4FUN

"The FUture of FUlly integrated human exposure assessment of chemicals: Ensuring the long-term viability and technology transfer of the EU-FUNded 2-FUN tools as standardised solution"

Grant agreement No.: 308440 (Collaborative Project)

Deliverable 4.4: Standard documentation describing the 2-FUN tool: model documentation based on defined standard protocol

Due date of deliverable: 31 September 2015
Actual submission date: 30 October 2015

Start date of project: 1st October 2012 Duration: 36 months

Coordinator	AEIFORIA
Deliverable Leading Partner	EDF
Contributing Partners	FACILIA, INERIS, ASI
Task	4.3: Standard documentation
Revision	

Project co-funded by the European Commission under the Seventh Framework Programme (FP7)		
Dissemination Level		
PU	Public	X
PP	Restricted to other programme participants (including the Commission Services)	
RE	Restricted to a group specified by the consortium (including the Commission Services)	
CO	Confidential, only for members of the consortium (including the Commission Services)	

Table of Contents

1 Introduction

The MERLIN-Expo (**M**odelling **E**xposure to chemicals for **R**isk assessment: a comprehensive **L**ibrary of multimedia and PBPK models for **I**ntegration, Prediction, u**N**certainty and Sensitivity analysis) tool was developed under the seventh Framework Program of the European Union (grant agreement n° 308440) within the 4FUN project (The FUture of FUlly integrated human exposure assessment of chemicals: Ensuring the long-term viability and technology transfer of the EU-FUNded 2-FUN tools as standardised solution). MERLIN-Expo aims to provide decision-makers with state of the art tools to analyse the current and future trends in environmental conditions and pressures that may lead to health problems. Its main objective is to support the evaluation and ranking of management options through a range of functionalities able to generate outputs of high concern for health risk assessment: building of long-term environmental and socio-economic scenarios, exposure assessment, provision of uncertainty margins, and identification of sensitive pathways and risks. The MERLIN-Expo multimedia modelling tool allows the user to assemble several models for a specific scenario, to enter input data and parameter values for selected contaminants and finally to run deterministic (best or worst-case estimate) or probabilistic (Monte Carlo) simulations.

MERLIN-Expo is based on a library of models for exposure assessment, coupling environmental multimedia and pharmacokinetic models. One of the objectives of the 4FUN project was to provide standard documentation for each of the models included in the library, guaranteeing their transparency and the long-term technical viability of the tool. Contrary to analytical 'simple' models, the multimedia and PBPK models that are included in the MERLIN-Expo library involve a large set of entities, i.e. a large set of compartments, state variables, forcing variables, parameters, equations, variables, and several regulatory outputs. They are then difficult to communicate in a comprehensive, unambiguous and accessible way. This situation could be shared with other complex models, but despite this background, it can be observed that no standard documentation protocol has been followed so far for describing large multimedia and/or PBPK models. In the 4FUN project, transparency was identified as a key criterion for evaluating models included in the MERLIN-Expo tool. In this context, an action was undertaken in the frame of the project in coordination with CEN (European Committee for Standardisation) to propose a standard documentation protocol (SDP) for exposure models. The SDP can be defined as a generic format and a standard structure by which all MM models could be documented. The main benefits that were expected from a SDP are: the promotion of a more rigorous formulation of models as the SDP intends to provide a comprehensive checklist covering the key features of a given model; a better communication of the theoretical background and assumptions of the model; an unambiguous use and reproduction of models by the end-users who are not originally involved in the development of models.

This deliverable intends to briefly describe the process followed for defining the SDP.

Documentation of all exposure models on the MERLIN-Expo platform is written according to this SDP. As documentation is comprehensive, it may contain several tens of pages for each model. Documentation of the MERLIN-Expo models then not provided in this summary report. Nevertheless, this report provides a brief summary of the models that were incorporated in the library available in the MERLIN-Expo tool.

2 The standardisation process

This section describes the process that was followed in the frame of the 4FUN project for defining a standard for exposure model documentation.

2.1 Literature review

To start, literature dealing with the documentation of exposure models as well other complex models was collected and reviewed. In particular, we reviewed documents that were used as a resource and reference material for the development of a more general and broadly applicable standard documentation framework for large exposure models, i.e.

- the ‘Guidance on the development, evaluation and application of environmental models’ by US EPA (US-EPA, 2009) related to the process of creating modeling tools for environmental regulatory modeling. The guidance lists recommended elements for environmental model documentation, in particular for the communication of ‘Problem identification and specifications’ and ‘Model development’ issues’;
- Several publications by Grimm et al. (Grimm and Railsback, 2005, Grimm et al, 2006 and Grimm et al, 2010) on the ‘Overview, Design concepts, and Details’ (ODD) framework for the documentation of ecological models. Grimm and Railsback (2005) initially proposed the basic idea of a standard protocol for explaining simulation models used in ecological field. The proposed standard protocol was developed and tested by 28 modelers who cover a wide range of fields with ecology. However, the ODD framework was developed to be applied for modelling of ecological systems, which contains aspects not relevant for multimedia models while missing others that would be relevant;
- a report on ‘Development and application of models of chemical fate’ published by the Canadian Environmental Modelling Network (CEMN) (Canadian Environmental Modelling Network, 2005) to support the novice model-user in understanding when, why, and how to use models of chemical fate in the environment;
- the Guidance document on the validation of quantitative structure-activity relationship (QSAR) models by OECD (OECD, 2007) that covers the majority of aspects related to a standard documentation framework for statistical QSAR models;
- research work performed by Bilitewski et al. (2013) that describes nine complex environmental models and evaluates them by predefined principal characteristics;
- the CEN/TR 16364 that provides a concrete standardized modelling procedure relying on a software tool. However, it is applicable only to a very small area, the migration of organic substances into water;
- the WHO report “Harmonisation Project Document No. 3: Principles of characterizing and applying human exposure models” that contains collective views of an international group of experts and provides clear and structured recommendations for characterizing exposure models. It is however focusing on human exposure and does not consider aspects for environmental multimedia models.

In order to define the exact structure and sub-elements to propose for standardized documentation framework, in addition to the literature search, a review on currently existing large environmental models and on their documentation was carried out. This review allowed to identify the main flaws in existing practice.

2.2 The CEN approach for standardisation

The approach taken by the 4FUN project was to build up on existing knowledge to cover the needs of wider chemical exposure models community by suggesting a structured documentation framework that would provide necessary model information at different levels of complexity. From the literature review presented above, the specifications that were expected for a user-focused SDP applicable to exposure models were detailed and allowed to propose a first version of the SDP.

In order to widely share views on exposure models documentation, to integrate the perspectives and requirements of several stakeholders in the construction of a consensus-based SDP, the 4FUN project set up a CEN workshop. The initial SDP that was built by 4FUN partners was provided as a basis for workshop opened to all interested parties, along with the sample documentation of the first documented models from the MERLIN-Expo tool. The CEN workshop was publicly advertised and also communicated to CEN technical committees dealing with chemicals, inviting participation specifically from public administrators and regulators dealing with risk assessment and chemicals; from producers of chemicals/manufacturers using chemicals.

In a first step, the MERLIN-Expo standard documentation framework was transferred into the standard format foreseen by CEN for European standards, including a clear definition of the scope and applicability of the standard and a section on terms and definition to be used consistently throughout. The body of the text of the framework was changed from descriptive to prescriptive, rephrasing the text to contain requirements and recommendations rather than descriptions or rationales. The latter renders a standard easy to use by giving clear instructions.

At the core of the workshop process to deliver the workshop agreement were cycles of reviews and comments by participants of the workshop until a general consensus had been reached on a draft text. Important new perspectives have been integrated from participants from outside the 4FUN project, from the point of view of consumer exposure models and worker exposure models.

The draft workshop agreement was then submitted to a public review, inviting comments from anyone outside the workshop. After giving full consideration to the comments received from public review, the workshop agreement was formally accepted on by the participants of the workshop. On this basis, the workshop could then develop a consensus-based SDP for exposure models.

This CEN Workshop Agreement (CWA) (CWA n. 16938 – available on web pages of national members of the CEN) establishes terms and definitions for exposure models and their elements, specifies minimum requirements for the amount and type of information to be documented on exposure models, and proposes a structure for communicating the documentation to different users.

3 Models of the MERLIN-Expo library

All the models that were included in the MERLIN-Expo library are described according the CEN standard previously indicated. The complete description of the models can be found on the MERLIN-Expo webpage (http://merlin-expo.eu/learn/documentation/). This section lists all the models that are 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.

3.1 The River model

- Goal: to dynamically simulate the distribution of organic contaminants and metals in abiotic media (i.e. water, suspended particulate matter and sediments) of river systems;
- Potential decision and regulatory frameworks:
  - ✓ to provide an estimation of the time-dependent concentration of the targeted contaminant(s) in raw water or filtered water. This/these output(s) can be used for evaluating the risk to exceed a given regulatory threshold for environmental risk (e.g. Predicted Non Effect Concentration (PNECs), Environmental Quality Standards (EQS) for individual pollutants defined by the European Water Framework Directive);
  - ✓ to provide an estimation of the time-dependent concentration of the targeted contaminant(s) in bottom sediments. This output can be used for evaluating the risk to exceed a given regulatory threshold for environmental risk dedicated to benthic organisms (e.g. Predicted Non Effect Concentration (PNECs), Environmental Quality Standards (EQS) for individual pollutants defined by the European Water Framework Directive);
  - ✓ to provide an estimation of the time-dependent concentration of the targeted contaminant(s) in drinking water. This output can be used for evaluating the risk to exceed a given regulatory threshold for human health or to provide an input for PBPK models;
  - ✓ to provide an estimation of contaminant inputs onto soils and plant leaves originating from irrigation practices;
- Main processes:
  - ✓ Simulation of the Suspended Particulate Matter (SPM) concentration by a rating curve relationship relating the flow rate of the river and SPM;
  - ✓ Sorption/desorption between water and SPM;
  - ✓ Deposition of particulate contaminants to bed sediments;
  - ✓ Resuspension of particulate contaminants from bed sediments;
  - ✓ Diffusion between water and sediment pore water;
  - ✓ Diffusion between water and atmosphere;
  - ✓ Degradation.

3.2 The Soil model

- Goal: to dynamically simulate the distribution of organic contaminants and metals in abiotic media (i.e. soil particles, pore water) of soil systems, with a description of their depth profile in the root zone;

- Potential decision and regulatory frameworks:
    - ✓ to provide an estimation of the time-dependent concentration of the targeted contaminant(s) in total soil and/or soil pore water over a given depth. This/these output(s) can be used for evaluating the risk to exceed a given regulatory threshold for environmental risk (e.g. Predicted Non Effect Concentration (PNECs), Environmental Quality Standards (EQS) for individual pollutants defined by the European Soil Directive(s));
    - ✓ to provide an estimation of the time-dependent concentration of the targeted contaminant(s) in the soil profile. This output can be used for evaluating the residence time of contaminant(s) in soil and the risk over time to exceed a given regulatory threshold for environmental risk dedicated to soil organisms (e.g. Predicted Non Effect Concentration (PNECs), Environmental Quality Standards (EQS) for individual pollutants defined by the European Soil Directive(s));
    - ✓ to provide an estimation of contaminant inputs into plant crops originating from root uptake;
    - ✓ to provide an estimation of contaminants emitted from soils to the atmosphere (especially relevant for contaminants directly deposited onto soil and able to reach atmosphere through volatilization);
    - ✓ to provide an estimation of the time-dependent concentration of the targeted contaminant(s) in soil available for e.g. pica children. This output can be used for evaluating the risk to exceed a given regulatory threshold for human health or to provide an input for PBPK models.

  Main processes:
    - ✓ Sorption/desorption between pore water and soil particles;
    - ✓ Evapotranspiration;
    - ✓ Water mass balance in soil and loss by infiltration;
    - ✓ Retardation factor and advection within soil;
    - ✓ Diffusion between water and atmosphere;
    - ✓ Bioturbation;
    - ✓ Diffusion within soil;
    - ✓ Wash-off from soils to river;
    - ✓ Degradation.

3.3 The Fruit model

- Goal: to estimate the time-dependent accumulation (in mass and concentration bases) of organic/metals in the edible part in fruits at harvest;
- Potential decision and regulatory frameworks: Coupled with the information about the ingestion rate of fruit crops (kg fresh weight d^{-1}), the fruit model can estimate the human exposure to organic substances/metals through the ingestion of fruit crops. This output can be used for evaluating the risk to exceed regulatory thresholds for human health or used as an input for PBPK models.
- Main processes:
    - ✓ Sorption/desorption between pore water and soil particles;
    - ✓ Partition between concentrations in roots and in water (xylem water), and concentrations in fruits and in water;
    - ✓ Xylem influx from soil to root driven by plant transpiration;
    - ✓ Xylem outflux from root to fruit driven by plant transpiration;

- ✓ Phloem outflux from leaves to fruit driven by fruit growth;
- ✓ Diffusion between fruit and air;
- ✓ Dry and wet deposition from air to fruits;
- ✓ Degradation in roots and fruits;
- ✓ Root uptake (for metals).

3.4 The Root model

- Goal: to estimate the time-dependent accumulation (in mass and concentration bases) of organic/metals in the edible part in root (e.g. carrots) at harvest;
- Potential decision and regulatory frameworks: Coupled with the information about the ingestion rate of root crops (kg fresh weight d^{-1}), the root model can estimate the human exposure to organic substances/metals through the ingestion of root crops. This output can be used for evaluating the risk to exceed regulatory thresholds for human health or used as an input for PBPK models.
- Main processes:
  - ✓ Sorption/desorption between pore water and soil particles;
  - ✓ Partition between concentrations in roots and in water (xylem water);
  - ✓ Xylem influx from soil to root driven by plant transpiration;
  - ✓ Degradation in roots;
  - ✓ Root uptake (for metals).

3.5 The Leaf and Grass models

- Goal: to estimate the time-dependent accumulation (in mass and concentration bases) of organic/metals in the edible part in leafy crops (e.g. salads) at harvest;
- Potential decision and regulatory frameworks: Coupled with the information about the ingestion rate of leafy crops (kg fresh weight d^{-1}), the leafy model can estimate the human exposure to organic substances/metals through the ingestion of leafy crops. This output can be used for evaluating the risk to exceed regulatory thresholds for human health or used as an input for PBPK models.
- Main processes:
  - ✓ Sorption/desorption between pore water and soil particles;
  - ✓ Partition between concentrations in roots and in water (xylem water), and concentrations in leaves and in water;
  - ✓ Xylem influx from soil to root driven by plant transpiration;
  - ✓ Xylem outflux from root to leaves driven by plant transpiration;
  - ✓ Diffusion between leaves and air;
  - ✓ Dry and wet deposition from air to leaves;
  - ✓ Degradation in roots and leaves;
  - ✓ Root uptake (for metals).

3.6 The Grain model

- Goal: to estimate the time-dependent accumulation (in mass and concentration bases) of organic/metals in the edible part in grain (e.g. wheat) at harvest;
- Potential decision and regulatory frameworks: Coupled with the information about the ingestion rate of grain crops (kg fresh weight d^{-1}), the grain model can estimate the human exposure to organic substances/metals through the ingestion of grain crops.

This output can be used for evaluating the risk to exceed regulatory thresholds for human health or used as an input for PBPK models.

- Main processes:
  - ✓ Sorption/desorption between pore water and soil particles;
  - ✓ Partition between concentrations in roots and in water (xylem water), and concentrations in grain and in water;
  - ✓ Xylem influx from soil to root driven by plant transpiration;
  - ✓ Xylem outflux from root to grain driven by plant transpiration;
  - ✓ Phloem outflux from leaves to grain driven by fruit growth;
  - ✓ Diffusion between grain and air;
  - ✓ Dry and wet deposition from air to grain;
  - ✓ Degradation in roots and grain;
  - ✓ Root uptake (for metals).

3.7 The Tuber model

- Goal: to estimate the time-dependent accumulation (in mass and concentration bases) of organic/metals in the edible part in tubers (e.g. potatoes) at harvest;
- Potential decision and regulatory frameworks: Coupled with the information about the ingestion rate of tubers crops (kg fresh weight d^{-1}), the tubers model can estimate the human exposure to organic substances/metals through the ingestion of tubers crops. This output can be used for evaluating the risk to exceed regulatory thresholds for human health or used as an input for PBPK models.
- Main processes:
  - ✓ Sorption/desorption between pore water and soil particles;
  - ✓ Partition between concentrations in tubers and in water;
  - ✓ Diffusion from soil to tubers driven by concentration gradient;
  - ✓ Degradation in tubers;
  - ✓ Root uptake (for metals).

3.8 The Fish model

- Goal: to estimate the time-dependent accumulation (in mass and concentration bases) of organic/metals in the edible part in fish at fishing time;
- Potential decision and regulatory frameworks:
  - ✓ to provide an estimation of the time-dependent concentration of the targeted contaminant(s) in fish. 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 fish for individual pollutants);
  - ✓ to provide an estimation of the time-dependent concentration of the targeted contaminant(s) in fish available for food ingestion. This output can be used for evaluating the risk to exceed a given regulatory threshold for human health (e.g. daily Reference Dose) or to provide an input for PBPK models.
- Main processes:
  - ✓ Respiratory uptake of chemicals;
  - ✓ Dietary uptake of chemicals;
  - ✓ Respiratory elimination of chemicals;
  - ✓ Dietary elimination of chemicals;
  - ✓ Elimination of contaminants through biomass production;
  - ✓ Metabolic biotransformation.

3.9 The Invertebrates model

- Goal: to estimate the time-dependent accumulation (in mass and concentration bases) of organic/metals in invertebrates living in water ;
- Potential decision and regulatory frameworks: to provide an estimation of the time-dependent concentration of the targeted contaminant(s) in invertebrates. 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 invertebrates for individual pollutants);
- Main processes:
  - ✓ Respiratory uptake of chemicals;
  - ✓ Dietary uptake of chemicals;
  - ✓ Respiratory elimination of chemicals;
  - ✓ Dietary elimination of chemicals;
  - ✓ Elimination of contaminants through biomass production;
  - ✓ Metabolic biotransformation.

3.10 The Phytoplankton model

- Goal: to estimate the time-dependent accumulation (in mass and concentration bases) of organic/metals in phytoplankton ;
- Potential decision and regulatory frameworks: to provide an estimation of the time-dependent concentration of the targeted contaminant(s) in phytoplankton. 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 phytoplankton for individual pollutants);
- Main processes:
  - ✓ Respiratory uptake of chemicals;
  - ✓ Respiratory elimination of chemicals;
  - ✓ Elimination of contaminants through biomass production;
  - ✓ Metabolic biotransformation.

3.11 The Mammals model

- Goal: to estimate the time-dependent accumulation (in mass and concentration bases) of organic/metals in mammals meat and milk ;
- Potential decision and regulatory frameworks: to provide an estimation of the time-dependent concentration of the targeted contaminant(s) in meat and milk available for food ingestion. This output can be used for evaluating the risk to exceed a given regulatory threshold for human health (e.g. daily Reference Dose) or to provide an input for PBPK models
- Main processes:
  - ✓ Dietary uptake/elimination of chemicals;
  - ✓ Water uptake/elimination of chemicals;
  - ✓ Soil uptake/elimination of chemicals;
  - ✓ Milk elimination;
  - ✓ Diffusion between the gastro-intestinal tract and blood;

- ✓ Blood circulation and partition between blood and target organs (muscle, liver, kidney, milk);
- ✓ Metabolic biotransformation.

3.12 The Human intake model

- Goal: to dynamically simulate the intake of organic contaminants and metals by humans from intentional ingestion of drinking water, crops and animal products, non intentional ingestion of dust and soil particles (for pica children) and inhalation of air contaminants ;
- Potential decision and regulatory frameworks: to estimate the time-dependent intake of the targeted contaminant(s) by humans. This/these output(s) can be used for evaluating the risk to exceed a given regulatory threshold for human health risk (e.g. Reference Dose) or to provide an input for PBPK models;
- Main processes:
  - ✓ Dietary uptake of food by humans of different age classes.

3.13 The PBPK model

- Goal: to simulate the toxicokinetics of contaminants in humans, i.e. the amounts or concentrations in different organs/tissues, under various exposure conditions;
- Potential decision and regulatory frameworks:
  - ✓ Simulation of the internal kinetics of the targeted contaminant(s) in several tissues/organs of the human body;
  - ✓ Computation of toxicokinetic properties in each compartment (e.g. the maximal concentration C_{max}, the time at maximal concentration T_{max});
  - ✓ Prediction of the amount of contaminant that will be excreted or/and metabolised;
  - ✓ Thes outputs can be used for evaluating the risk to exceed a given regulatory threshold for human health (e.g. Equivalent Biomonitoring Reference Doses).
- Main processes:
  - ✓ Growth of human individuals influencing anatomy, physiology and metabolism, and thus PBPK parameters;
  - ✓ Absorption by inhalation (i.e. route of administration: absorption in the lung tissues);
  - ✓ Absorption by ingestion (i.e. route of administration: oral absorption and transport to the gastrointestinal tract);
  - ✓ Distribution of chemicals among organs (i.e. partitioning of a compound into the various tissues of the body from the systemic circulation);
  - ✓ Metabolism (i.e. irreversible transformation of a parent compound into metabolites by enzymatic reactions);
  - ✓ Excretion (i.e. removal of the compound and its metabolites from the body, occuring predominantly via the kidneys in urine).

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