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Modelling the exposure to chemicals for risk assessment: a comprehensive library of multimedia and PBPK models for integration, prediction, uncertainty and sensitivity analysis – the MERLIN-Expo tool

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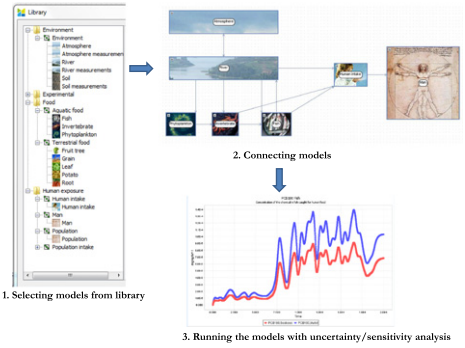
HIGHLIGHTS

- MERLIN-Expo is a library of models that provides integrated exposure assessment.
- MERLIN-Expo integrates multimedia (MM) environmental models and PBPK models.
- MERLIN-Expo contains many functionalities for uncertainty/sensitivity analysis.
- MERLIN-Expo targets both humans and wildlife biota through common fate models.
- MERLIN-Expo was tested on three realistic case studies.

GRAPHICAL ABSTRACT



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ABSTRACT

MERLIN-Expo is a library of models that was developed in the frame of the FP7 EU project 4FUN in order to provide an integrated assessment tool for state-of-the-art exposure assessment for environment, biota and humans, allowing the detection of scientific uncertainties at each step of the exposure process. This paper describes the main features of the MERLIN-Expo tool. The main challenges in exposure modelling that MERLIN-Expo has tackled are: (i) the integration of multimedia (MM) models simulating the fate of chemicals in environmental media, and of physiologically based pharmacokinetic (PBPK) models simulating the fate of chemicals in human body. MERLIN-Expo thus allows the determination of internal effective chemical concentrations; (ii) the incorporation

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of a set of functionalities for uncertainty/sensitivity analysis, from screening to variance-based approaches. The availability of such tools for uncertainty and sensitivity analysis aimed to facilitate the incorporation of such issues in future decision making; (iii) the integration of human and wildlife biota targets with common fate modelling in the environment.
MERLIN-Expo is composed of a library of fate models dedicated to non biological receptor media (surface waters, soils, outdoor air), biological media of concern for humans (several cultivated crops, mammals, milk, fish), as well as wildlife biota (primary producers in rivers, invertebrates, fish) and humans. These models can be linked together to create flexible scenarios relevant for both human and wildlife biota exposure. Standardized documentation for each model and training material were prepared to support an accurate use of the tool by end-users.
One of the objectives of the 4FUN project was also to increase the confidence in the applicability of the MERLIN-Expo tool through targeted realistic case studies. In particular, we aimed at demonstrating the feasibility of building complex realistic exposure scenarios and the accuracy of the modelling predictions through a comparison with actual measurements.

1. Introduction

The paradigm for assessment of risks to biota and humans from chemicals is based on two main pillars: the exposure assessment and dose-response assessment. Exposure assessment involves the process of estimating or measuring the magnitude, frequency and duration of exposure to chemicals, along with the number and characteristics of the population exposed. Exposure assessment is generally considered as a weak point in risk assessment due to a lack of data and the inherent natural variability in exposure levels, leading to uncertainty in the estimates. Big advancement in risk assessment can therefore be achieved by improving exposure assessment with innovative approaches.

Exposure to chemicals through multiple pathways is typically estimated by the so-called 'multimedia models' (MM models) that calculate the distribution of chemicals over environmental media. As far as human exposure is concerned, the targeted environmental media correspond to sources of interest for human exposure, like e.g. drinking water, inhaled air, vegetables, meat, fish, milk and other foodstuffs. When combined with data describing human behaviour (diet composition, time activity pattern, etc.), such MM models provide an estimation of the daily dose inhaled or ingested by the population of interest.

From a regulatory point of view, exposure estimation in general, and exposure modelling in particular, must face (or will have to face) new challenges. Results of cost-benefit analyses of environmental policy decisions are indeed often subject to debates (e.g. in the frame of REACH application that aims at promoting sustainable chemicals), because of high uncertainties throughout the health risk assessment chain (including in particular the exposure assessment stage). Such uncertainties are recognized but rarely explicitly quantified and integrated over the full impact assessment pathway. In addition, the (e.g. under REACH) recommended MM model SimpleBox in EUSES does not include the latest scientific insights and advancements on MM modelling of the past 20 years. Thus, for improving future environmental and health regulations and associated debates with stakeholders, the implementation of recent scientific developments for the construction of robust exposure scenarios and integrated models and the evaluation of uncertainties in the whole chain of assessment into a tool is requested. The integration of a full-chain approach integrating uncertainties would allow optimizing efforts towards environment and health impact prevention, hence contributing to the promotion of sustainable products/technologies/activities.

In this particular context, the MERLIN-Expo tool was developed in the frame of the FP7 EU project 4FUN in order to provide an integrated assessment tool for state-of-the-art exposure assessment for environment, biota and humans, allowing the detection of scientific uncertainties at each step of the exposure process.

This paper describes the main features of the MERLIN-Expo tool. In a first section, the main challenges in exposure modelling that MERLIN-Expo has tackled are described. In the second section, models that are available in the MERLIN-Expo library are briefly described, as well as the documentation and support that is available for end-users. In the third section, the main features and capabilities of the MERLIN-Expo user interface are presented. Finally, a brief description of key case studies that were investigated with MERLIN-Expo is proposed in order to illustrate the flexibility of the tool and the kind of assessments that could be performed with the tool.

2. Challenges in exposure modelling and solutions proposed by MERLIN-Expo

2.1. Internal human exposure

The terminology 'exposure assessment' can be defined in different ways. It can refer to intake rates of chemicals through ingestion, inhalation or contact of/with contaminated media like air, water, dust, food. This is the definition generally considered by the so-called multimedia (MM) or exposure models, which provide information only on concentrations in environmental media and provide an estimation of daily quantity ingested/inhaled by humans. However, beyond the estimation of daily intakes, the determination of internal effective concentrations, i.e. in the target tissues where toxic effects arise, is also required to comprehensively assess 'exposure' and to characterize accurately the link between the intake from the environment and health effects. The exposure concept should then be extended to the environment and human body in order to actually cover the full exposure chain that is of interest for evaluating health effects (Sheldon and Cohen Hubal, 2009). The importance of internal exposure assessment is highlighted in detail in Ciffroy et al. (companion paper, 2016a–in this issue). In short, the incorporation of pharmacokinetic issues in exposure assessment will become more crucial in the future with the development of 'Equivalent Biomonitoring Reference Doses' that provide concentration thresholds of chemicals in human tissues (instead of thresholds in environmental media only) (Schulz et al., 2007; Hays et al., 2008). Exposure assessment tools must then anticipate such current progress in effect assessment to be able to actually compare contaminant levels in human tissues with 'Equivalent Biomonitoring' thresholds (Angerer et al., 2011). Besides, as internal concentrations account for the concentration to which target organs or systems are actually exposed to, they allow a more relevant extrapolation between species, between levels of biological organizations or between laboratory tests and field monitoring. Internal concentrations also aggregate the contributions of many routes of exposure (ingestion, inhalation, etc.), may account for the bioavailability of the chemicals, and facilitate the understanding of relationships between tissue residues and adverse outcome.

Physiologically based pharmacokinetic (PBPK) models are dedicated tools that satisfy this need because they describe the fate of chemicals (and mixtures of chemicals) in the body and thus can predict their levels in the internal tissues. They consist of a series of mathematical equations with parameters based on the specific physiology of an organism and on the physicochemical properties of a substance, which are able

to describe the absorption, distribution, metabolism and elimination (ADME) of the compound within this organism. The solution of these equations provides the time-course of the parent compound and possibly some of its metabolites in the organs and allows for a sound mechanistic description of the kinetic processes including accumulation in tissues (Andersen, 2003; Brochot et al., 2007; Peters, 2012). Substance-dependent parameters like partition coefficients between blood and organs, uptake, excretion or metabolism rates can be extrapolated from one species based on allometric factors (Campbell et al., 2012). As such, PBPK models are, for instance, well-suited for integrating available information on age- or gender-dependent changes and then the evaluation of the influence of these changes over the course of an individual's lifetime on the internal dosimetry (Beaudouin et al., 2010; Bois et al., 2010). They can also be used in a reverse way, i.e. deducing exposure concentrations from measured internal ones. This is the basis of dose reconstruction based on human biomonitoring (Clewell et al., 2008), based for instance on measurements performed in urine, blood or breast milk (Ulaszewska et al., 2012).

So far however, models dedicated to contaminant fate in the environment and in human body respectively were developed in parallel by different scientific communities and, at our knowledge, they have rarely been coupled in the same platform, so that comprehensive risk assessments cannot be performed over the full exposure chain. In the 4FUN project, specific contributions were dedicated to MM environmental modelling and PBPK modelling respectively and all the models developed for the environment and human body were then integrated in the common and flexible modelling platform MERLIN-Expo. MERLIN-Expo was thus designed to allow internal exposure assessments (and not only intake rates) for different human populations (general population, children at different ages) integrating exposure through multiple pathways. Integrated evaluations over the full chain were tested on case studies presented in this issue (XXX).

2.2. Uncertainty/sensitivity analysis

Uncertainty and sensitivity are issues that are now systematically identified as essential in all the guidelines referring to health risk assessment (WHO, 2008, 2014; RIVM, 2013; ECHA, 2012; FERA, 2010). It is indeed stressed that more attention should be drawn to the nature and extent of scientific uncertainty associated to risk assessments and that uncertainty should be taken into account in the decision-making process (Cowan-Ellsberry et al., 2009). In particular, exposure assessment is associated with many sources of uncertainty: in complex scenarios such as environmental and/or human exposure assessment, where more than one scientific discipline is considered (e.g. fate of chemicals in atmosphere, soils, surface waters, biological media, human pharmacokinetics), where a large number of data are necessary, and where the system investigated is very wide (interactions between environment and humans), many sources of natural variability and incompleteness of knowledge are introduced. In such complex situations, uncertainty analysis (UA) is an essential tool for improving the governance of risks. This is the reason why WHO (2008) has recently proposed a tiered approach for assessing uncertainty in the frame of exposure assessment. Sensitivity analysis (SA) is complementary to uncertainty and provides information on how uncertainty in a model output can be systematically apportioned two different sources of uncertainty in the model input. In other words, sensitivity can be used to identify the important drivers (parameters, processes) contributing most to uncertainty, and in contrast identify non influential drivers; it thus identifies priorities in term of research activities, model refinements and potential countermeasures.

The wording 'uncertainty' and 'sensitivity' covers however different meanings and can be used to answer different questions like: (i) what is the range of variation of model outputs when inputs randomly cover their global space of variation; (ii) which input parameters/variables contribute most to the output variation; (iii) which processes are the important drivers of model outputs; (iv) which input parameters are "non influential"; (v) what is the critical parameter space leading to threshold excess? Some of the existing exposure assessment tools actually contain options for conducting uncertainty analysis, but methods that are incorporated are generally limited to purely random samplers (like Monte Carlo approach) and are not suitable for answering all the above-mentioned questions. For example, in a report dealing with human exposure models, WHO (2005) writes that 'rather simple stochastic models can be accurate […] if the input variables […] are independent of each other and if the sequences of the exposure events are irrelevant to the exposure. If these conditions are violated, the models either become more complex or may produce erroneous outputs. More advanced probabilistic modelling techniques can deal with intercorrelated input variables'. This citation shows that uncertainty/sensitivity techniques have to be used with caution because the most 'generic' ones are not necessarily suitable for all the questions that a risk assessor has to answer. An exposure model can instead propose a set of different uncertainty/sensitivity options to cover a wide range of issues. To answer each of the above-mentioned questions, several sensitivity methods are actually available like: (i) local SA methods, performed by varying one-parameter-at-a-time (OAT) around a nominal value. The majority of published sensitivity analyses are based on such local or OAT methods. The problem with this kind of approach is that it sometimes relies on unjustified assumptions of model linearity and additivity. Besides, changing one factor at a time in a multi-dimensional space of uncertain factors leaves the majority of that space unexplored. Also, no interaction between factors can not be identified because for this one needs to vary more than one factor at a time (Ferretti et al., in this issue); (ii) screening methods based on optimized experimental designs (e.g. Morris method), aiming at identifying non influential parameters at low computational cost; (iii) global regression methods, relying on the strong assumption that the relationship between outputs and inputs is linear or monotonic (e.g., Standardized Regression Coefficients (SRC)); (iv) global variance-based methods (e.g., FAST, EFAST, Sobol'), considered as the most robust, but computationally expensive.

MERLIN-Expo contains a set of functionalities for uncertainty/sensitivity analysis, including all the methods indicated above, as well as a guidance document, allowing flexibility in the methods used according to the question that has to be addressed. These methods are in line with the tiered approach recommended by WHO (2008) that suggested to conduct uncertainty/sensitivity analysis according to a three-step approach based on the subsequent use of qualitative, semi-quantitative and quantitative methods successively. The two last stages may require a set of methods for sensitivity analysis (e.g. screening and variance-based methods) that are rarely available in most existing models. The availability of such options and guidance for uncertainty and sensitivity analysis in MERLIN-Expo aimed to facilitate the incorporation of such issues in future decision making for a wide range of stakeholders/end-users.

2.3. Biota exposure versus human exposure

Integrated Risk Assessment (IRA) has been defined in a recent White paper (Wilks et al., 2015) as "the mutual exploitation of Environmental Risk Assessment for Human Health Risk Assessment and vice versa in order to coherently and more efficiently characterize an overall risk to humans and the environment for better informing the risk analysis process". As discussed in Ciffroy et al. (2016a–in this issue), integrating Environmental Exposure assessment (EEA) (i.e. exposure of biota) and Human Exposure assessment (HEA) would be a major benefit for the IRA framework. So far however, EEA and HEA have generally used and developed their own models in parallel, with poor linkage between them. EEA and HEA pursue different targets, protection goals and timeframes that could explain such discrepancies. Indeed, 'on site' exposure (i.e. local exposure to chemicals that are emitted into the

environment under non-intentional or controlled conditions) is mainly of concern for biota, while exposure to humans can be extended to chemical production (occupational exposure), regional and global use of resources (imported products) and intentional and/or non-intentional use of products by consumers (e.g. cosmetics). Despite such differences, human and wildlife species also share the same environment and they similarly inhale/ingest air, water and food. For many chemicals, exposure of humans mainly originates from environmental pathways that are common to biota living in similar environments (i.e. ingestion of contaminated foodstuffs). Then exposure pathways may in part overlap between humans and wildlife species, and models will use the same concepts for simulating the transport and fate of chemicals and for predicting chemical concentrations in e.g. surface waters, outdoor air, soils, sediments, or biological targets.

It was then identified that there is a need for the development of exposure tools integrating both human and wildlife biota targets with common fate modelling in the environment. That is why MERLIN-Expo is composed of a library of fate models dedicated to non biological receptor media (surface waters, soils, outdoor air), biological media of concern for humans (cultivated crops, cow milk, fish seen as foodstuff, etc.), as well as wildlife biota (primary producers in rivers, invertebrates, fish seen as targeted organism for EEA). These models can be linked together to create flexible scenarios relevant for both human and wildlife biota exposure and can be a promising way to better integrate EEA and HEA. As MERLIN-Expo is an open platform, the option remains also to extend the library and incorporate new models as required by site-specific investigations.

2.4. Easy-to-use, easy-to-understand, flexible and difficult-to-abuse

In its guideline dedicated to exposure modelling, WHO (2005) identified the priority criteria affecting the selection of an exposure model, i.e. mathematical simplicity, computational simplicity, interpretability, consistency and accuracy in prediction. It can be stated that some of these criteria are sometimes in direct conflict, e.g. good accuracy in prediction can require quite complex models that are not mathematically and computationally simple. Actually, many existing exposure tools do not solve conflicts between such antagonist criteria: some of them are mathematically simple, but are adapted only for screening situations and accuracy is not their main priority; some others are computationally complex, but their numerical robustness has not been validated; some others act as 'black boxes' and are then difficult to interpret. Some of the WHO recommendations could be translated in simple goals; to enable a software to be used by a wide range of stakeholders and end-users, it should be: (i) easy-to-use, (ii) easy-to-understand, (iii) flexible and (iv) difficult-to-abuse. Developing a tool based on these criteria is far from obvious. Indeed, many existing exposure models do not fit these requirements either because they were primarily designed for exploratory research or for "proof of principle" assessment where no regulatory action was expected, or because they are only accessible as 'black boxes'. The use of exposure tools becomes then troublesome when model concepts, components, scientific background, parameter sources, mathematics and/or numerical schemes are not transparent and/or when the domain of applicability can easily be transgressed by end-users.

The choice of the MERLIN-Expo platform was actually driven by the four criteria indicated above. Exposure models were thus implemented on the same platform (i.e. Ecolego® - see www.facilia.se) in order to facilitate integrated full-chain assessments for combined exposures. One of the main characteristics of Ecolego® is the use of Interaction Matrices to create and visualize models (see below), similar to what is written down 'on the paper' when building the conceptual models ('easy-to-understand' criteria). By grouping sub-models into hierarchical compartments, a large model can be cleanly separated into independent modules that represent a certain part of the model and that can be easily coupled ('easy-to-use' and 'flexible' criteria – see below). Finally, alerts can be included for avoiding misuse of the model ('difficult-to-abuse' criteria).

Quality Assurance (QA) and standardization is also essential for guaranteeing a robust use of the tool. Developing a QA plan for documenting all the MERLIN-Expo models was conducted in the frame of the 4FUN project in coordination with CEN (European Committee for Standardization) (Ciffroy et al., 2016b–in this issue). To tailor the communication to the needs of different users and to overcome the barrier of non-transparency to third party users, a standard documentation protocol was developed, providing guidance on what should be the content of an exposure model documentation (CEN CWA 16938), and is available online (see next section).

3. Models available in the MERLIN-Expo library

This section lists all the models that are currently available in the MERLIN-Expo library, with a short description of the goals, potential decision and regulatory frameworks, and main processes incorporated in the model. A complete documentation of each model can be consulted on the MERLIN-Expo web site (http://merlin-expo.eu/learn/documentation/model-documentation/). This section presents also the support material that is available to end-users.

3.1. The 'Surface water' model

The goal of the 'Surface water' model is to dynamically simulate the distribution of chemicals in non-biological media of surface water systems (i.e. water, suspended particulate matter (SPM), sediment particles, sediment porewater). Thus, the model provides an estimation of the time-dependent concentration of the targeted chemical(s) in raw water, filtered water and bottom sediments. This/these output(s) can be used for instance for evaluating the risk to exceed a given regulatory threshold for environmental risk (e.g. Predicted Non Effect Concentration (PNECs), and/or Environmental Quality Standards (EQS) defined in some regulations like the European Water Framework Directive). The model provides also inputs for other models, e.g. for simulating bioaccumulation in phytoplankton/invertebrate/fish, for evaluating the risk to exceed a given regulatory threshold for human health (drinking water) and/or for evaluating chemical inputs to soils and plants through irrigation.

The main processes included in the model are (Fig. 1): (i) the simulation of temporal SPM variability that is related to flow rate according to a rating curve model (see e.g. Syvitski et al., 2000); (ii) sorption/desorption between water and SPM and between sediment particles and sediment porewater, described by distribution (or partition) coefficients, expressed as the concentration ratio at equilibrium between the particulate phase and the dissolved phase respectively; (iii) deposition of particulate contaminants to bed sediments, and inversely resuspension of particulate contaminants from bed sediments, simulated according to mechanistic dynamic models that were developed in sediment science (see e.g. Ha and Maa, 2009). They are based on the assumption that the gravitational settling velocity of particles plays the dominant role for deposition, and that the bed shear stress exerted by the flow plays the dominant role for resuspension; (iv) diffusion between water and sediment pore water, represented by a two film diffusion model, where the transport into the sediment is assumed to happen through two layers of resistance (the first layer representing the laminar water-side film and the second one sediment-side boundary layer); (v) diffusion between water and atmosphere, especially relevant for highly volatile chemicals (or Semi Volatile Organic Compounds – SVOCs). Absorption/volatilization of SVOCs at the air-river interface is modeled using the stagnant boundary theory (two-film model), the pollutant being assumed to diffuse across two layers (stagnant water layer and stagnant air layer) characterized by two resistances in series; (vi) degradation. Several processes can contribute to the degradation of a chemical in water and sediments and to the

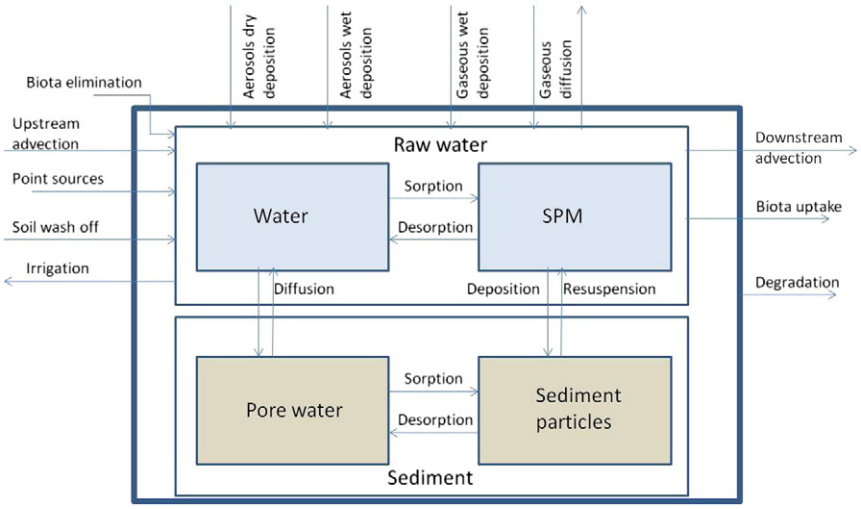


Fig. 1. Conceptual representation of the Surface water model available in the MERLIN-Expo library.

formation of metabolites: biodegradation, photolysis, hydrolysis. Most of these degradation processes require a large number of parameters that are poorly available for most of the chemicals. Therefore individual degradation processes are not distinguished in MERLIN-Expo but are added into an aggregated loss rate parameterized through a read-across approach developed by Kühne et al. (2005).

3.2. The 'Soil' model

The goal of the 'Soil' model is to dynamically simulate the distribution of chemicals in non-biological media of soils (i.e. soil particles and soil porewater), as well as to simulate their depth profile in the root zone. Thus, the model provides an estimation of the time-dependent concentration of the targeted chemical(s) in total soil and/or soil porewater over the depth profile. This/these output(s) can be used for instance for evaluating the risk to exceed a given regulatory threshold for environmental risk (e.g. Predicted Non Effect Concentration (PNECs), and/or Environmental Quality Standards (EQS) for soil organisms). It can also be used for evaluating the residence time of chemicals in soil. The model provides inputs for other models, e.g. for simulating root uptake to plant crops, or for evaluating the risk of soil ingestion by e.g. pica children.

The main processes included in the model are (Fig. 2): (i) sorption/desorption between pore water and soil particles, described by distribution (or partition) coefficients, expressed as the concentration ratio at equilibrium between the particulate phase and the dissolved phase respectively; (ii) advective transport of chemicals to deep soil layers, driven by the water mass balance in soil (i.e. inputs from rain + inputs from irrigation – loss by infiltration – loss by evapotranspiration). The downward water flux (i.e. infiltration) and the associated advective transport of chemicals to deep soil layers can be assumed to occur preferentially for excess water, i.e. for the fraction exceeding field capacity. However, because the chemical is partly sorbed on the solid phase, only the dissolved phase is assumed to move along the depth profile, resulting in a retardation factor. This latter is a dimensionless parameter defined as the amount by which a chemical is held back by the soil in comparison to the water velocity. In other words, how much the flow of the contaminant is delayed as compared to flow of the infiltrating water; (iii) diffusion between water and atmosphere. Absorption/volatilization of Semi-Volatile Organic Compounds (SVOCs) at the air-soil interface are modeled using the stagnant boundary theory (two-film model), the chemical being assumed to diffuse across two layers (stagnant soil layer and stagnant air layer) characterized by two resistances in series; the soil resistance results itself of the combination of two resistances in parallel representing resistances in soil porewater and in soil gas respectively; (iv) Bioturbation. Bioturbation refers to the disturbance of soil layers by biological activity. Bioturbation can thus be seen as the process that is responsible for the sorbed phase transport of chemicals in soil depth and it is simulated as an additional diffusion process applicable to the solid phase. By analogy with diffusion in gas and water phases, bioturbation can then be represented by a vertical diffusion coefficient (see e.g. McLachlan et al., 2002); (v) Diffusion within soil. Diffusion within soil (i.e. along the vertical soil profile) is governed by the general 1D transport model, and is directed according to the concentration gradient within soil (Fick's law). Diffusion in water and gas in a porous media like soil differs from diffusion in free water and pure gas. Effective diffusion coefficients in gas and water D_{gas} and D_{water} are defined from diffusion coefficient in pure phases corrected by a tortuosity factor to account for the reduced flow area and increased path length of diffusing gas and water molecules in soil; (vi) Wash-off from soils to river. 'Wash-off' of chemicals designates the transport of contaminants in water flowing over the soil surface and finally reaching surface water systems. The approach chosen in MERLIN-Expo for simulating

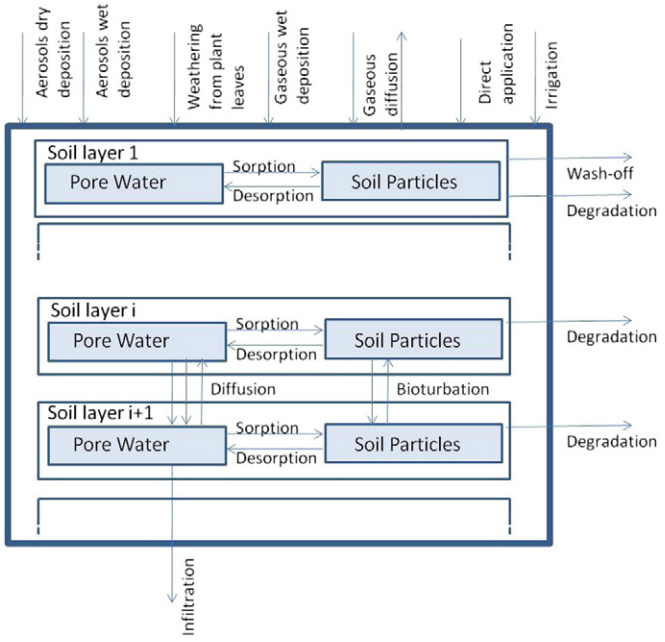


Fig. 2. Conceptual representation of the Soil model available in the MERLIN-Expo library.

wash-off is based on global wash-off rate constants directly relating concentrations in soils and inputs into surface waters. Such global rate constants were fitted especially in the field of radioecology where nuclear accidents represent a good source of tracers for following global transfer from watersheds to surface water systems (see e.g. Garcia-Sanchez, 2008); (vii) Degradation. As previously described for surface waters, degradation of chemicals in soils can be driven by hydrolysis, photolysis and/or microbial degradation. In MERLIN-Expo, they are added into an aggregated loss rate assuming linear first-order kinetics. The effect of temperature on degradation rate is taken into account through the approach described in EFSA, 2007.

3.3. The Atmosphere model

The goal of the 'Atmosphere' model is to dynamically simulate the distribution of chemicals in gaseous and particulate atmospheric phases and interactions with terrestrial surfaces. Thus, the model provides an estimation of the concentration of the targeted chemical(s) in gas and aerosols, as well as of deposition/volatilization to/from surface waters, soils and vegetation. The model provides thus inputs for other models, e.g. for simulating chemical inputs to rivers, soils and plant crops.

The main processes included in the model are: (i) partition of chemicals between gaseous and particulate atmospheric phases, described by distribution (or partition) coefficients. The distribution of organic non polar chemicals between gas and particles can occur by adsorption to active sites and be described by the sub-cooled liquid vapor pressure (P_{vs}), and/or can occur by absorption on aerosols' organic matter and be described by the octanol-air distribution coefficient and the fraction of organic matter in the particle phase; (ii) chemical reactions like photolysis with atmospheric photooxidants (e.g. hydroxyl radical OH), that can be integrated in a first-order degradation process. On the basis of existing experimental data for the tropospheric degradability of organic compounds, approaches based on QSAR can be investigated for predicting half-lives (or degradation rates) of chemicals in the atmosphere; (iii) dry exchanges of gaseous chemicals between the atmosphere and earth surface (bare soil, vegetation and/or surface waters), that can be seen as the composition of a dry deposition (or absorption) flux and a (re)emission (or volatilization) flux. Dry exchange flux of gaseous chemicals can be described by the Fick's law, with a global diffusive transfer coefficient $K_{dry,g}$ between atmosphere and terrestrial surface. $K_{dry,g}$ represents the different mechanisms involved in the mass transfer, i.e. the atmospheric turbulence that governs the transport via the aerodynamic resistance R_a, Brownian diffusion, inertial impaction and interception in the quasi-laminar layer that are grouped into a quasi-laminar resistance term R_b, and the surface or canopy resistance $R_{s,g}$ that combines all uptake processes involving individual elements of the surface (soil, vegetation, surface water); (iv) dry exchange of particles, expressed as the product of a deposition velocity by the atmospheric concentration in the particulate phase. The dry deposition velocity of particles can be expressed by resistances to deposition as for gases but there is an additional term corresponding to the gravitational settling velocity. The surface resistance for particles $R_{s,p}$ represents also other mechanisms, i.e. the collection due to Brownian diffusion (i.e. process by which aerosol particles move randomly due to collisions with gas molecules), impaction (related to the inertia of the particles) and interception(related to the size of the particles); (v) wet deposition, i.e. the mechanism leading to the removal of chemicals from the atmosphere by precipitating hydrometeors. Chemicals are captured by particles of condensed water which grow to become hydrometeors (rain, snow and hail) and precipitate on surfaces. This process is simulated by scavenging coefficients representing removal rates from the atmosphere. Below-cloud wet scavenging of gas and particles can be described by semi-empirical formulations that depend on raindrops radius, raindrop falling velocity, diffusivities and chemical Henry's law constant.

3.4. The Phytoplankton/Invertebrate/Fish models

The goal of the 'Fish', 'Invertebrates', and 'Phytoplankton' models is to dynamically simulate the bioaccumulation of organic contaminants and metals in a single aquatic species and along aquatic food webs. This/these output(s) can be used for evaluating the risk to exceed a given regulatory threshold for environmental risk (e.g., Environmental Quality Standards (EQS) in aquatic organisms for individual pollutants) and also to provide inputs for Human Intake and PBPK models.

Bioaccumulation models are based on the OMEGA model proposed by Hendriks et al. (2001), Hendriks and Heikens, 2001), which has been adapted to fit specific MERLIN-Expo features. In MERLIN-Expo these models can be used independently or linked to create an 'Aquatic food web' model, allowing to recreate aquatic food webs and dietary preference matrices of various dimensions and complexity, supporting the analysis of, for instance, biomagnification of chemicals in trophic chains.

The 'Fish' and 'Invertebrate' models include two systems that correspond to two input/output pathways for chemical accumulation in aquatic organisms, namely the respiratory system and the gastro-intestinal tract (GIT) system (Fig. 3), whereas bioaccumulation in phytoplankton is represented by a one-compartment model. The main processes included in the models are: (i) chemical uptake by aquatic species through respiration. The process is based on allometric scaling and on the assumption that uptake is controlled by the physicochemical properties of respiratory surfaces (e.g., gills, cell membrane). The uptake rate depends on the properties of the substances, organism weight, and resistances that substances encounter in lipid and water layers of the organism; (ii) Uptake of chemicals through ingestion is described as an exchange taking place across the gastro-intestinal tract (GIT). It is driven by diffusion gradients, i.e. the concentration differences between phases within the organism and its food/feces (Fisk et al., 1998). These exchanges between phases are represented by partial resistances from water and lipid layers, species weight, and chemical affinity to lipid and water fraction of food; (iii) Elimination processes including excretion, egestion, growth and metabolism account for loss of chemicals from animal's body. Excretion can be seen as a release of chemicals from the organism in the water compartment via respiratory route. Chemical uptake via the respiratory surface of the organism (such as gills) is related to chemical excretion associated to the efflux of water via the respiratory surface. Both processes are influenced by the same factors connected with respiration. Likewise, ingestion and egestion rate constants are related: their ratio represents indeed the ratio between the assimilated and non-assimilated food. Another process affecting concentration of contaminants in the organism is growth. The production of new biomass actually contributes to the dilution of chemical, rather than causing a real elimination. Metabolism is another important factor affecting the overall accumulation of chemicals in the organism (Papa et al., 2014). In the models, a quantitative structure-activity relationship (QSAR) model is applied to predict biotransformation half-lives (Arnot et al., 2008, 2009).

3.5. The Plant models

The goal of the 'Plant' models is to dynamically simulate the concentration of chemicals in food crops that are of concern for human food. For physiological reasons leading to variation in the fate of chemicals, plants are subdivided in several categories: root vegetables, tubers (e.g. potatoes), leaf vegetables and grass, fruit trees, cereals. This/these output(s) can be used for instance for evaluating the risk to exceed a given regulatory threshold for human intake (e.g. Ingestion Reference Dose) and it provides also inputs for PBPK models.

The main processes included in the model are (Fig. 4): (i) transpiration stream and associated xylem flow that is a key process in the transfer of pollutants from soil to root. The uptake of chemical from soil to root is indeed governed by the transpiration stream that

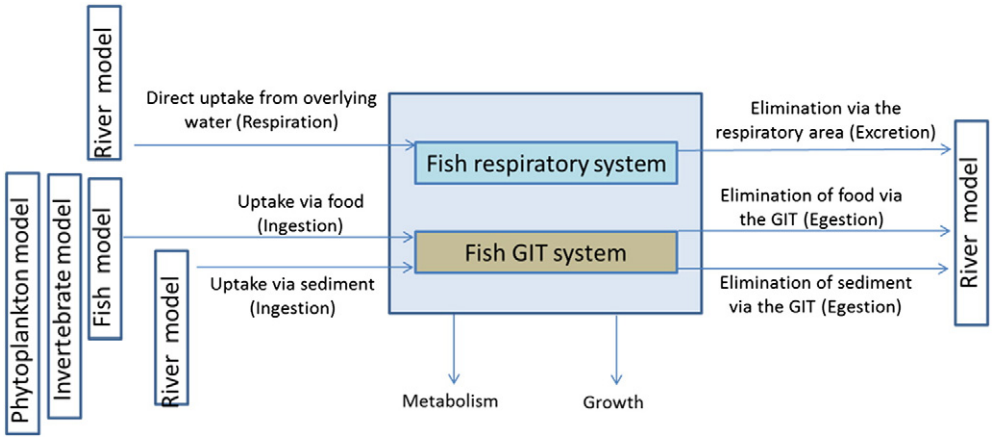


Fig. 3. Conceptual representation of the Fish model available in the MERLIN-Expo library.

drives the movement of dissolved chemicals in the continuum soil-root-stem-leaves/storage organs. As transpiration alone is not commonly measured, it can be estimated from evapotranspiration (i.e. the sum of soil evaporation and plant transpiration) by taking into account an extinction factor (representing fraction of solar radiation that can reach soil) and Leaf Area Index (Sau et al., 2004; Francisco et al., 2008). Once the transpiration stream is evaluated, the xylem influx of chemicals from soil to root and from root to stem can be estimated. It is assumed that only chemicals that are dissolved in soil porewater can contribute to xylem influx; (ii) phloem flow. A fraction of chemicals accumulated in storage organs like fruits is originated from the phloem flow originating from leaves. Despite their different functions, xylem and phloem streams are however neighbored and then a diffusive exchange may occur between these transport systems. For this reason, it can be assumed that there is no difference between chemical concentration in phloem and in xylem flows (Trapp, 2007); (iii) diffusive exchange between plants and air (except for root vegetables and tubers). Some pollutants can be exchanged between above-ground plant surfaces (in particular leaf surfaces) and atmosphere through stomata and cuticle.

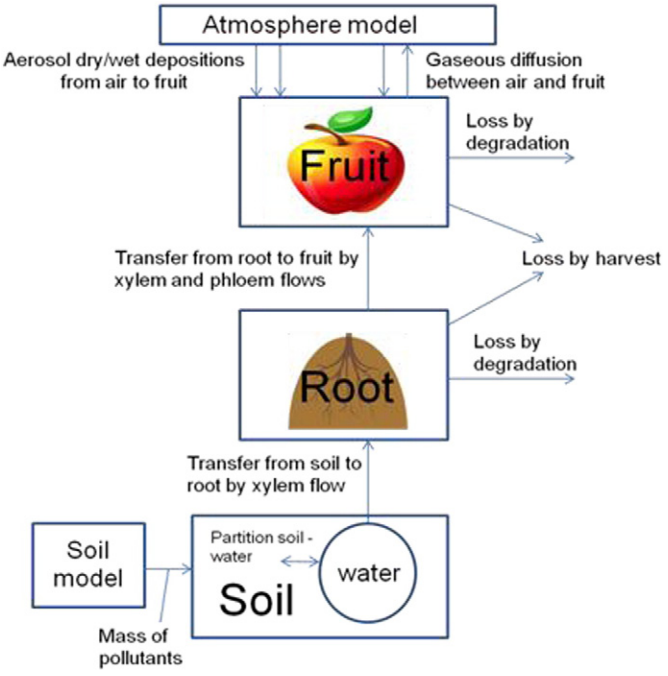


Fig. 4. Conceptual representation of the Fruit tree model available in the MERLIN-Expo library.

Diffusion of chemicals between air and leaf is controlled by the conductance of leaf that can be estimated by considering that several resistances control the exchange between plant and air, i.e., cuticle resistance, air boundary layer resistance, and stomata resistance; (iv) deposition and interception of chemicals on above-ground plant (except for root vegetables and tubers). Both the fractions of dry and wet deposits intercepted by leaf can be quantified by semi-empirical relationships reflecting the fact that the interception fraction increases as the plant grows (and the surface of leaves increases) (Chamberlain, 1970). Such relationships relate the interception fraction (i.e. the ratio between the intercepted chemical quantity and the total deposited quantity) and the above-ground biomass (or Leaf Area Index); (v) diffusion between soil and tubers. A tuber like potato is botanically seen as a part of stem. The uptake of hydrophobic organic pollutants into potato is, therefore, most likely to take place from soil by diffusion, governed by diffusion coefficients in water and gas (Trapp, 2007).

Specific processes for electrolytes (not yet included in MERLIN-Expo, but under development) must also to be mentioned. For these compounds indeed, transfers are partially governed by lipophilic interactions, but also partially by ionic interactions.

3.6. The Mammal model

The goal of the 'Mammals' model is to dynamically simulate the concentration of chemicals in mammals organs that are of concern for human food (i.e. muscle, liver, kidney, milk). This/these output(s) can be used for instance for evaluating the risk to exceed a given regulatory threshold for human intake (e.g. Ingestion Reference Dose) and it provides also inputs for PBPK models.

The main processes included in the model are (Fig. 5): (i) the advective transport and diffusion of chemicals in/across the gastro-intestinal tract (GIT). Bioaccumulation first depends on the distribution of food between digested and undigested fractions respectively that is represented by the assimilated fraction of food (for water and lipids respectively). The distribution of food between digested and undigested food respectively allows quantifying the fraction of chemical able to be transport across the GIT membrane. Chemical exchanges across the GIT are then driven by passive diffusion gradients i.e. the concentration differences between animal blood and its food/feces. Diffusion is governed by resistances to diffusion in series or in parallel corresponding to different layers in the membrane (O'Connor et al., 2013): the partial resistance from water layer; the partial resistance for passive diffusion from outer polar lipid layer; the partial resistance for passive diffusion from inner apolar lipid layer; eventually, the partial resistance for carrier-mediated transport; (ii) the circulation of blood in tissues and partition of chemicals between blood and fat/tissue. Once chemicals have cross the GIT barrier, their accumulation in animal organs is mainly

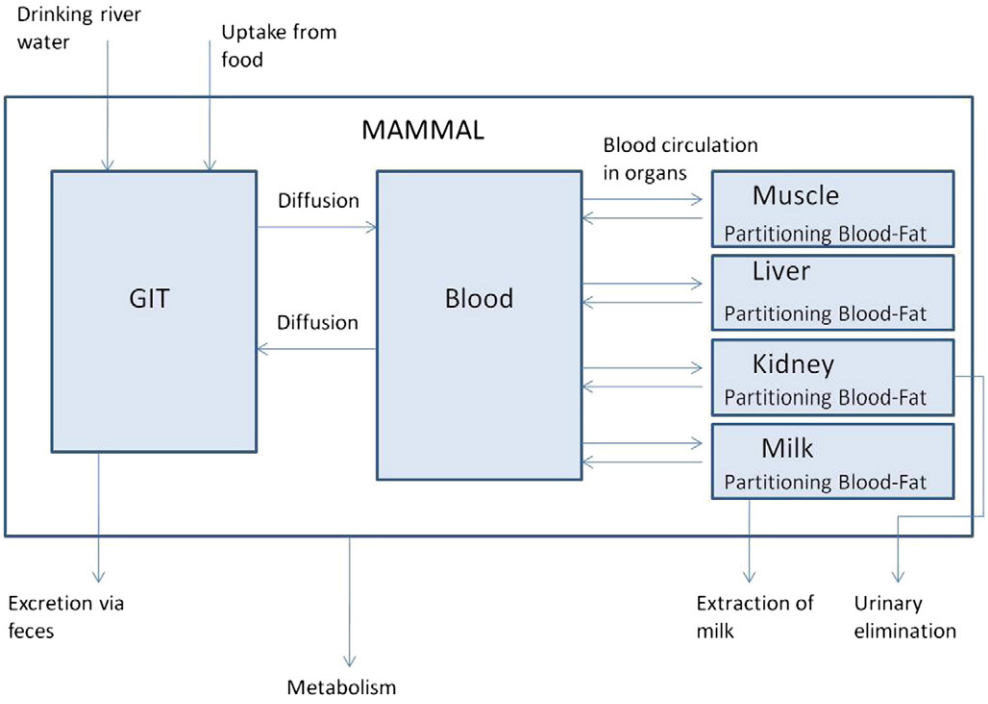


Fig. 5. Conceptual representation of the Mammals model available in the MERLIN-Expo library.

governed by two processes: the circulation of bloody fluids through organs which mainly depends on the perfusion rate of the tissues; once blood is circulating within the organ, the partition of chemicals between blood and fat contained in the organ that is represented by partition coefficients; (iii) the elimination of chemicals by growth, milk lactation, urinary excretion and/or metabolism. Elimination via biomass production occurs due to weight increase. Metabolism (or biotransformation) is defined as a change of the parent substance to another molecule or a conjugated form of the parent substance. The formation of metabolites can be represented by first-order processes or by non-first-order processes through a Michaelis-Menten approach. Urinary excretion is calculated considering the urine volume and the concentration of chemicals in kidneys. For milk compartment, the losses by outflux can be calculated considering the milk cattle lactation as sum of lipids and water in milk.

3.7. The Human model

The Human model is a physiologically based pharmacokinetic (PBPK) model that aims to describe the fate of chemicals in the human body. This model allows simulating the time evolution of the amounts or concentrations of chemical substances in the different organs or tissues of the body under various exposure conditions. Together with an exposure scenario, the Human model is able to predict internal dosimetry of the compound, in the form of either concentrations in target tissues that can be linked to the toxic effects, or biomarkers of exposure (as the concentrations in blood or urine) that are measured in human population in biomonitoring studies. These latter can then be compared to biomonitoring equivalents that are concentration of biomarker consistent with existing exposure guidance or reference values such as tolerable daily intakes.

The PBPK model implemented in MERLIN-Expo subdivides the body in 22 compartments representing organs connected through blood (Beaudouin et al., 2010). The main processes included in the Human model are (Fig. 6): (i) evolution of the anatomy and physiology over the lifetime of the individuals. The PBPK model accounts for the physiological or biochemical variations that arise throughout the growth and the development of an individual. Mathematical functions were

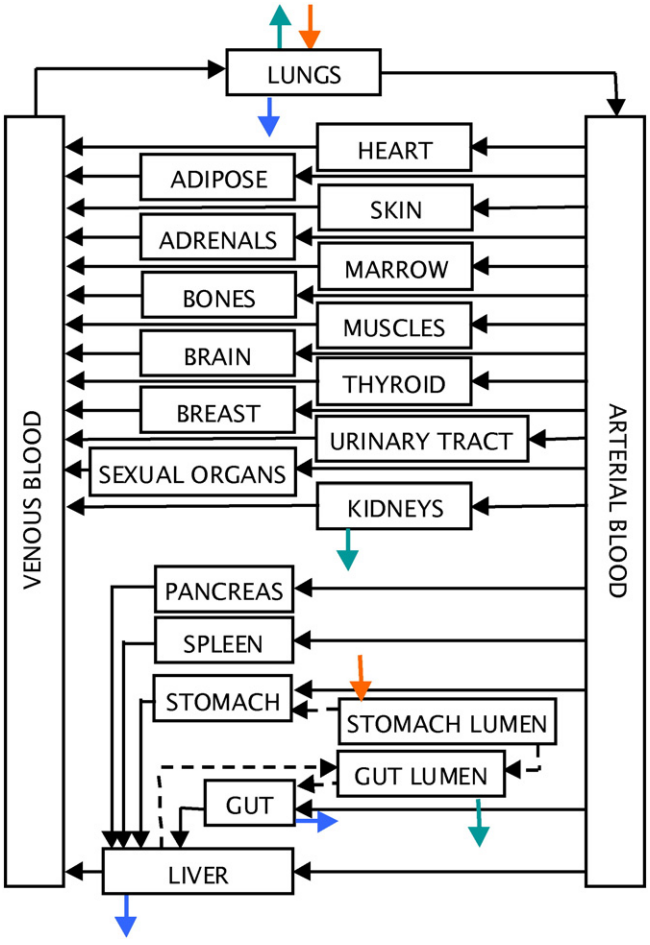


Fig. 6. Conceptual representation of the Human PBPK model available in the MERLIN-Expo library.

assigned to the model parameters that are known to vary during lifetime, as bodyweight, volumes and flows of organs, enzymatic capabilities…; (ii) absorption of the contaminants via inhalation. Gas exchanges (inhalation and exhalation of contaminant, oxygenation of blood…) were modeled in the alveolar space and were assumed to be very rapid. The alveolar space is located between the venous blood and the lungs modeled as an organ. A simple model describes gas exchanges based on a one-directional airflow in the region of gas exchange and a rapid equilibrium between lung air and blood in the alveoli (Reddy et al., 2005). A Blood-Air partition coefficient controls the uptake of the contaminant via inhalation; (iii) absorption by ingestion. The gastrointestinal tract was subdivided into the stomach and the guts. Each of these was divided into 2 compartments: the lumen (in which the contaminant enters) and the wall (linked to the systemic circulation). The exchanges between the lumen and the wall were modeled as a diffusion by a first order reaction dependent of the concentration of contaminant in the stomach or gut lumen. Alternatively, a direct input can be made in the liver; (iv) distribution of the compound in the body organs. Distribution refers to the reversible partitioning of a compound into the various tissues of the body from the systemic circulation. Each organ or tissue can receive different doses of the compound and the compound can remain in the organs or tissues for a varying amount of time. The compound can be moved from the plasma to the tissue until equilibrium is established. The distribution is assumed to be evenly and homogeneously throughout the compartment volume and to be limited by perfusion, i.e., the tissue membranes present no barrier to diffusion. Blood flow is then the limiting factor to distribution in the various organs or tissues. The extent of tissue distribution is controlled by a partition coefficient that is a measure of the compound's affinity to the tissue: (v) metabolism of the compound by enzymatic reactions. Metabolism is the irreversible transformation of a parent compound into metabolites by enzymatic reactions. Nearly all metabolic transformations result in more polar products than the parent compound to facilitate the removal from the organism (excretion in bile or urine). In our PBPK model, metabolism can occur in all compartments except in the gut and stomach lumen and in the alveolar space. Two equations are proposed to model metabolism either as a saturable (Michaelis-Menten equation) or a linear process (a first order reaction). The linear model assumes that the rate of metabolism is proportional to the change rate in the chemical concentration in the organ. The saturable Michaelis-Menten reaction implies that the reaction is essentially first order at low concentrations of the compound, and it approaches zero order after a certain high concentration; (iv) excretion of the compounds that refers to the removal of the compound and its metabolites from the body. As metabolism, excretion can occur in all organs/compartments except in the gut and stomach lumen and in the alveolar space and is described by a first-order reaction. This model assumes that the rate of excretion is proportional to the rate of change of the amount of the contaminant in the organ. Two specific excretion routes were also modeled: the biliary excretion and the excretion in feces. Contaminants excreted by bile enter in the gut lumen and can be reabsorbed.

4. Support for end-users

With such a wide-ranging scope of processes in MERLIN-Expo, it is likely that users will not have expertise in all scientific areas that are of interest to them. Therefore it was thought necessary to prepare standardized documentation and user support to facilitate accurate use of the tool by all users.

4.1. Documentation available for end-users

MERLIN-Expo has developed a comprehensive framework for documenting exposure models (see CEN CWA 16938) with the objective to provide clear and comprehensive information at the required level of detail to all users. The framework has been agreed in a workshop with representatives of regulatory authorities and potential users of the MERLIN-Expo tool (Ciffroy et al., 2016b–in this issue). The framework consists of (1) definitions of model components and terms used when modelling which are applied consistently throughout all model descriptions ensuring clarity and consistency; (2) a list of aspects that must be covered on each model in the documentation ensuring and exactly what information must be provided on each aspect ensuring full transparency; and (3) guidelines for the structure of the documentation that facilitates quick retrieval of the desired information thereby enabling ease of communication for all types of user groups. The proposed framework not only makes it easy to find unambiguous information, but also to compare alternative models and also facilitates the coupling of models. This documentation framework has been applied to the documentation of all the MERLIN-Expo models and can be freely consulted online http://merlin-expo.eu/learn/documentation/model-documentation/

The first section of the documentation always focuses on the purpose and applicability of the model to prevent abuse or misinterpretation of results. Other sections focus on the scientific background of the chosen model, and on numerical and mathematical information to be provided in a clear structure. Finally, a section on model evaluation is also recommended where data for verification are available.

4.2. Training online

The MERLIN-Expo website has a range of options for support with the software. These include a list of Frequently Asked Questions, a user forum, the documentation on the models themselves and training videos. The training videos cover key elements of the software. The user who follows all the videos through to the end will receive 3 introductory presentations (to cover the need for the tool, the interface for the tool and processes that are simulated); several presentations on the models (e.g. river, fish, fruit tree and human); and presentations based on examples. These presentations are available to view on http://merlin-expo.eu/learn/tutorials/ and have also been included in an online training programme where there is a quiz, additional background information, access to webinars and certification (http://www.opentea.eu/en/e-learning/courses-The-Future-of-Environmental-and-Human-Health-Exposure-Modelling-of-Chemicals.10/).

The MERLIN-Expo website will be maintained in the future by one of the 4FUN project partner (FACILIA) and will host the updated documentation and models.

4.3. Face-to-face training

During the development of the MERLIN-Expo tool, a set of training events was organized across Europe. These events lasted 1–2 days and covered practical use of the tool with realistic scenarios. Further events are planned to be held in 2016 and beyond in order to allow users to develop their use of the tool and discuss how the tool can be applied to individual research questions.

5. The MERLIN-Expo interface

The MERLIN-Expo user interface consists of a number of screens that are sequenced in the order they are meant to be used (even though the user can freely move between them).

One innovative feature of MERLIN-Expo is the decoupling of software developers from model developers. The sub-systems of the MERLIN-Expo library are created with the modelling software Ecolego (http://ecolego.facilia.se/ecolego/show/HomePage). The sub-system files are uploaded to a Subversion (http://merlin-expo.eu/) repository and are then automatically downloaded to the end-users' computers. By making the model developers independent of the programmers,

the model library can be updated without having to make new software releases. Also, MERLIN-Expo could survive without software developers.

We expect that many more models will be added to the MERLIN-Expo library. The user interface has been designed to fit any model that meets the following characteristics.

- It is packaged as an Ecolego sub-system, which means it can be connected to other sub-systems.
- It may be vectorised in some manner; by contaminants, spatially, by food type, etc.
- It may have inputs – such as constants or forcing variables – to be provided by the user.
- It produces some type of output data.

5.1. Flexible construction of an exposure scenario via the model library

The model library of MERLIN-Expo consists of a set of sub-systems that represent the different stages in the fate of chemicals from release to human exposure. Each sub-system is in itself a stand-alone model and has been verified and benchmarked against other similar models.

A sub-system has inputs (data that must be provided by the user), and outputs (calculation endpoints). For example, a plant sub-system could have "concentration in soil", "dry deposition" and "precipitation" as inputs and offer "concentration in fruit" as an output. When a user lacks data, another sub-system can provide it instead. For instance, "concentration in soil" could be provided by a Soil sub-system and "dry deposition" by an Atmosphere sub-system. By aggregating sub-systems in this fashion, a large model for a complex scenario can be assembled from simpler units.

The 'Model' screen (Fig. 7) is used to assemble a model by fetching and connecting sub-systems from the model library. A right click on the drawing panel gives access to the models library and the Auto-Connect option allows the user to quickly add and connect sub-systems; however, it is also easy to add connectors by dragging line between boxes and editing the connectors' inputs and outputs. This screen also allows the user to browse the model to see all equations and relationships between different model building blocks. The constructed scenario is then visualized as a classic diagram showing the sub-systems as boxes connected by arrows representing the interaction.

MERLIN-Expo also allows visualizing the model within an interaction matrix. In the Matrix view the sub-systems are arranged on the main diagonal of the matrix and the interactions (processes) are placed clockwise on the off-diagonal elements. The interaction matrix greatly facilitates construction of large and complex model.

The next step in the construction of the scenario is the definition of the context. The Context screen (Fig. 8) is located after the Model screen, as the model components determine which contaminants are available, which types of food can be included, or if it is possible to model for different individuals.

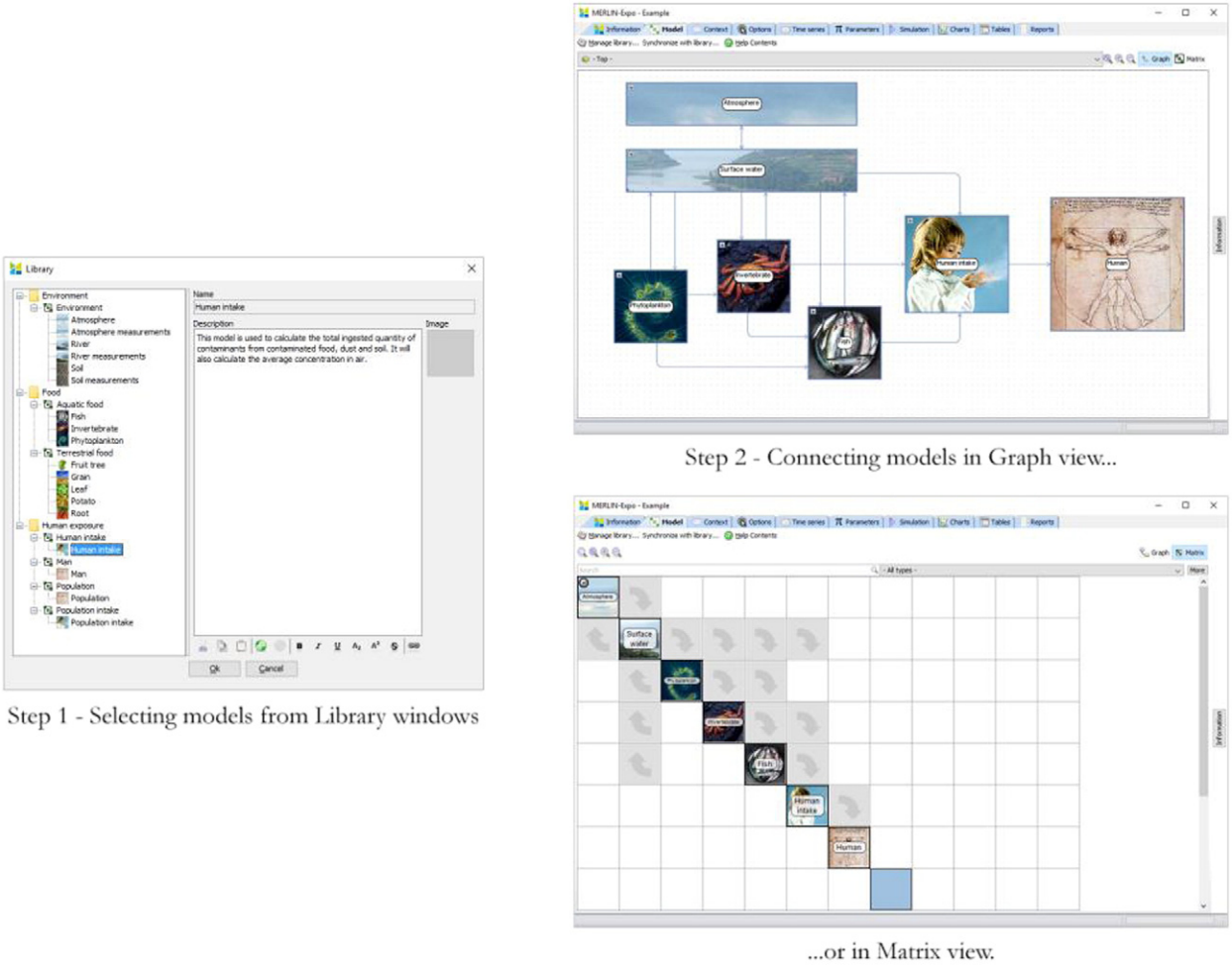
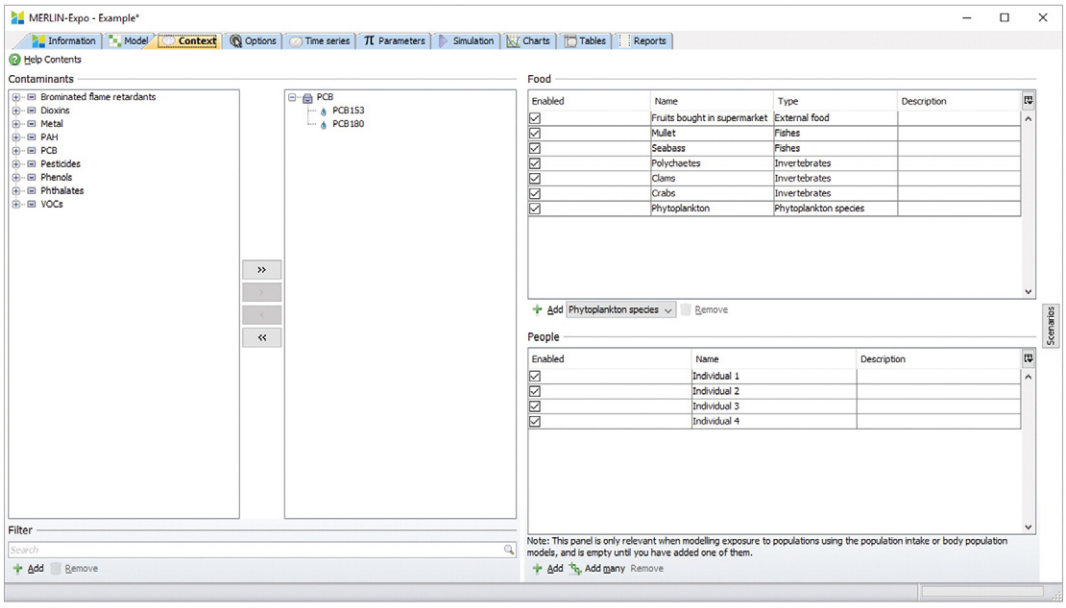


Fig. 7. Model screen in MERLIN-Expo.



Step 3 - Selecting chemicals, species/food items, and human individuals.

Fig. 8. Context screen in MERLIN-Expo.

5.2. Adapting parameter values and forcing variables for customer tailored scenario building

There are three screens for providing inputs to the model; options, time-series and parameters. When an item is selected, the right hand side of the screen will detail all information about the object and allow the user to enter or change data.

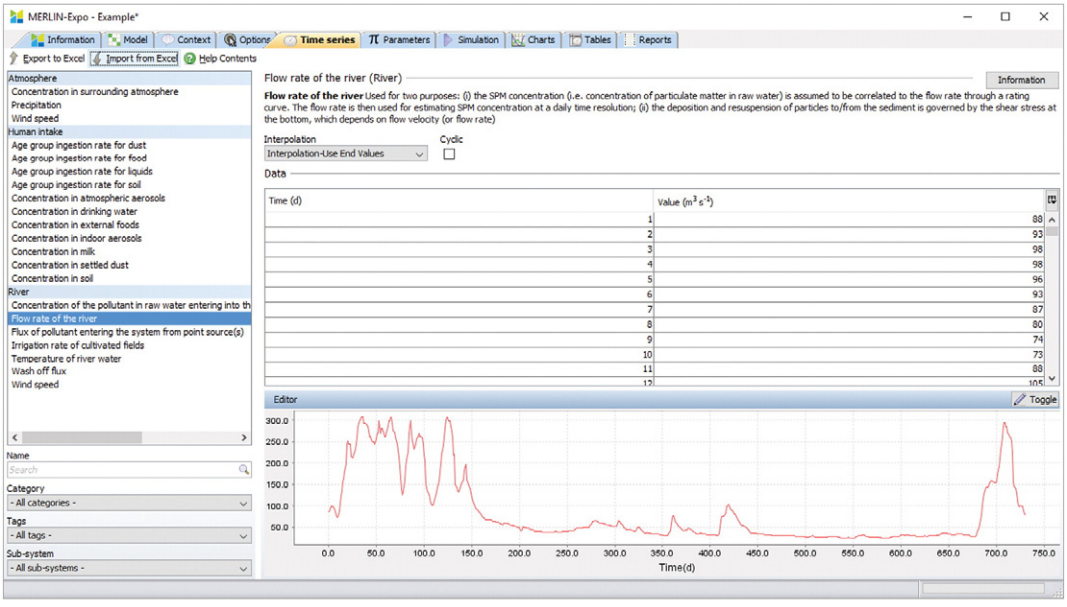
The option screen will present the user with a question and several alternatives to choose from. For instance, the Human model will ask – for each contaminant – if it attaches to red blood cells or not.

The time series screen (Fig. 9) will display a table where the user can enter (typically time dependent) data such for forcing variables such as meteorological data (e.g. precipitation, sunlight duration), concentrations for different media, age-dependent diet, etc.

The parameters screen (Fig. 10) displays all parameters that the model developer has made available to the user. Some parameters are specific to a given scenario and must be given by the user. The documentation of the models in the library often provides guidance on how to select values for parameters. A parameter can be assigned both a best estimate and a probability density function. MERLIN-Expo also contains a library of substances for which default values are provided and justified for each compound-specific parameter (e.g. partition coefficients).

5.3. Running a simulation and visualizing results

The simulation screen is used to set up and to run a simulation. This window also displays a list of errors that need to be dealt with before a



Step 4 - Entering forcing variables (e.g. meteorological data, chemical concentrations from point sources, etc).

Fig. 9. Time series screen in MERLIN-Expo.

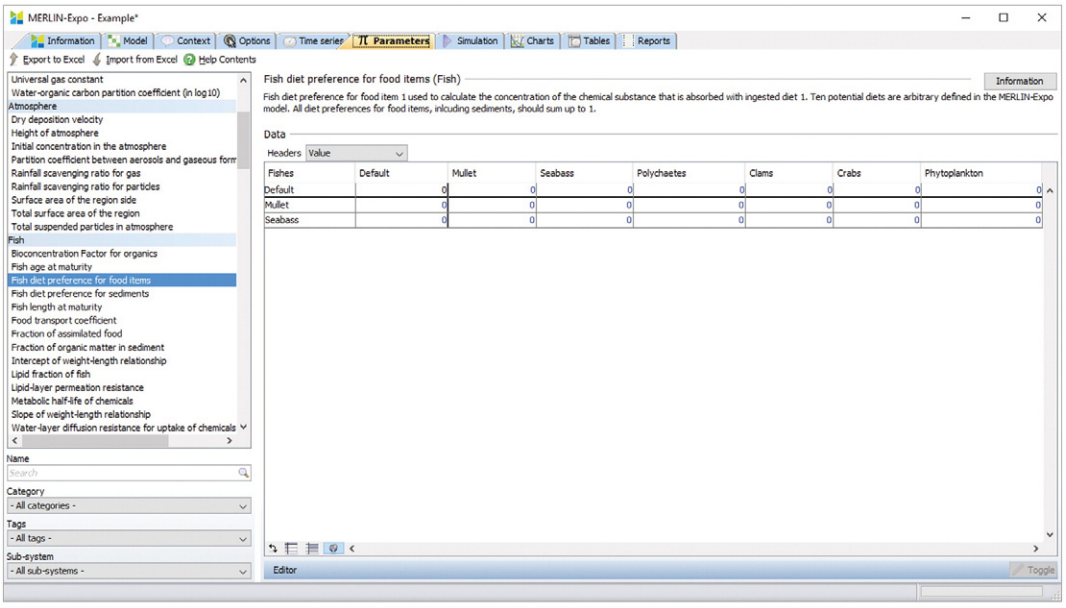


Fig. 10. Parameters screen in MERLIN-Expo.

simulation can be run and warnings that should be considered. Three types of simulations are available; deterministic (single run), probabilistic (Monte Carlo) and sensitivity analysis.

Within the charts and table screens the user is able to review the result of a simulation. The charts screen allows plotting simulation results. There are different sorts of charts available depending on the type of simulation that has been run. A chart is created by first selecting outputs in the list. MERLIN-Expo will attempt to create a chart which suites the selected output, but the user can also select the chart type in the toolbar. The tables screen lets create tables with data from simulation outputs. It is very similar to the charts screen. When running probabilistic simulation there are several types of tables that are dedicated to probabilistic results and sensitivity analysis. Depending on the type of simulation the user can select the table type in the toolbar.

5.4. Conducting an uncertainty analysis

An uncertainty analysis in MERLIN-Expo starts with identifying uncertain parameters. These parameters are assigned probability density functions that describe the knowledge the user has about each parameter value.

Many of the uncertain parameters in the MERLIN-Expo library have been given probability density functions (PDFs). The documentation of each model describes not only how the PDFs have been derived but also suggest how to proceed to improve the data of a site and how to derive PDFs for contaminants that are not included in the library.

MERLIN-Expo provides the user with a PDF editor which appears when clicking a cell in the table for which a PDF is required. From the Distribution functions drop-down list the user can choose a probability density function and the input fields will appear depending on the number of arguments required for the selected function. The Upper trunc and Lower trunc fields are always available and can be used to truncate the function. Lower trunc is often used to avoid negative values for parameters (e.g. in case of normal PDFs). An editor toolbar displays graphs and statistics of the current selected PDFs.

Once PDFs are selected for each of the uncertain parameters, the user defines the features of the simulation, i.e. (i) the number of random samples of parameter values that have to be generated. Two random generators are available, i.e. Monte Carlo and Latin Hypercube; (ii) the correlations between uncertain parameters, allowing to avoid the generation of irrelevant combination of parameter values; (iii) the endpoints to be studied in the uncertainty analysis.

MERLIN-Expo then runs simulations with all the parameters samples that were previously generated and provides summary statistics for describing the uncertainty of each selected endpoint.

5.5. Conducting a sensitivity analysis

The first steps in sensitivity analysis are common to those described for uncertainty analysis, i.e. definition and selection of PDFs for each of the uncertain parameters, generation of a random sample of parameter values (except for the Morris' approach), probabilistic simulation with each of the parameters sample previously generated. For some methods, the number of samples that have to be generated for producing a relevant sensitivity analysis is preselected by the software according to ad hoc requirements. Results can be analysed by a variety of approaches for providing summary statistics that measure the sensitivity of each parameter on the chosen endpoint:

- The Morris approach, which is a one-factor-at-a-time (OAT) screening design. The Morris method is qualitative, as it does not provide a decomposition of the output variance but instead provides a ranking of input parameters in order of importance. This method is considered global because the design intends to cover the entire space of the parameters and allows to identify parameters with (a) negligible effects (non-influential parameters), (b) linear and additive effects, or (c) non-linear effects or interactions with other parameters (Saltelli et al., 2008).
- Regression-based approaches. For monotonic and linear models, a regression between the selected output and the untransformed input parameters is calculated and several coefficients can used to control the quality of the regression (e.g. the determination coefficient). For monotonic but non linear models, the same analysis can be made after a rank transformation.
- Variance-based approaches, like Sobol, FAST and EFAST. These are variance-based methods, independent of any assumptions regarding the relationship (linearity or monotonicity) between input parameters and outputs. They provide the fraction of the output variance that is due to variation in each input parameter. These methods explore the entire range of variation of parameters, while the Morris

method applies only to several discrete values of the sampling space. This characteristic makes them more computationally expensive, but also more informative. Some methods (e.g. EFAST) can compute first order and total order sensitivity indices.

5.6. Editing a report

The report screen lets the user generate a report for the conducted assessment. Like with a webpage, the report uses links which allows the reader to navigate in the report. A MERLIN-Expo user can control what to include in the report by editing the report settings.

Once a report is generated, the user can save it as an html file (which can be opened in Microsoft Word or OpenOffice), or as an Adobe PDF file.

6. Key illustrative case studies (CS)

One of the objectives of the 4FUN project was to increase the confidence in the applicability of the MERLIN-Expo tool through targeted demonstration activities based on complex realistic case studies. In particular, we aimed at demonstrating the feasibility of building complex realistic exposure scenarios satisfying the needs of stakeholders, the accuracy of the modelling predictions through a comparison with actual measurements, and how uncertainty margins can improve risk governance. The case studies can be seen as reference cases that provide guidance to future users on how to apply the tool in different situations and how to interpret the results from the assessments with the tool taking into account relevant regulatory frameworks.

6.1. Integrating EEA and HEA (Venice)

MERLIN-Expo was applied and tested on a case study in the lagoon of Venice, with the aim of assessing ecological and human exposure to Persistent Organic Pollutants (POPs). The rationale of this case study was: i) to demonstrate the feasibility of performing integrated exposure assessment with MERLIN-Expo, that is, combining the evaluation of ecological and human exposure in the same assessment; ii) to test the capability of MERLIN-Expo to explore long term exposure scenarios (several decades, covering an entire human life), needed to realistically reconstruct historical exposure to persistent, bioaccumulating chemicals; iii) to demonstrate the capability of the tool to approximate real biota and human biomonitoring data, providing useful information on modelling performance.

Specifically, the study aimed at simulating the bioaccumulation of some PCBs and dioxins in target aquatic species, as well as reconstructing human internal exposure associated to the consumption of local fish and seafood from the lagoon. The lagoon of Venice was seriously impacted by pollutant emissions, mainly from Porto Marghera industrial area (Bellucci et al., 2000), and lagoon sediment keeps a trace of historical contamination and still represents a secondary source of POPs and a potential hazard to ecosystems and human health (Dalla Valle et al., 2003; Micheletti et al., 2007). The implementation in MERLIN-Expo library of three new models, namely Phytoplankton, Invertebrate and Fish models, allowed to build a rather complex aquatic food web, including 15 different species, representative of Venice lagoon ecosystem. Past concentration trends of selected PCBs and dioxins in sediment and water were reconstructed from dated sediment cores (Frignani et al., 2005) and used as inputs to simulate for several decades (from 1930's to 1990's) the accumulation of chemicals in individual species, including the trophic transfer along the food chain (considering prey-predator relationships). Then, simulated concentrations in edible species (such as clam, crab, mullet, goby and seabass) together with daily fish/seafood dietary intakes for Venice municipality (Pedenzini, 1996) were used to calculate lifetime daily intake of target chemicals (Human Intake model) and internal concentrations in blood (Man PBPK model) for local population, considering the whole life of each individual.

Model results were evaluated against available monitoring data to assess model reliability and its applicability to complex exposure scenario. In particular, evaluation was performed for the end of the 1990's, using chemical concentrations measured in five aquatic species (data from Venice Water Authority, 2000) and data of chemical concentrations in blood serum for men living in Venice municipality (Raccanelli et al., 2007). Detailed results and discussion are presented in Giubilato et al. (in this issue).

6.2. Reconstruction of human biomonitoring (Belgium)

The rationale of this CS was: (i) to demonstrate the extent of the applicability domain of MERLIN-Expo models. While most CSs focused on organic chemicals, the Belgium CS dealt with inorganic chemicals (metals); (ii) to show the flexibility of complex scenario building, including both direct and indirect exposures for several individuals; (iii) to demonstrate the capability of MERLIN-Expo to reconstruct human biomonitoring data, thus providing information on model performance.

Then, human exposure to lead (Pb) and arsenic (As) has been studied in a site-specific residential setting. Both direct exposure through ingestion and/or inhalation of soil, dust, and air particulate matter and indirect exposure via consumption of home-grown vegetables and purchased food stuff, were included in the scenario and the associated conceptual exposure model. Apart from showing the flexible use of the tool and a first verification of the model performance as compared to real-world measurement data the intent of these case studies was also to make the required model adjustments so as to be able to accommodate site-specific exposure assessment at an aggregated population level, i.e. exposure assessment of a large number of participants each showing individual time-activity patterns (e.g. moving between areas with varying levels of inorganics in the environmental media) and each showing different consumption patterns (both with respect to the quantity and variety of purchased food items as to the consumption of locally grown vegetables and/or ground water). Input data on Pb and As in environment matrices as well as concentrations of Pb and As in blood of preschool children and urine in adults, respectively, were obtained from a large monitoring campaign conducted between 2006 and 2008 in the Northern Campine region of Belgium with a long history of polluting zinc smelting industry, most of which has been closed down or has been modernised, but leaving a trail of historical heavy metal pollution, mainly in soil and dust (Van Deun et al., 2008a, 2008b; Van Holderbeke et al., 2008; Vlaamse Overheid, 2008). The monitoring campaign entailed exposure assessment of 337 preschool children (2–6 years old) and 1220 adults (19–79 years old) living at varying distances of the former industrial hot spots as compared to individuals living in a reference area (Vlaamse Overheid, 2008). Questionnaires on time-activity and consumption of food items allowed to further differentiate between individuals. In order to gain confidence in the model performance several scenarios were built and simulated varying from very simple to rather complex (i.e. deterministic vs. probabilistic, with vs. without considering local food consumption, population vs. individual level, etc.). Results on the comparison of model predictions with the actual measurement data and the contribution of the different exposure pathways to the final external and internal exposure as identified via sensitivity analysis are discussed in more detail in this issue (Fierens et al., in this issue; Van Holderbeke et al., in this issue).

6.3. Investigating emergent chemicals (Spain)

This CS focuses on the perfluorinated compounds (PFOA-Perfluorooctanoic acid and PFOS-Perfluorooctanesulfonic acid) in the Ebro River basin. Its main objective is to estimate the environmental exposure of the PFC compounds that are present in water, sediments and

fish using the MERLIN-Expo model. Monitoring data were provided from the European project AQUATERRA in different zones along the Ebro River basin (4 sampling campaigns), and the spanish project Consolider-Ingenio 2010 CSD2009–00,065 Scarce (2 sampling campaigns). Forcing variables required for the simulations (e.g. daily flow measurements, irrigation, water temperature and point sources) were provided by the national water authority.

The River model provides an estimation of the time-dependent concentration of the targeted contaminant(s) in raw water, filtered water and bottom sediments. This/these output(s) can be used for evaluating the risk to exceed Environmental Quality Standards (EQS) for individual pollutants defined by the European Water Framework Directive. EQS for the PFOS was established for inland surface waters (EQS $= 6.5 * 10^{-4}$ μg/L) and for biota (9.1 μg/kg wet weight). The environmental regulations still needs to be established for the PFOA. PFCs represent an example of emerging contaminants for which the MERLIN-Expo could be used in future for policy making.

Simulated Predicted Environmental Concentrations (PECs) were compared to monitoring data in river stretches (Oca, Miranda de Ebro and Tudela) where the data set was complete (i.e. concentrations in upstream river stretch, sediments and two fish species Cypsinus Carpio and *Barbus Graellsii*). Simulated PECs for PFOA and PFOS were found to be in the same order of magnitude as Measured Environmental Concentrations (MECs) in river water for two stretches (Oca and Miranda del Ebro), while they overestimate MECs for the third stretch (Tudela). Deterministic simulation in fish and sediments showed a good agreement between simulated PECs and MECs for all river stretches. Monte Carlo probabilistic simulations and sensitivity analysis were performed. Sensitivity analysis showed the percentage of how much a certain parameter influences the entire process of modelling. Detailed results and discussion are presented in Banjac et al. (in progress).

7. Conclusion

MERLIN-Expo was developed in the frame of the 4FUN European project in order to tackle new challenges in exposure modelling, i.e. (i) the combination of multimedia models simulating the fate of chemicals in environmental media, and of PBPK models simulating the fate of chemicals in human body, in the perspective of calculating internal effective concentrations; (ii) the integration of a wide set of functionalities for uncertainty and sensitivity analysis; (iii) the integration of human and wildlife biota targets for both environmental and human exposure assessments. In collaboration with CEN, a specific effort was dedicated to the standardization of documentation, guaranteeing a comprehensive and transparent access to all the material required for deeply understanding and running models. The main features and capabilities of the MERLIN-Expo user interface are presented in this paper, which was designed to be easy-to-use, easy-to-understand, flexible and difficult-to-abuse.

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