2-FUN

***F**ull-chain and **UN**certainty Approaches for Assessing Health Risks in*

***FU**ture **EN**vironmental Scenarios*

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Summary

The following pages present the content of the conference on uncertainty analysis given by P. Ciffroy during the joint final conference of the INTARESE-HEIMTSA-2-FUN projects.

Uncertainty in human health risk assessment
The experience of the 2-FUN project

Philippe Ciffroy, EDF

with special thanks to the 'Uncertainty Winter School' organizers and participants providing ideas and material for this presentation

Uncertainty: a shared issue

- HIA is fundamentally about clarifying uncertainty – characterising the most sensitive sources of uncertainty and the effect on follow up measures **(Health Development Agency, UK, 2008)**

- In order to acknowledge limitations of data and methods in HIA, assessors should describe the uncertainty in predictions **(North American HIA Practice Standards Working Group, 2009)**

- Acceptance of unpopular public policy decisions is more likely when decision-makers acknowledge uncertainty and commit to monitoring and evaluating outcomes **(WHO, 2008)**

- WHO IPCS Harmonization Project published a guidance monograph on Characterizing and Communicating Uncertainty in Exposure Assessment (2008) **http://www.who.int/ipcs/publications/methods/harmonization/exposure_assessment.pdf**

Why Uncertainty analysis?

- Avoiding worst case approach and improving decision making
- Accounting for the limitations of the knowledge available
- Identifying the main data gaps and research priorities (which can be filled further to improve the accuracy of estimation)
- Accounting for the ‘Minority opinions’ in the construction of scenarios
- More generally, increasing transparency of underlying assumptions and credibility of the process

Uncertainty analysis: a tiered process (1/2)

- Tier 1: **Qualitative assessment of uncertainty**
  - ✓ Subjectivity of choices (space, similarity among stakeholders, prior sensitivity of choices, etc)
  - ✓ Adequacy of the available knowledge base (reliability of data, plausibility of knowledge, acknowledging ignorance, maturity of science)
  - ✓ Level of uncertainty (measurement uncertainty, reducible vs irreducible ignorance, etc)

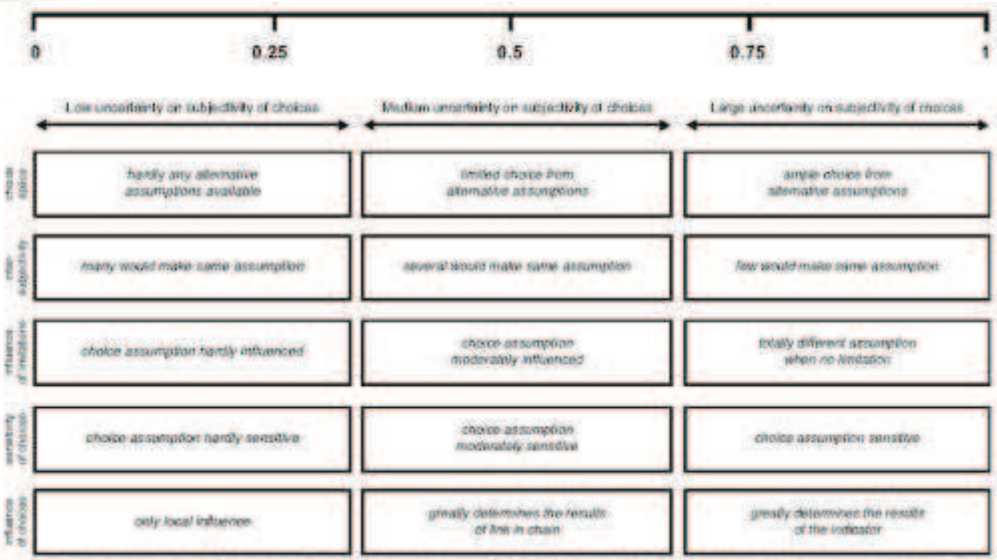


Figure 9: The scale of uncertainty related to subjectivity of choices (adapted from van der Sluijs et al., 2005)

→ **Low vs Medium vs High**

Uncertainty analysis: a tiered process (2/2)

- Tier 2: **Semi-quantitative assessment of uncertainty and sensitivity**
  - ✓ based on One-At-A-Time (OAT) variations of each input variable/parameter

⇩

Percentage change around the baseline scenario because of incremental change

⇩

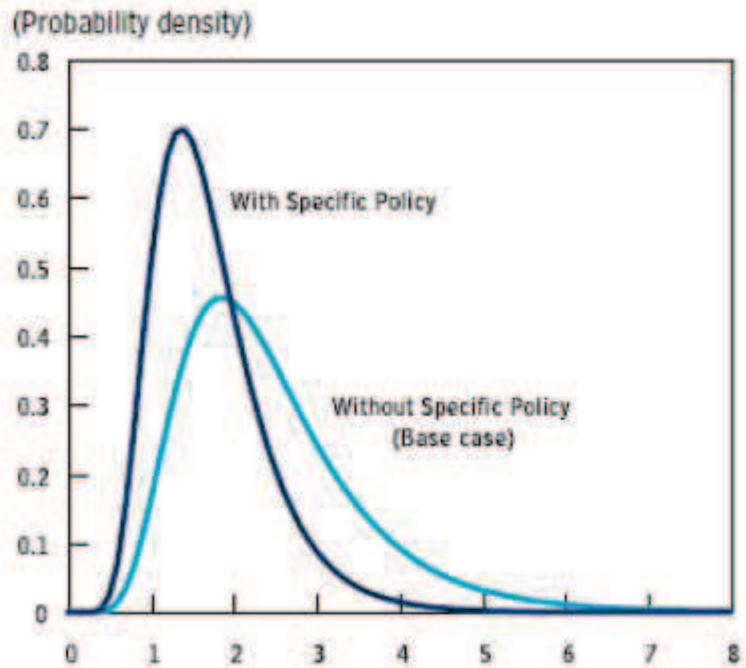
✓ Local uncertainty and not global (i.e. no coverage of the input variables/parameters space)

✓ Does not account for dependencies between model inputs

✓ Does not account for actual parameter probabilities

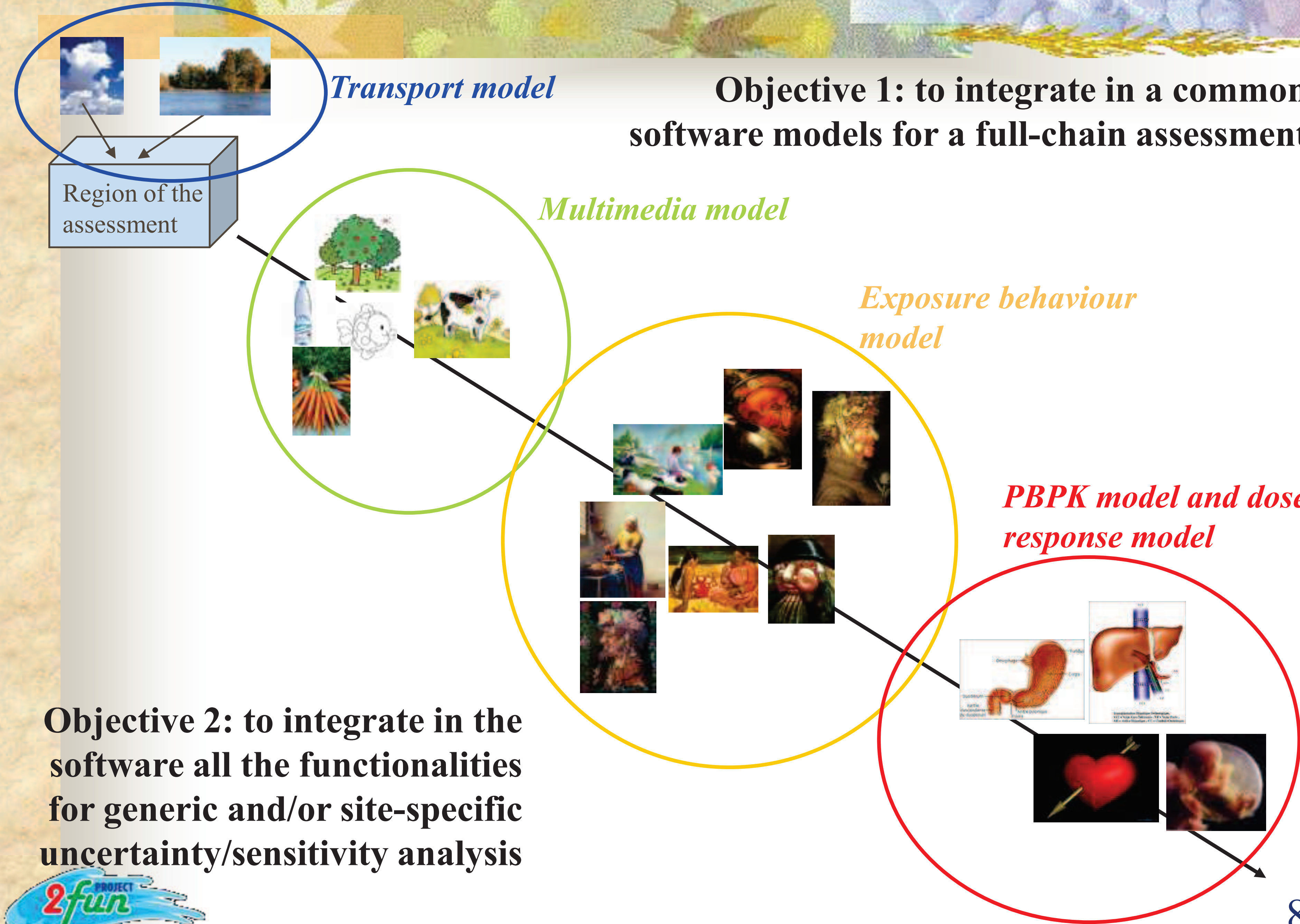
Uncertainty analysis: a tiered process (2/2)

- Tier 3: **Quantitative assessment of uncertainty**
  - ✓ based on probabilistic description of input variables/parameters
  - ✓ based on random samples generations (e.g. Monte Carlo) and uncertainty propagation



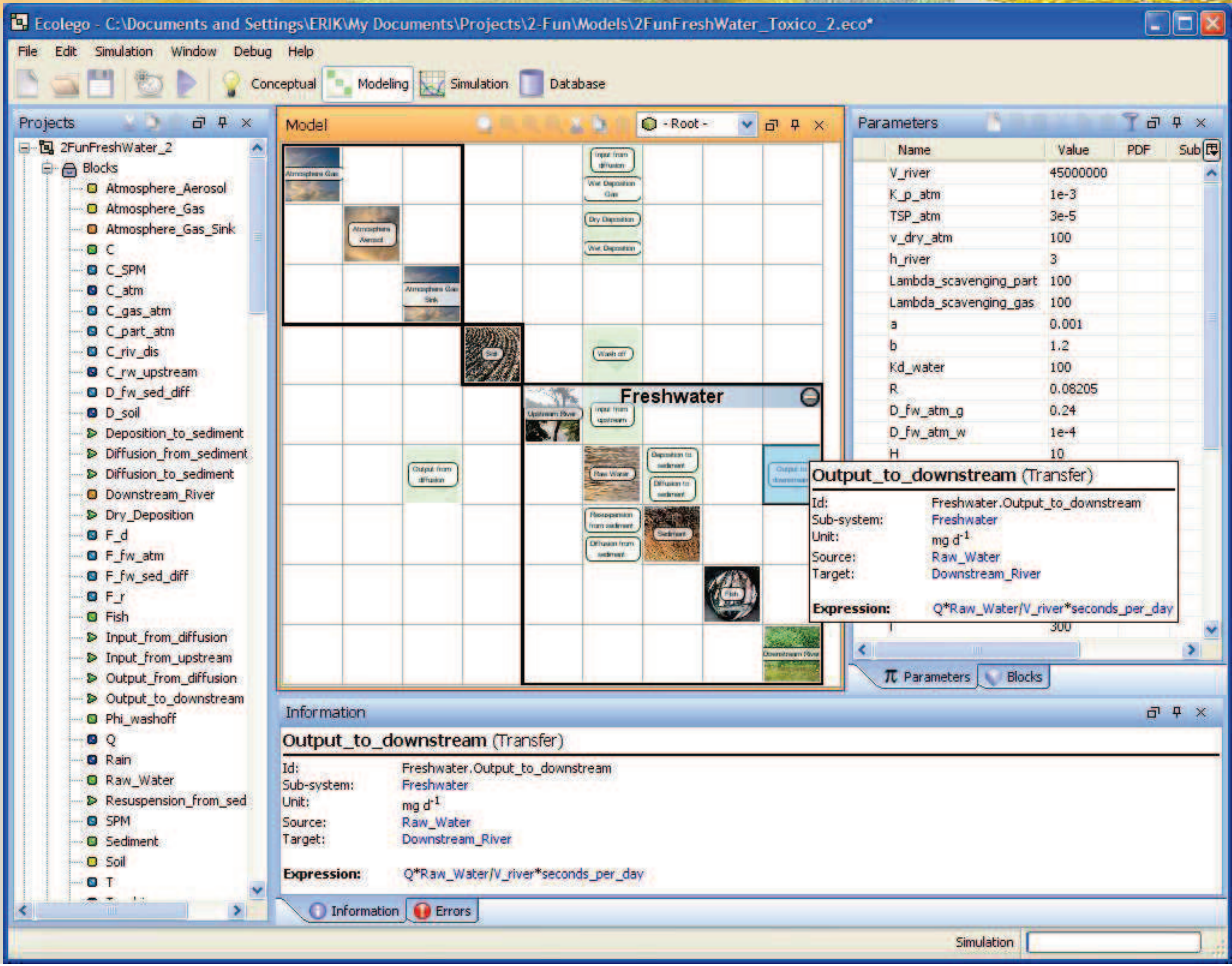
Uncertainty in the 2-FUN project

Objective 1: to integrate in a common software models for a full-chain assessment

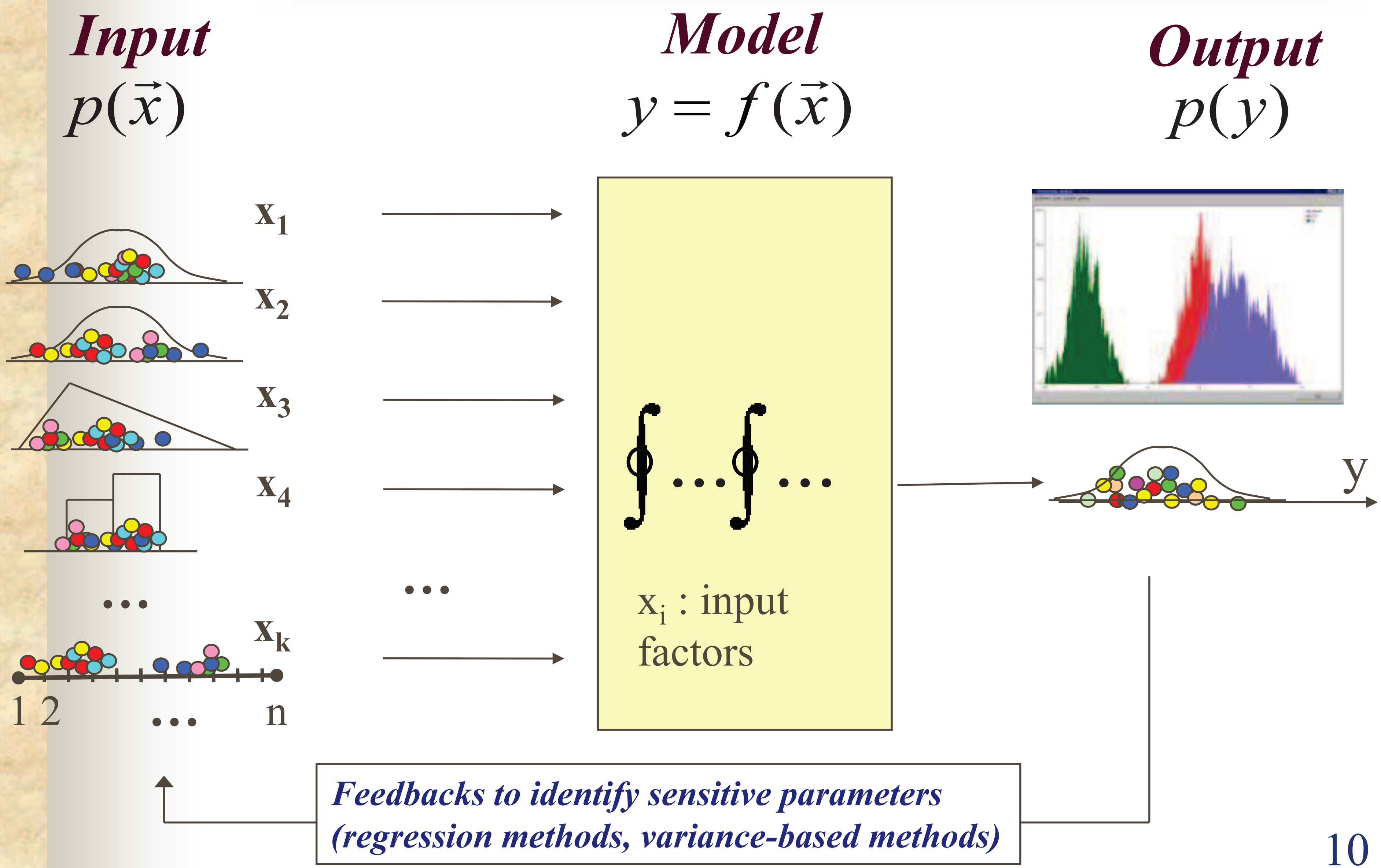


Objective 2: to integrate in the software all the functionalities for generic and/or site-specific uncertainty/sensitivity analysis

The 2-FUN software

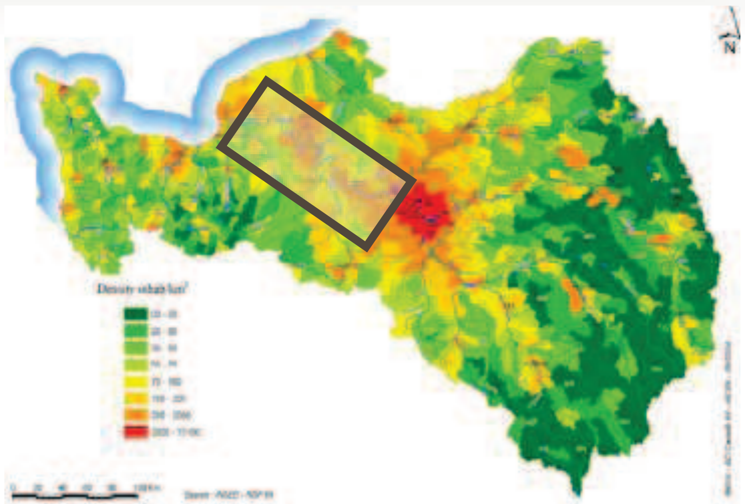


The 2-FUN software: sensitivity functionalities

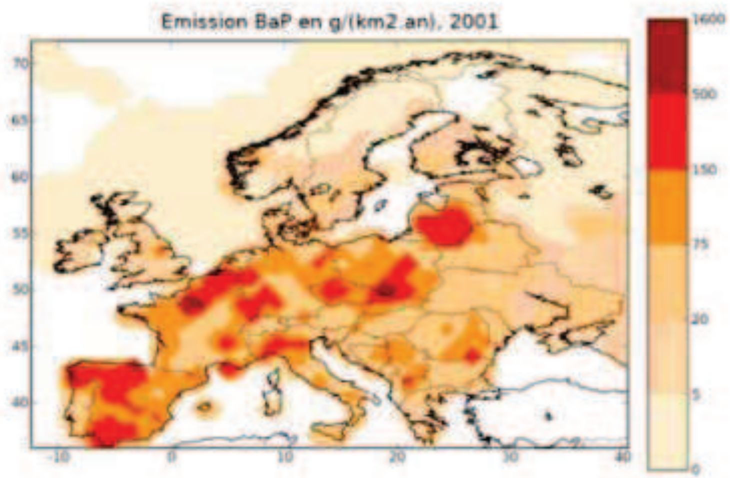


Concrete Uncertainty/sensitivity analysis with the 2-FUN tool

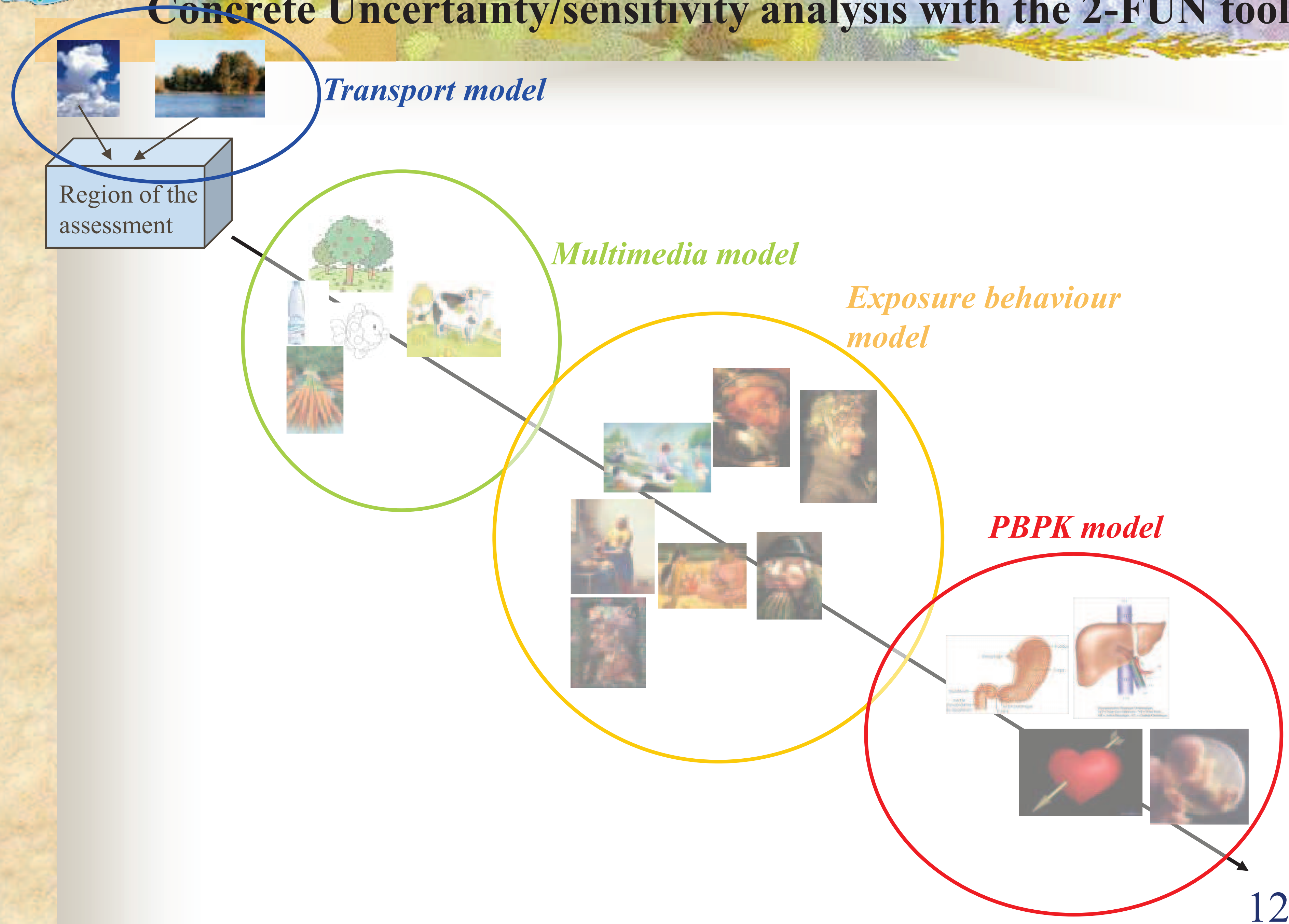
Target region: A region situated on **the Seine river watershed**, just downstream of Paris, France



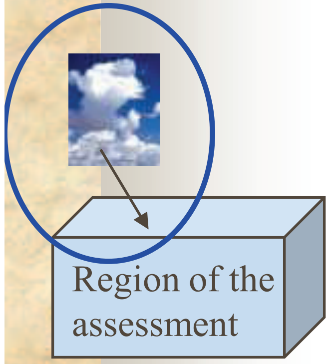
Target substance: **Benzo (a) Pyrene** (one of Polycyclic aromatic hydrocarbons (PAHs))

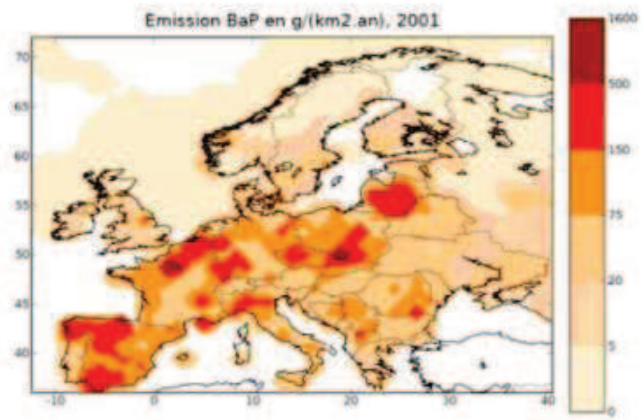


Concrete Uncertainty/sensitivity analysis with the 2-FUN tool



Uncertainty of input data (scenario: atmosphere contamination)

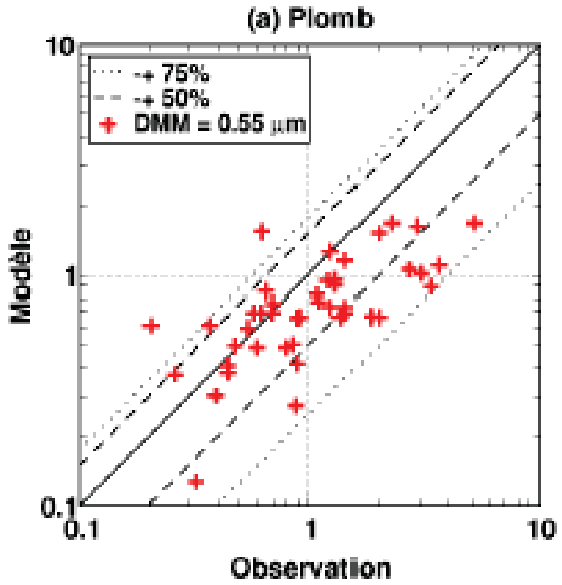




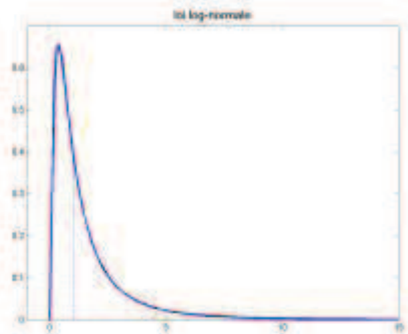
Polair3D

vs

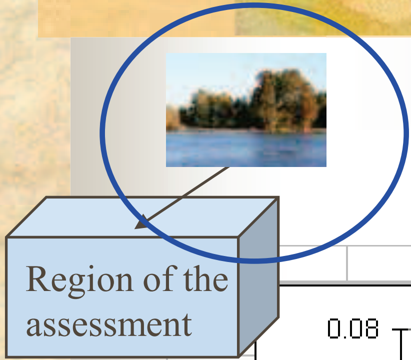
Monitoring

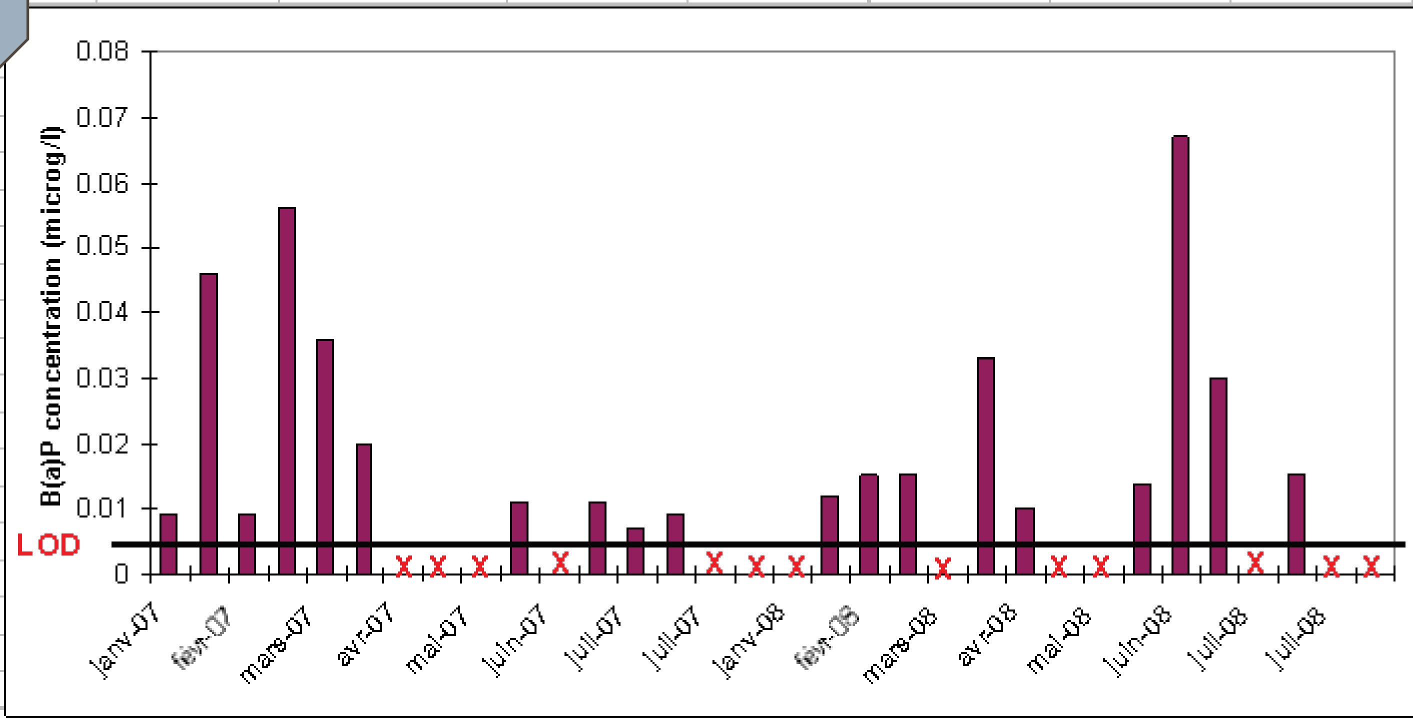


Accuracy function ε



Uncertainty of input data (scenario: river contamination)





How to build PDF for ‘B(a)P concentration in raw water’ accounting for non-detects?

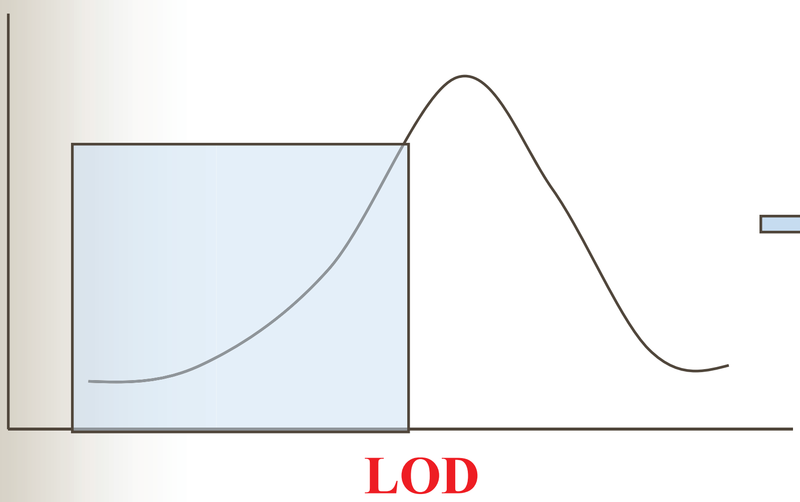
Uncertainty of input data (scenario: river contamination)

Methods of substitutes:

non-detects = 0
non-detects = LOD
non-detects = LOD/2

→ over- or underestimation of the mean
over- or underestimation of the variance

Parametric methods (Cohen's approach)

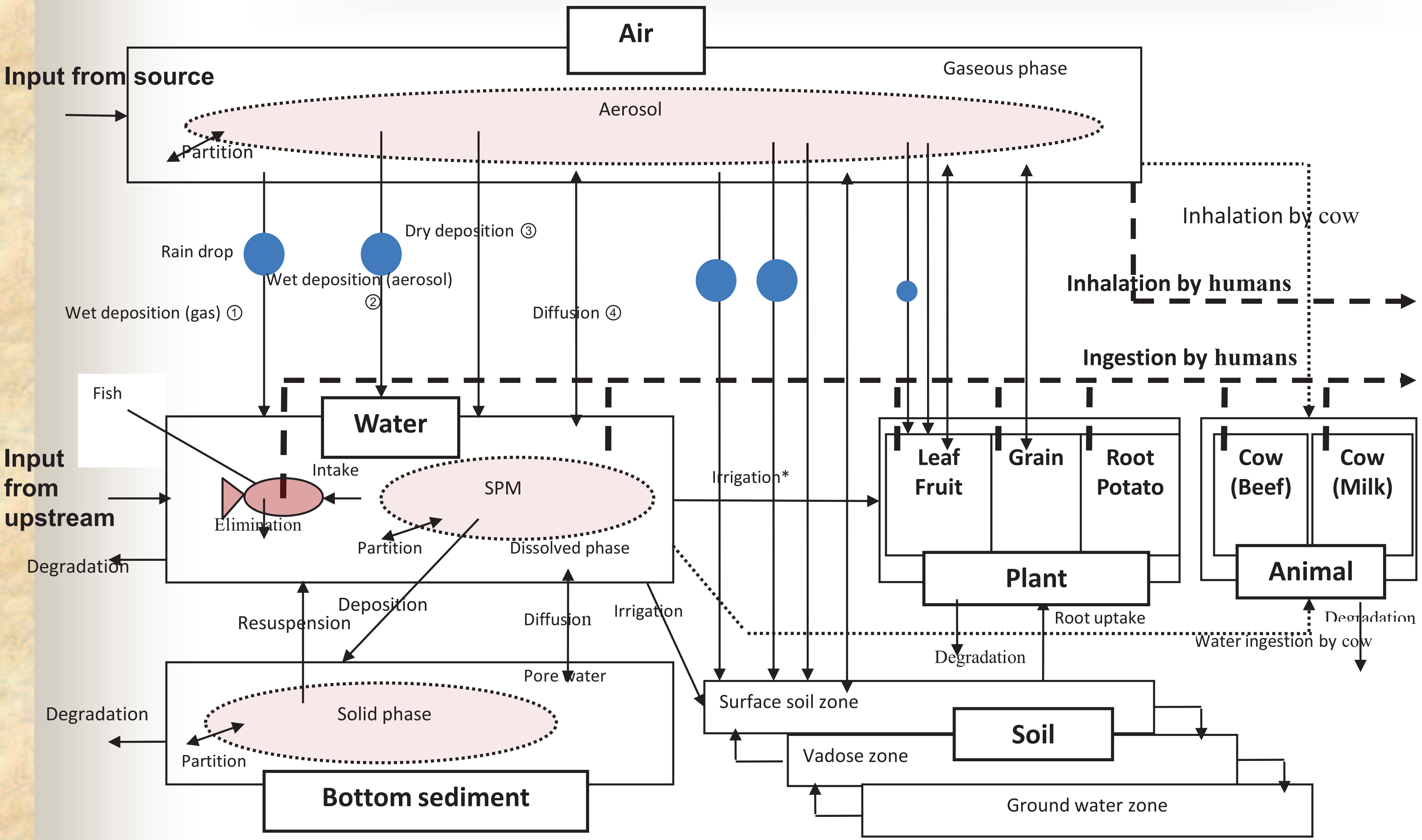


$$\hat{\mu} = \bar{y} - \lambda(\bar{y} - LOD)$$

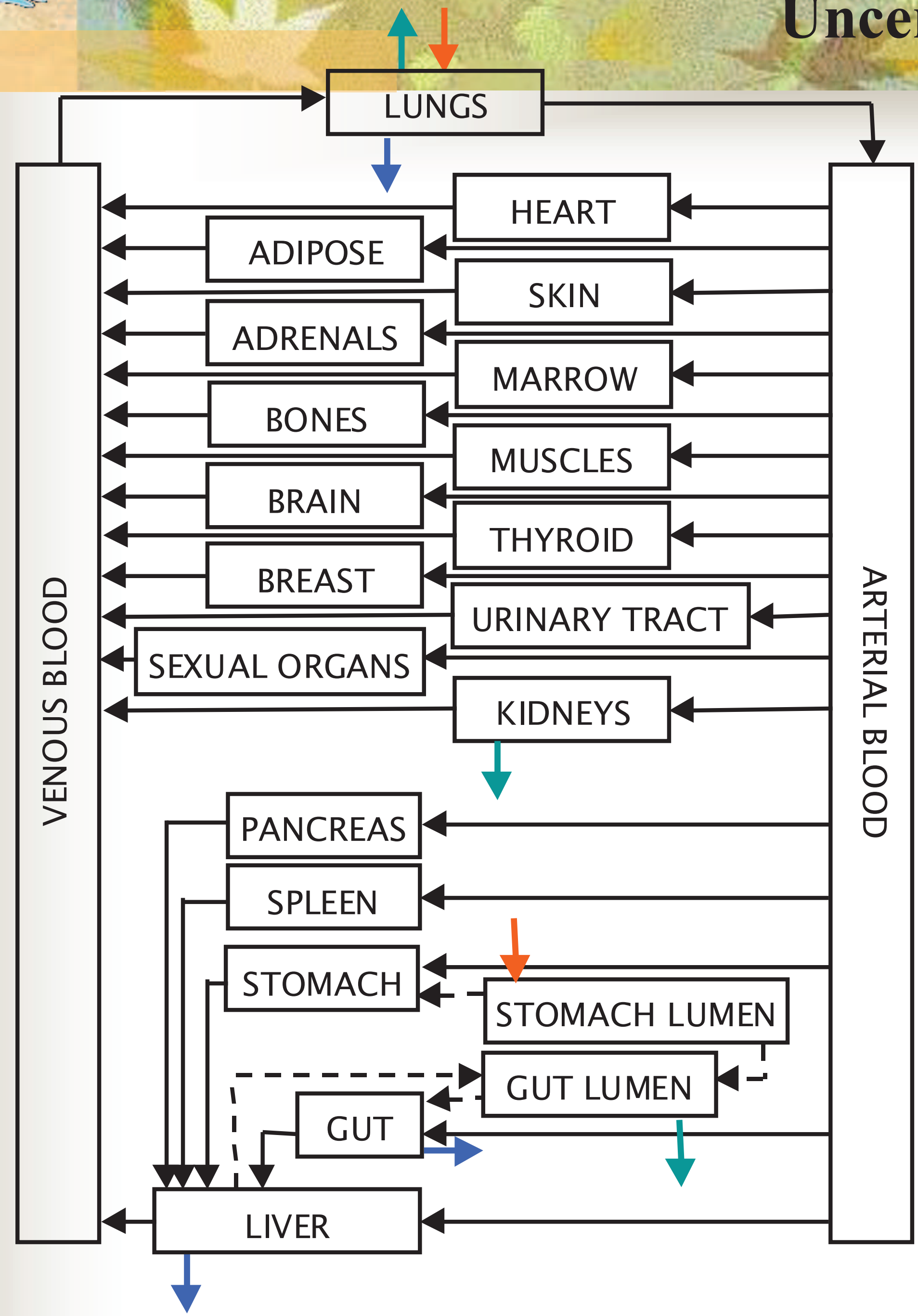
$$\hat{\sigma} = \sqrt{s^2 + \lambda(\bar{y} - LOD)^2}$$

$$PDF_{B(a)P\ raw\ river\ water} = N(4.2.10^{-3};2.3.10^{-2})\ \mu g/l$$

Uncertainty of environmental parameters + …



Uncertainty of PBPK parameters



Describe the human body in detail and the redistribution processes of a substance:

- 2 routes for administration (inhalation and ingestion)
- The substance is distributed in 23 tissues or organs
- 3 sites of metabolism (lungs, liver and gut)
- 3 sites of elimination (via faeces or urine, exhalation)

How to build parametric PDFs?

When collecting information related to a given parameter of interest, several situations can be met:

1. **a large set of homogeneous data is available;**
2. **a large set of data is available, but the quality of these latter is heterogeneous (e.g. data obtained under different experimental protocols);**
3. **A large dataset set of data is available, but with a large fraction of non-detects;**
4. **only a limited set of data is available, but prior information is known;**
5. **No data at all, but analogies with other substances can be assumed**

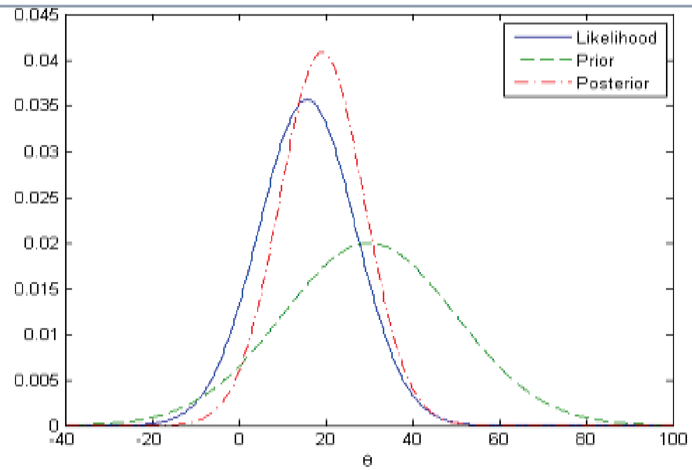
How to combine prior knowledge and site measurements?

Bayes' theorem:

Well adapted to build PDFs when theoretical prior knowledge is available and when **only a limited set of measurements are available for a parameter.**

$$p(\mu,\sigma^2 | Data) = \frac{p(Data | \mu,\sigma^2).p(\mu,\sigma^2)}{p(Data)}$$

$p(\mu,\sigma^2/Data)$: **posterior distribution**
$p(Data/\mu,\sigma^2)$: function of **measurement dataset** (called likelihood)
$p(\mu,\sigma^2)$: **prior distribution** (derived from **expert knowledge or models**)
$p(Data)$: Normalizing factor



How combining prior knowledge and site measurements?

Example: Wc: settling velocity of particles in rivers

1. Prior knowledge: Stokes law

$$W_c = 86400.\frac{g.d^2.\rho_e}{18.\mu} \Rightarrow PDF_{prior} = LN(GM=6.6;GSD=1.53)$$

2. Integration of site-specific measurements

ELSEVIER

Ecological Modelling 127 (2000) 99–117

ECOLOGICAL MODELLING

www.elsevier.com/locate/ecolmodel

A model simulating the transport of dissolved and particulate copper in the Seine river

P. Ciffroy *, C. Moulin, J. Gaillard

Calibration of the particles settling velocity W_c (in mm.s^{-1})

Sampling point	Best estimate	Variation
Kilometric Point 6.5—middle of the Seine river	0.4	0.3–0.6
Kilometric Point 6.5—right bank of the Seine river	0.3	0.1–0.5
Kilometric Point 8.5—middle of the Seine river	0.3	0.2–0.4
Kilometric Point 8.5—right bank of the Seine river	0.1	0.1–0.2

$$\Rightarrow PDF_{site\text{-}specific} = LN(GM=8.7;GSD=2.6)$$

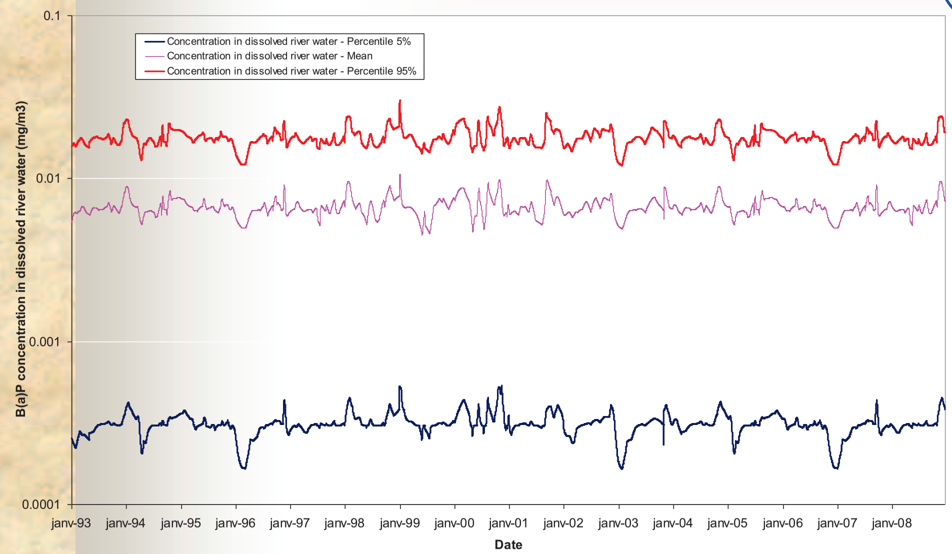
How to build parametric PDFs?

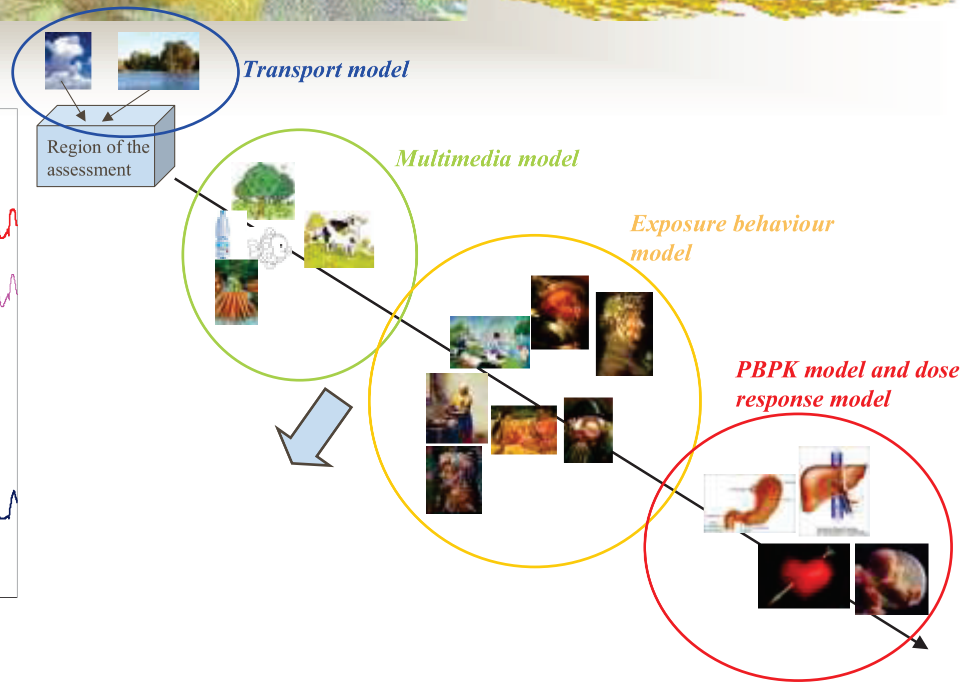
When collecting information related to a given parameter of interest, several situations can be met:

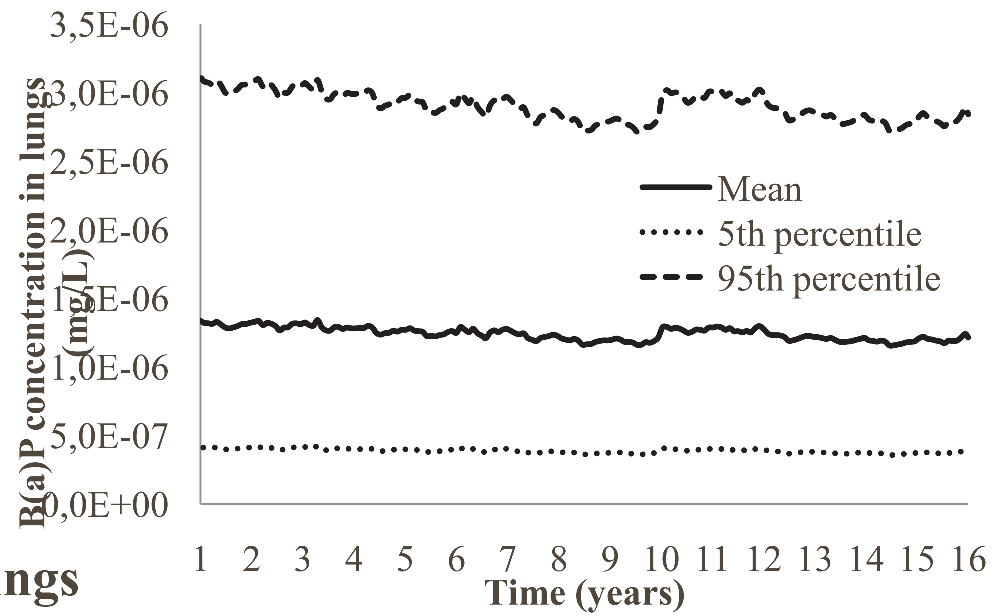
1. a large set of homogeneous data is available;
2. a large set of data is available, but the quality of these latter is heterogeneous (e.g. data obtained under different experimental protocols);
3. A large dataset set of data is available, but with a large fraction of non-detects;
4. only a limited set of data is available, but prior information is known;
5. No data at all, but analogies with other substances can be assumed ⟹ e.g. QSAR (validity domain, etc)

Some uncertainty results

BaP conc. in drinking water

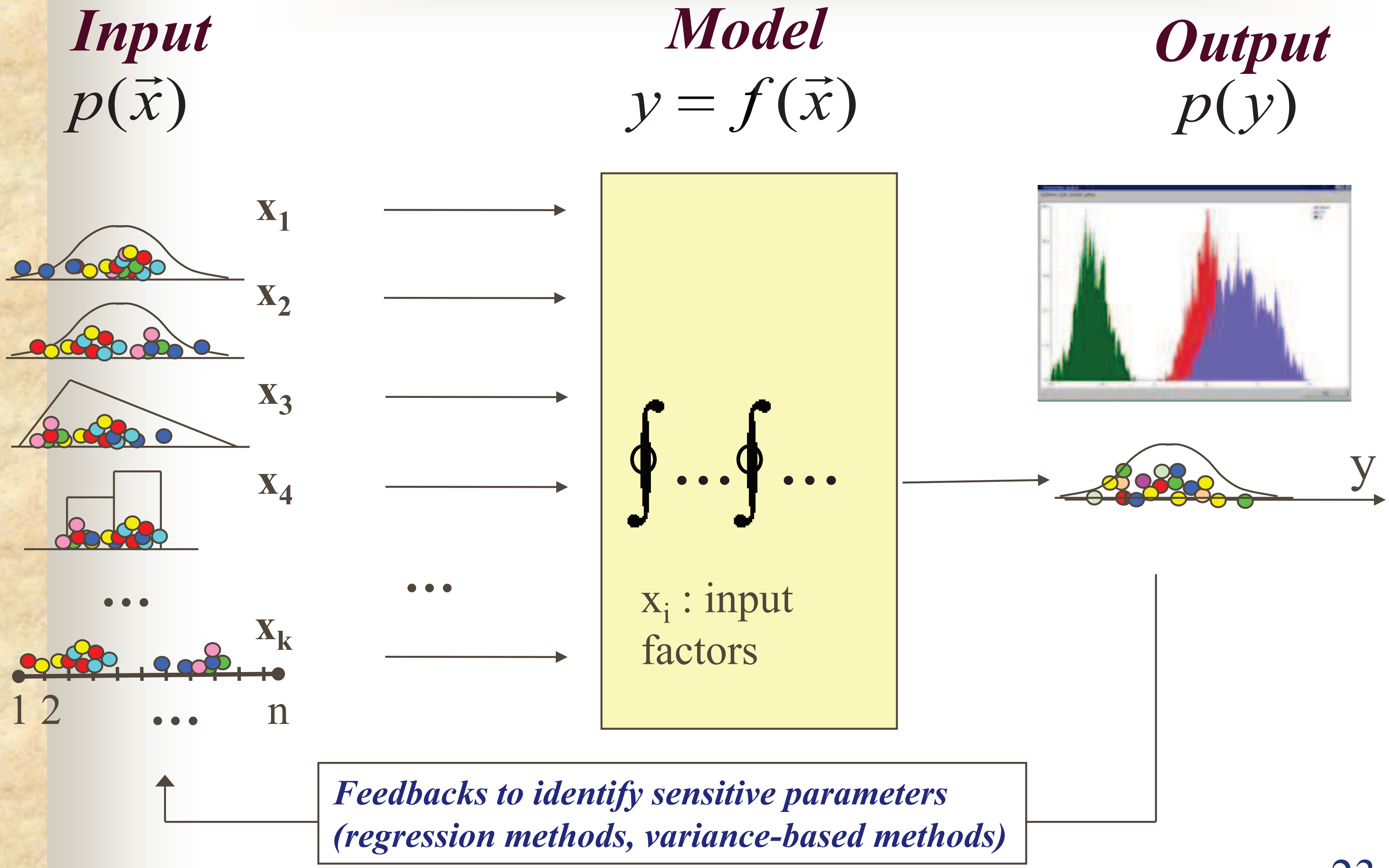






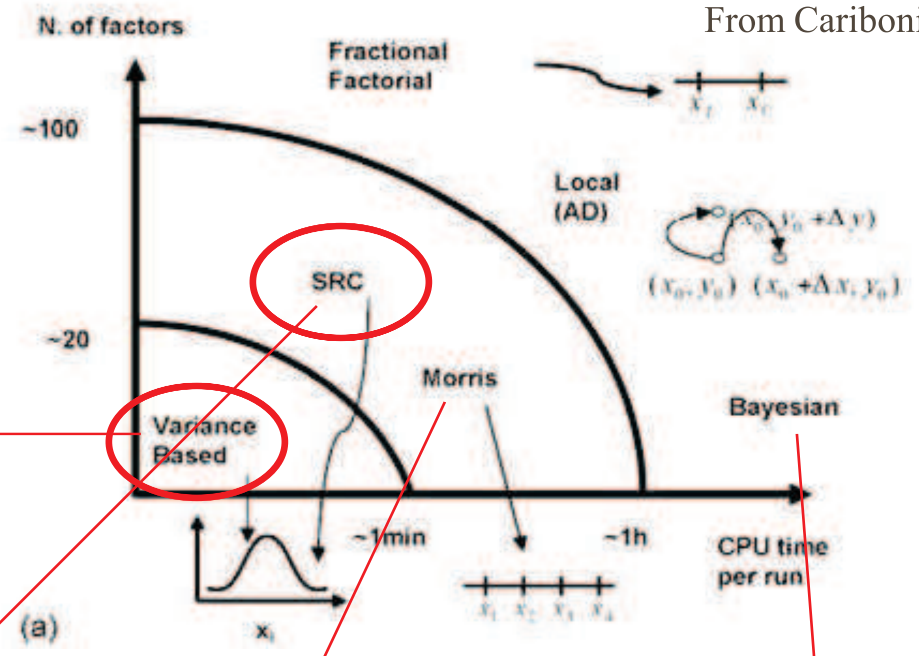
BaP conc. in lungs

Sensitivity approaches



Sensitivity approaches

From Cariboni et al, 2007



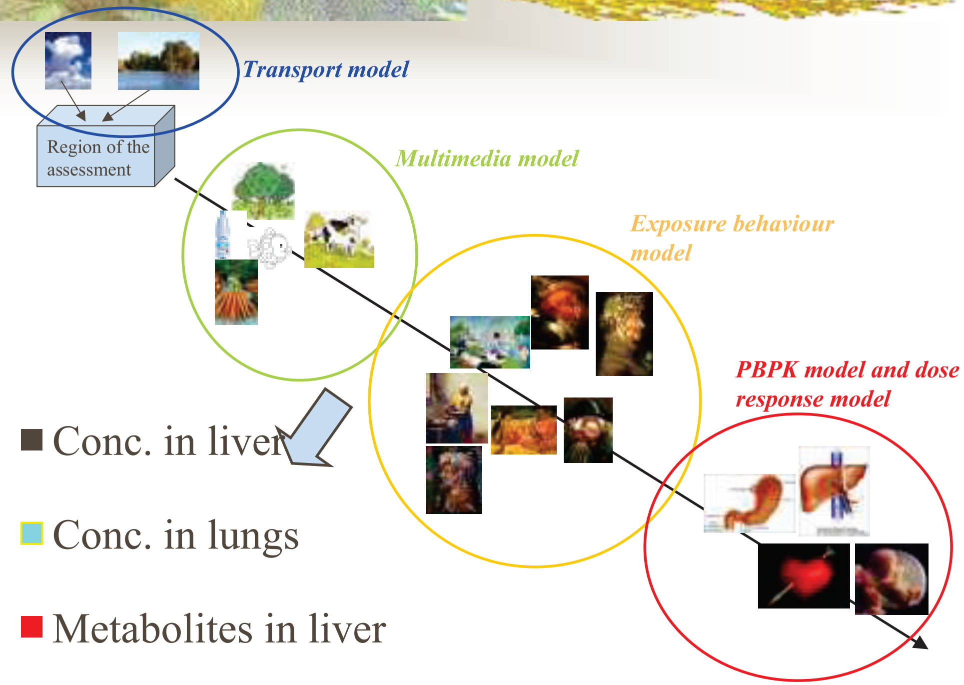
Variance decomposition

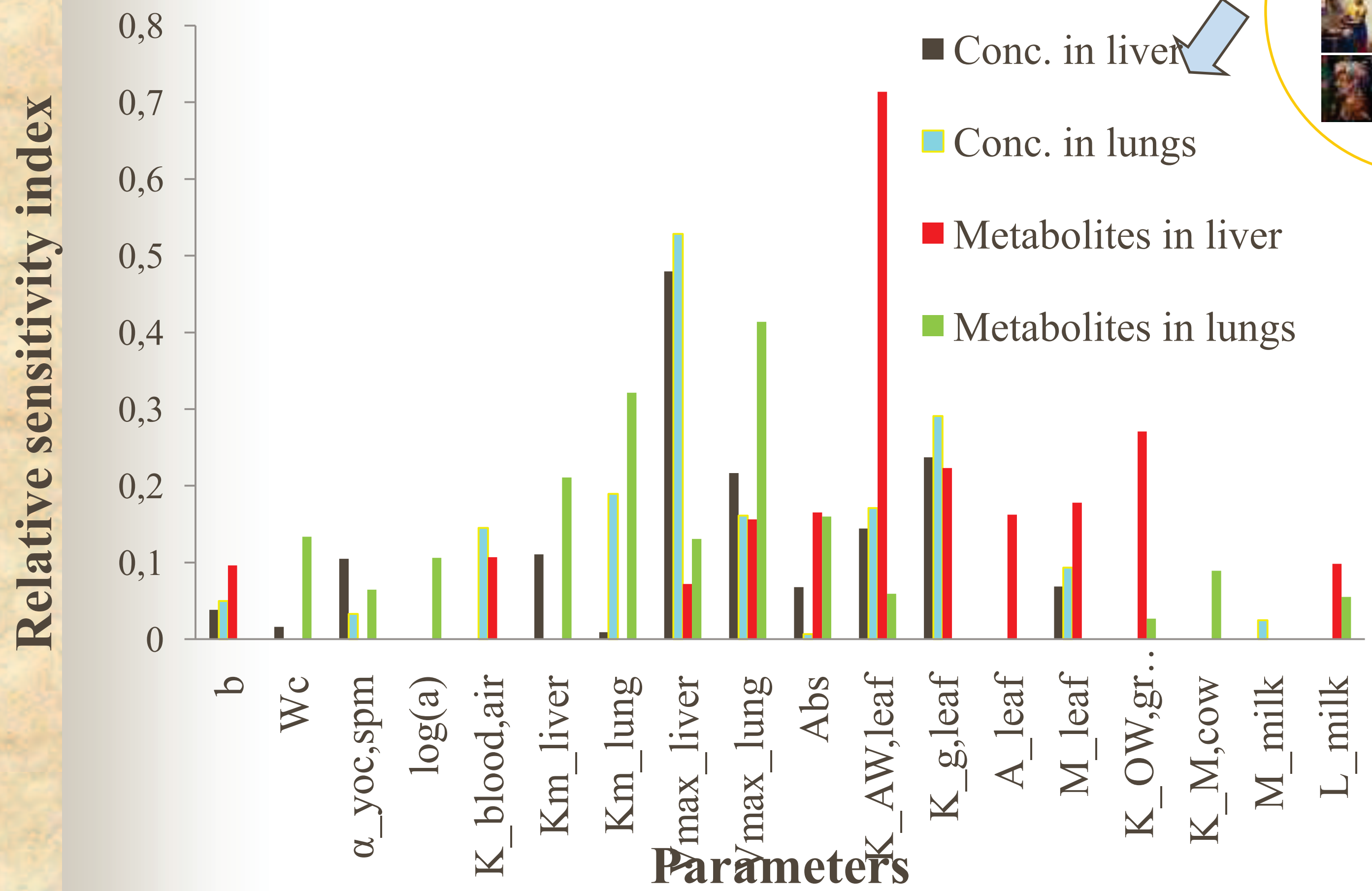
Regression-based methods

Experimental designs

Prior updating by Bayes theorem

Some sensitivity results





Some conclusions

- Ability to conduct a **‘full-chain’** uncertainty analysis (input data, multimedia models, PBPK model)

- Results of the global sensitivity analysis allows to focus on **predominant input parameters** and exposure pathways, and then to improve more efficiently the performance of the modeling tool for the risk assessment

- Developments in the **derivation of parameter PDFs** (Bayesian approaches, etc)