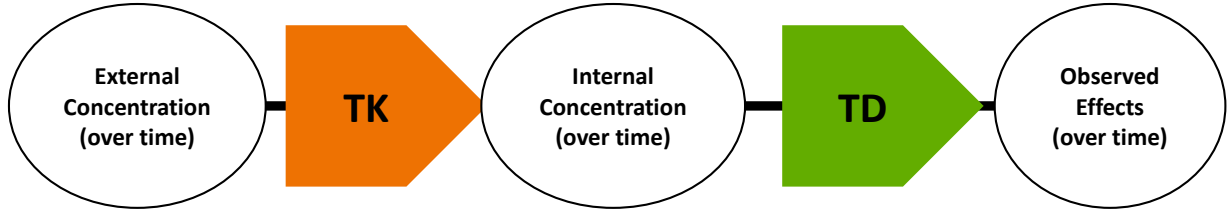
https://mosaic.univ-lyon1.fr/

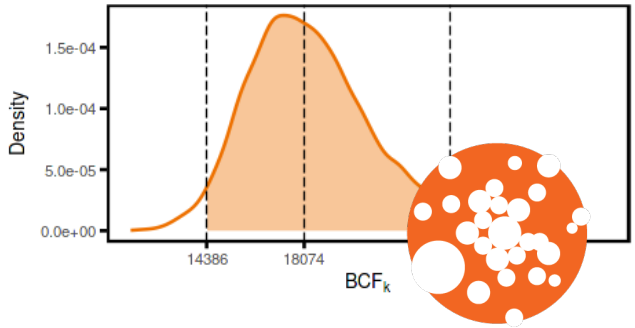
Dose-response



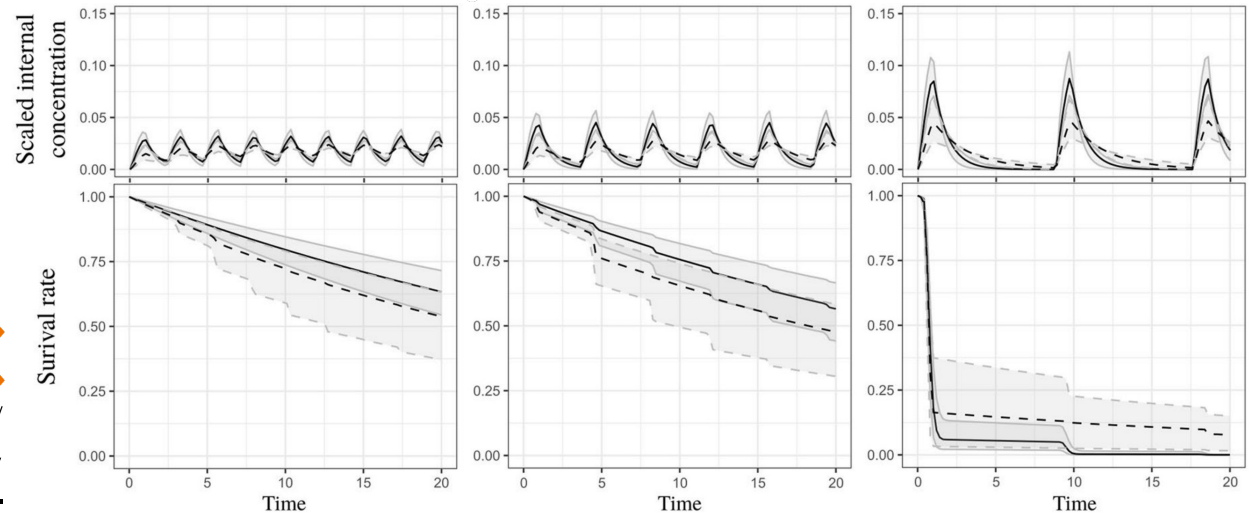
MOSAIC
modeling and statistical tools for ecotoxicology

https://mosaic.univ-lyon1.fr/

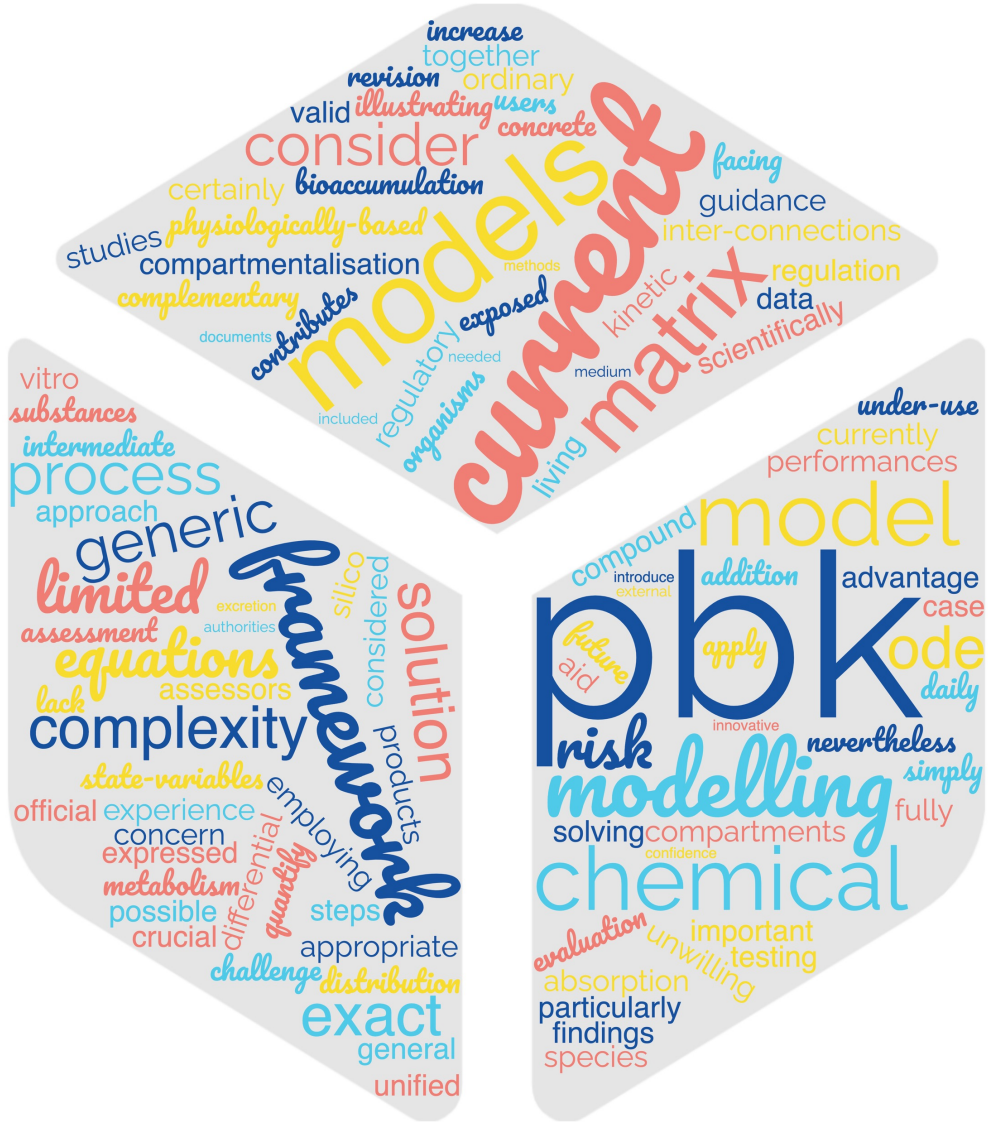




GUTS - predict



What's next?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regulation
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nevertheless
risk
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confidence
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unwilling
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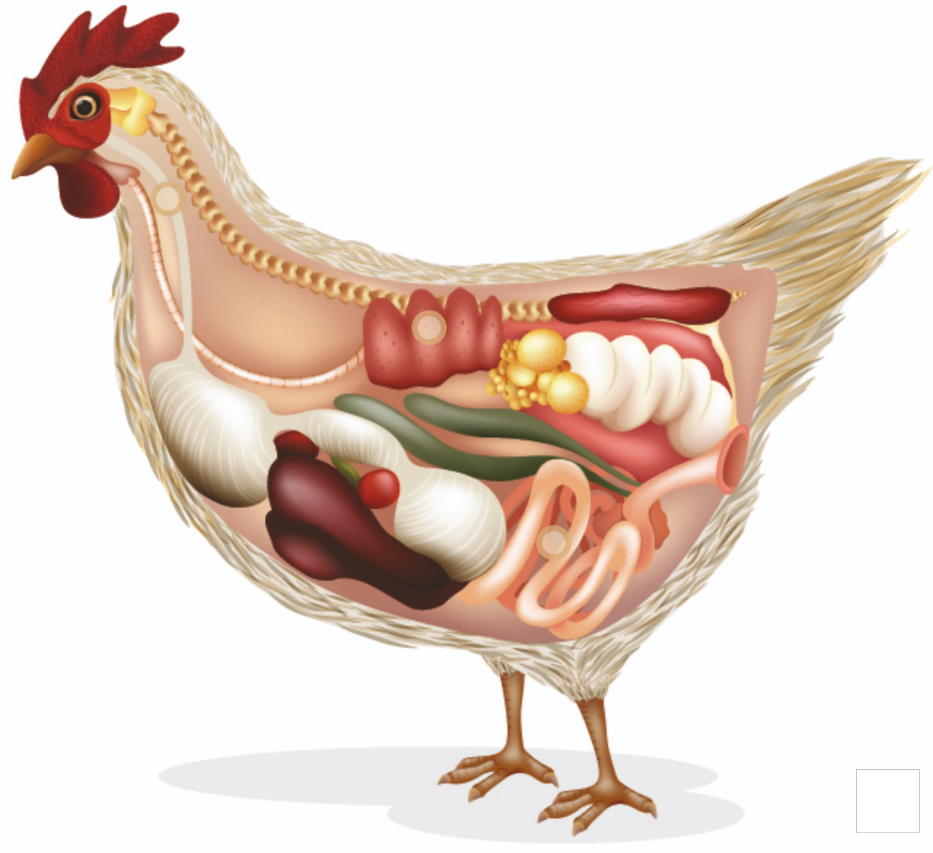
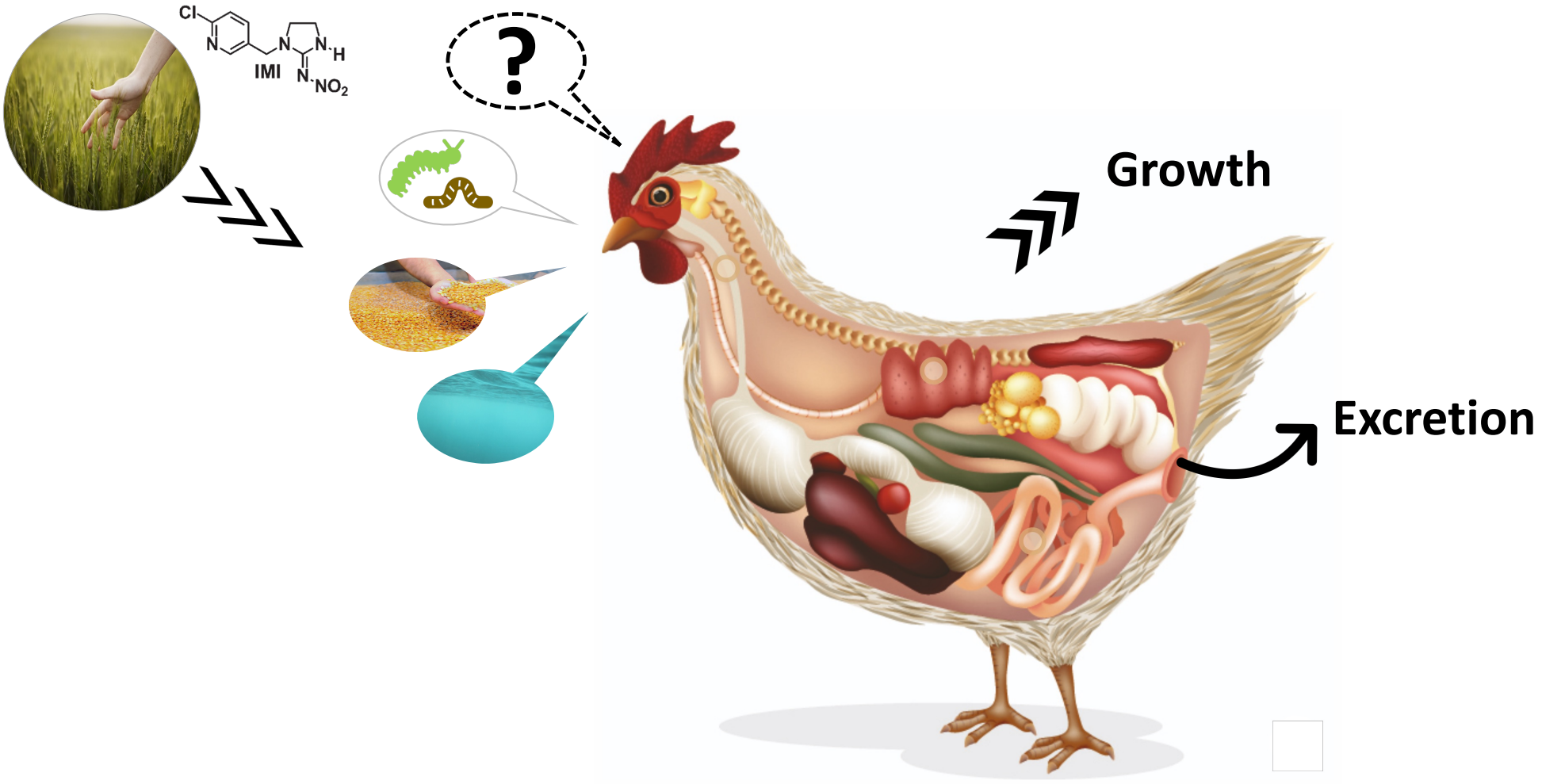
absorption
particularly
findings
species

What's next?

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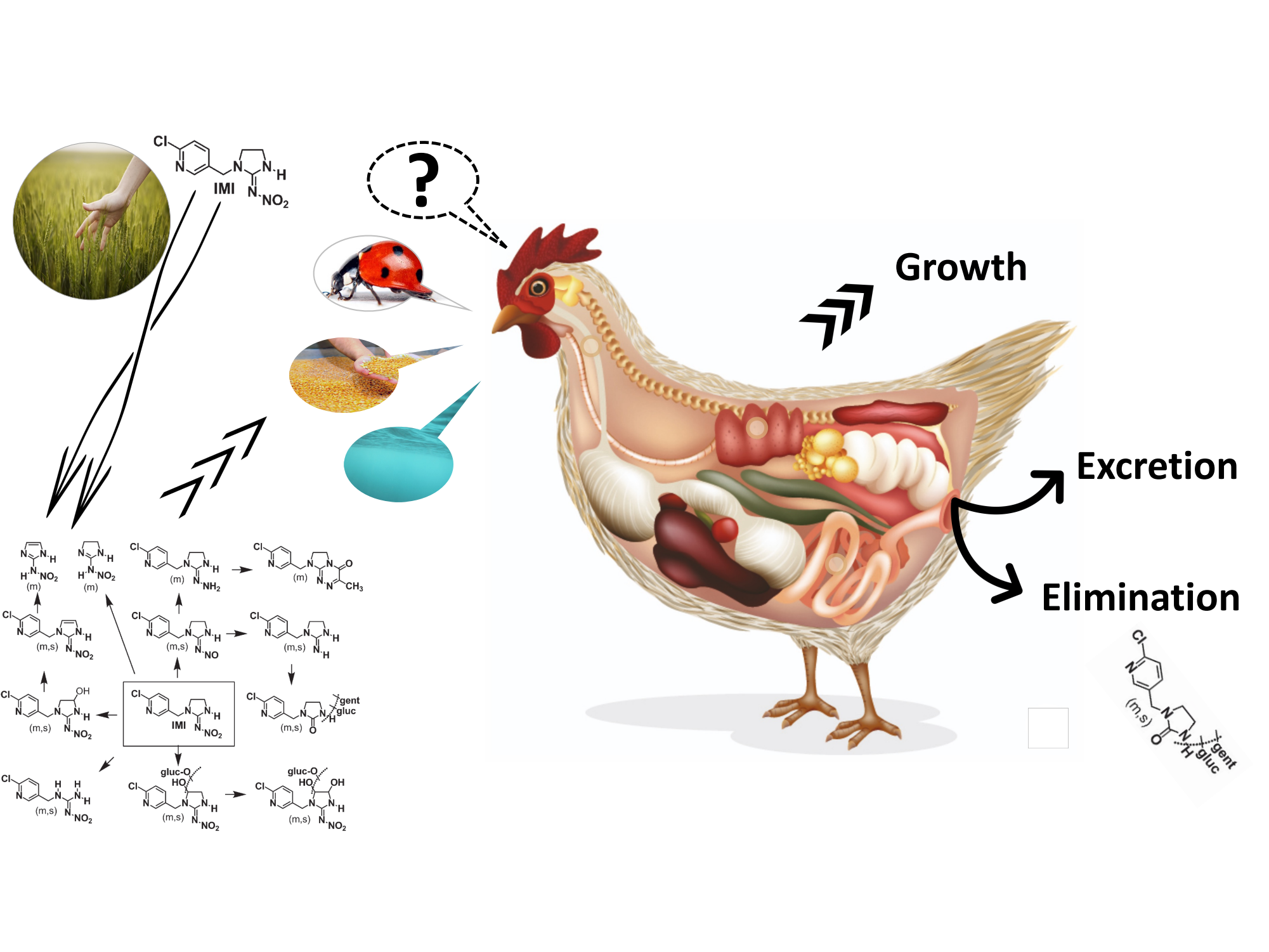
Growth
Excretion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Growth
Excretion
Elimination
(m)
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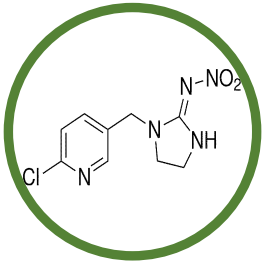
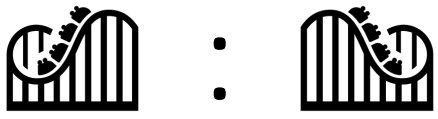


Change of paradigm…

From
“one-compound
versus one species”
:
:
:

to

chemical mixtures

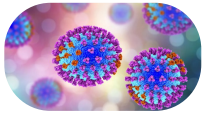


Change of paradigm…




to the exposome

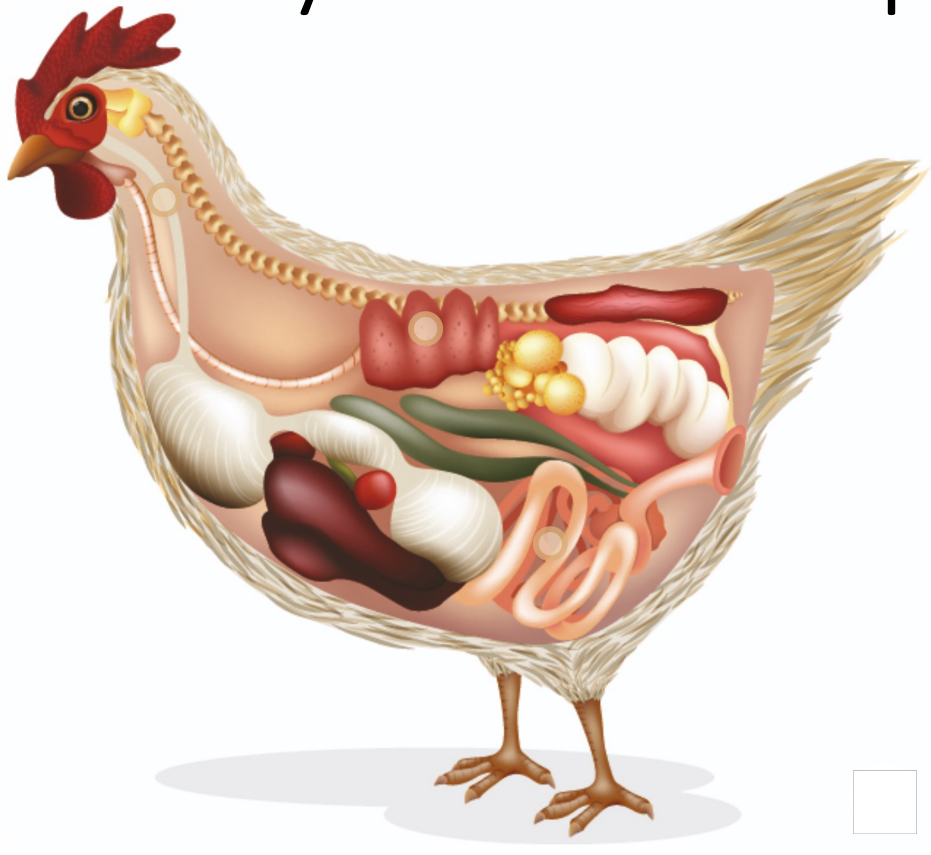


Change of paradigm…




...towards a systems-based approach

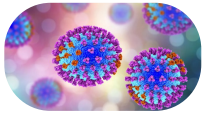


...

with an organ-based view

...



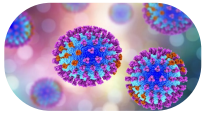






.towards a systems-based approach

until ecological interactions





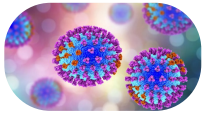

.towards a systems-based approach

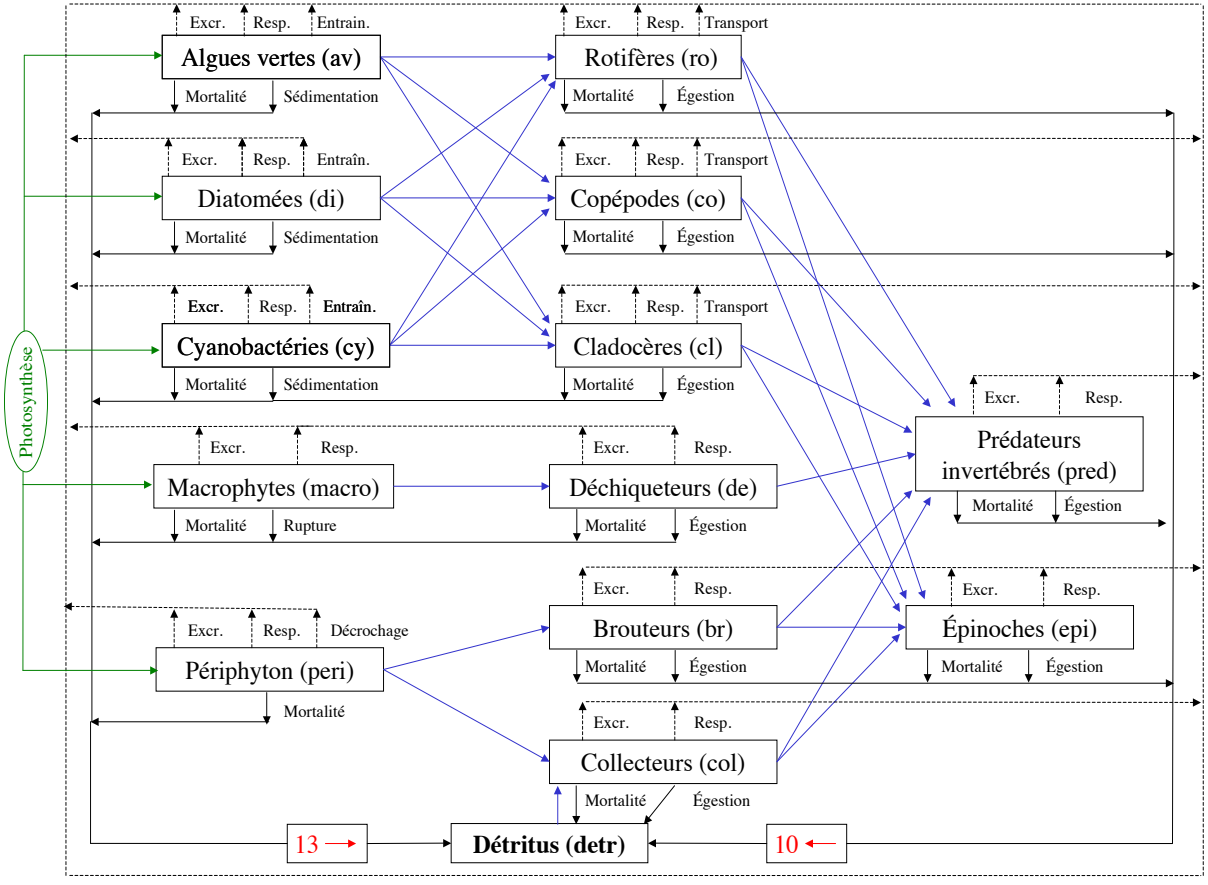
. . .

until ecological interactions

. . .

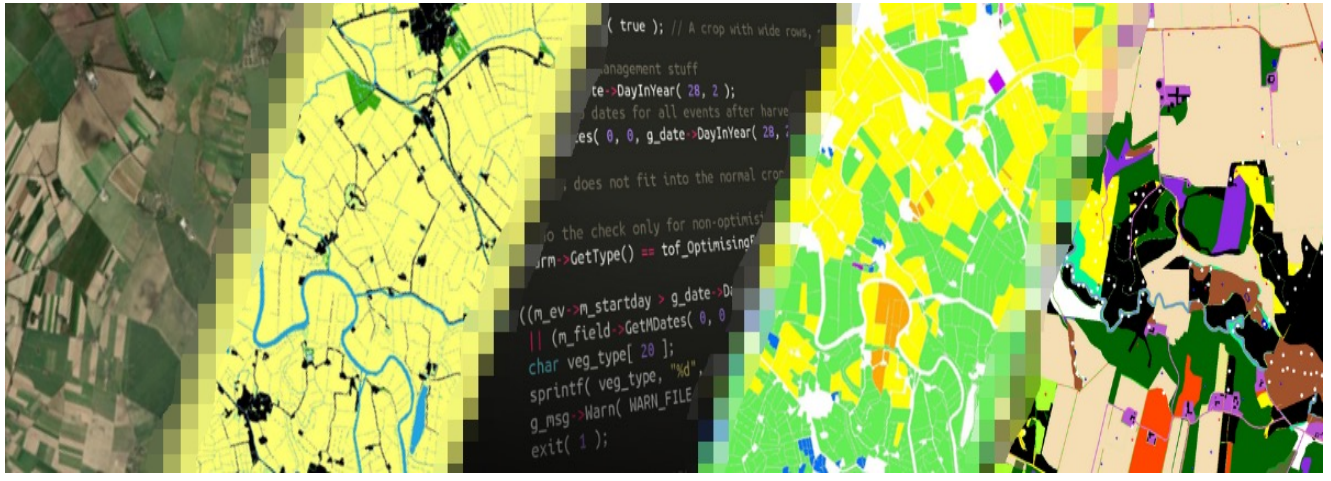






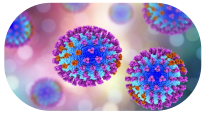

..towards a systems-based approach



including space & time

!



ALMaSS

Change of paradigm
↳ move towards a systems-based approach

- Sustain researchers
- Closely collaborate on demand and supply
- Work under the umbrella of Open Science
- Comply with FAIR principles

GO FAIR

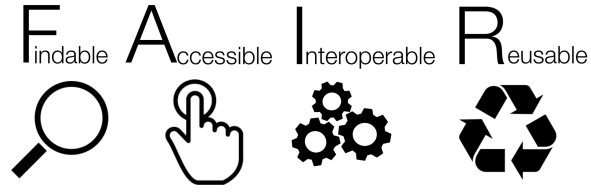


Table of content

TK plate 2.0

European Food Safety Authority

- **Technical offer to call for tender**

  #OC/EFSA/SCER/2021/07

- **Six partners**:
  - University of Utrecht (UU, The Netherlands)
  - University Lyon 1 (UCBL, France)
  - University of Turin (UNITO, Italy)
  - University of Parma (UNIPR, Italy)
  - ANSES (France)
  - Federal Institute for Risk Assessment (BfR, Germany)
  - Wageningen Food Safety Research (WFSR, The Netherlands)
- **Three sub-contractors:**
  - Qonfluens (Montpellier, France)
  - Quinten Healthcare (Paris, France)
  - Osnabrück University (OU, Germany)

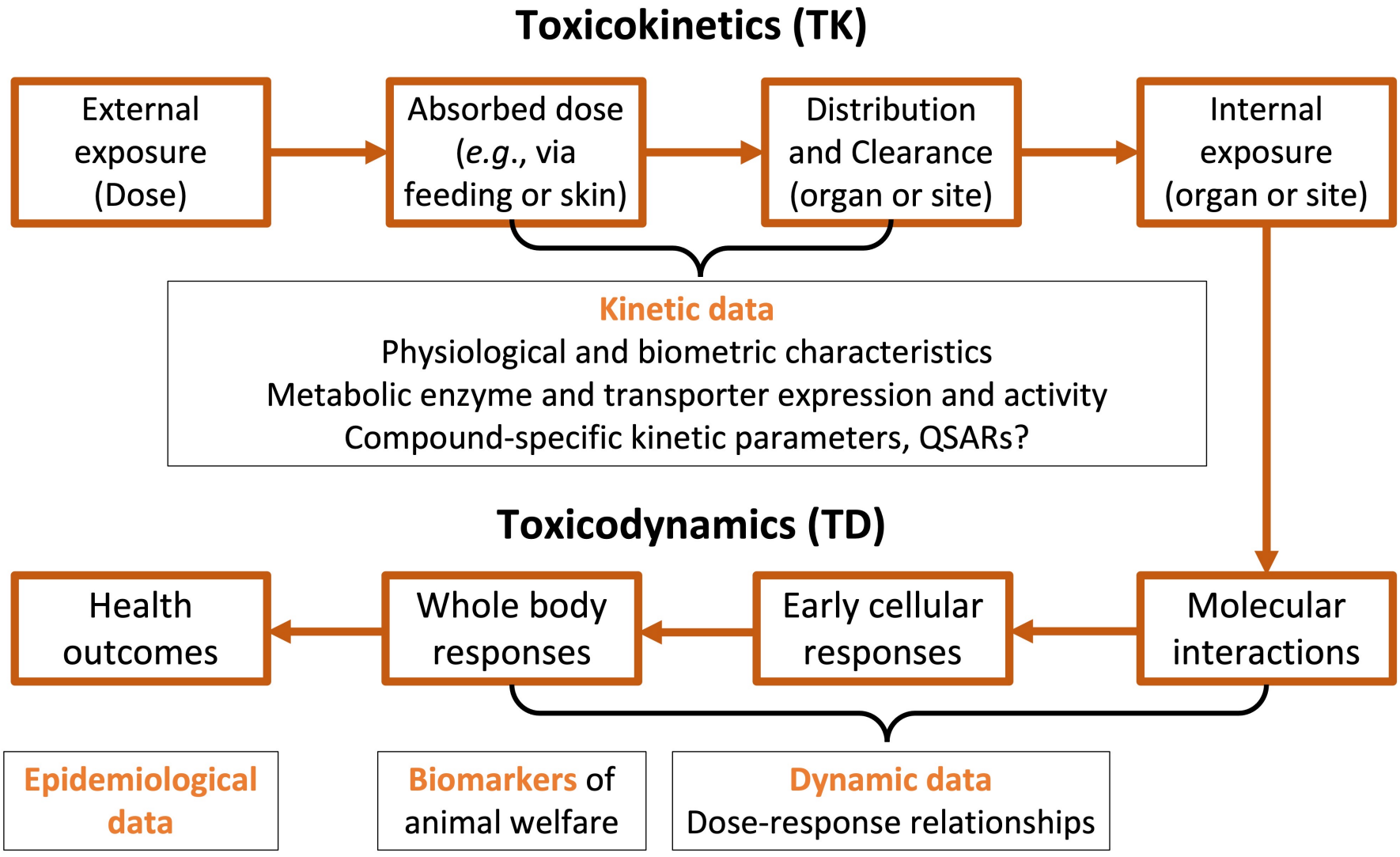
TK plate 2.0

efsa
European Food Safety Authority

TK Plate is a pilot, open-source platform that already integrates PBK, PBKD, TKTD and DEB models for humans and food-producing animals (single compound).

It is used for risk assessment of pesticides, food additives, feed additives and contaminants

There is a need to further develop TK Plate, for multiple chemicals and biological stressors in farm and wild mammalian species, as well as in birds


Toxicokinetics (TK)
External exposure (Dose)
Absorbed dose (e.g., via feeding or skin)
Distribution and Clearance (organ or site)
Internal exposure (organ or site)
Kinetic data
Physiological and biometric characteristics
Metabolic enzyme and transporter expression and activity
Compound-specific kinetic parameters, QSARs?
Toxicodynamics (TD)
Health outcomes
Whole body responses
Early cellular responses
Molecular interactions
Epidemiological data
Biomarkers of animal welfare
Dynamic data
Dose-response relationships

Three objectives

1. Data collection on structured physiological, kinetic and dynamic for chemical and biological stressors in animal species;
2. Development of generic K and KD as well as ML models for animal species and implementation of the algorithms in TK plate 2.0 to support transparency in risk assessment;
3. Validation of models using case studies relevant to EFSA panels for single chemicals, multiple chemicals and biological hazards to support transparency in food and feed safety.

1. Collect data on physiological, K and D of chemical and biological stressors

- Review available database resources and scientific literature
- **Create pilot databases on physiological data and expression and activities of enzymes, transporters**
- **Create pilot databases on kinetic and dynamic data including toxicity, epidemiological data and welfare conditions**

→ **in farm, wild mammalian and bird species**

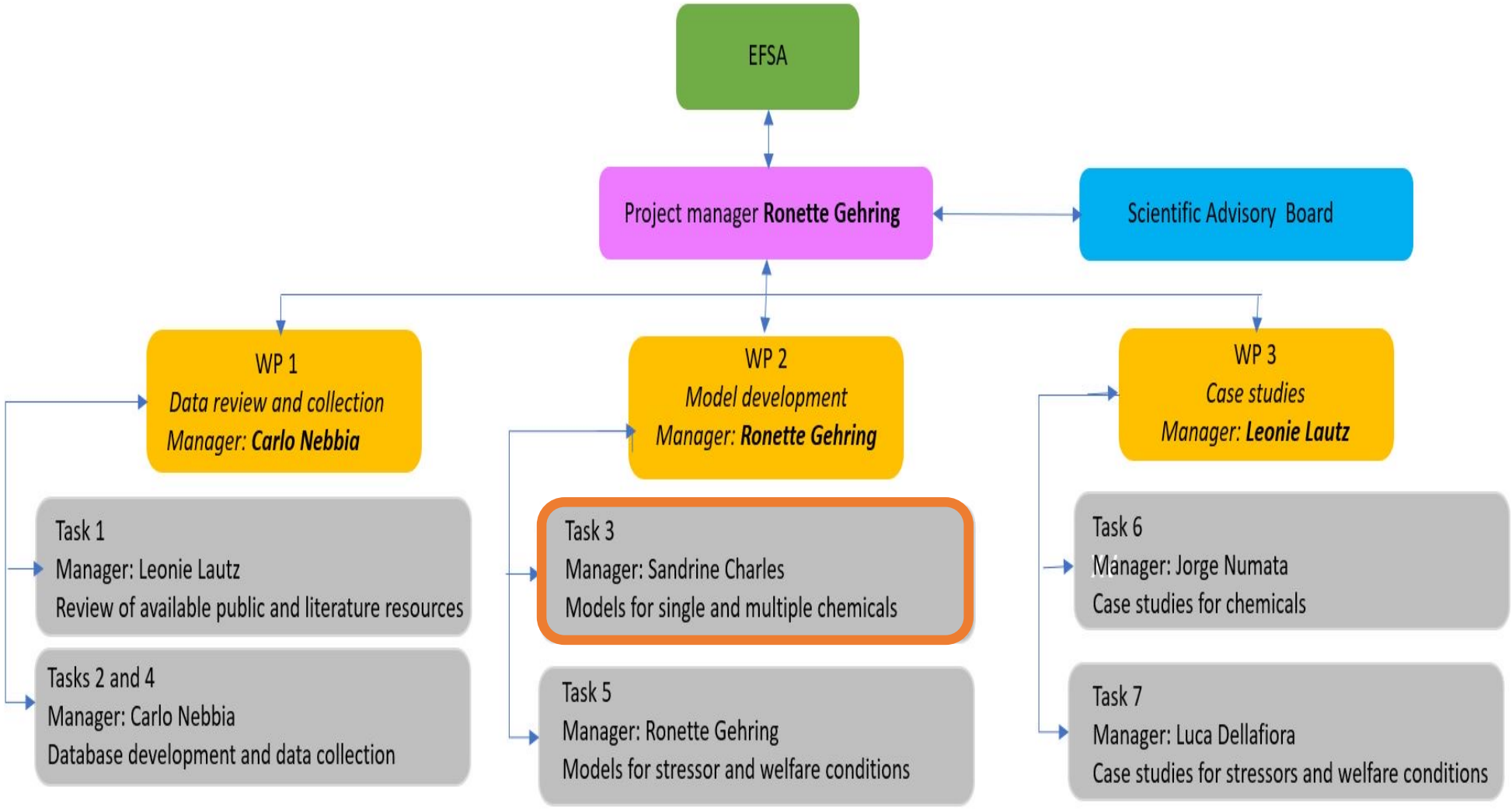
- Train stakeholders to the final tool via webinar or workshop

2. Generic K, K-D and ML model implementation in TK plate 2.0

- Review available Kinetic and/or Dynamic models and Machine Learning methods for all our animal species of interest
- **Build a K-D tool for chronic ERA of single PPPs in birds within the spirit of Open Science + Train stakeholders**
- **Develop PB-K, PBK-D and other biologically-based models for ERA of multiple chemical effects**
- Develop PB-K, PBK-D and other biologically-based models for ERA of biological stressors, welfare conditions and multiple stressors.
- Develop ML models for predicting K and D properties of chemical and biological stressors.

3. Validation of models using case studies

- **Case studies for the use of PB-K, PB-K and ML models under single chemical exposure (all animal species)**
- **Case studies for the use of PB-K, PB-K and ML models under multiple chemical exposure (all animal species)**
- Case studies for the use of PB-K, PB-K and ML models under multiple biological hazards and welfare conditions exposure
- Case studies for the use of PB-K, PB-K and ML models) under multiple multiple stressors exposure

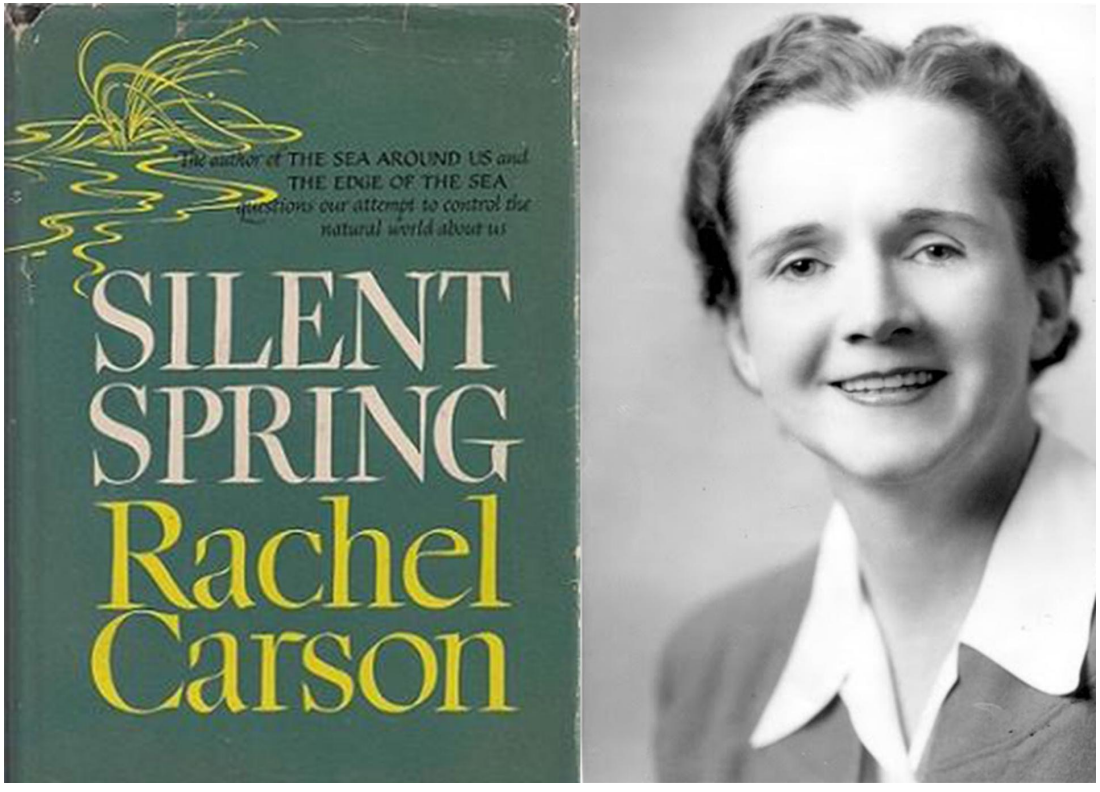

EFSA
Project manager **Ronette Gehring**
Scientific Advisory Board
WP 1
Data review and collection
Manager: ***Carlo Nebbia***
WP 2
Model development
Manager: ***Ronette Gehring***
WP 3
Case studies
Manager: ***Leonie Lautz***
Task 1
Manager: Leonie Lautz
Review of available public and literature resources
Tasks 2 and 4
Manager: Carlo Nebbia
Database development and data collection
Task 3
Manager: Sandrine Charles
Models for single and multiple chemicals
Task 5
Manager: Ronette Gehring
Models for stressor and welfare conditions
Task 6
Manager: Jorge Numata
Case studies for chemicals
Task 7
Manager: Luca Dellafiora
Case studies for stressors and welfare conditions

Scientific Advisory Board (SAB)

- **Dr. Jim Riviere**
  https://iccm.k-state.edu/people/riviere/index.html
- **Dr. Ronald Baynes**
  https://cvm.ncsu.edu/directory/baynes-ronald/
- **Dr Keyvin Darney**
  https://www.researchgate.net/profile/Keyvin-Darney/publications
- **Dr. Chris Rackauckas**
  https://chrisrackauckas.com/

- **Kansas State University, US**
  Institute of Computational Comparative Medicine
- **North Carolina State Veterinary Medicine, US**
- **ANSES, France**
  Agence nationale de sécurité sanitaire
- **Massachusetts Institute of Technology, US**
  SciML Open Source Software Organization


Why avian species?



1st edition in 1962

Impassioned, poetic and brilliantly written, ***Silent Spring*** is now recognized as one of the most influential books of the 20th century.

Rachel Carson exposes the destruction of wildlife through the widespread and indiscriminate use of pesticides.

She described:

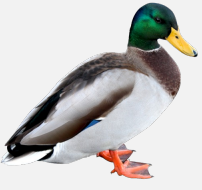
- the nests full of eggs that would never hatch,
- the rivers bloated with poisoned fish
- the children killed by the very chemicals which had previously been lauded as miracle potions, and sprayed without reservation across the country.

Dr. Rachel Carson

https://www.ecodisciple.com/blog/the-enduring-legacy-of-silent-spring/

Generalities about avian species

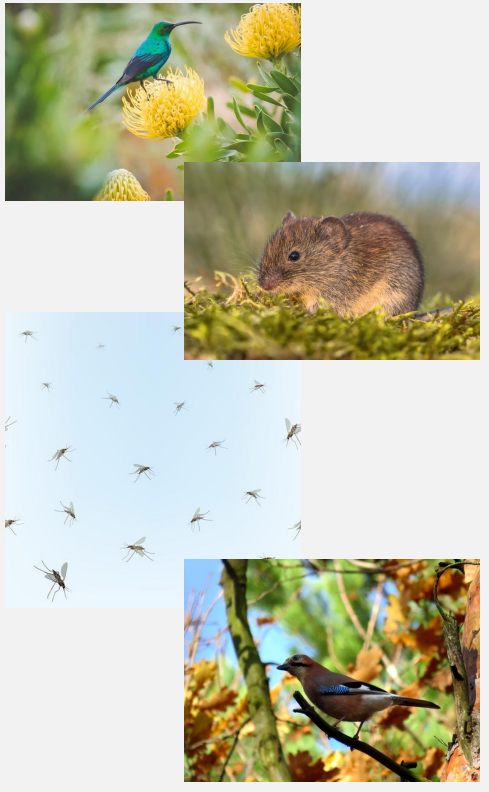
- There are 11 000 species of birds documented around the world
- Avian species serve as pollinators, predators, and secondary consumers
- Their life processes are closely linked with agricultural activities
- They can be used as biomarkers for polluted sites
- One out of seven (1/7) species is threatened for extinction, according to IUCN
- Worldwide pesticide use has risen from 3.04 – 4.11 million tons (between 2000-2017)



https://www.iucn.org/fr

Why specifically focus on pesticides?

- Plants Protection Products (PPP) pose a tremendous adverse effects on birds, due to their key role within ecosystems.
- Pesticides induce reduced growth rate, decrease in fertility, hence low reproduction of birds.
- Bioaccumulation of chemicals may appear within target organs of birds



Why it matters?

- Analyze the effects of Persistent Organic Pollutants
- Plan for the future, *i.e.*, management and mitigation
- Provide data to support claims
- Study new pollutants entering market

Example: *DDT use in the US and avian mortality*

The circle of all dangers for birds

Reduced quantity of cereals

Poor quality of crops

Less viable eggs

Increased bird mortality

Cocktails of chemical mixtures

Arya, A.K., Singh, A., Bhatt, D., 2019. Pesticide applications in agriculture and their effects on birds: An overview, in: Contaminants in Agriculture and Environment: Health Risks and Remediation. pp. 129–137.

Current status

- Literature search
- Review paper (ESPR)
- PBTKTD modelling

A total of 120 papers

((bioaccumulation AND model*) OR (toxicokinetic* AND model*) OR PBTK OR PBPK OR (toxicodynamic AND model*) OR GUTS OR (DEBtox AND model*) OR (DEBkiss AND model*) OR (dose response AND model*) OR (exposure-effect AND model*) OR (Effect* concentrat* AND model*) OR (modelling AND ecotoxicology) OR (modelling AND toxic*) OR (modelling AND contamina*)) AND (birds OR avian OR hen OR chicken OR poultry)

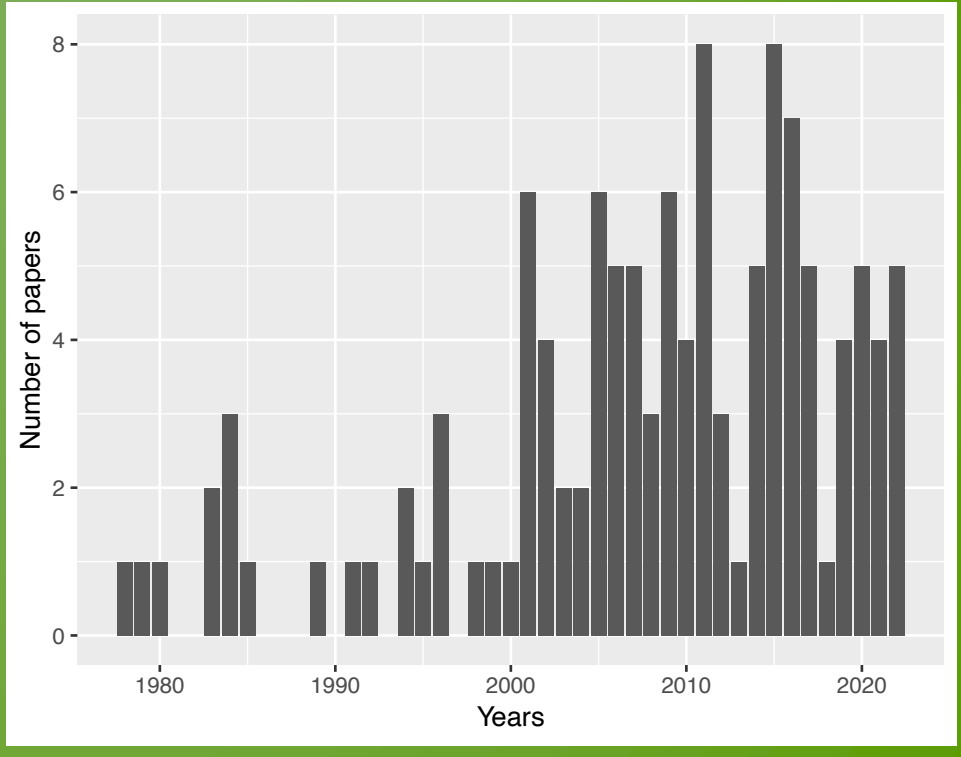
Scopus keyword equation

Excluded → book, book chapter, editorial and note

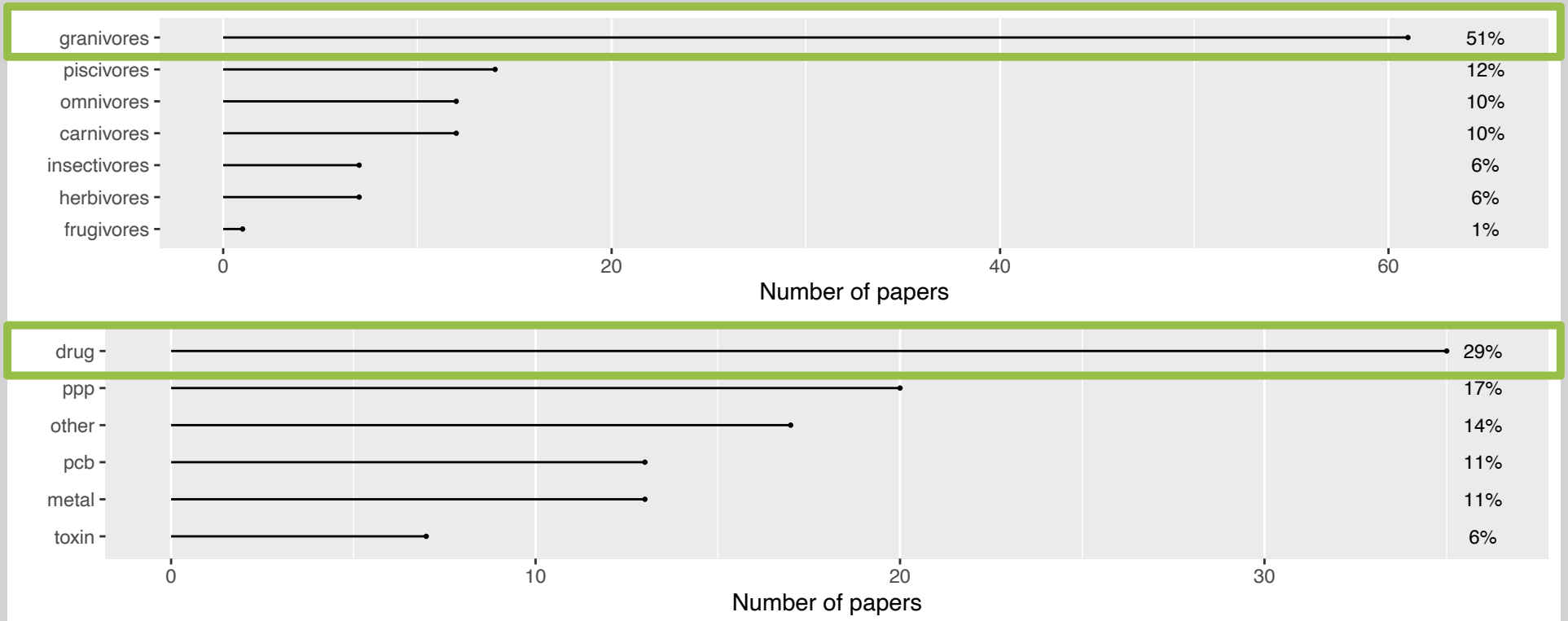
Excluded → no modelling, pure descriptive models, basic statistical/hypothesis tests, generic modelling issues without case studies

Literature review

- Quite a few papers
- Most after 2000



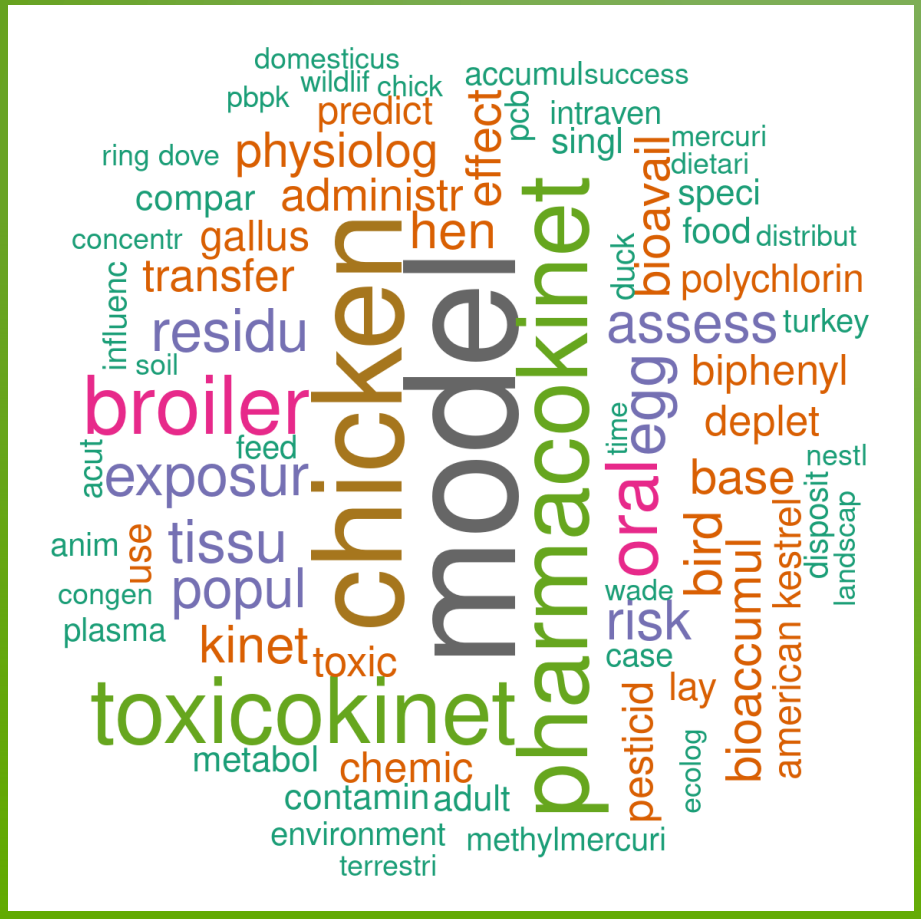
A majority of papers on granivores / drugs



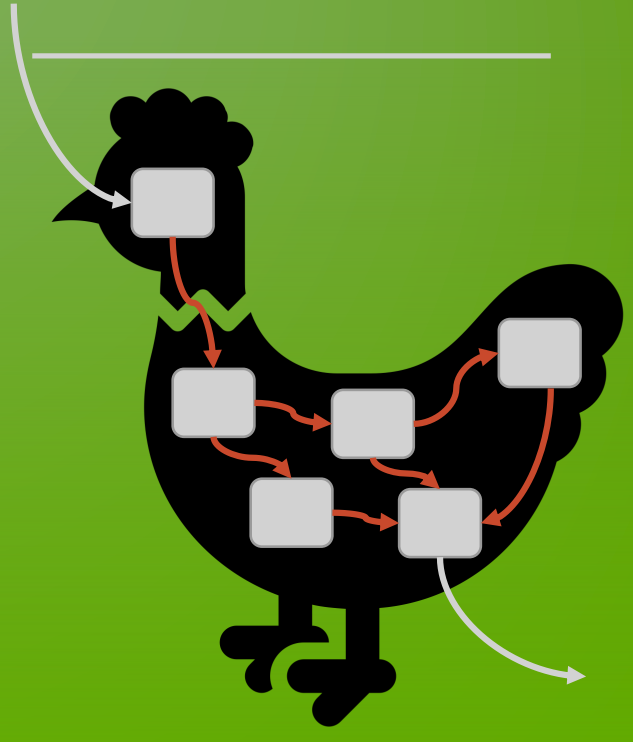
A majority of papers on individual PBK models

Level of organization	#
Individual	102
Population	14
Community	2
Landscape	3

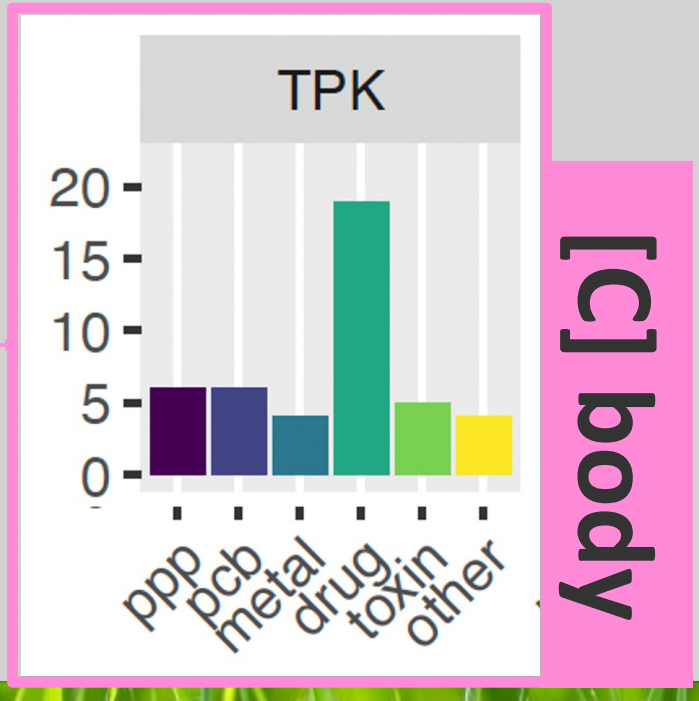
Type of model	#
PBK	89
PD/TD	12
Dose-response	2
Energy-based	5
EDO-based	8
IBM	3
Food-web	2
Spatially- explicit	3

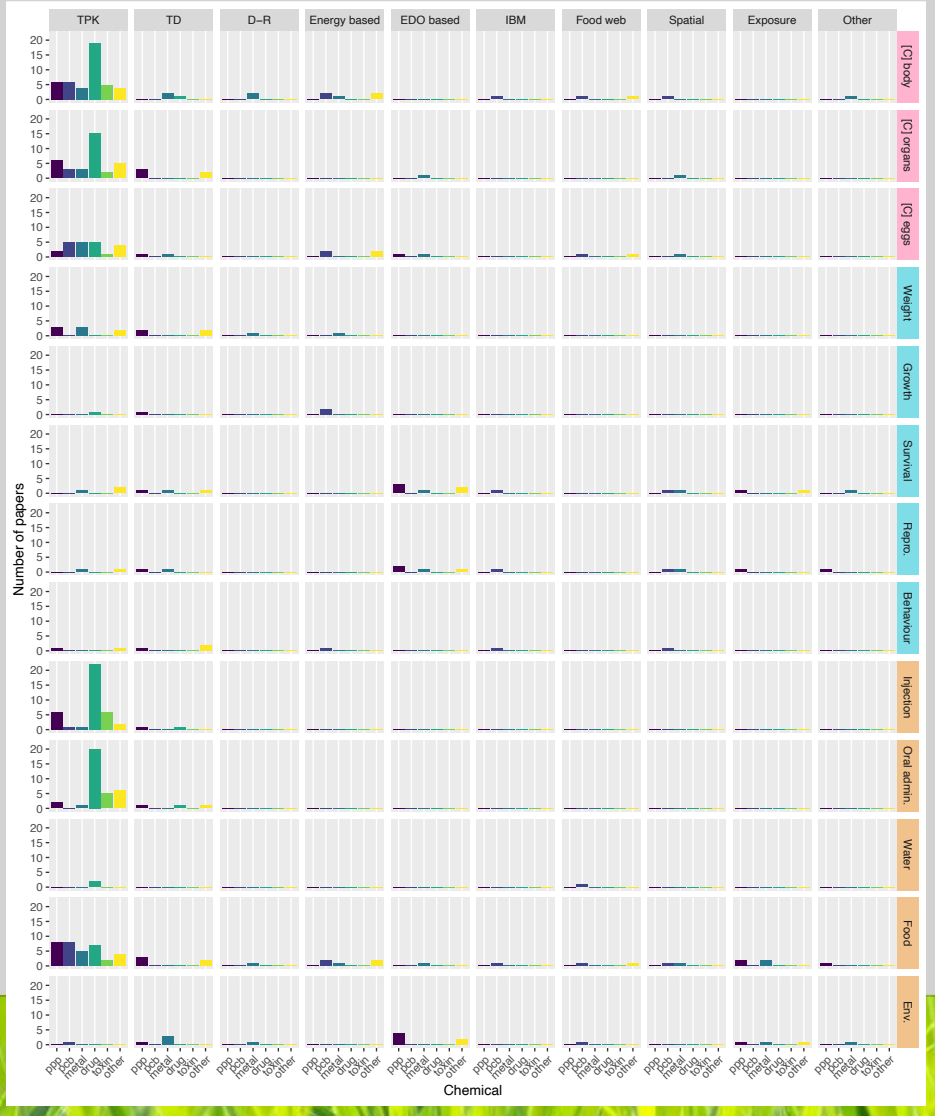


Word cloud on titles



Crossed view of data availability

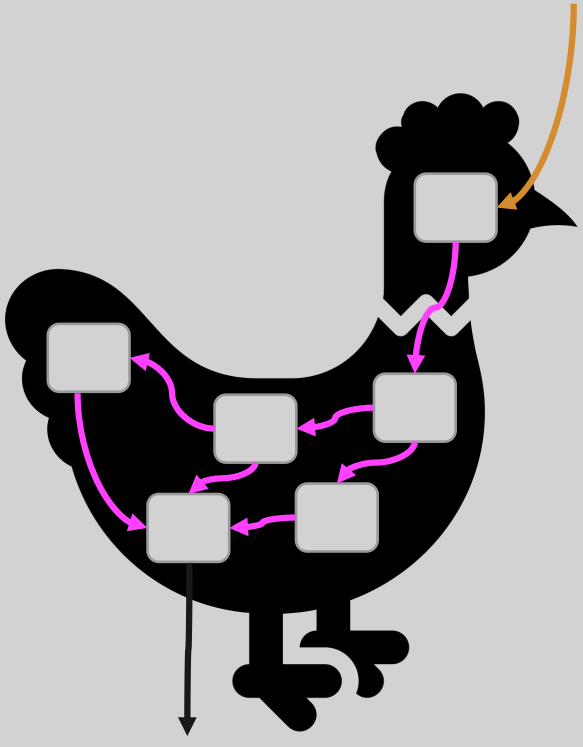




Concentration measurements

Measured endpoints

Exposure routes



Thank you
for your attention