

INTEGRATING MULTIMEDIA ENVIRONMENTAL MODELS AND EFFECT MODELS ON A COMMON PLATFORM FOR RISK ASSESSMENT

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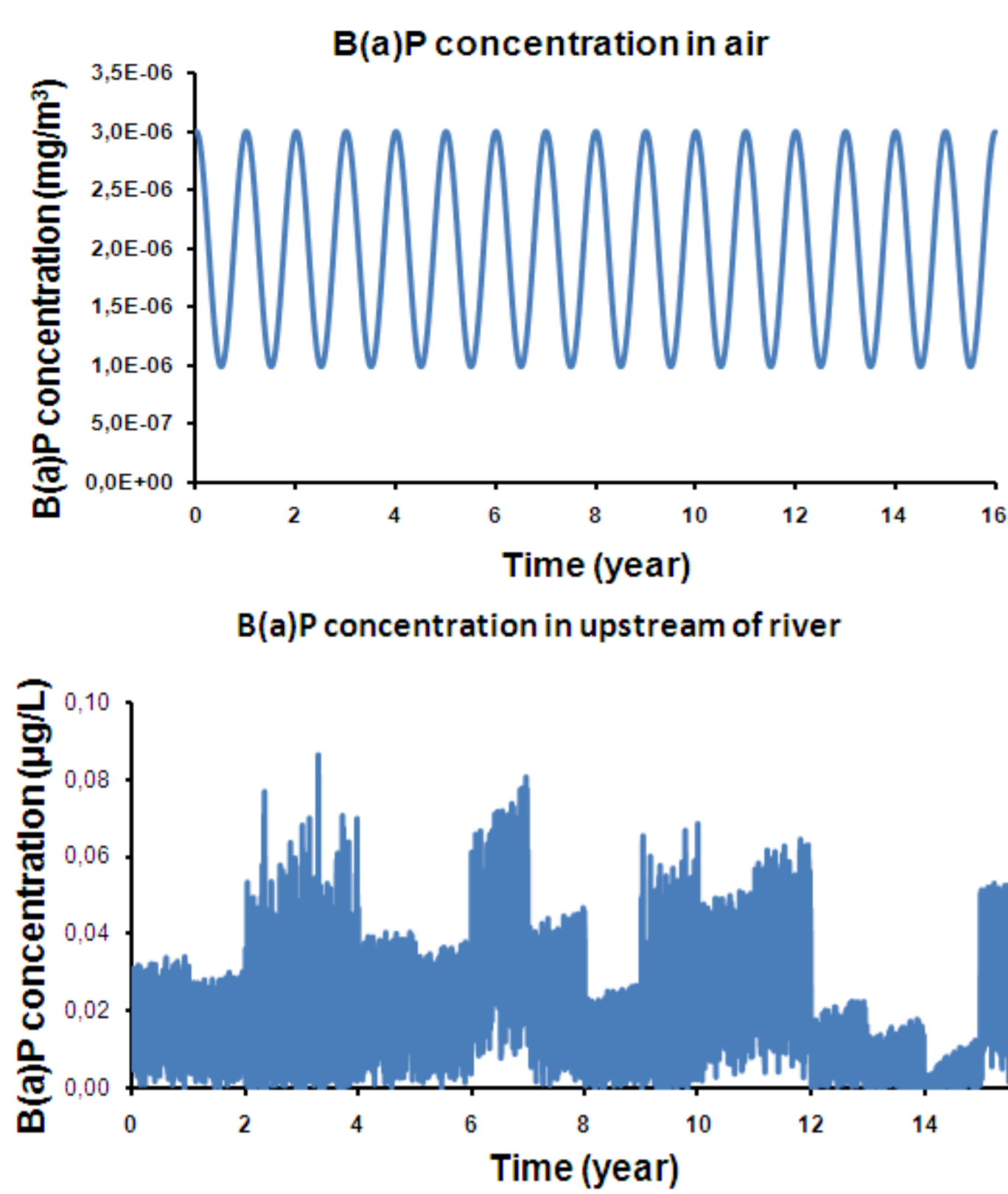
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INTRODUCTION

The European project 2-FUN (Full-chain and UNcertainty Approaches for Assessing Health Risks in FUTURE ENvironmental Scenarios) aims at improving the methodologies currently used in exposure and dose-response assessments. Human exposure through multiple pathways is classically estimated by **multimedia models**, calculating the distribution of contaminants among the different routes of exposure (e.g., drinking water, inhaled air, food). Combined with data describing human behaviour, such models provide an estimate of the daily quantity inhaled or ingested by humans. Dose-response modelling aims at determining the relationship between the dose and the probability of an effect. **Physiologically based pharmacokinetic (PBPK) models** are an adequate tool to predict internal effective concentrations, *i.e.* in the target tissues where toxic effects arise. A dose-response model is then applied to link the effective concentration to the adverse effects.

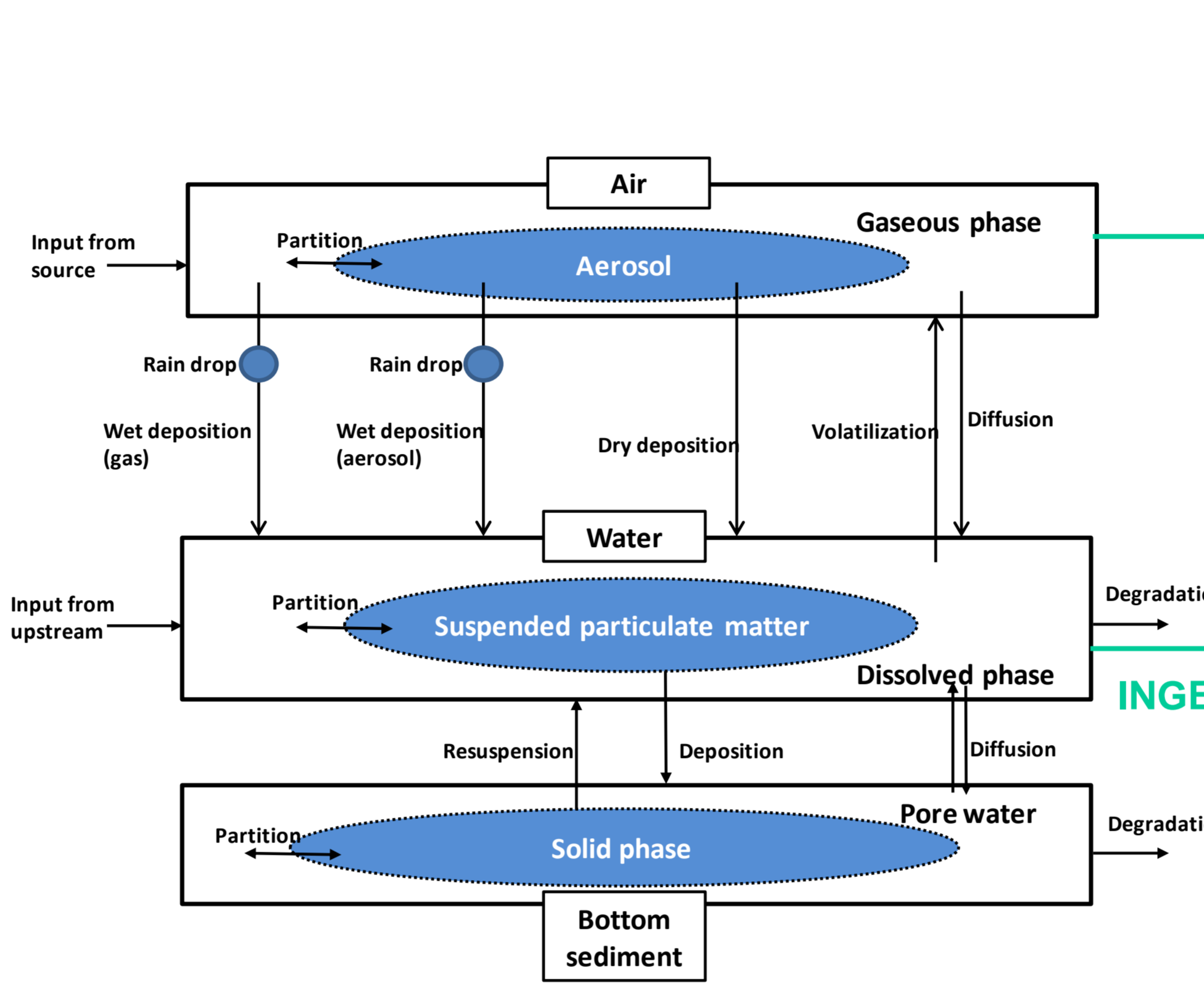
In the 2-FUN project, multimedia and PBPK models were integrated on a common platform, Ecolego™. We show here the application of these integrated risk assessment models to benzo(a)pyrene, a polycyclic aromatic hydrocarbon. We study in particular the **propagation of uncertainty and inter-individual variability** along the modelling chain. As a case study, a region situated on the Seine river watershed, just downstream of the Paris megacity was selected. It is characterized by strong industrialization and urbanization, with industries and domestic anthropogenic activities potentially releasing B(a)P. In this case study, only riverine and atmospheric inputs of B(a)P were considered.

INPUT DATA AND MODELS



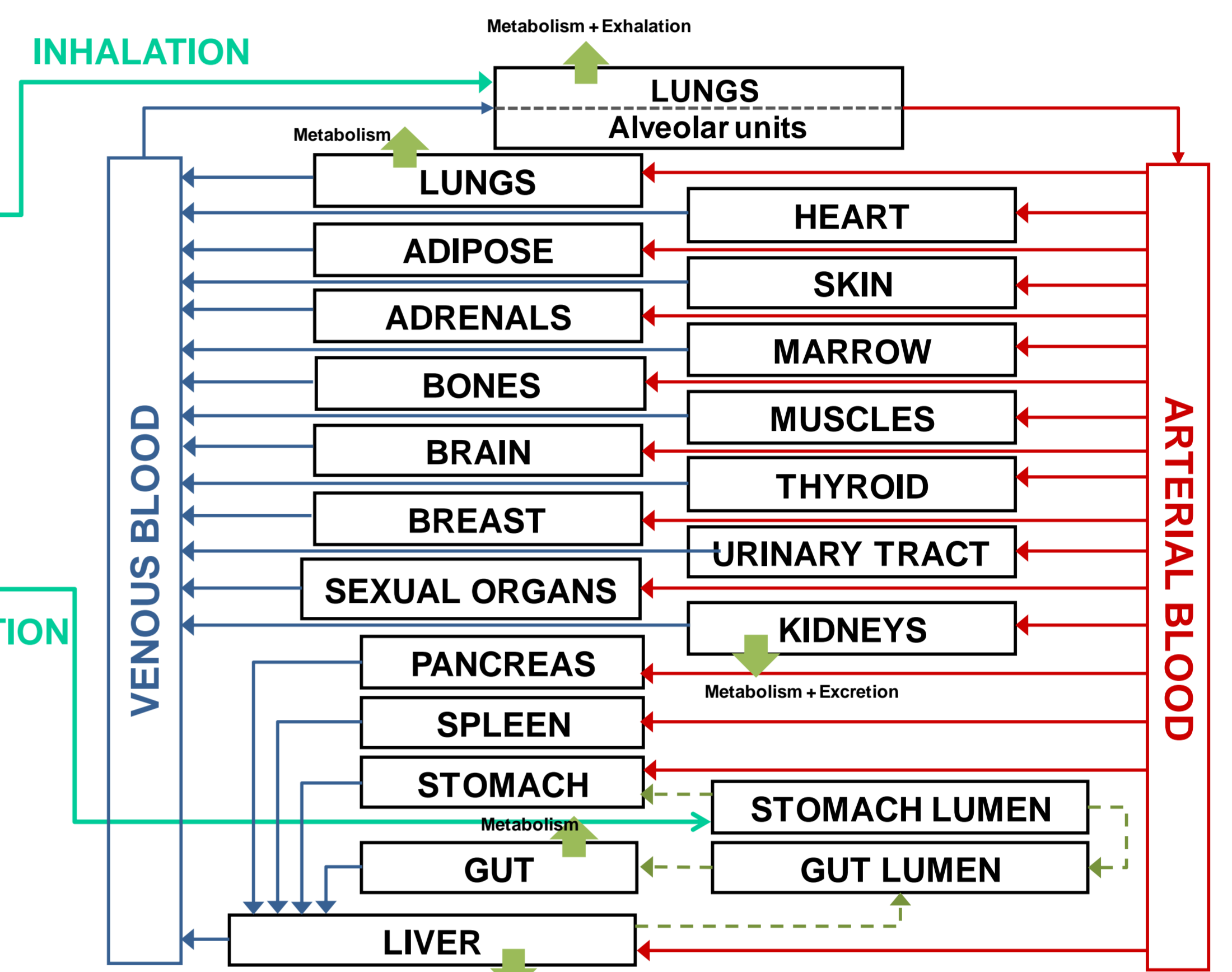
Input data for the freshwater and air models

Contamination levels in river were estimated based on the data collected by the 'Seine-Normandie Water Management Agency' (SNWMA). The data were obtained at the monitoring station Poissy from 1993 to 2008 (except 1995 and 2004). The estimation method is described in Ciffroy et al. (2010). Air concentration of B(a)P was obtained referring to Quéguiner et al. (2010).



A multimedia model for fresh-water and air compartments

A multimedia model consisting of fresh-water and air compartments simulates chemical distribution in each compartment taking into account physical and chemical interactions in and between the compartments. In this study, the multimedia model was used to simulate the concentrations of B(a)P dissolved in water and of B(a)P in air.



A PBPK model for humans

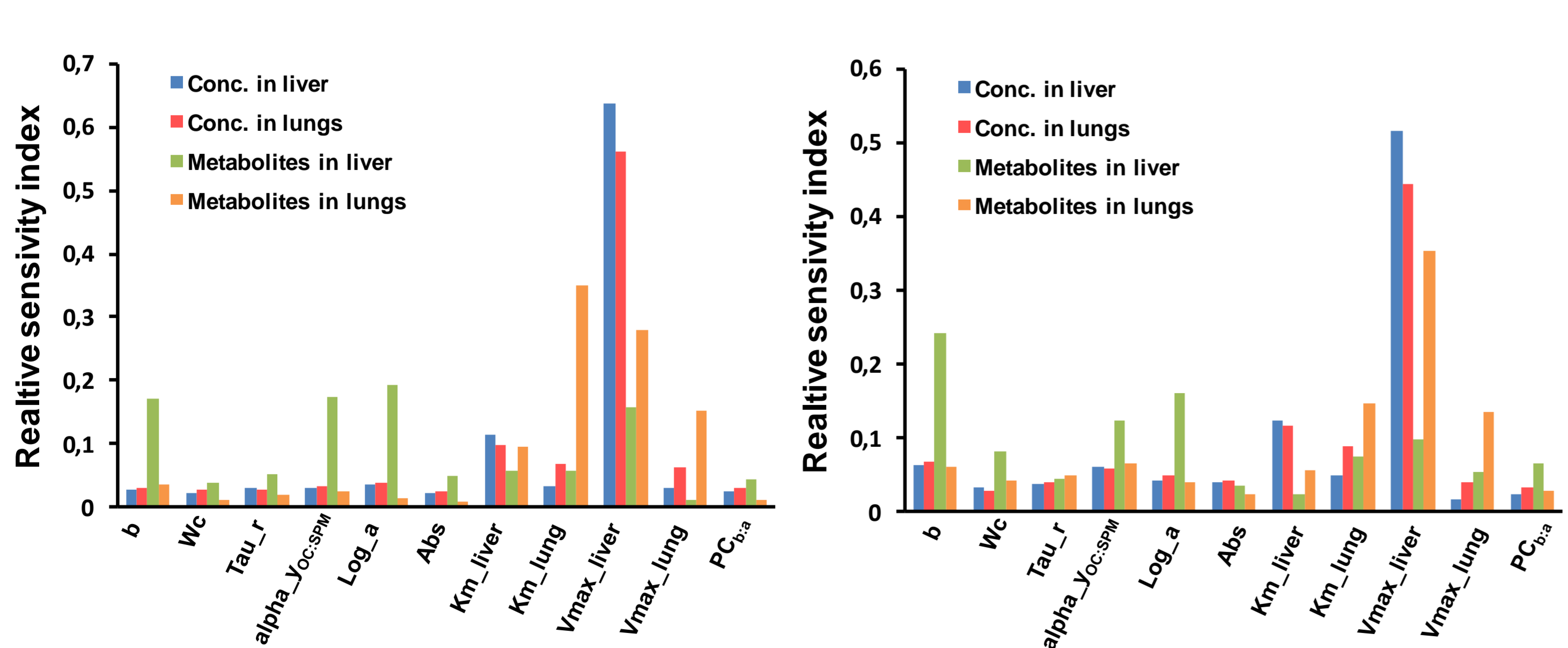
A PBPK model for men and women was developed to simulate the body burden of various xenobiotics throughout the entire human lifespan integrating the evolution of the physiology and anatomy from childhood to advanced aged. The PBPK model describes the ADME (absorption, distribution, metabolism, and excretion) processes and is expressed as a set of first-order differential equations.

PROBABILITY DISTRIBUTIONS FOR SA and UA

Probability distributions were defined to perform a global sensitivity analysis and an uncertainty analysis. Only the key parameters of the multimedia and PBPK model were considered for those analyses. The model outputs of interest are the concentration of B(a)P in the liver and lungs, and the total quantity of metabolites formed in liver and lungs.

Parameter	Unit	PDF	Relevant process
1 st empirical parameter for the rating curve relating suspended particulate matter (SPM) and flow rate in river (log _a)	-	N(-4.19, 0.33)	Concentration of time-dependent SPM
2 nd empirical parameter for the rating curve relating SPM and flow rate in river (b)	-	N(0.99, 0.13)	Concentration of time-dependent SPM
1 st empirical parameter for the relationship between time-dependent organic fraction in SPM and time-dependent SPM (α _{Y_{oc,SPM}})	-	Trian(0.15, 0.55)	0.96, Time-dependent organic fraction in SPM
Settling velocity of particles (W _c)	m d ⁻¹	LN(18.9, 3.0)	Deposition from water to sediment phase
Critical shear stress for resuspension (tau _r)	N m ⁻²	LN(0.18, 3.78)	Resuspension from sediment to water phase
Percentage of the chemical absorbed (Abs)	-	Uniform[0.8;1]	Chemical absorption
Michaelis constant for metabolism in liver (Km _{liver})	mg.L ⁻¹	Normal[1.39; 1.39]	Chemical metabolism in liver
Michaelis constant for metabolism in lungs (Km _{lung})	mg.L ⁻¹	Normal[0.06; 0.06]	Chemical metabolism in lungs
Maximal velocity for metabolism in liver (Vmax _{liver_vivo})	mg.min ⁻¹	Normal[4.42; 4.42]	Chemical metabolism in liver
Maximal velocity for metabolism in lungs (Vmax _{lung_vivo})	mg.min ⁻¹	Normal[0.0017; 0.0017]	Chemical metabolism in lungs
Partition coefficient between blood and air (PC _{blood_over_air})	-	Normal[590; 295]	Inhalation and exhalation of the chemical

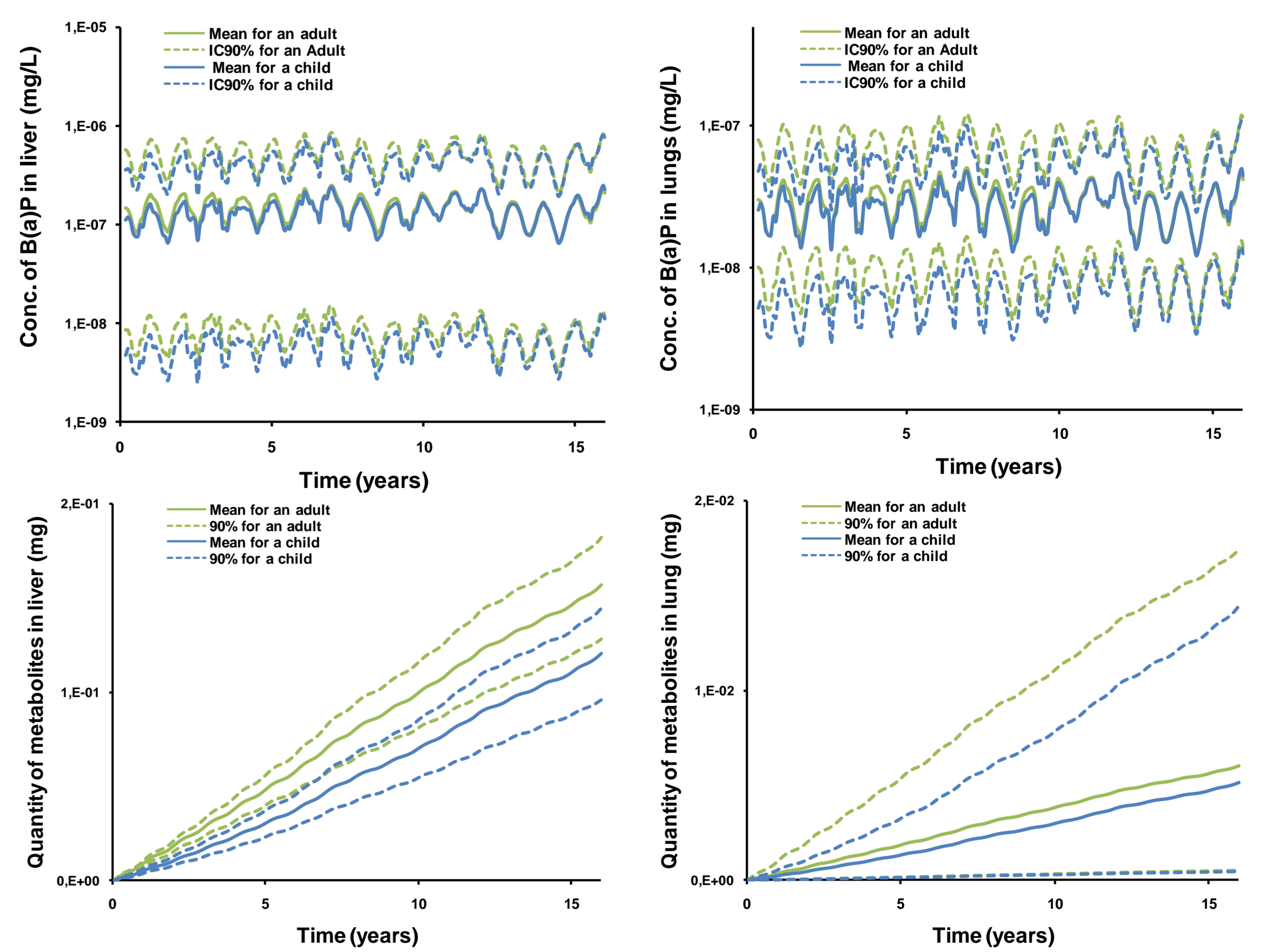
GLOBAL SENSITIVITY ANALYSIS



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UNCERTAINTY ANALYSIS



CONCLUSION

This study is a "prototype case study" aiming at demonstrating the feasibility of the 2-FUN software for conducting a full-chain risk assessment involving both environmental multimedia and PBPK models, with uncertainty analysis.

A case study concerning the exposure of humans to B(a)P in a French area was proposed. The global sensitivity analysis and the uncertainty analysis were performed to evaluate the impact of the model parameters and their associated uncertainty or variability on outputs of interest (the formation of B(a)P metabolites). These analyses showed that some parameters of multi-media models have a high influence on the internal dosimetry of humans.

Future developments concern the coupling of the PBPK model with dose-response functions and the integration of other sources and pathways of exposure in order to complete the modeling chain and to allow a **complete risk analysis**.