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Mixing apples and oranges

Problems, approaches and solutions in mixture risk assessment

Leo Posthuma and many colleagues

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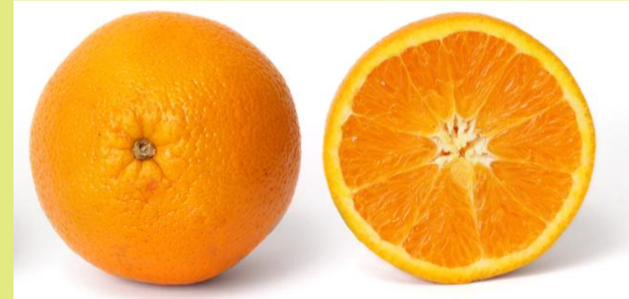
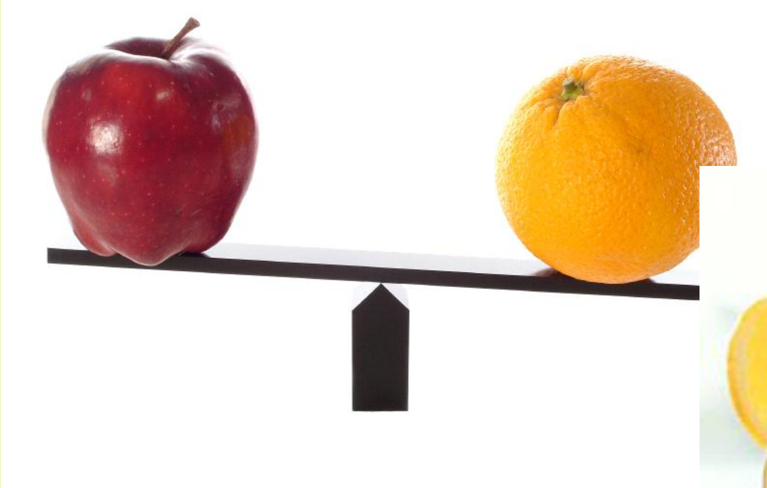
Keep separate

and study



Weigh. One heavier or healthier?



Act as if the same

(but wrong?)

Nice mixture …..

Whatever

This basket is healthy

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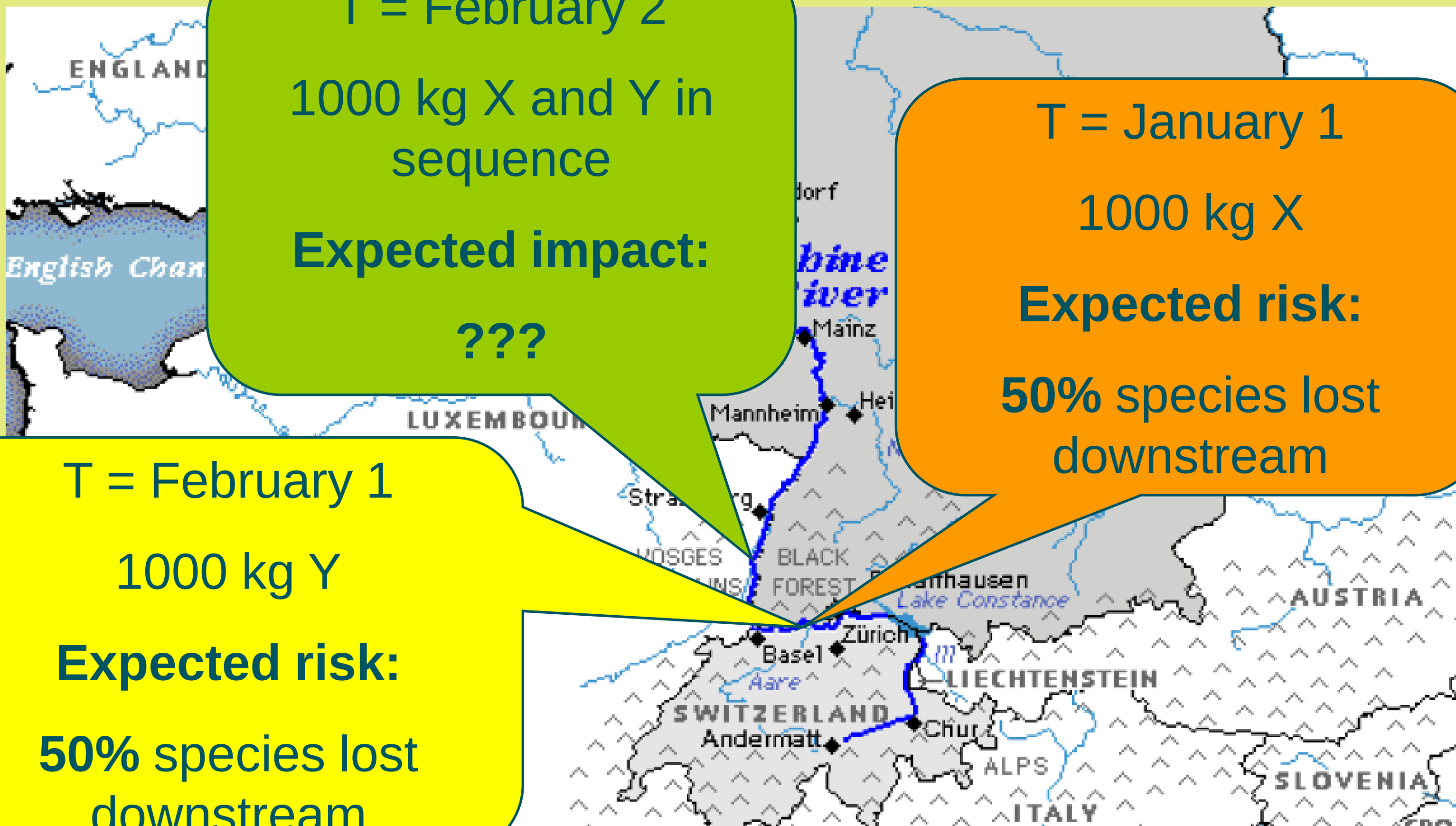
Thought experiment; “random compounds, “the” ecosystem



T = February 2

1000 kg X and Y in sequence

Expected impact:

???

T = January 1

1000 kg X

Expected risk:

50% species lost downstream

T = February 1

1000 kg Y

Expected risk:

50% species lost downstream

Net impact downstream??

(Assuming: no mixture, no recovery, no breakdown, no further dilution)

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Net impact

1. I am sure I cannot know
2. I don't know
3. I am sure it is 50%
4. I think it is 50%
5. I am sure it is not 50%, but some bit higher
6. I guess it is more than 50%
7. I think it is more than 50%
8. I am nearly sure it is near 75%
9. I am not fully sure, but it is likely between 70 and 80%
10. I am sure it is 100%
11. …

Thought experiment 2 (1 day apart)

T = January 3

1000 kg X and Y in sequence

Expected risk:

???

T = January 1

1000 kg X

Expected risk:

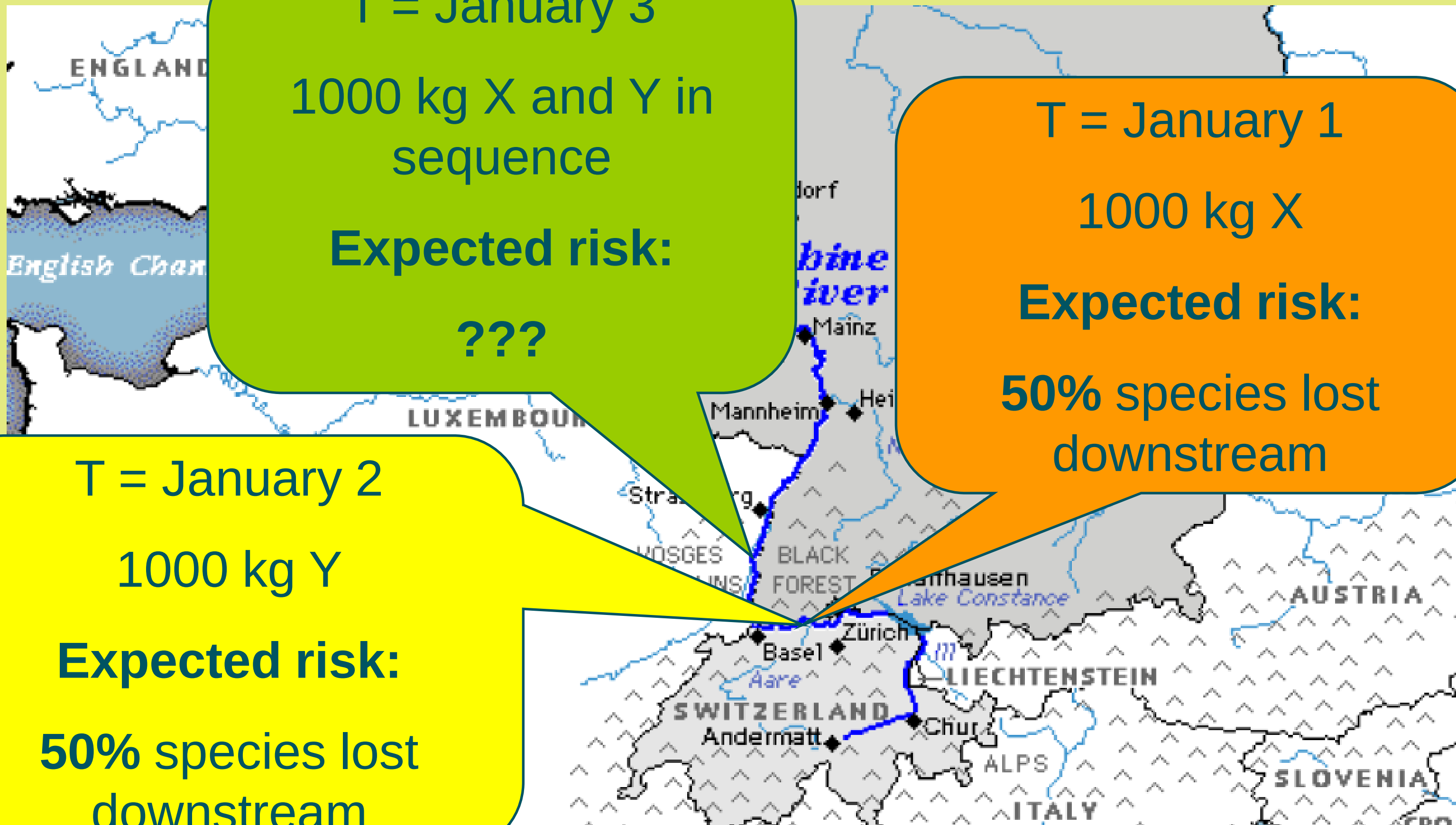
50% species lost downstream

T = January 2

1000 kg Y

Expected risk:

50% species lost downstream



Net impact downstream??

(Assuming: no recovery, no breakdown, no further dilution)

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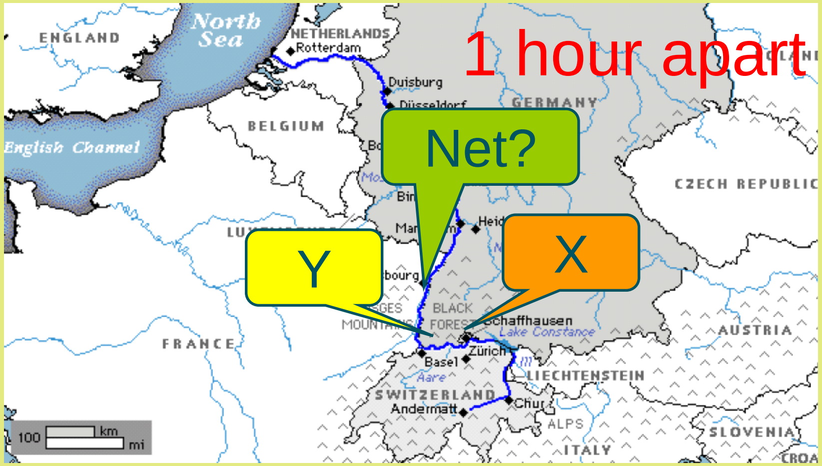
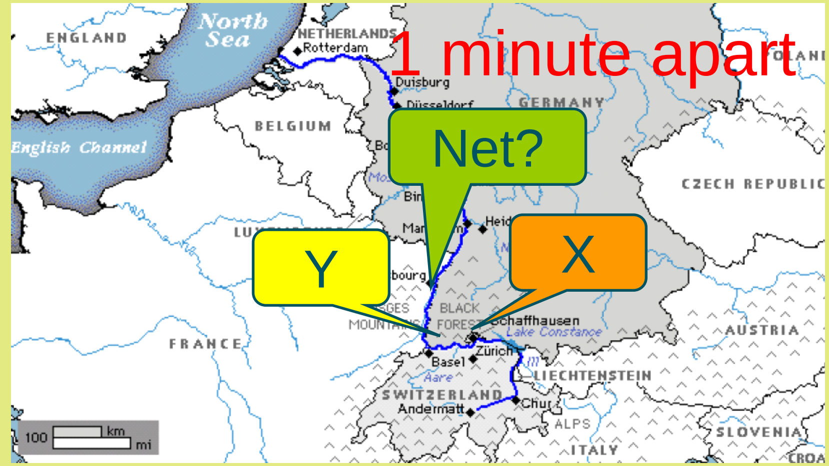
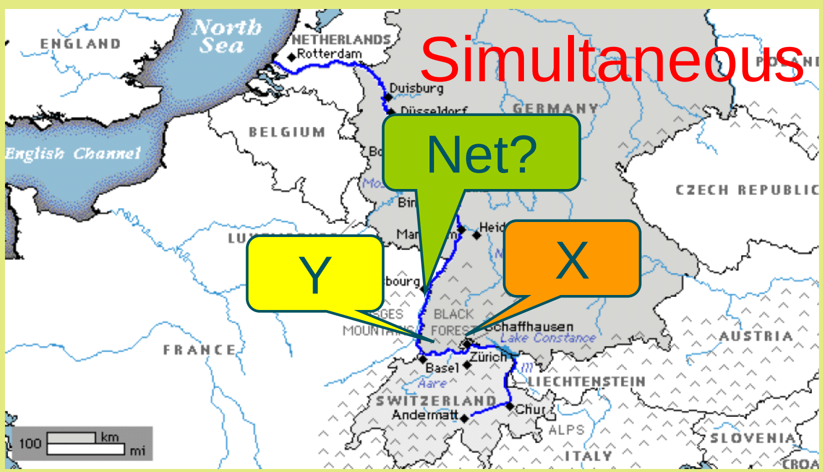
Thought experiment 3, 4, 5 ….







= mixture problem

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NORMAN – objectives

To create a network of (expert) reference laboratories ….for….

- Improve data collection and management
- Concerning emerging environmental contaminants

- From monitoring institutes $\Rightarrow$ End-users (finally risk management)
- Improve and validate tools along this chain

- Eventually: spatially and temporally explicit risk information (man and eco)

Eventually: permanent HERA network on emerging environmental contaminants

And all those emerging environmental contaminants

may co-occur – how to address that?

(this workshop's theme)

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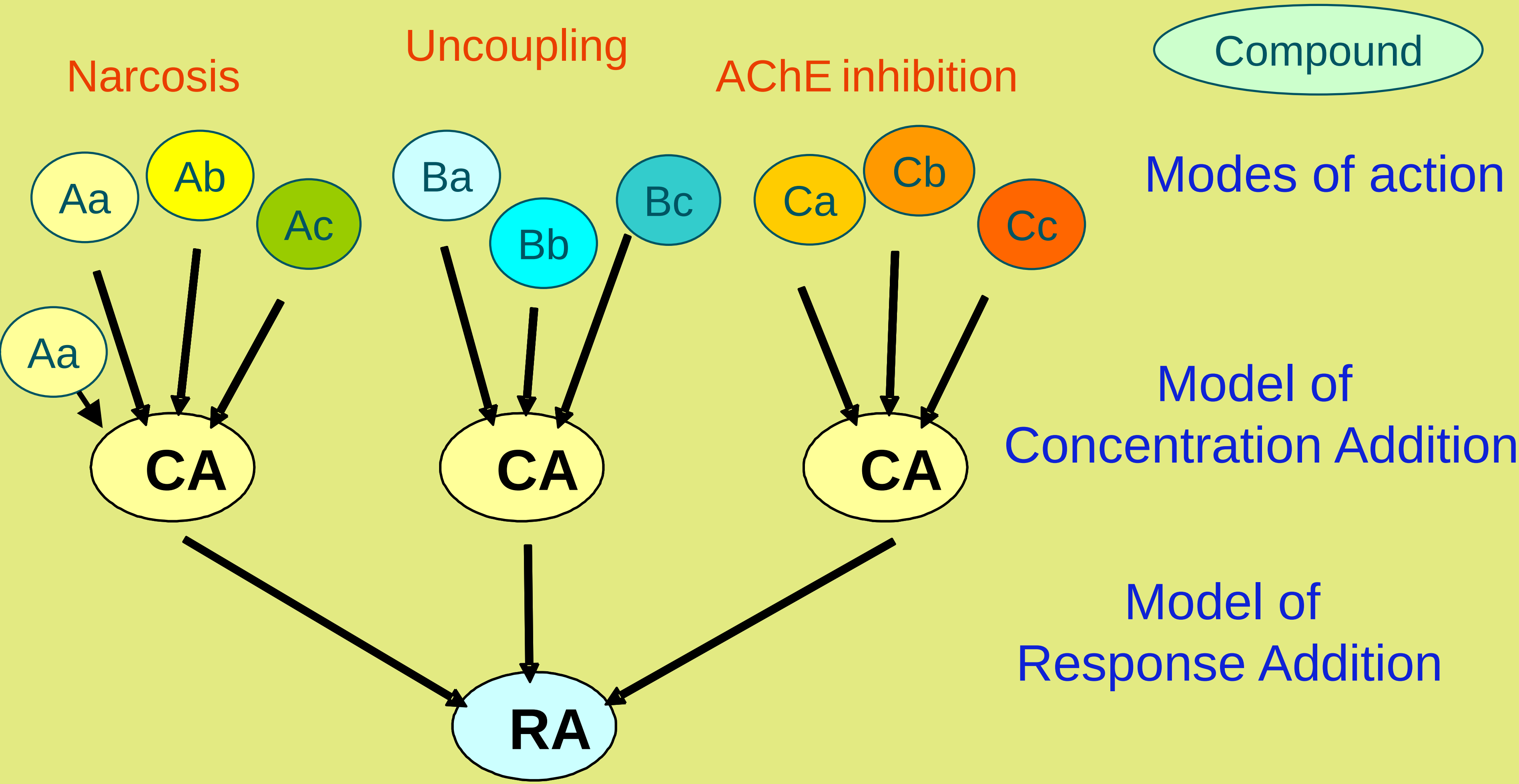
This presentation

- How to address apples and oranges: mixture risks
- To eventually serve risk management
- Using established techniques and models
- While critical on validation
- Recognizing strengths and weaknesses

- …. practical examples to show risk management benefits

Basic mixture issues (physiology, mechanistic)



Jager et al. (2007)

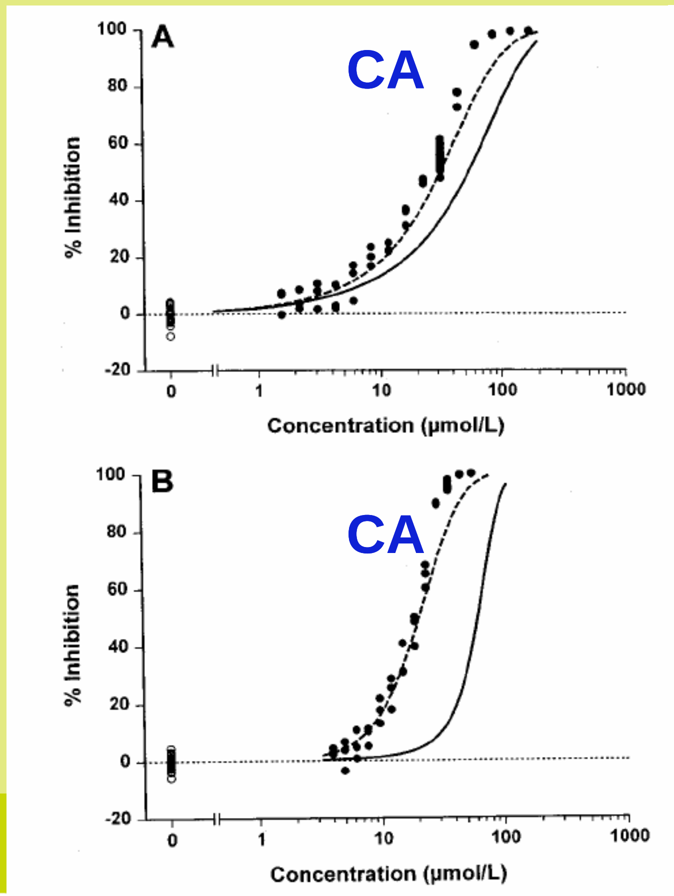
At species level: Altenburger et al. 2004/2005

At community level: De Zwart & Posthuma 2005

Mixture tests on *Vibrio fischeri*

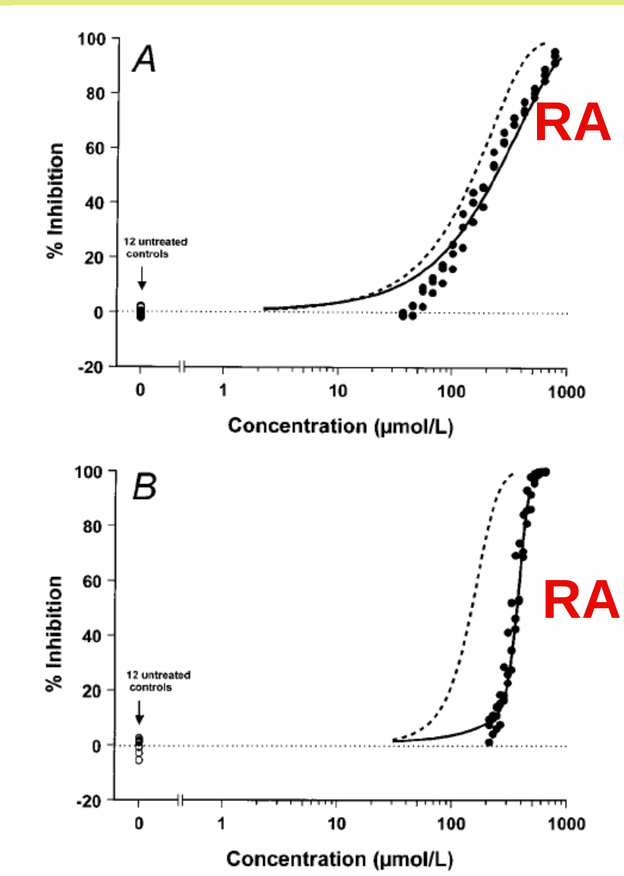
(• = data point, lines are model predictions)

Various compounds
Similar MOA



Altenburger et al., 2000

Various compounds
Dissimilar MOA



Backhaus et al., 2000

- - - - CA
—— RA

Equitoxic (EC50)

Equitoxic (EC1)

Observations fit to expected model

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Mathematical properties of CA and RA

Drescher, K., and Bödeker, W. (1995).

Assessment of the combined effects of substances – the relationship between Concentration Addition and Independent Action *[RA].*

Biometrics. 51, 716–730

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Mathematical properties of CA and RA

- At "moderate" slopes, divergence between mixture null models limited !!
- "No mixture effect" is "most wrong"

CA-prediction ≅ RA-prediction ≅ Mixed-Model prediction

- Statement:
  "For <u>some</u> practical problems it is better
  → to use either mixture model (CA and/or RA and/or "mixed model"), rather than
  → neglect mixtures (using "limitations in scientific evidence" as argument)

  ……. provided that assumptions need be tested

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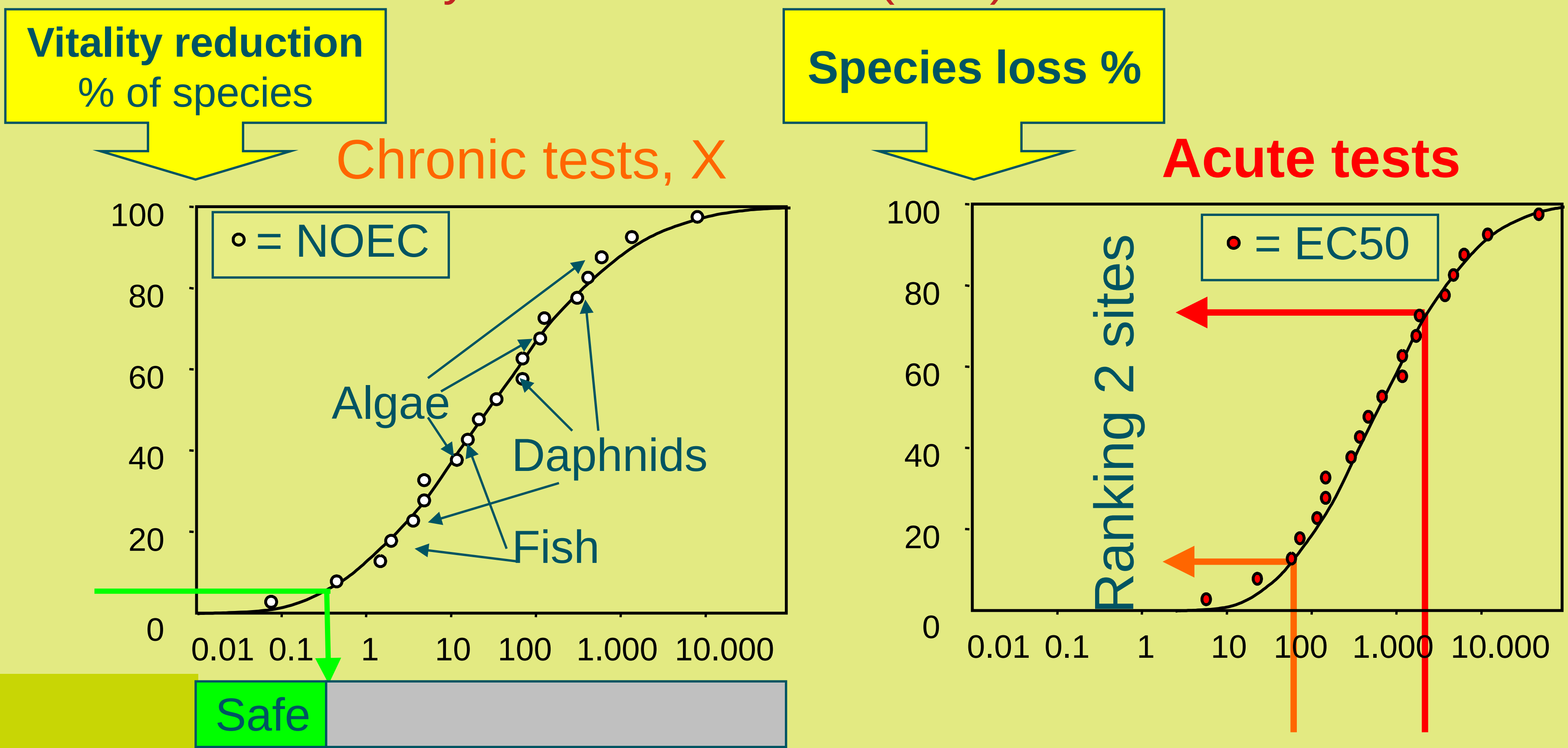
From mechanism to ERA-use

Apparently, we have:

- Frequent mixtures in environment
- Mechanism-based, numerically validated species-level models
- ….and our 75%-guestimate (Rhine – thought experiment) at the species assemblage level

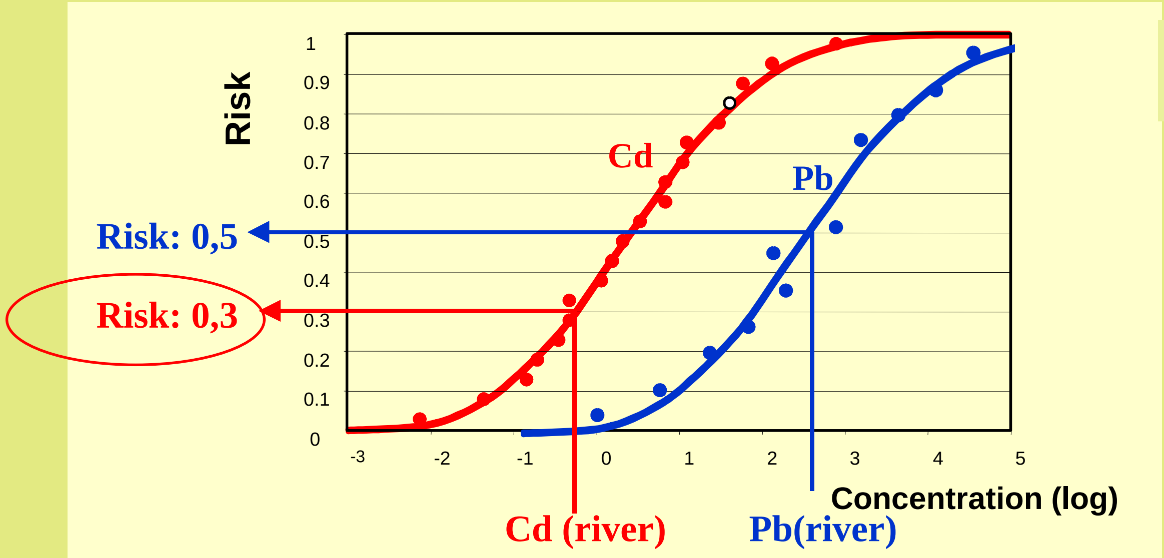
Assemblage-level modeling

- Species differ in sensitivity for a compound
- SSD = Species Sensitivity Distribution
- Y = Potentially Affected Fraction (PAF)



Environmental concentration

Back to thought experiment:mixture



- Mixture risk according to dissimilar Mode of Action:
- Risk = PAF = Potentially Affected Fraction of species
- Multi-substance PAF = 1 – (1 – 0.3)*(1 – 0.5) = 0.65

msPAF = 0.65

- 65% of the species would be affected in this river
- ranking of sites possible → management information !

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Risk assessment paradigm

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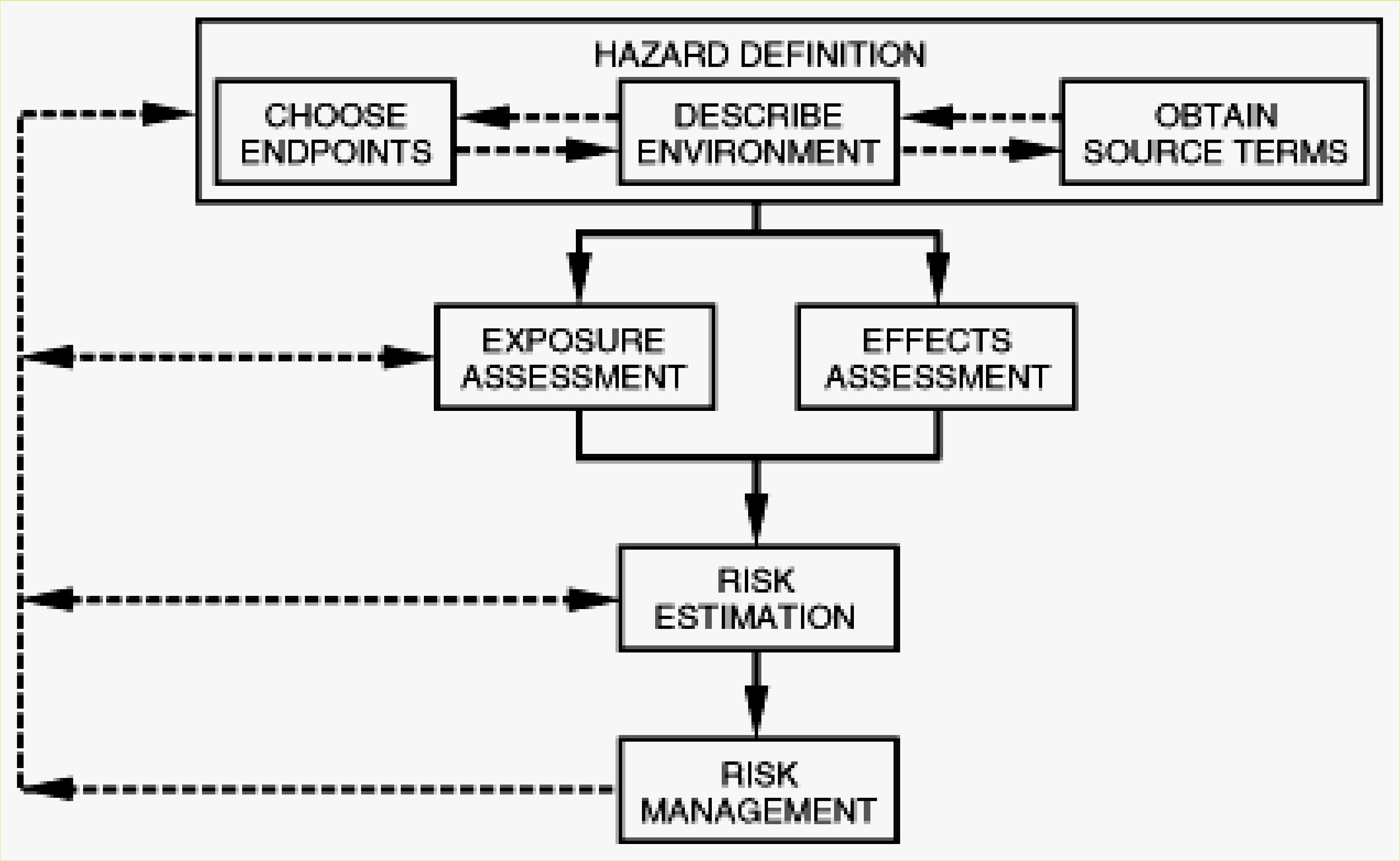
The ERA paradigm



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Currently two policy lines

E.g., EU-Water Framework Directive

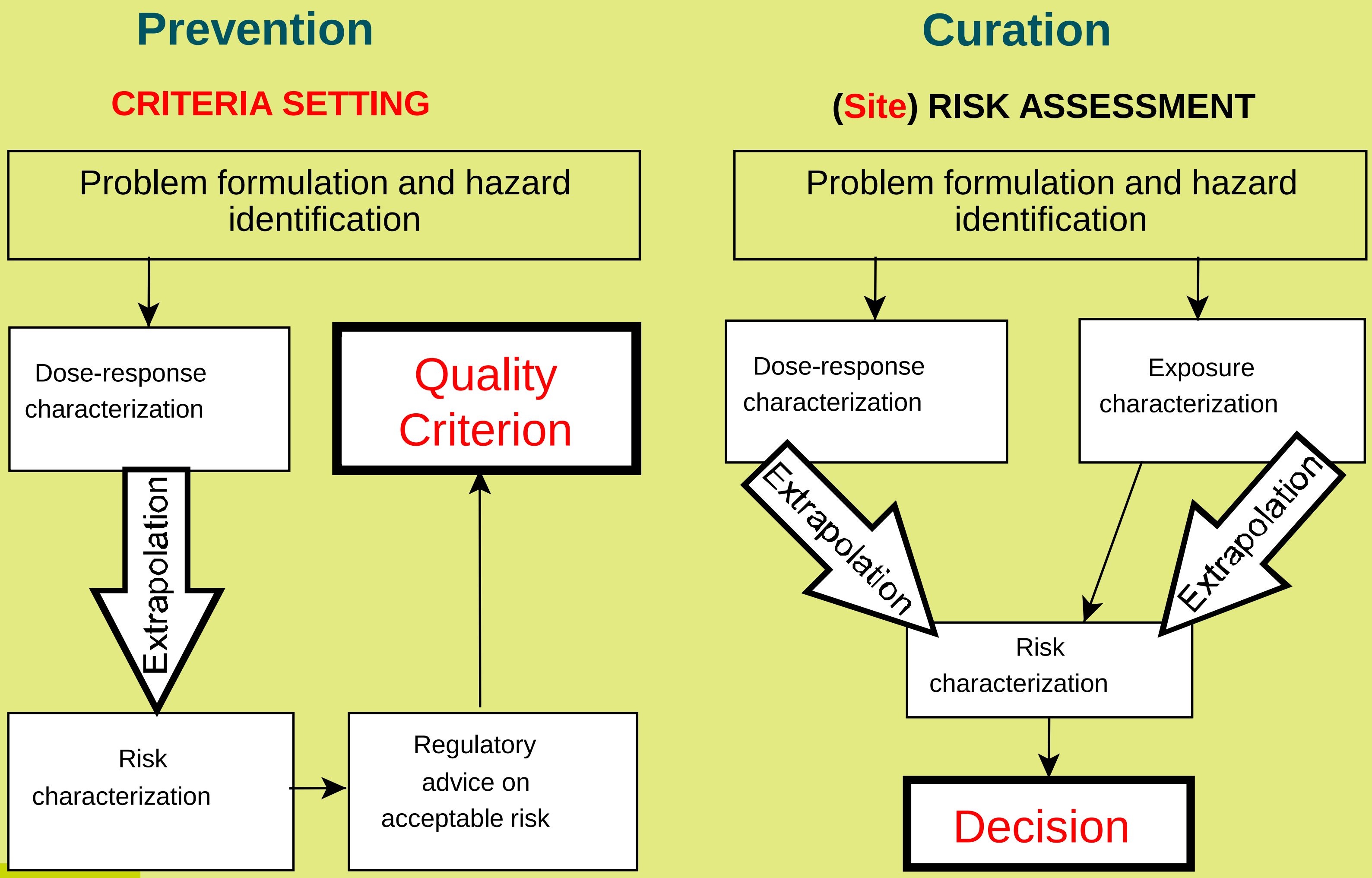
- Good Chemical Status …..priority compounds
  → Chemical Quality Criteria

  If not met → *Reduce emissions*

- Good Ecological Status ….. Species assemblages OK
  → Diagnosis of mixture (?) problem

  If not GES → diagnosis → Integrative site management

Double use ERA-paradigm …..



Refinement when needed

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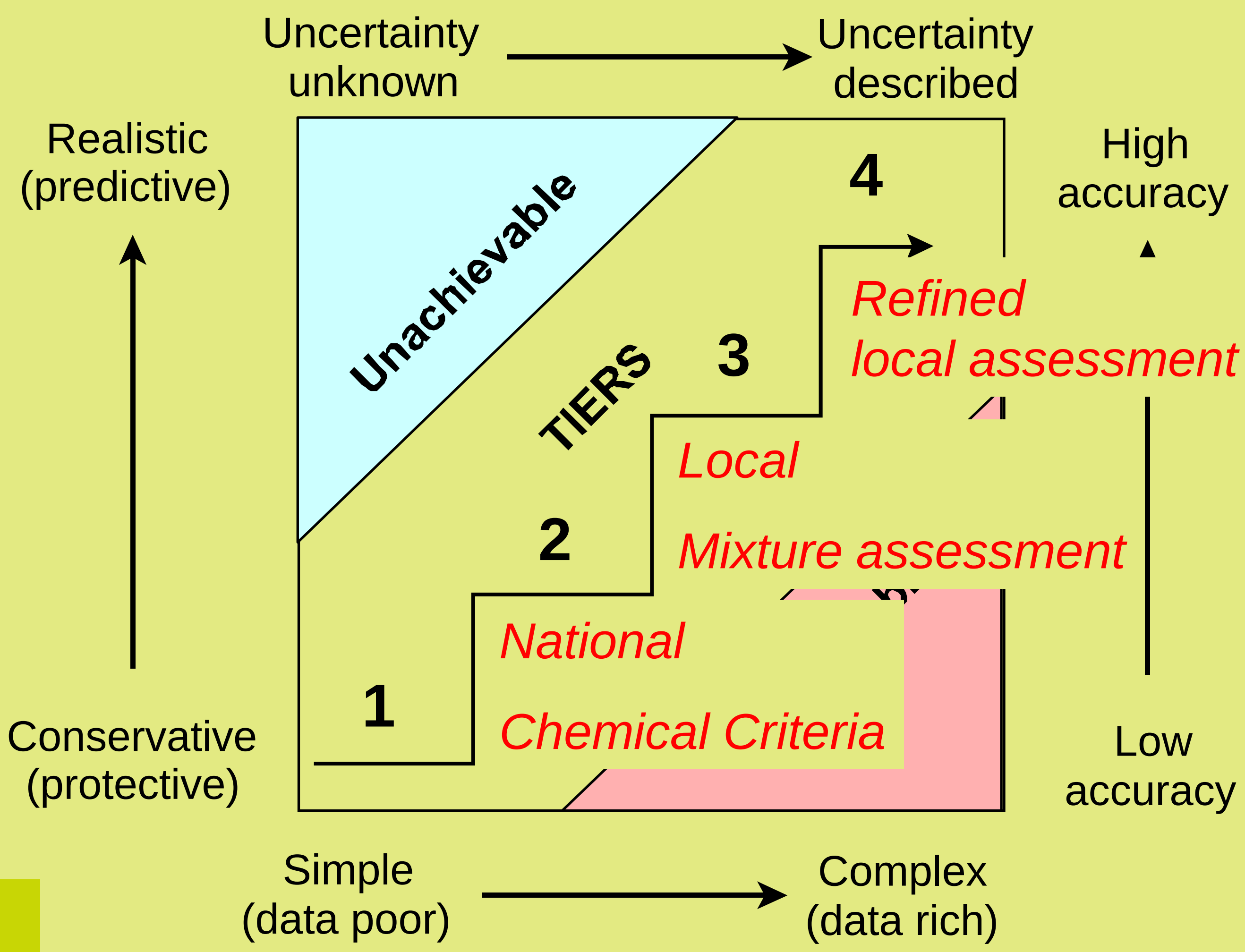
….that is: consistent, tiered system



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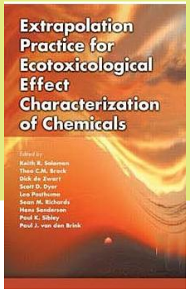
Solomon et al. 2008



And now: follow context not details

Examples highlighting tiering, flexibility,….

….imagine consequences for ERA-practices

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Net risk for adjacent ditches and watersystems?

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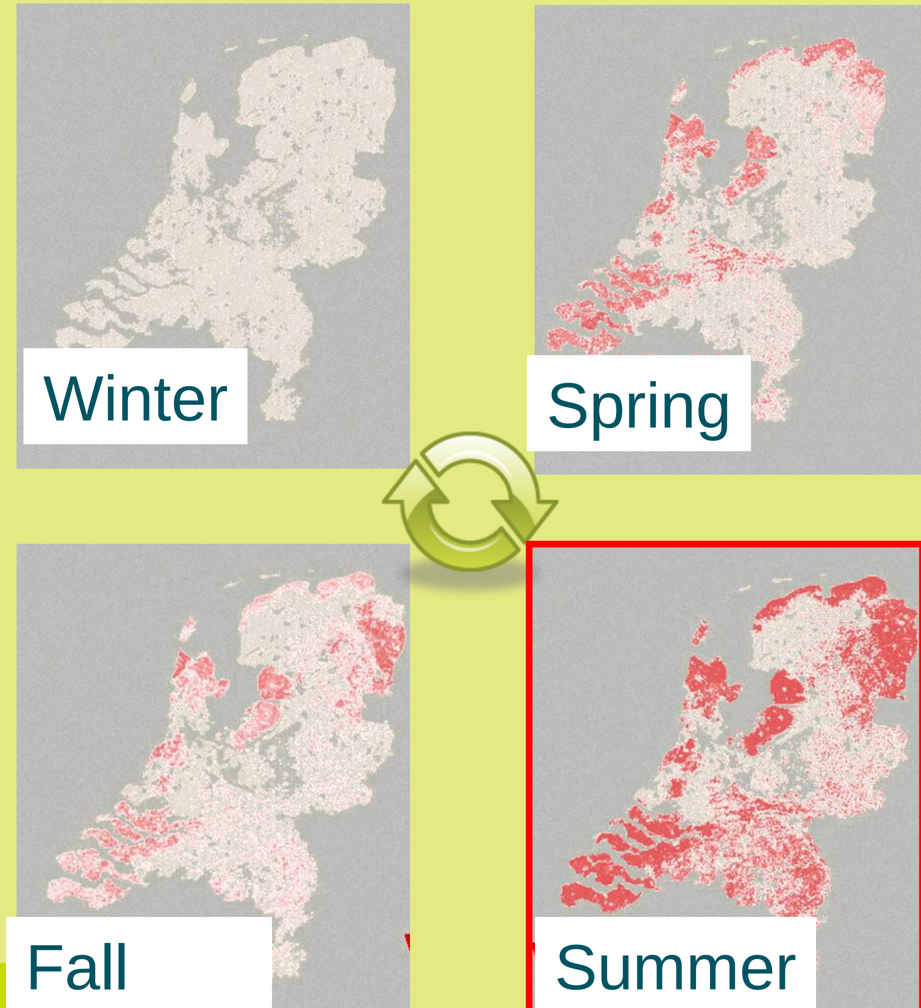
Compounds only: Evaluate net expected impact + rank



- **Vitality** loss (ditches)
- Model:
  Predicted ditch concentrations

- Summer: Max. 51% of species
- 7 compounds link to 96% of loss

Contribution by Crop Type:
- Potatoes 58%
- Bulbs 14%
- Other

- **Ranking informs priority**
  - **Δ Environment / € ?**

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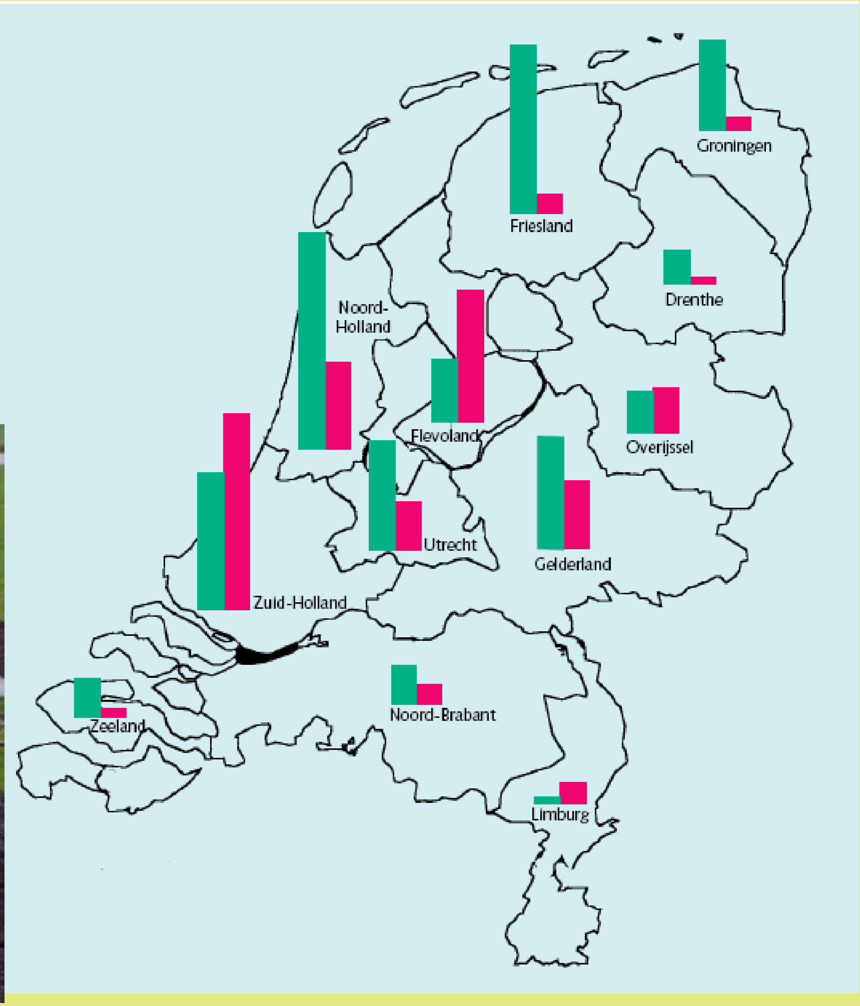
Contaminated sediment in rural areas



Policy plan: phase out class-2 pollution (green) in yr 2000

→ Currently: millions of m^3 backlog

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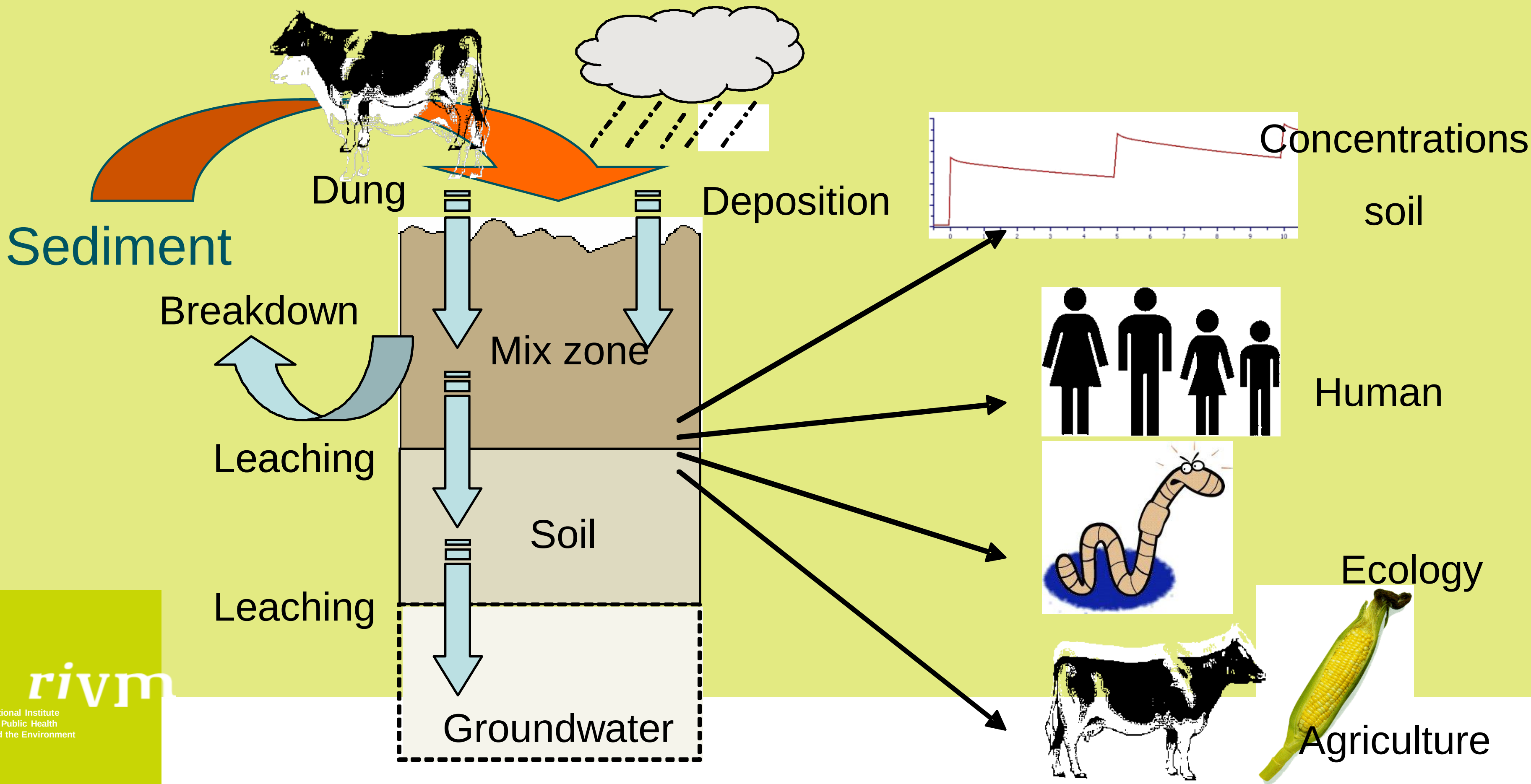
Compounds + Local System

Where can we safely deposit slightly contaminated sediment on land, regularly, and at acceptable cost?

- From “per chemical + safety factor” to a local systems approach



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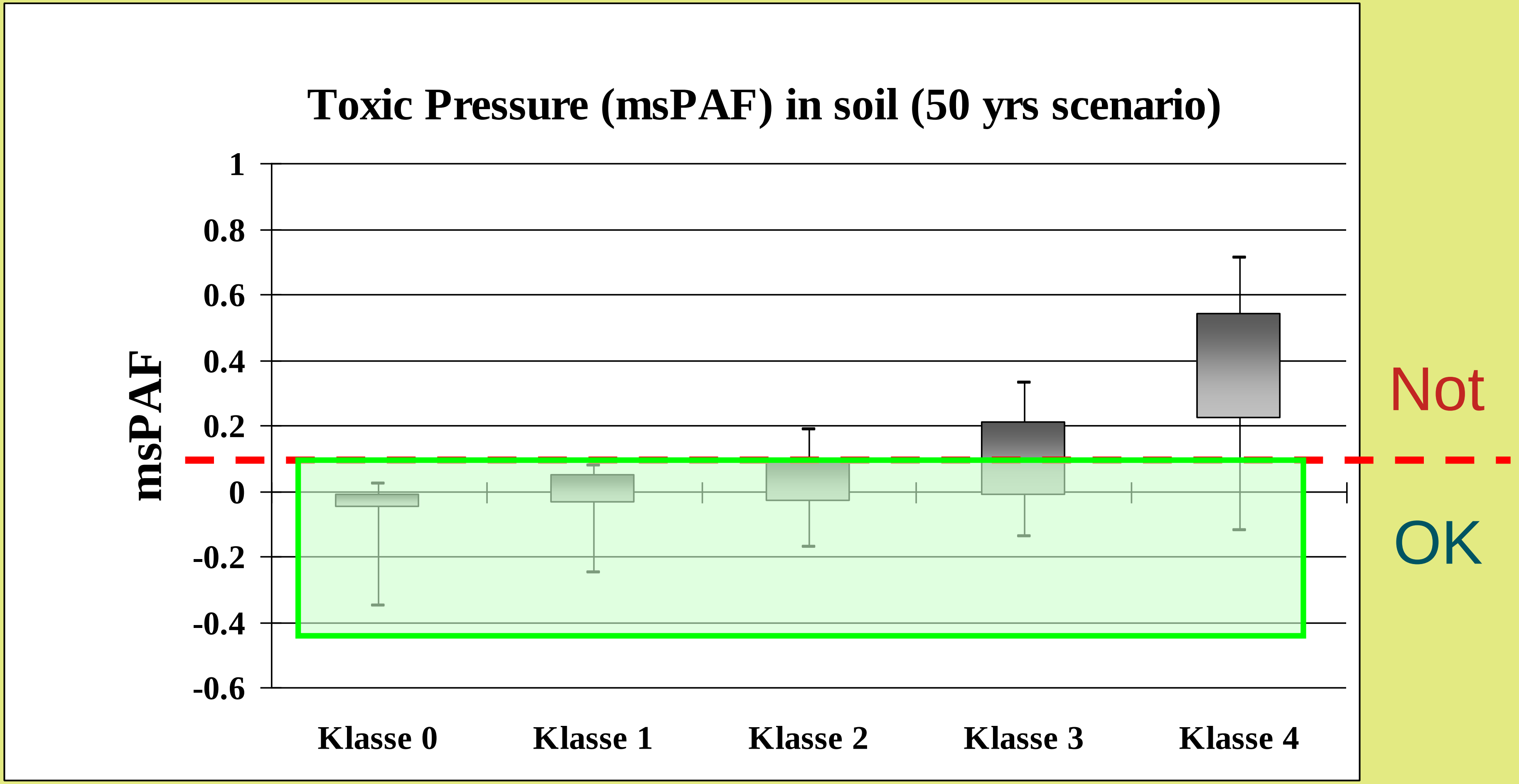
Example output (> 1000 sites, Boxplot risk variance)



- Ranking situations and management
  - Δ Environment / € ?

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Good / bad Ecological Status: diagnosis?

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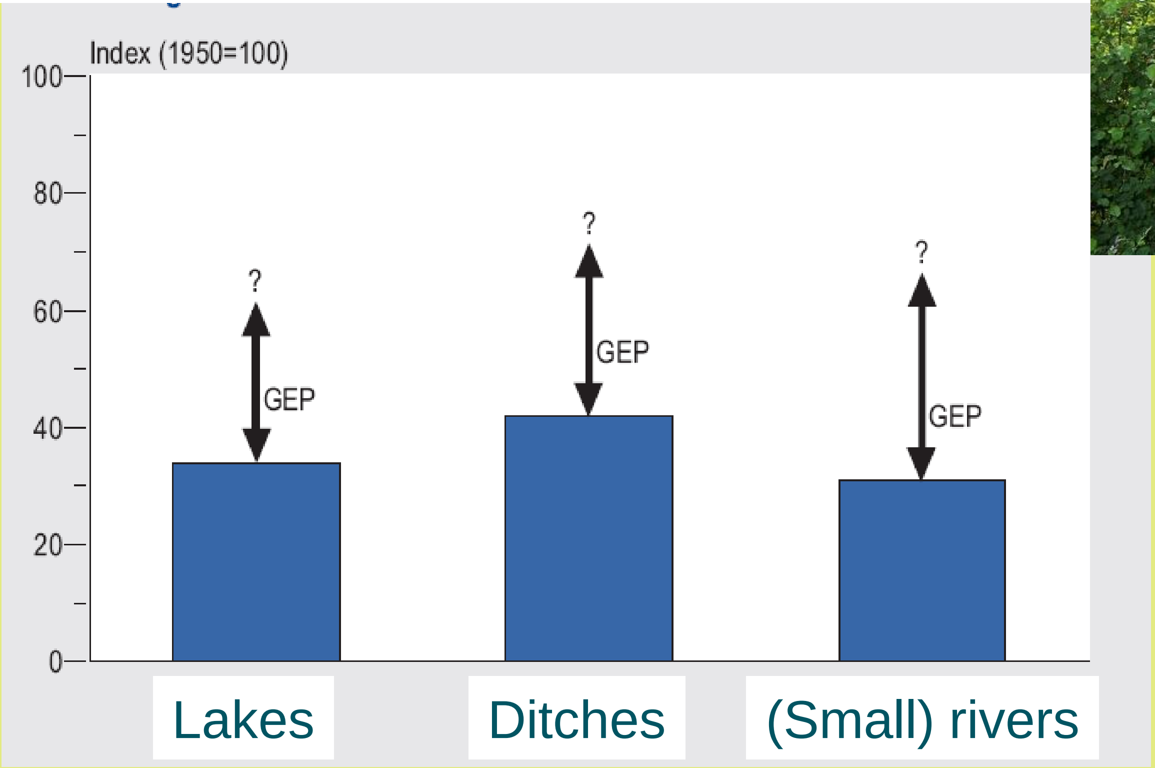
Diagnosis

Deviation of Good Ecological Status / Potential



Water (Water Framework Directive): Good Ecol. Status by 2015

Deviations observed….. What are the causes of impacts?

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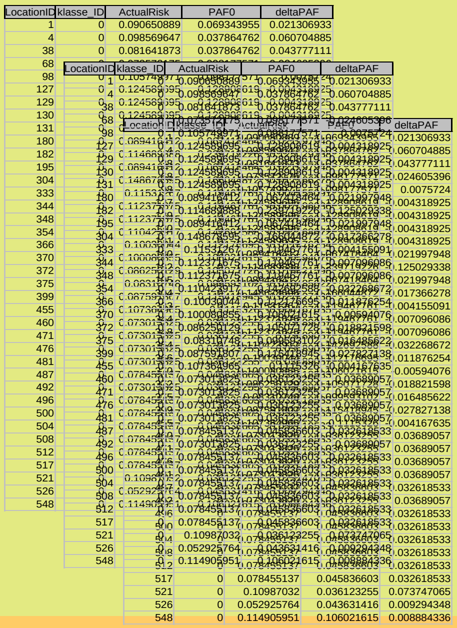
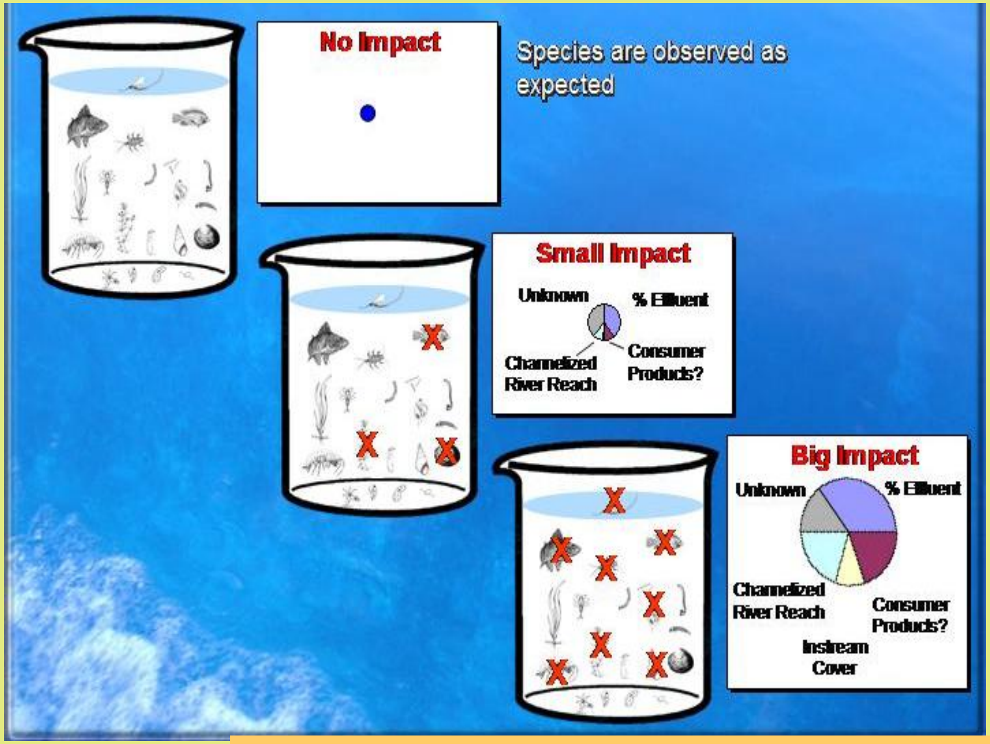
Eco-epidemiology

From monitoring data → local causes → Program of Measures





Monitoring data

- 700 sites
- 100 species of fish
- 25 stressor variables +
- msPAF for all toxicants

Outline of diagnostic product

-Impact per site

-Causes per site

-(Ohio, Scheldt)

Not only for chemicals for which we have

Water , Soil or Sediment Quality Criteria

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Chemicals + site + natural variability

- Good Ecological Status is final target (EU-2015)
  ….but species composition varies between sites

UK-monitoring data:

14 main types of

minimally disturbed

aquatic

sites

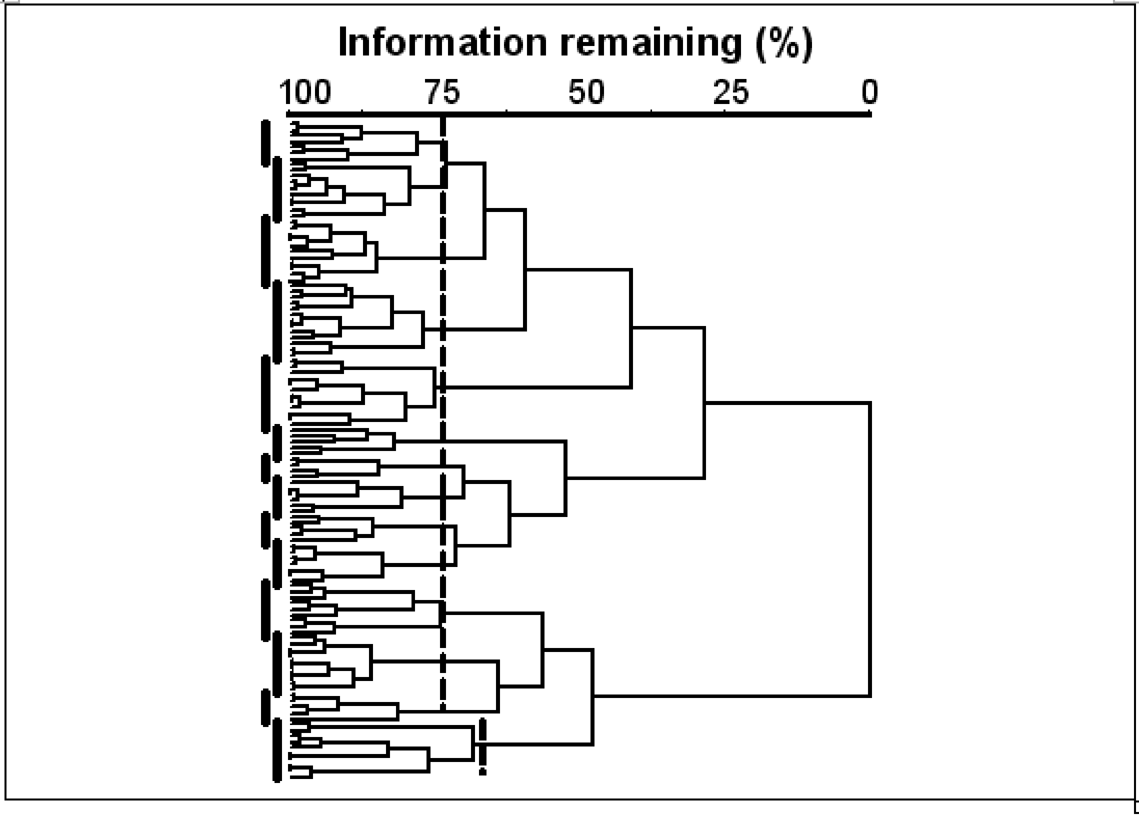
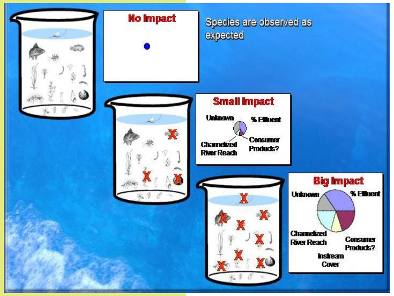
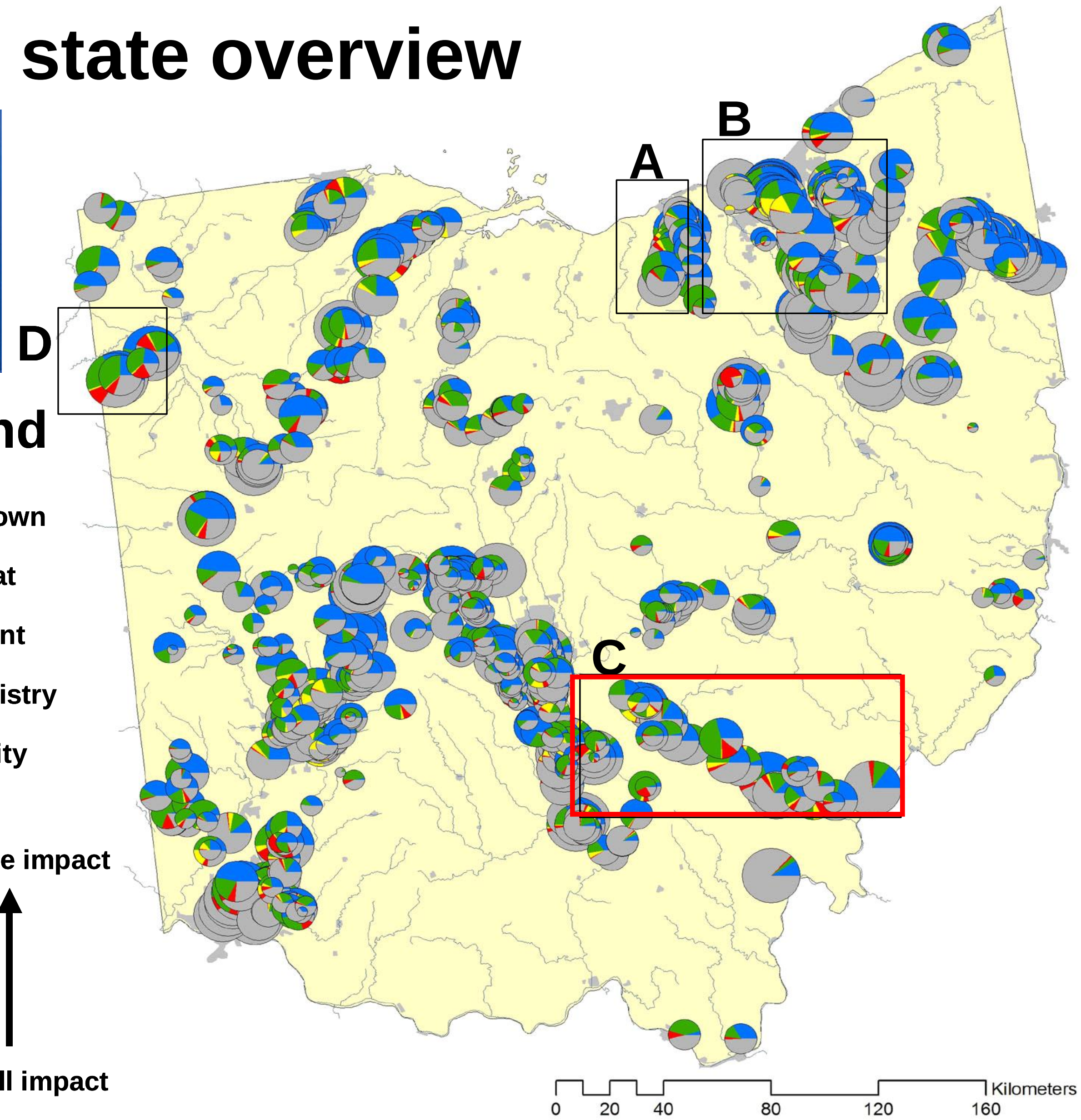


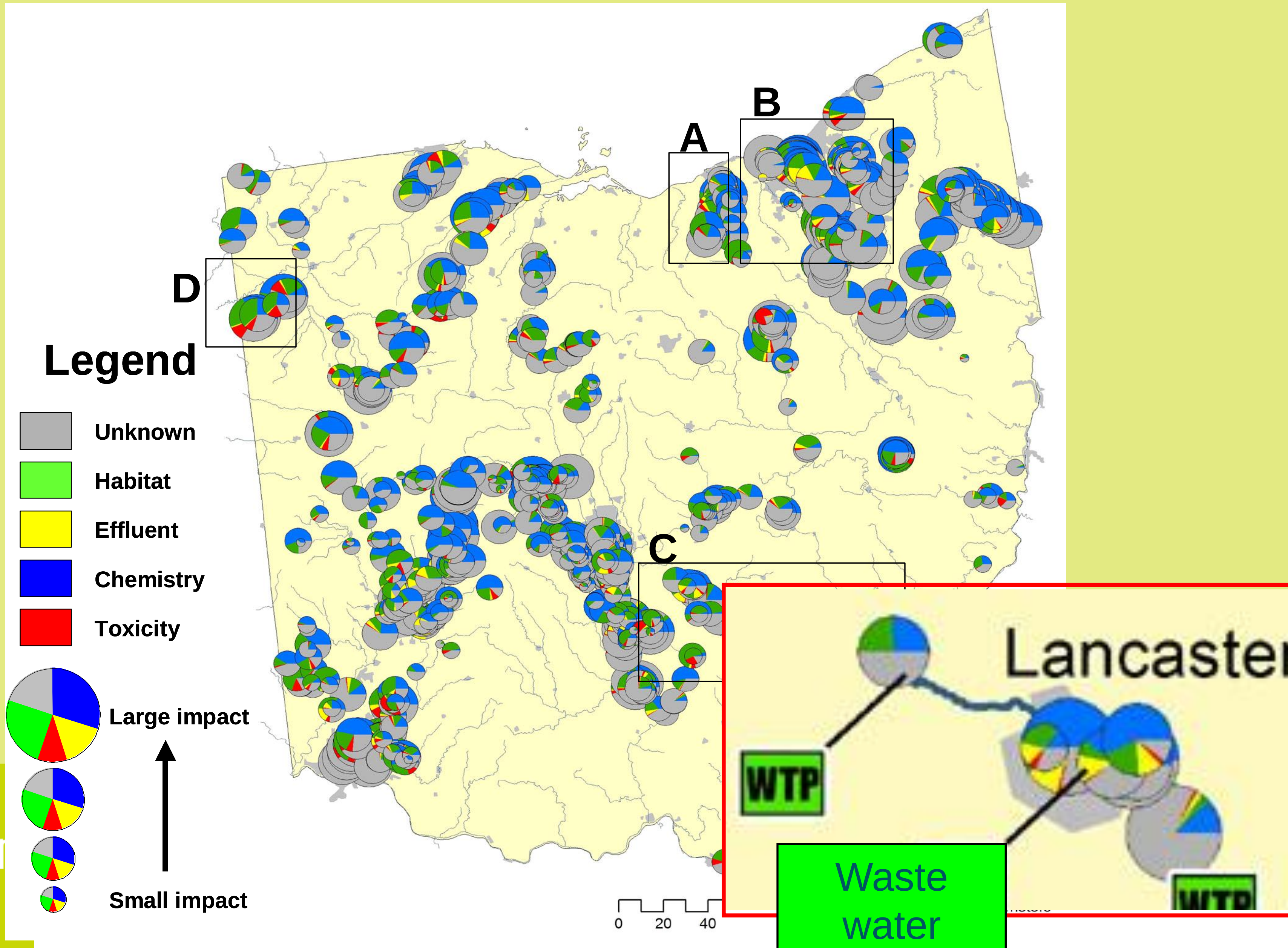
Figure 3.1 Example of a TWINSPAN presentation of RIVPACS-grouping of reference site

Chemicals + site + stressors + natural variability





Ohio – local diagnostics



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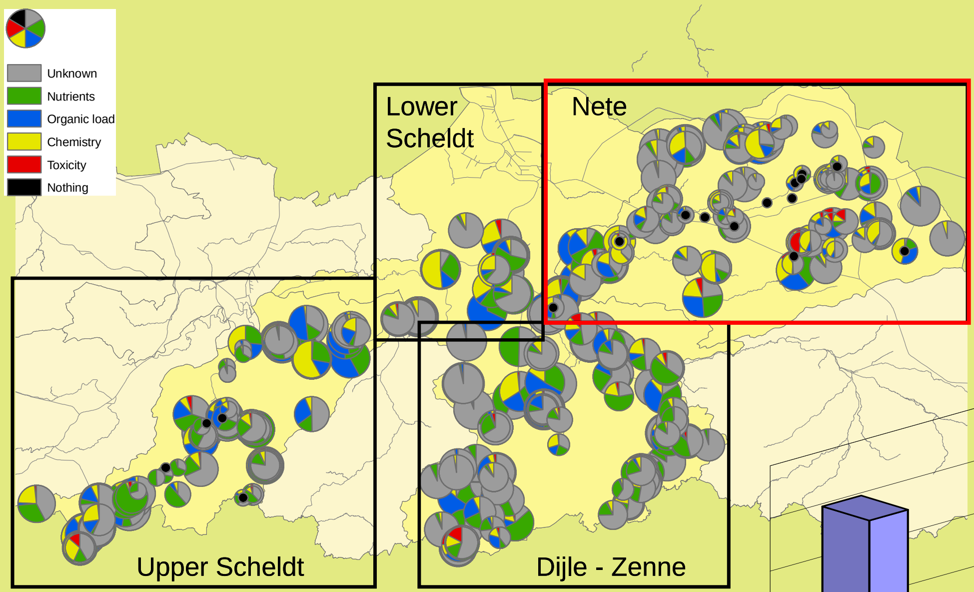
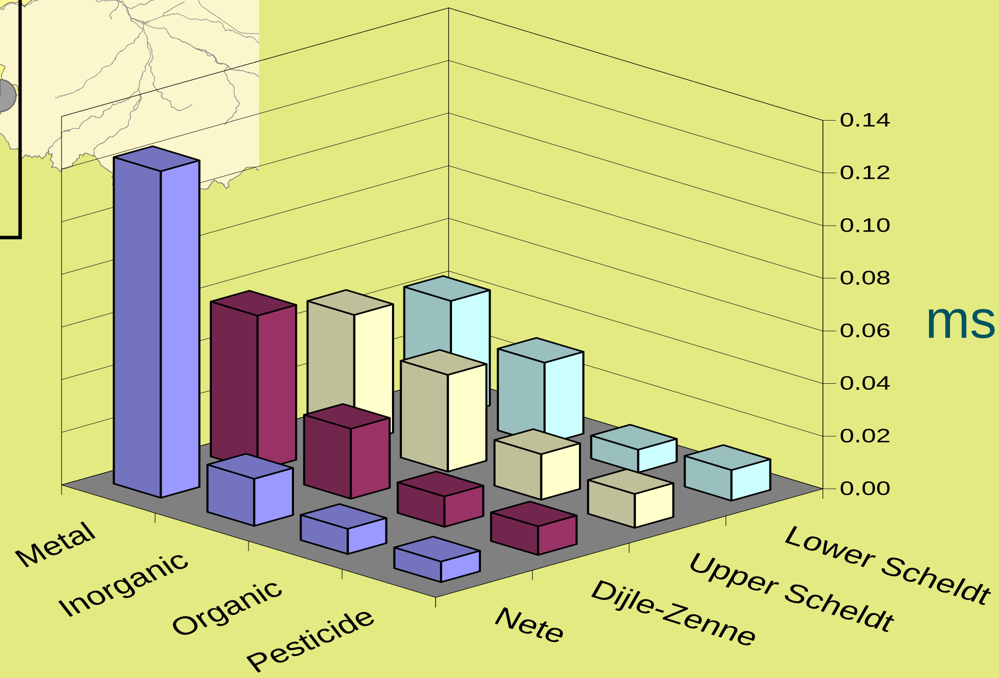
Disaggragation of mixture impacts
(River Scheldt, 4 subcatchments)





→ Focus on "keystone compounds" !!!

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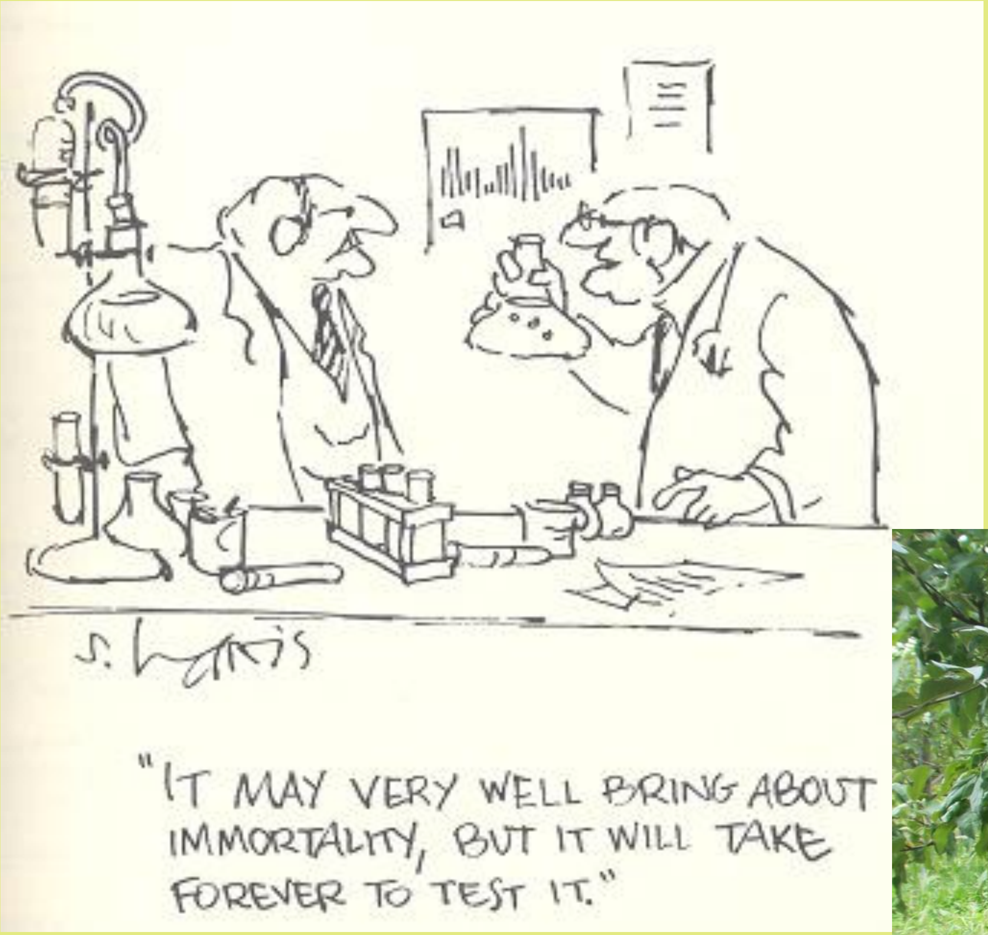

Further research

to reduce uncertainties

Manage risks

despite uncertainties

Validation, remember?

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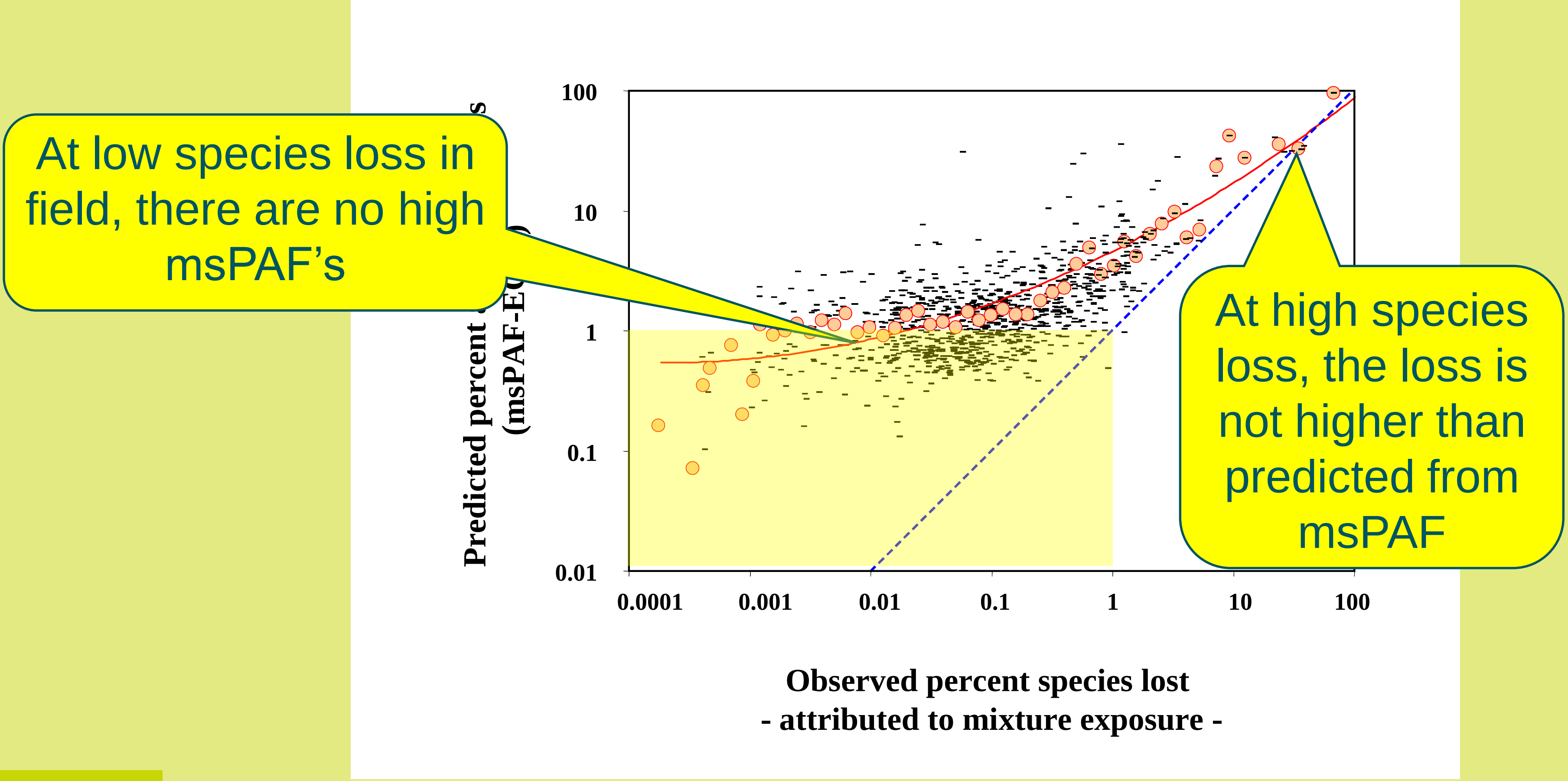
Validation as constant focus in science

- Monitoring (species loss) data and msPAF approach



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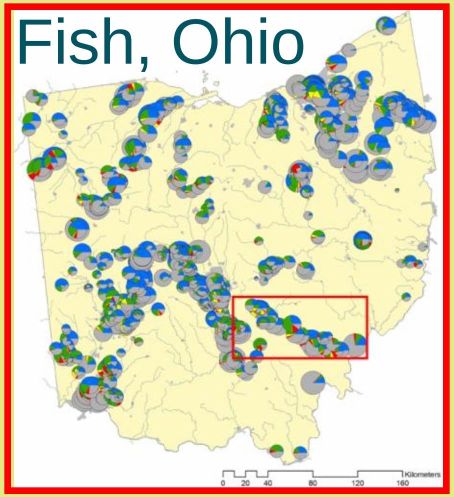
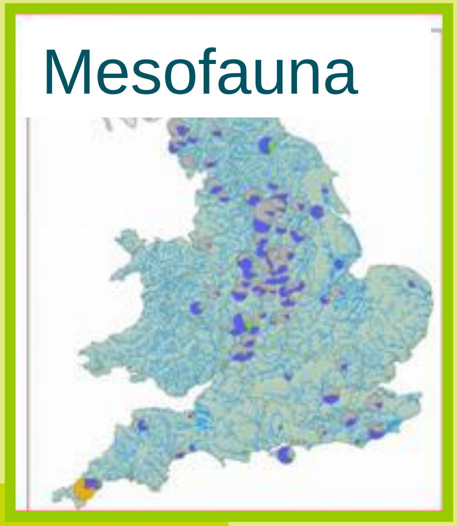
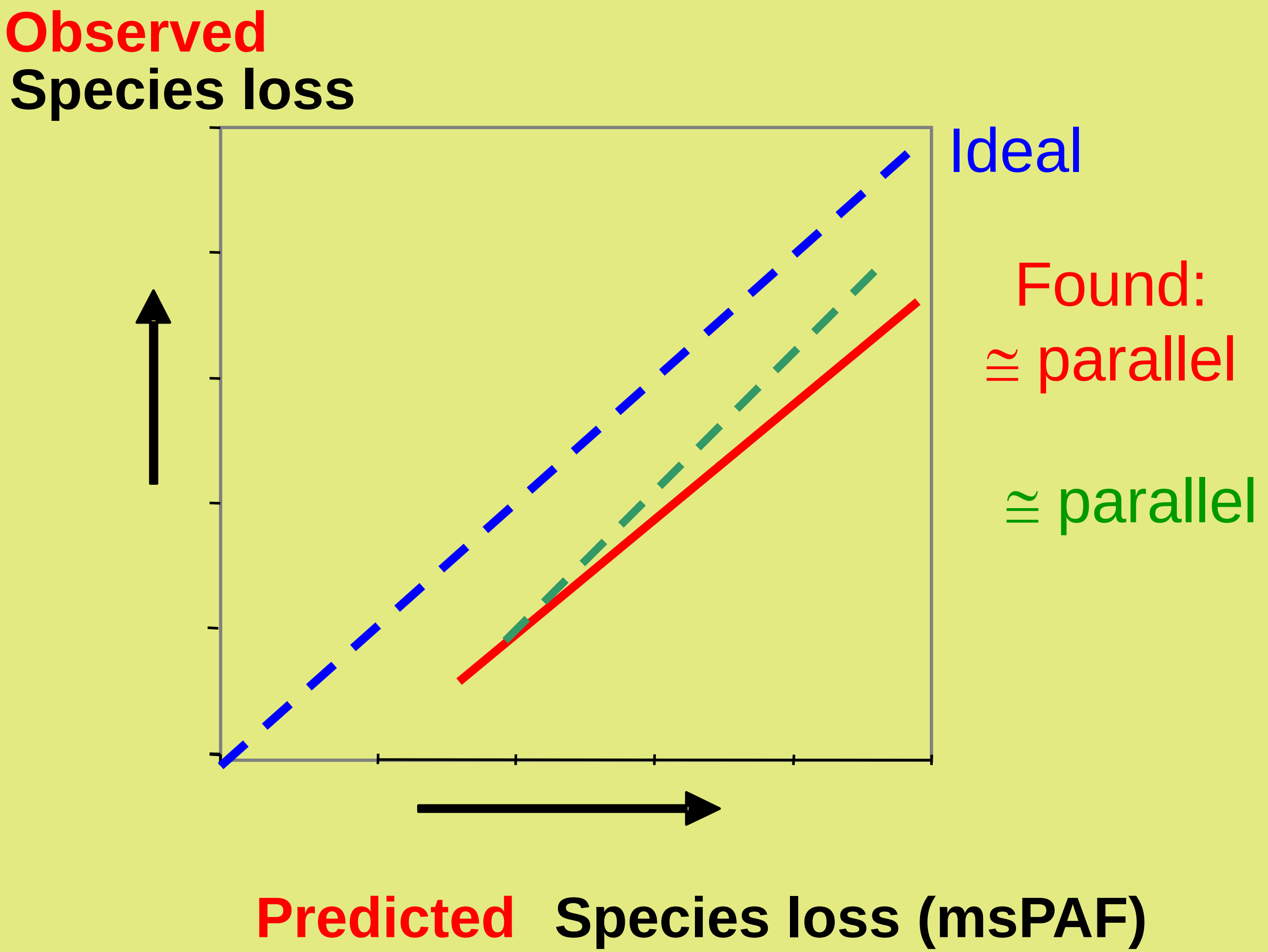
msPAF$_{EC50}$ associated to species loss
But “natural variability” and other stressors

Validity: Monitored species loss vs msPAF







OK for ranking and management priority

msPAF and species abundance change

Regression term	Category	Percent of species with term	Significance of regression terms p < 0.001	p = 0.01	p = 0.05
LongpDEV	Natural	73%	100%	0%	0%
DCatpDEV	Natural	72%	98%	0%	2%
AATRpDEV	Natural	72%	96%	2%	2%
	Nutrient	71%	96%	4%	0%
Industrial msPAF	Toxic pressure	71%	96%	4%	0%
SiltpDEV	Natural	69%	98%	0%	2%
DisSpDEV	Natural	67%	100%	0%	0%
SlopepDEV	Natural	67%	98%	2%	0%
pHpDEV	Water chemistry	67%	96%	4%	0%
LatpDEV	Natural	65%	100%	0%	0%
AltpDEV	Natural	64%	100%	0%	0%
CaCO3pDEV	Natural	64%	98%	0%	2%
TSSpDEV	Water chemistry	64%	100%	0%	0%
DepthpDEV	Natural	63%	100%	0%	0%
BolCobpDEV	Natural	63%	100%	0%	0%
NH4pDEV	Nutrient	63%	98%	2%	0%
PebGravpDEV	Natural	61%	98%	2%	0%
PhipDEV	Natural	61%	98%	0%	2%
MATpDEV	Natural	61%	98%	2%	0%
ClpDEV	Water chemistry	61%	98%	2%	0%
WidthpDEV	Natural	60%	98%	2%	0%
	Nutrient	57%	100%	0%	0%
Pesticides msPAF	Toxic pressure	56%	100%	0%	0%
SandpDEV	Natural	55%	95%	5%	0%

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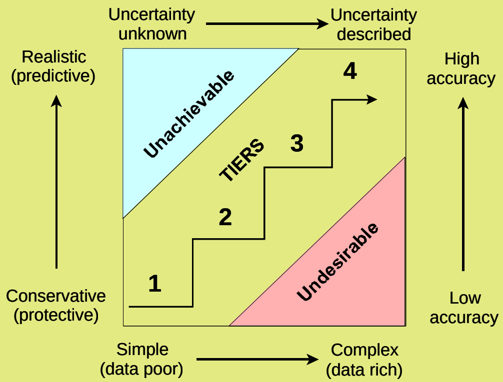
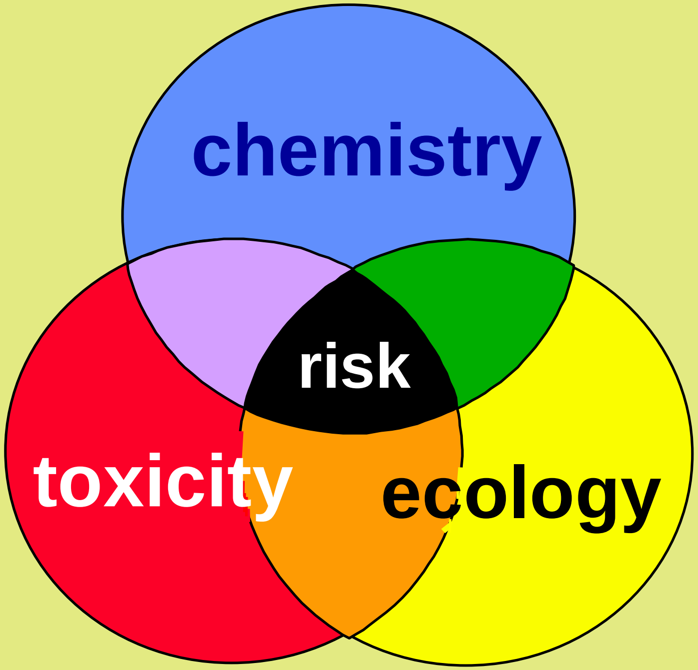
msPAF highly significant “shaper of abundance”

Further methods



- So far: model explorations; useful for "big workloads" & ranking
- Empirical 2nd and higher tiers
  - TIE (Sequential exclusion of stressor relevances)
  - BDF
  - ….
  - Weight of Evidence (Simultaneous Triad of approaches)
  - …..

Triad – multiple lines of evidence (to verify local impacts)



	Parameter	Samples		
Chemistry		**Skagen L**	**Skagen M**	**Skagen H**
	Sum TP organic chemicals	0.00	1.00	1.00
	Sequential Supercritical Fluid Extraction (SSFE)			0.24
	Leaching test in hand -packed colums			0.03
	Solid Phase Micro Extraction (SPME)			
	Concentration in plant shoots (mg/kg)			0.68
	Risc	**0.00**	**1.00**	**0.88**
Toxicology				
	Plant growth test			0.48
	Springtail reproduction test	0.00	0.18	0.37
	Microtox acute (BSPT)	0.00	0.00	0.07
	Ostracodtoxkit mortality	0.00	0.07	0.32
	Ostracodtoxkit growth inhibition	0.00	0.61	0.64
	Daphnia survival 24 hours	0.00	0.10	0.15
	Daphnia survival 48 hours	0.00	0.10	0.20
	Daphnia survival	0.00	0.43	0.37
	Dahnia offspring	0.00	0.15	0.30
	Risc	**0.00**	**0.24**	**0.34**
Ecology				
	Microarthropodes	0.00	0.26	0.33
	Vegetation	0.00	0.17	0.34
	Biolog	0.00	0.19	0.18
	Risc	**0.00**	**0.21**	**0.29**

judgement chemistry:	0.00	1.00	0.88
judgement toxicology:	0.00	0.24	0.34
judgement ecology:	0.00	0.21	0.29
final judgement	0.00	0.92	0.62
deviation	0.00	0.78	0.56

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Conclusions

- We can mix apples and oranges – in “fruit units” (kg, or vitamines, or….)
- We (I hope) showed a good gut feeling on mixtures (Rhine thought experiment)
- We have robust numerical models, derived from pharmacology and fundamental mixture toxicology
- Those can be “extrapolated” to compounds of concern, to predict probable impacts of mixtures
- At least useful for ranking impacts between sites
- Also in complex diagnostic (bio)monitoring dataset
- Various lines of evidence support sufficient validity
- When uncertain, apply local empirical approaches, mechanism-based approaches (many…)


RISKS
BENEFITS
HAMBURGER $2.35
CHEESEBURGER $2.95
TUNA SALAD $2.75
EGG SALAD $2.65
OMELETTE $3.10
BEEF STEW $3.45
S. Harris