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Concawe workshop report “PAH integrated exposure modelling”

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Prepared for the Concawe Health Management Group’s Special Task Force on Exposure Assessment (STF-29).

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ABSTRACT

This report summarizes the discussions held during the "Polycyclic Aromatic Hydrocarbons (PAHs) integrated exposure modelling" 2-day workshop organized by the Flemish Institute for technological research (VITO) together with Concawe on 8 - 9th October 2015 at Concawe in Brussels.

Currently, Concawe aims to address the challenge of assessing the contribution of Petroleum Substances (PS) to aggregated PAH exposure. In this context, there is an opportunity to identify integrated multi-source, multi-route (MSMR) exposure model(s) suitable for characterising exposure to PAHs including those that may derive from PS. The ultimate goal is to have a reliable, validated, integrated source-to-receptor PAH exposure modelling tool capable of generating realistic predictions of PAH exposure, which enables the determination of the relative proportion of PAHs exposures over different routes and sources (and which also extends beyond petroleum sources).

The overall aim of the workshop was to explore whether (and which of the) existing MSMR models meet the goal outlined above, and to identify databases (such as PAH monitoring in air, food and biomonitoring) that could be used to support and verify model predictions. The focus of the workshop was general population exposure modelling tools (including consumer exposure and indirect exposure via the environment).

This workshop report aims to reflect 1) the interaction and discussion between model developers and other workshop participants from a model user perspective, 2) the discussion on the potential bottlenecks and gaps when applying the models for PS scenarios, and 3) the way forward when using MSMR modelling in addressing Concawe's challenge to assess the contribution of PS to aggregated PAH exposure.

KEYWORDS

Integrated exposure modelling, Polycyclic Aromatic Hydrocarbons (PAHs), petroleum substances, biomonitoring.

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This report is available as an Adobe pdf file on the Concawe website (www.concawe.org).

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SUMMARY

This report presents the discussions held during the "Polycyclic Aromatic Hydrocarbons (PAHs) integrated exposure modelling" workshop organized by the Flemish Institute for technological research (VITO) on 8 - 9th October 2015. This 2-day workshop was held at Concawe offices with participation of model users and developers, Concawe secretariat, Concawe member companies and VITO.

Currently, Concawe aims to address the challenge of assessing the contribution of Petroleum Substances (PS) to aggregated PAH exposure. In this context, there is an opportunity to identify integrated multi-source, multi-route (MSMR) exposure model(s) suitable for characterising exposure to PAHs including those that may derive from PS. The ultimate goal is to have a reliable, validated, integrated source-to-receptor PAH exposure modelling tool capable of generating realistic predictions of PAH exposure, which enables the determination of the relative proportion of PAHs exposures over different routes and sources (and which also extends beyond petroleum sources).

The overall aim of the workshop was to explore whether (and which of the) existing MSMR models meet the goal outlined above, and to identify databases (such as PAH monitoring in air, food and biomonitoring) that could be used to support and verify model predictions. The focus of the workshop was general population exposure modelling tools (including consumer exposure and indirect exposure via the environment); occupational exposure was out of scope.

The features and applications of five models were presented by their developers (presentations can be found in Appendix). In particular, the intended model use was discussed as well as the general impressions in relation to the currently used models (tiered level, comparison with biomonitoring data, transformation and degradation, cumulative exposure, model uncertainty and variability, sensitivity analysis, data gaps and model documentation and tutorials). Additionally, particular aspects of the models were highlighted and practical model considerations were outlined. The availability of biomonitoring data for model verification was also presented. Concluding, the way forward was discussed, and recommendations on how to proceed with the potential use of MSMR models within Concawe were developed.

In summary, this workshop report aims to reflect 1) the interaction and discussion between model developers and other workshop participants from a model user perspective, 2) the discussion on the potential bottlenecks and gaps when applying the models for PS scenarios, and 3) the way forward when using MSMR modelling in addressing Concawe's challenge to assess the contribution of PS to aggregated PAH exposure.

1. BACKGROUND AND AIM OF THE WORKSHOP

Exposure to polycyclic aromatic hydrocarbons (PAHs) is ubiquitous. There are many sources and many routes by which human exposure to these substances occurs. The contribution of petroleum substances (PS) to population PAH exposures, however, has not been widely characterised and therefore the impact is not fully established. In view of the potential for PS to be included in the different REACH processes (notably Evaluation and Authorisation), Concawe aims to identify integrated multi-source, multi-route (MSMR) exposure model(s) suitable for characterising exposure to PAHs including those that may derive from PS. Concawe is particularly interested in the abilities of the model(s) to predict direct PAH exposures arising from the use of substances, as well as those occurring indirectly.

The ultimate goal is to have a reliable, validated, integrated source-to-receptor PAH exposure modelling tool capable of generating realistic predictions of PAH exposure, which enables the determination of the relative proportion of PAHs exposures over different routes and sources (and which also extends beyond petroleum sources).

Since the experience of model users and developers is essential to achieving this aim, a workshop was organized in Brussels on 8 - 9th October 2015.

The overall aim of the workshop was: 1) to explore whether (and which of the) existing multi-route, multi-sources models meet the goal outlined above, and 2) to identify databases (such as monitoring of PAHs in air, food and biomonitoring) that could be used to support and verify model predictions. The focus of the workshop was general population exposure modelling tools (including consumer exposure and indirect exposure via the environment); occupational exposure was out of scope.

As part of the preparation for the workshop, VITO performed a screening of MSMR models that potentially fit the above described purpose. As an outcome of this task, the five most likely useful models appeared to be INTEGRA, MERLIN-Expo, EUSES, USEtox and SHEDS-multimedia. Model developers of INTEGRA, MERLIN-Expo, EUSES and SHEDS-multimedia attended the workshop and gave presentations highlighting their model features and applications (see Appendix 3). It is remarked that EUSES is designed as a screening tool, while the other mentioned models are designed as higher tier models. Notwithstanding, it was preferred to include EUSES in the overview of the MSMR models given the dominant use of EUSES in the context of REACH.

This workshop report aims to reflect: 1) the interaction and discussion between model developers and other workshop participants from a model user perspective, 2) the discussion on the potential bottlenecks and gaps when applying the models for PS scenarios, and 3) the way forward when using MSMR modelling in addressing Concawe's challenge to assess the contribution of PS to aggregated PAH exposure.

2. PAH SUBSTANCES IN SCOPE FOR CONCAWE – RELATION TO MODELS

2.1. PAH SUBSTANCES IN SCOPE

The choice of appropriate exposure models depends on the application domain of the models. Therefore, it should be considered for which PS and PAHs the model(s) are intended to be used.

Several hundreds of PAHs exist, and therefore, the (groups of) PAH substances that are of most relevance for Concawe were discussed. From this wide range of PAHs, the US Environmental Protection Agency (EPA) and the EU have prioritized 16 and 24 PAHs, respectively.

Consequently, the environmental monitoring programmes (in air, food, dust, soil and water) are focussed on these 16 – 24 PAHs; within both of these groups, pyrogenic and petrogrenic PAHs are included.

Pyrogenic PAHs are formed during rapid high temperature combustion processes (>700 °C) of vehicle motors, shipping and combustion of fossil energy sources and are dominated by 4-6 ring PAHs, although, 3-ring PAHs may be also formed during combustion. Lower temperature combustion processes (e.g., burning of wood) generally result in low molecular PAHs.

Petrogenic PAHs mainly originate from PS and are being formed during low long-lasting temperatures (100 -300 °C). Crude and refined PS contain mainly 2-4-ring PAHs. Besides the exception of chrysene, 4-6-ring PAHs hardly occur in PS. Alkylated PAHs are generally dominating in PS.

The type of PAH (low or high molecule weight) also influences the dominance and routes of exposures: for larger PAHs (> benzo[a]pyrene, BaP), food is the dominant exposure source, while for smaller PAHs, inhalation is generally the dominant route of exposure [1, 2, 3, 4].

Therefore, the performance of the models might also differ across different types of PAHs. A MSMR model consisting of a simple –low tier dietary module and a higher tier (time-activity based) inhalation module might be appropriate for smaller PAHs, though less appropriate for 4-6 ring PAHs (and vice versa).

Obviously, there is a need for identification of relevant PAH substances that are of interest to Concawe.

As an outcome of the discussion, it was advised to interact with other Concawe working groups (e.g., Ecology, Air Quality and Health Management Groups) to identify the most relevant PAHs components to Concawe. Based on this outcome, a set of marker/signature PAHs would be identified to cover both pyrogenic and petrogenic sources. This set of marker/signature PAHs could be used in the exposure scenarios (see further).

It was discussed and agreed that, for the purposes of estimating human PAH exposures, naphthalene would be out of scope. Under Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures (CLP Regulation), naphthalene is classified H351 (Carcinogenic Cat. 2). However, as indicated in Concawe report 1/15R (Appendix 5), there is evidence that strongly

supports a cytotoxic threshold mode of action in rodents and low risk for human respiratory cancer at typical and occupational exposure levels [5].

2.2. CHEMICAL SPACE DOMAIN OF MODELS

Both the INTEGRA and MERLIN-Expo models have pre-set lists of chemicals (INTEGRA: about 150 substances; MERLIN-Expo: about 30 substances) for which the models are parameterised.

Stochastic Human Exposure and Dose Simulation (SHEDS)-multimedia has been parameterized and applied for several substances (groups), covering a wide range of chemical properties (e.g. PCBs, metals, pesticides).

For each of these three models, it is also possible to add new substances to the models; thereto, model functionalities are foreseen prompting users to fill in the fundamental substance properties.

In INTEGRA and Merlin Expo, Quantitative Structure–Activity Relationship (QSAR) functions in several model compartments (e.g. environment – food transfer functions and estimation of physiologically based pharmacokinetic parameters, PBPK) enable the prediction of exposure for a rather wide range of chemicals. However, an important aspect, herein, is to check the application domain of the QSARs underpinning the models. It is unclear whether such a check can be performed within INTEGRA. In MERLIN-Expo, a dedicated step to verify whether the substance falls within the application domain of the model is not foreseen. However, as MERLIN-expo has been developed in accordance with the European Committee for Standardization (CEN) specifications for model documentation, there will be some indication of the application domain for each module/equation implemented in MERLIN-Expo.

According to the developers of the INTEGRA model, the QSARs for the estimation of PBPK modelling parameters in INTEGRA have been validated by means of a test dataset, independent of the training set on which the QSAR has been built. A publication of this validation is foreseen.

SHEDS-multimedia is linked with structure-based PBPK models and are used together to quantify target tissue dose, and conduct linked exposure-dose model evaluations.

3. INTENDED MODEL USE

Both MERLIN-Expo and INTEGRA have been developed as exposure modelling tools that are not dedicated to be used in one specific policy context domain.

INTEGRA was initially developed to address consumer exposure. This is reflected in the fact that INTEGRA provides the option to give rather detailed consumer use scenarios, and hereby accounting for dermal, oral and inhalation pathways. INTEGRA was in a later phase expanded to account for (in)direct environmental exposure. Furthermore, INTEGRA was not developed specifically in the context of REACH, however the model includes REACH use descriptors as an option to calculate exposure.

MERLIN-Expo was mainly developed to address (in)direct environmental exposure, as a high tier exposure model. This is reflected in the rather advanced way of addressing environmental exposure (including aquatic and terrestrial food web). Notwithstanding this, it is possible to add aspects of consumer exposure, though in a less sophisticated way compared to INTEGRA (e.g. the ability to account for usage patterns). Benchmarking MERLIN-Expo against EUSES revealed that both models are comparable in their exposure predictions.

SHEDS-multimedia has been developed within the US EPA Policy, Regulation and Risk Assessment context, to support to EPA in performing cumulative and aggregate assessments for multiple chemicals. The model gives equal importance and tiered level to dietary exposure as well as to residential exposure, i.e. non dietary exposure, including exposure via hand-mouth contact, indoor air exposure, etc.). Given the nature of the model, and the database underpinning the model, SHEDS-multimedia is intended to be used on a probabilistic basis only, and cannot readily be simplified into a deterministic version. The model is not intended to be used as a full chain source to receptor model to predict impact of several policy options, since the model does not include an environmental fate model (for predicting impact of environmental on contaminant levels in food). Since the model is based on large records on (food) monitoring data in the US, the model may rather be used as a tool to assess ‘true, current’ aggregated exposure in the US populations, reflecting current environmental conditions and exposure situations in the US.

4. GENERAL IMPRESSIONS OF PRESENTED MODELS – IN RELATION TO CURRENTLY USED MODELS (EUSES, PETRORISK)

4.1. TIERED LEVEL

SHEDS-multimedia, MERLIN-Expo and INTEGRA were perceived as high tier exposure models, acknowledging the scientific complexity of the nature, and routes of exposures. All three models have clear advantages in terms of their ability to address concurrent exposures to PAHs from multiple sources and via multiple routes compared to the standard lower tier tools (EUSES, Petrorisk and ECETOC TRA). Specifically, they show the capacity of: 1) integrating of exposure pathways by translating exposure into internal doses, 2) as a consequence, there is the possibility to compare predictions with biomonitoring data, which serve as a gold standard for validation of integrated exposure modelling predictions, 3) including tools and data for probabilistic assessments, 4) implementing appropriate mechanisms to underpin exposure routes and pathways, and 5) including tools for reverse dosimetry modelling, and hence may allow the identification of main exposure sources. The models MERLIN-Expo and INTEGRA appeared to be very flexible in use. As a drawback, however, these models might be too flexible, and therefore time and effort-consuming to set up, parameterize and run scenarios. Validation of very complex models is commonly also very challenging.

Setting up scenario runs based on SHEDS-multimedia for the EU population, would a be very time-consuming exercise since it would require gathering of a huge number of person-oriented records for dietary exposure, human activities database, usage database, and monitoring levels in environmental media (water, dust, air, soil) and food in the EU.

It was argued that the development of a tiered approach in selecting the appropriate models would be of benefit; it is likely that in several situations, (conservative) lower tier models would be capable of providing an assessment and hence would be preferred.

As mentioned by Philippe Ciffroy (MERLIN-Expo), higher tier types of models should not be used for lower tier assessments.

4.2. COMPARISON WITH BIOMONITORING DATA

The strongest point of the higher tier models of INTEGRA, MERLIN-Expo and SHEDS-multimedia is that the output, i.e., predictions of levels in target organs, allows for a comparison with measured data collected during biomonitoring campaigns; this provides a solid foundation against which of the models can be validated.

Indeed the strong correlation between available biomonitoring data for pyrethroids and predictions made by SHEDS-multimedia was noted.

An example presented by the developers of INTEGRA demonstrated that the INTEGRA tool predicts a 6-fold increase in BaP intake if BaP levels in ambient air increase by a factor of 2.5 (not verified against biomonitoring data).

4.3. TRANSFORMATION AND DEGRADATION

None of the models (SHEDS-multimedia, INTEGRA and MERLIN-Expo) take into account transformation and degradation of compounds throughout the source – environment – receptor chain.

The models have been mainly tested and verified for metals or organic substances that are persistent or do not readily degrade (e.g., PCBs, dioxins and phthalates). The models' lack of validation for readily metabolised, degradable substances might form a constraint for readily degradable substances.

4.4. CUMULATIVE EXPOSURE

A second shortcoming is that both INTEGRA and MERLIN-Expo are single-substance oriented models, and lack the capability to assess exposure to mixtures or certain complex substances, including interactions between substances and metabolites.

In contrast, SHEDS-multimedia is capable to address cumulative exposure. For example, in a case study on 7 pyrethroids, SHEDS-multimedia provides as an outcome the cumulative doses of 7 pyrethroids. This feature of SHEDS-multimedia could be useful for a cumulative exposure to PAHs; however, it would require huge efforts to gather and implement data to parameterize SHEDs-multidmedia for PAHs exposure in the EU.

Petrorisk potentially offers a means for assessing exposure to mixtures of PAHs; however, the tiered level of Petrorisk is similar to EUSES; and thus is not capable to assess internal exposures or to perform reverse dose modelling to identify significant exposure sources. Moreover, the primary focus of Petrorisk lies with predicting environmental exposures.

It would be advised to explore how easy it may be to expand the single substance models MERLIN-Expo or INTEGRA into a mixtures' exposure tool; this would have the benefits of a high tier exposure model for predicting internal levels, and the benefits of a mixture model. An alternative would be to explore the extent to which the Assessment Entity concept could be captured and processed by such models (as is also likely to be required within REACH Chemical Safety Assessments (CSAs).

4.5. MODEL UNCERTAINTY, VARIABILITY

MERLIN-Expo, INTEGRA and SHEDS-multimedia have the advantage of allowing probabilistic assessments, compared to the deterministic-oriented models like EUSES and Petrorisk.

In INTEGRA, it is possible to attribute probabilistic distribution functions for numerous model input parameters. In MERLIN-Expo, probability density functions (PDFs) can be added to all input parameters of interest.

The architecture of the probabilistic nature of the SHEDS-multimedia differs strongly form MERLIN-Expo and INTEGRA: in SHEDS-multimedia, huge databases of person-oriented records (e.g. food patterns, time-activity) form the core of the platform, and these person-oriented databases include inherently the populations' variability. These person-oriented records are used in Monte-Carlo simulations.

According to the model developers of INTEGRA and MERLIN-Expo, mechanisms are foreseen to avoid unrealistic combinations' of distribution tails; this is an important aspect since several parameters are inter-correlated, and not accounting for this would render the tails of the predictions unrealistic; for example, fish consumption data are correlated with meat consumption. However, these mechanisms have not been demonstrated in the presentations of the INTEGRA and Merlin-Expo models.

Whereas parameter variability has been extensively addressed in the distribution functions, the aspect of model uncertainty is less addressed. In none of the tools, it is currently possible to distinguish between variability and uncertainty.

In order to run a probabilistic assessment in MERLIN-Expo or INTEGRA, model users should describe distribution functions of input parameters. For the INTEGRA model, it is so far unclear to what extent certain (generic) model parameters distribution functions have been pre-filled in the models. For MERLIN-Expo, this is clearly described in the model documentation.

4.6. MODEL SENSITIVITY ANALYSIS

INTEGRA, MERLIN-Expo and SHEDS-multimedia provide the possibility to perform an initial sensitivity analysis. The outcome of the sensitivity analysis allows the model user to identify the parameters which benefit most from refining (gathering better data as input) and from treatment by a probabilistic approach since they strongly affect the variability of the overall outcome. For other less sensitive parameters, conservative default values are sufficient (refining to more realistic values would hardly affect the outcome) and a deterministic approach may be followed. The latter reduces the computing time compared to a full-blown probabilistic approach where all input parameters have a distribution function.

4.7. DATA GAPS

A sensitivity analysis might also lead to the identification of data gaps and uncertainties. In an example presented by the INTEGRA model developers, i.e., a scenario combining environmental exposure and consumer products, it was suggested that exposure to BaP in rubber boots dominated strongly the exposure (contribution from rubber boots via dermal exposure is > 100 fold higher than oral and inhalation exposure).

However, one could question whether the predicted high contribution of dermal exposure from rubber boots reflects reality, or whether overprediction based on (too) conservative assumptions has led to the predicted exposure levels. For this particular case, the information on PAH release from rubber boots could be considered as a data gap because the applied PAH release data from rubber boots are based on results from testing procedures which probably do not adequately mimic realistic release rates of PAH from rubber boots and transfer to the skin. Appropriateness of such test results require further investigation.

4.8. MODEL DOCUMENTATION AND TUTORIALS

All equations and values for parameterization of MERLIN-Expo are extensively documented according to the CEN documentation standards. Documentation and online tutorials (videos) are available from the 4-FUN website[1]. Additionally, an

[1] http://4funproject.eu/en/content/MERLIN-Expo.15/

extensive wiki-function within the MERLIN-Expo reflects the equations and parameters.

Model documentation of INTEGRA is available for registered users on the website of INTEGRA[2] (end 2015).

A Technical Manual and User Guide of SHEDS-multimedia is available at the website of EPA[3].

[2] http://www.integra.cperi.certh.gr/

[3]http://cfpub.epa.gov/si/si_public_record_report.cfm?dirEntryId=199844&simpleSearch=1&searchAll=SHEDS+multimedia

5. PARTICULAR HIGHLIGHTS OF MODELS

MERLIN-Expo, INTEGRA and SHEDS-multimedia show, on the one hand, similarities, such as the capability to predict internal exposures with QSAR-based PBPK models. On the other hand, differences were noticed, partially influenced by the model purpose: whereas INTEGRA was primarily designed to address consumer exposure, MERLIN-Expo initially focused on man via environmental exposure. This is reflected in the tiered level of the model building blocks. For example, INTEGRA is based on the rather simple EUSES food basket and environment to food transfer formulae; MERLIN-Expo demonstrates a higher complexity in transfer functions and food web composition. The current version of MERLIN-Expo does not allow predicting dermal exposure from consumer products. Nevertheless, both models have the flexibility to add additional sources of exposure.

In the paragraphs below, particular highlights appreciated by the workshop participants are described.

5.1. INTEGRA: HRT MODEL (HUMAN RESPIRATORY TRACT MODEL)

The model simulates the behaviour of bioaerosol particles of variable size and shape in the human respiratory tract. Additionally, it describes the deposition in the lungs, and translocation of airborne fraction to the mucous membranes and gastro-intestinal system. Mucociliary escalatory and gut translocation for particles might be relevant for PAHs since PAHS are commonly adhered to particles.

5.2. MERLIN-EXPO: CEN DOCUMENTATION

All equations and values for parameterization are extensively documented according to the CEN documentation standards. This benefits greatly to model transparency.

5.3. SHEDS-MULTIMEDIA: VALIDATION WITH BIOMONITORING DATA AND LONG LIST OF PUBLICATIONS AND USERS

The strong correspondence between available biomonitoring data for pyrethroids and predictions made by SHEDS-multimedia was noted.

SHEDS-multimedia has a long track record of publications and users: 20 peer-reviewed papers on SHEDS-multimedia methods, model applications, and evaluation have been published; SHEDS-multimedia has users in 26 countries and the US for different chemicals and applications from academia, industry, consultants and individual citizens.

6. AVAILABILITY OF BIOMONITORING DATA FOR MODEL VERIFICATION

Biomonitoring data are a key element in the verification of exposure predictions since biomonitoring measurements reflect integrated exposure, i.e. aggregate and across all routes.

In the presentation 'Biomonitoring data for PAHs' by Gudrun Koppen (see Appendix 3), an overview was given on the existing PAH biomonitoring data gathered in various scientific projects, and some national health monitoring programmes (e.g. http://biomonitoring.ca.gov/chemicals/polycyclic-aromatic-hydrocarbons-pahs).

It was noted that while parent compounds are present in small amounts in biological matrices (urine, blood), metabolites are more abundant. The vast majority of data are for the metabolite 1-OH pyrene. Data on other metabolites are less abundant and more difficult to analyse.

It was advised to write a review on the biomonitoring of PAHs.

7. PRACTICAL MODEL CONSIDERATIONS

7.1. SOFTWARE PLATFORMS

MERLIN-Expo, INTEGRA, EUSES and SHEDS-multimedia are online available free of charge. For the use of SHEDS-multimedia, users need to have installed the software package SAS (SAS v8 or higher), which is a commercially available statistical software package (significant costs may be associated for company licences). MERLIN-Expo and INTEGRA are built in the Ecolego and acslX software packages, respectively. To use MERLIN-Expo and INTEGRA, the end-user does not need to buy and/or install these software packages. MERLIN-Expo can be downloaded free of charge from the 4FUN website (http://merlin-expo.4funproject.eu/). On the other hand, INTEGRA is a web-based tool. Users are only required to register online to get access to the INTEGRA platform.

Whereas MERLIN-Expo performs and stores simulations on the model users' PC, all simulations with INTEGRA are performed online and model scenarios and results are stored on the servers of the model developers, i.e. at the Centre for Research and Technology Hellas (CERTH). It is, thus, not possible to use INTEGRA locally; a well-functioning internet connection is a prerequisite to carry out simulations with INTEGRA.

7.2. MODEL FLEXIBILITY / IMPLEMENTATION OF MODIFICATIONS

MERLIN-Expo consists of a library of models, so that a model user might select and implement the model compounds of interest for a specific case. For models not yet covered in the library of MERLIN-Expo (e.g. dermal exposure – consumers), it is possible to ask the model developers to add model(s) to the library. As a rough estimate, the implementation of the INERIS dermal exposure module in the software code would require one additional day (implementation by the MerlinExpo team), defining the model input parameters would be a more time-consuming task, while documentation of the module according to the CEN standard would take considerable time.

7.3. COMPUTING TIME

Once model construction is completed, deterministic model runs in INTEGRA and MERLIN-Expo are performed within a few seconds. Probabilistic model runs may require computing time up to several hours (or beyond), depending on the number of parameters which are addressed in a probabilistic way. For example, in INTEGRA about 100 model parameters may be described with PDFs.

In order to overcome time-consuming computing time and gathering of information to describe the distribution functions of input parameters, both INTEGRA and MERLIN-Expo provide the possibility to perform an initial sensitivity analysis. The outcome of this analysis allows the model user to identify those parameters which benefit most from a probabilistic consideration; for other less sensitive parameters, a deterministic approach may be sufficient. The latter reduces the computing time compared to a full-blown probabilistic approach.

7.4. DATA

One of the most time-consuming actions in applying MSMR exposure models is the search for relevant data to 'feed' the exposure models, the selection of relevant data for the considered exposure scenario's , and to load the data into the models.

Although both INTEGRA and MERLIN-Expo provide default values for key parameters, keeping these default values for all (and especially sensitive) parameters will likely result in unrealistic exposure estimates. For sensitive parameters, it is advised to find more realistic parameters, including variability. An overview of available data sources for PAHs was given in the presentation 'Exposure data sources' by Katleen De Brouwere (VITO) (see Appendix 3).

The model of SHEDS does not work with default parameter values. Instead, a database of exposure factors of a large number of individuals is underpinning the model. The SHEDS database in based on US population characteristics, such as the National Health and Nutrition Examination Survey (NHANES) data; adapting to the EU population would require the implementation of a EU representative dataset of individuals and their behaviours (e.g. time, activity, dietary patterns) and characteristics.

7.5. MODEL STATUS

SHEDS-multimedia and MERLIN-Expo have been finalized, released and already available for end users; a validation for MERLIN-Expo for BaP was presented by the model developers during the workshop. In addition, an extensive model documentation, tutorials and help functions have been completed and released for both models. Several case studies (including validation) of the use of MerlinExpo have recently been published in scientific peer-reviewed journals [e.g. 6, 7, 8, 9].

The INTEGRA model has been released in early 2016, and access to the model platform and documentation is available on the INTEGRA website. It is unclear to what extent validation has been performed, and whether case studies using INTEGRA have been published.

8. WAY FORWARD

The second day of the workshop was dedicated to the internal discussion within Concawe of the benefits and drawbacks of the presented models, and to develop recommendations on how to proceed with the potential use of MSMR models within Concawe.

The following suggestions were formulated:

- Recommendation to write a (scientific) **review paper on PAH biomonitoring data**. This would form a good basis for comparing predicted exposures (and hence model verifications), and backward dose modelling exercises.
- Notwithstanding that an exposure assessment based on EUSES and Petrorisk fulfils current regulatory expectations under REACH, it was agreed that higher tier MSMR models (INTEGRA, SHEDS-multimedia and MERLIN-Expo) have an additional value since these models are based on a more developed scientific approach, and hence account for several aspects ignored by lower tier models (e.g. variability, secondary poisoning). This would provide improved and more realistic insights in the current exposure scenarios for PS, both for a better understanding in refining industry as well as in a regulatory context.
- It is advised to develop a **tiered approach/decision tree** for MSMR modelling: in which cases are simple tools sufficient, and in which cases, are higher tiered approaches needed?
- Alternative approaches compared to the use of the presented MSMR models were suggested:
  - combine separate exposure models: e.g. dietary or consumer exposure models combined with standalone PBPK models (e.g. IndusChemFate: excel-based tools, parameterized for pyrene);
  - make add-ons to Petrorisk (e.g. use the output of Petrorisk as input for higher tier models such as MERLIN-Expo or INTEGRA (which include PBPK models) in order to be able to compare with biomonitoring data);
  - invest in measurement campaigns that enable certain critical parameters to be suitably described, instead of modelling.
- It is recommended to **interact with other Concawe groups** which may already have relevant exposure data, such as the Ecology, Air Quality and Health Management Groups. The Toxicology Sub Group could also work on the definition of sensitive toxicological reference values/toxic equivalents for groups of materials.
- It was suggested to connect to the consortium of the **H2020 call 'European Human Biomonitoring Initiative**' to explore the possibility for participation in the workpackage on PAH exposure assessment and biomonitoring.
- Although SHEDS-multimedia was regarded as an excellent tool, the efforts to use and parameterize it for PAHs in the EU are considered too demanding at this stage, and therefore, it is not foreseen to include the use of SHEDS-multimedia for a set of scenarios to be tested (see below).
- Based on the presentations of MERLIN-Expo and INTEGRA, it could not be judged at the moment which of the two models is the most appropriate to perform MSMR exposure modelling for PAHs present in PS. Therefore, it was suggested to **test both models in parallel for a set of scenarios.** Such practical

experience with both models will probably also give an impression on model use (how practical are the models to use, how time-consuming is it to set up a scenario and to run the model, and how do the model predictions relate to existing biomonitoring data?).

The **following 5-6 scenarios have been suggested as cases to model with MERLIN-Expo and INTEGRA**:

1. Consumer scenario: changing motor oil of a car (addressed in SCEDS; exposure data are available);
2. Consumer scenario: filling up a diesel car (some exposure data are available; can already be modelled with INTEGRA);
3. Environmental exposure: local exposure around oil refineries (indirect exposure, e.g. locally grown crops)
4. Consumer exposure: cosmetics (e.g. lipsticks) (Concawe started recently a project, some data are available);
5. Consumer exposure: playgrounds and soft (rubber) grips (some exposure data are available, e.g. PAH contents and releases to skin);
6. Depending on the available resources an additional environmental scenario (i.e. background exposure).

9. UPDATE 2016 - 2017

In 2016, the Concawe-funded project “Integrated exposure modelling PAHs arising from petroleum substances for 6 exposure scenarios” was launched and is currently run by VITO.

In the framework of this project, MerlinExpo and INTEGRA models are tested on the six exposure scenarios described in Section 8, to assess the contribution of consumer uses to integrated PAH exposure.

This project aims at investigating the applicability of the selected MSMR models for PS, to get good practical insight into model architectures and practical performance, to test the promising features of INTEGRA (e.g. HRT) and MerlinExpo and to identify potential bottlenecks when using the models.

A report on the outcome of this project is expected in 2017.

10. GLOSSARY

BaP: Benzo[a]pyrene

CEN: European Committee for Standardization

EPA: Environmental Protection Agency

QSAR: Quantitative Structure–Activity Relationship

PAH: Polycyclic Aromatic Hydrocarbon

PBPK: Physiologically Based Pharmacokinetic

PDF: Probability Density Functions

PP: Petroleum Products

PS: Petroleum Substances

SHEDS: Stochastic Human Exposure and Dose Simulation

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8. Van Holderbeke, M. et al (2016) Assessing multimedia/multipathway exposures to inorganic arsenic at population and individual level using MERLIN-Expo. *Sci Total Environ 568, 794-802*

9. Radomyski, A. et al (2016) Modelling ecological and human exposure to POPs in Venice lagoon - Part II: Quantitative uncertainty and sensitivity analysis in coupled exposure models. *Sci Total Environ 569, 1635-1649*

APPENDIX 1: LIST OF WORKSHOP PARTICIPANTS

Gerald Bachler	SHELL
Sarah Barber	representing P66
Peter Boogaard	SHELL
Philippe Ciffroy	EDF
Katleen De Brouwere	VITO
Lize Deferme	EXXONMOBIL
Tatsiana Dudzina	EXXONMOBIL
Tine Fierens	VITO
Eddy Goelen	VITO
Anna Hedelin (by WebEx)	NYNAS
Ashish Jachak	EXXONMOBIL
Spyros Karakitsios	CERTH
Gudrun Koppen	VITO
Carol Lee (WebEx)	EXXONMOBIL
Chris Money	CONSULTANT
David Morgott	LYONDELLBASEL
Gunther Niemeck	OMV
Giulia Pizzella	ENI
Jan Urbanus	SHELL
Rosemary Zaleski (by WebEx)	EXXONMOBIL
Valarie Zartarian (by WebEx)	US EPA
Klaas den Haan	CONCAWE
Gillian Federici	CONCAWE
Hans Ketelslegers	CONCAWE

APPENDIX 2: WORKSHOP AGENDA

Concawe workshop "PAH integrated exposure modelling"
8-9 October 2015

Venue:
Concawe meeting room
Boulevard du Souverain 165 B-1160 BRUSSELS

Day 1 (full day): 8 October 2015

Participants: Concawe participants and model developers

Welcome, Safety & Competition Law Reminders

09.30 – 09.45 Introduction and aim of the workshop (*Chris Money/ Jan Urbanus- Concawe)*

09.45 – 10.00 Overview of integrated multi-source, multi-route (MSMR) models (*Katleen De Brouwere – VITO)*

10.00 – 11.00 The Merlin Expo tool – 7th FP 4 -FUN (*Philippe Ciffroy; EDF)*

11.00 – 11.15 Coffee break

11.15 – 12.15 The INTEGRA tool – CEFIC LRI B 11 (*Spyros Karakitsios; CERTH)*

12.15 – 12.45 Exposure data sources for PAHs (*Katleen De Brouwere – VITO*)

12.45 – 13.30 Lunch

13.30 – 14.00 SHEDS multimedia – US EPA (Valerie Zartarian; US EPA; remote participation via WebEx)

14.00 – 14.30 Biomonitoring data for PAHs *(Gudrun Koppen – VITO)*

14.30 – 15.00 EUSES (Carolyn Lee – ExxonMobil)

15.00 – 16.00 Discussion and summary

16.00 – 16.30 Reception

Day 2 (half day): 9 October 2015

Participants: Concawe participants

Welcome, Safety & Competition Law Reminders

09.30 – 09.45 wrap-up of day 1 outcome

9.45 – 10.30 participants perspectives concerning integrated models for PAH exposures: tour de table

10.30 – 12.00 targetted discussions, addressing following topics:

- current practices and context of using MSMR: experiences from industry perspective
- upcoming challenges (REACH evaluation and authorization?): the role of MSMR modelling?
- (mis?)match between existing MSMR models and industry perspective's needs? if relevant: how can we bridge the gap?

Suggestions for other topics are welcomed

12.00 – 12.30 summary and the way forward?

12.30 workshop closure

APPENDIX 3: PRESENTATIONS

OVERVIEW OF INTEGRATED MULTI-SOURCE, MULTI-ROUTE MODELS

Definition

- Model for predicting human exposure arising from various sources
- Prediction based on mechanistic understanding of transfer processes
- Integration of various routes: oral, inhalation and dermal exposure
- Integration of various sources:
  - primary sources:
    - Consumer products and uses (e.g. lubricants, candles, motor oils, domestic woodstoves)
    - Industrial production and use → environment
  - intermediate 'sources': food, dust, soil, drinking water
- Ideally MSMR models integrate 3 routes of exposure, and a flexible list of sources

OVERVIEW OF INTEGRATED MULTI-SOURCE, MULTI-ROUTE MODELS

Focus

» General population, including vulnerable populations (children, pregnant women, elderly, asthmatic)

» Exposure directly or indirectly via the environment

+

consumer exposure

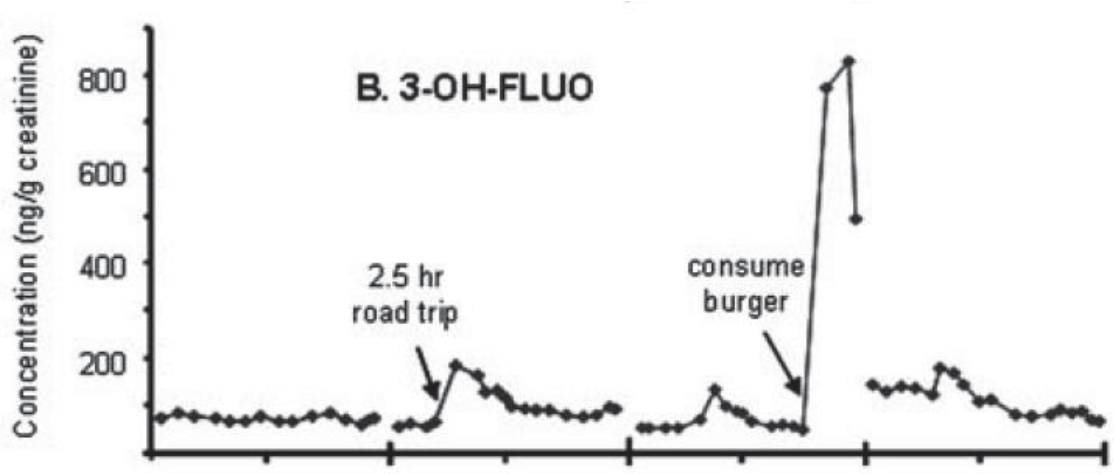
» Occupational exposure: out of scope

» Environmental exposure : in scope if in relation to transfer to human exposure

OVERVIEW OF INTEGRATED MULTI-SOURCE, MULTI-ROUTE MODELS

Why do we need MSMR models for PAH exposure assessment?

» Because exposure is resulting from multiple sources and routes



3-hydroxyfluorene levels in urine over 8 days period (Li et al., 2010)

OVERVIEW OF INTEGRATED MULTI-SOURCE, MULTI-ROUTE MODELS

Why do we need MSMR models for PAH exposure assessment?

» Relative importance of sources and routes, affected by: PAH type and exposure situation

Shin et al.,2013

Table 3
Median daily intake rate (nmol day^{-1}) and contribution of each exposure route to the total intake.

Compound	Outdoor inhalation intake based on NATA emissions (a)	CalTOX food intake based on NATA emissions (b)	Indoor inhalation intake based on indoor sources (c)	Total predicted intake from food and outdoor and indoor air (a + b + c) = (d)	Estimated intake based on NHANES biomarkers (e)	Ratio of predicted to estimated intake (d)/(e)
Naphthalene	0.4(0.7%)	0.001(<0.1%)	63.1(99.3%)	63.5	18.6	3.4
Fluorene	0.01(0.3%)	0.001(<0.1%)	3.7(99.6%)	3.7	3.3	1.1
Phenanthrene	0.03(1.8%)	0.01(0.4%)	1.8(97.9%)	1.8	3.1	0.6
Pyrene	0.01(9.7%)	0.003(2.5%)	0.1(87.8%)	0.12	0.4	0.3
Benzo(a)pyrene	0.002(2.1%)	0.09(95.2%)	0.002(2.7%)	0.09	0.06	1.5

» Flexible tools are needed to predict exposure in several situations and for several PAHs/petroleum substances

» Power of predictive models: anticipating, identifying appropriate risk reduction actions

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OVERVIEW OF INTEGRATED MULTI-SOURCE, MULTI-ROUTE MODELS

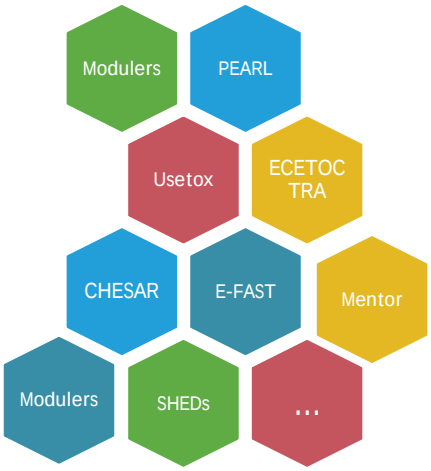
Overview of MSMR model

PROJECT 4FUN

The FUture of FUlly integrated human exposure assessment of chemicals

TAGS

Tiered Aggregate Exposure Assessment



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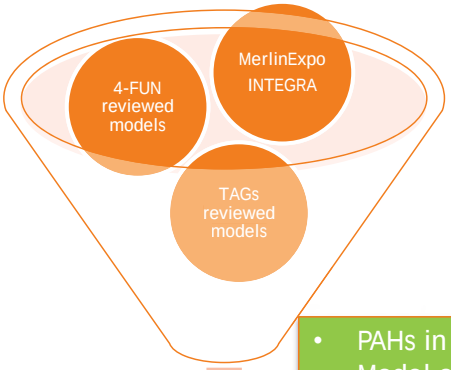
OVERVIEW OF INTEGRATED MULTI-SOURCE, MULTI-ROUTE MODELS



- PAHs in application domain
- Model availablity
- Aggregation of routes
- Multiple routes and sources
- Human exposure

Filter

10 models: inventory of model building blocks, parameters, etc.

5 most attractive models: EUSES, MerlinExpo, INTEGRA, SHEDs and Usetox

The MERLIN-Expo tool
General introduction

Content of the presentation

1. **The MERLIN-Expo tool: general purpose and scope**
2. Model structure
3. Model documentation and parameterization
4. Model scenarios

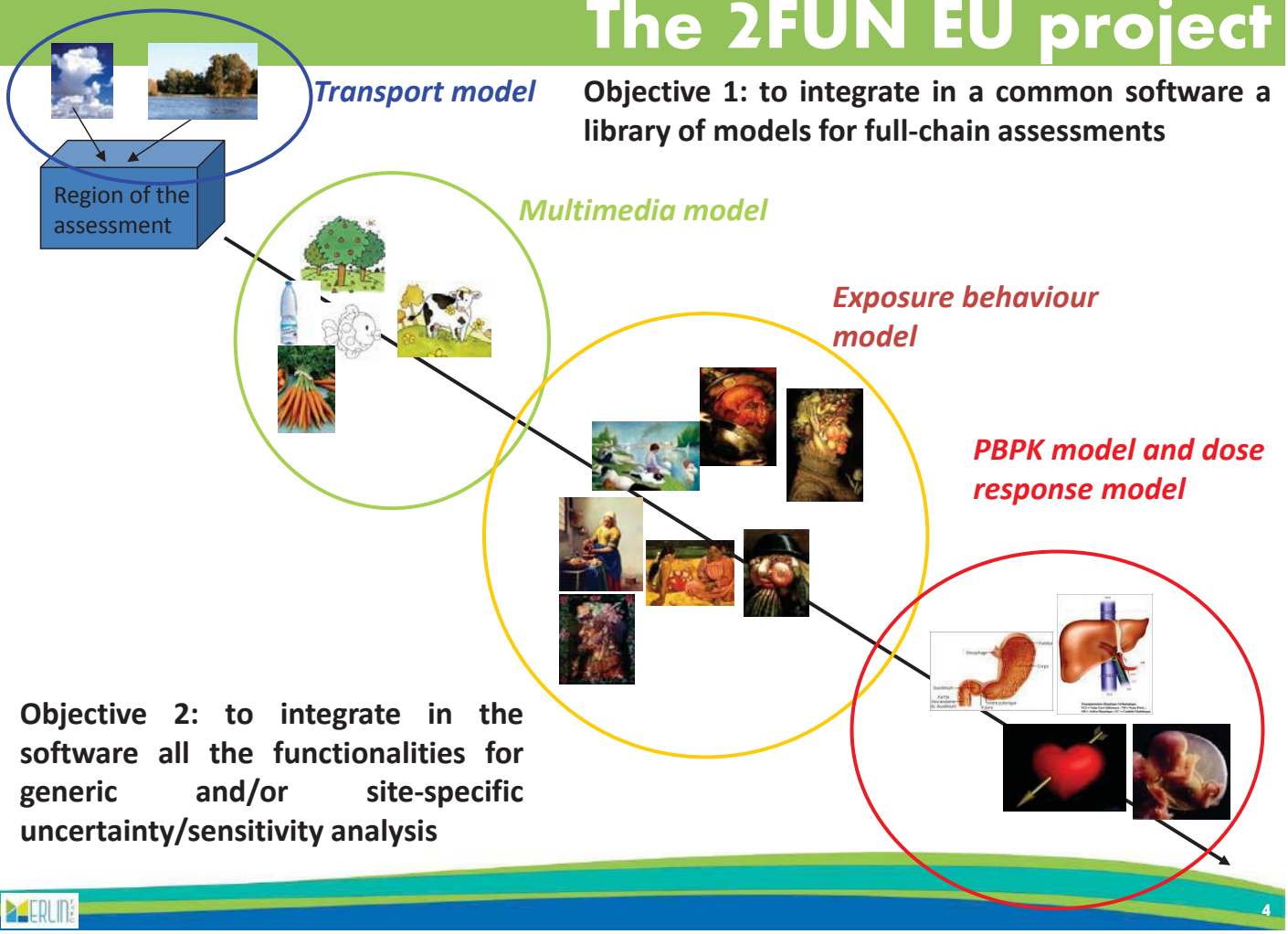
History

THE 2FUN EU PROJECT (2007-2010)

THE 4FUN EU PROJECT (2012-2015)

THE MERLIN-EXPO TOOL (2015-...)

The 2FUN EU project



Objective 1: to integrate in a common software a library of models for full-chain assessments

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

The 2FUN EU project

The 2FUN prototype: innovative issues

1: A library of models (river, soil, outdoor air, plants (root, fruits, etc), aquatic food web, PBPK for human, etc)

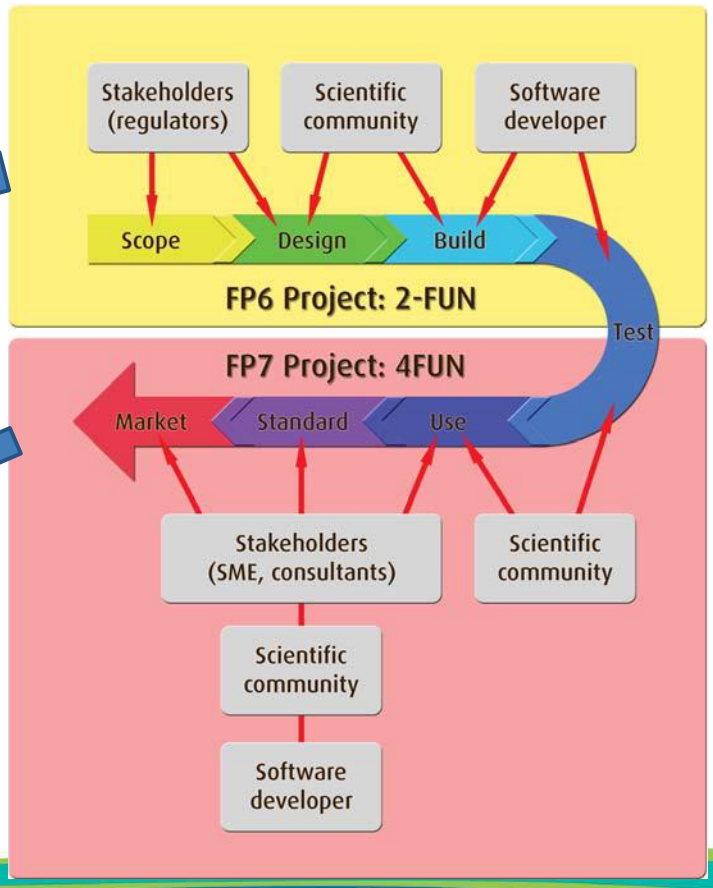
- ✓ that can be combined in a flexible way to build a wide variety of scenarios (including dynamic scenarios)
- ✓ for a wide range of chemical substances (metals, organics including PAHs)

2: Combining external exposure (environmental multimedia models) and internal exposure (PBPK) → dose to organs or biological targets (in the perspective of 'Equivalent Biomonitoring Reference Doses' or Adverse Outcome Pathways)

3: Advanced functions for uncertainty/sensitivity analysis (from screening to variance-based approaches → in agreement with WHO, 2008

The 2FUN and 4FUN EU projects

The life cycle of a software development



To provide all documentation, validation and demonstration elements for a standard tool

Why MERLIN-Expo?

Modelling Exposure to chemicals:

the tool intends to simulate the fate of chemicals in the environment and in human body to calculate exposure to chemicals

Risk assessment:

the tool can provide exposure estimates that can further be used in the general Risk assessment paradigm

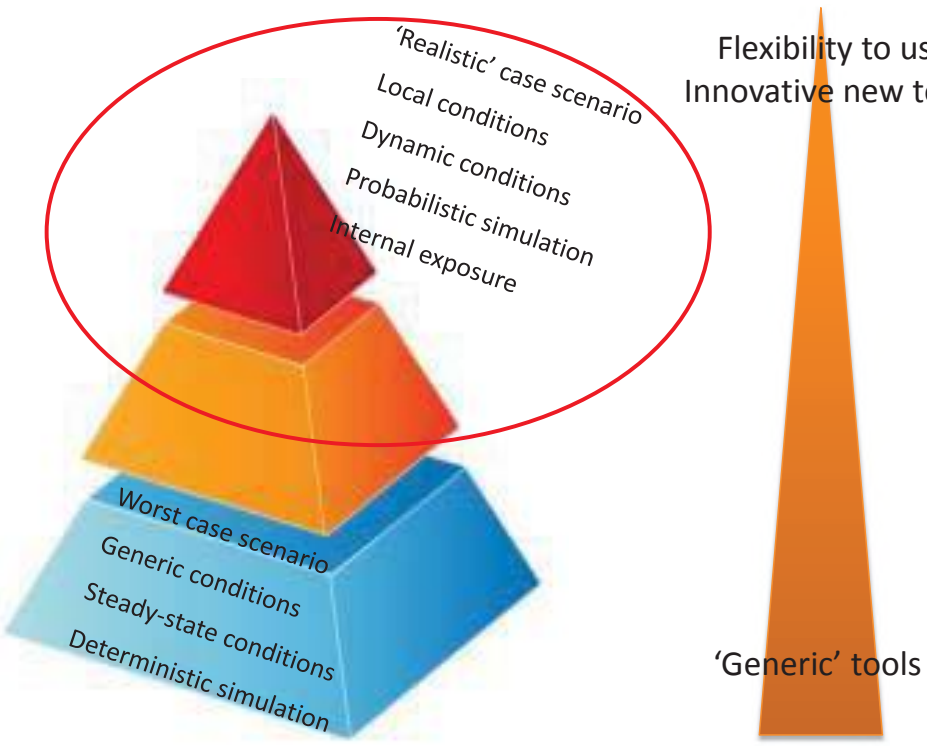
Comprehensive Library of multimedia and PBPK models:

the tool contains a large set of models for simulating the fate of chemicals in the environment (river, soil, fruits, etc) and PBPK models for simulating the fate of chemicals human body and for estimating internal exposures

Integration, Prediction, uNcertainty and sensitivity analysis:

the tool contains several functions for conducting parametric uncertainty and sensitivity analysis (from screening to global variance-based approaches)

MERLIN-Expo in the tiered approach?



Flexibility to use
Innovative new tools

'Generic' tools

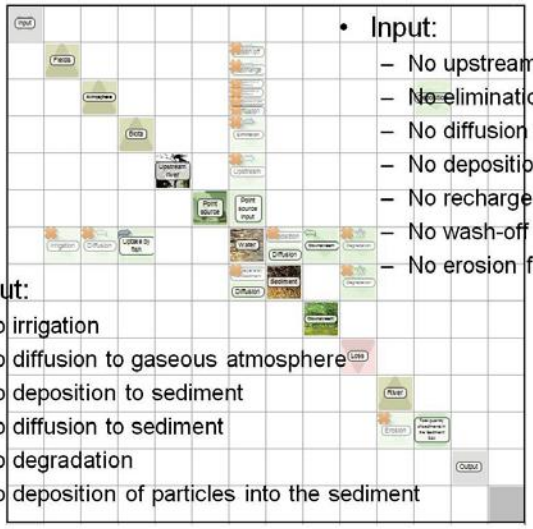
MERLINExpo benchmarking

EUSES European Union System for the Evaluation of Substances

versus

MERLIN EXPO

… with some deleted processes
… with updated 'worst case' parameter values



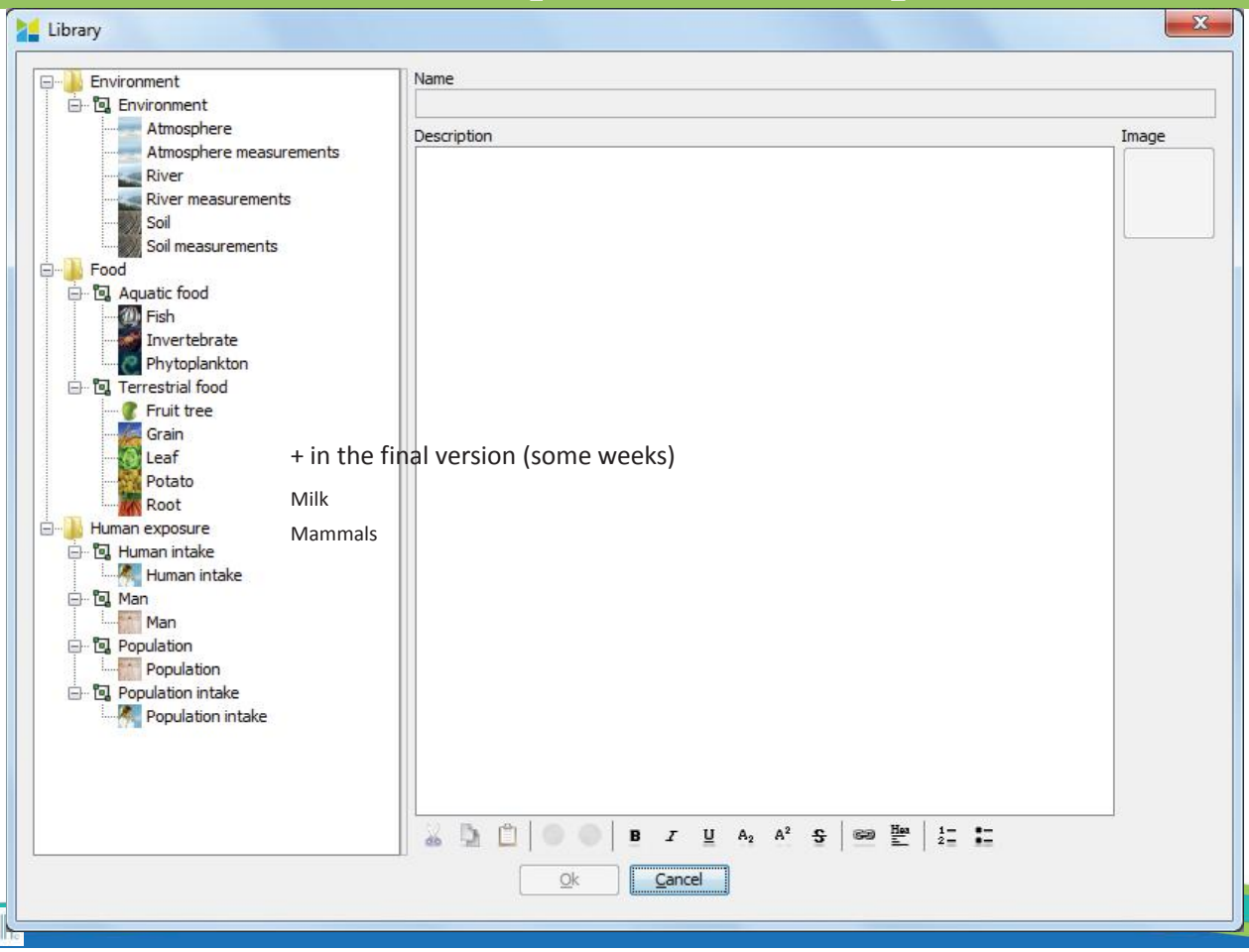
- Input:
  - No upstream river input
  - No elimination from fish
  - No diffusion from air
  - No deposition
  - No recharge from groundwater
  - No wash-off
  - No erosion from sediment
- Output:
  - No irrigation
  - No diffusion to gaseous atmosphere
  - No deposition to sediment
  - No diffusion to sediment
  - No degradation
  - No deposition of particles into the sediment

Similar results

Content of the presentation

1. The MERLIN-Expo tool: general purpose and scope
2. **Model structure**
3. Model documentation and parameterization
4. Model scenarios

MERLIN-Expo: library of models



+ in the final version (some weeks)

Milk

Mammals

MERLIN-Expo: library of models

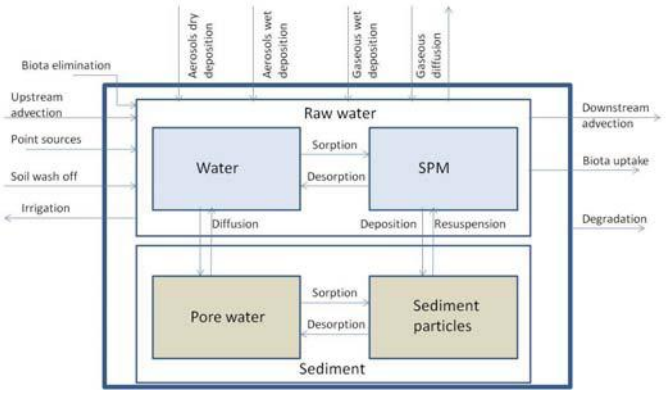
River model

Inputs/outputs from/to

- ✓*atmosphere*
- ✓*terrestrial system*
- ✓*aquatic biota*

Within River exchanges by

- ✓*Sorption/desorption*
- ✓*Deposition/resuspension*
- ✓*Diffusion*



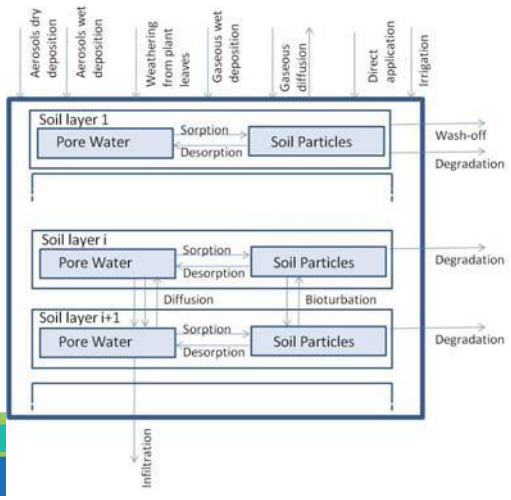
Soil model

Inputs/outputs from/to

- ✓*atmosphere*
- ✓*canopy*
- ✓*rivers*

Within Soil exchanges by

- ✓*Sorption/desorption*
- ✓*Advective transport*
- ✓*Diffusive transport*
- ✓*Bioturbation*
- ✓*Degradation*



MERLIN-Expo: library of models

Fish model

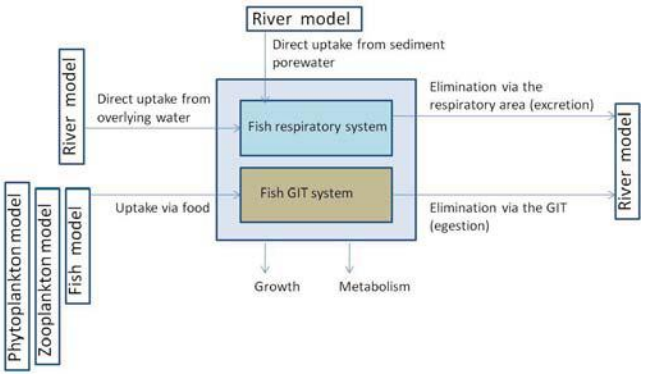
Inputs/outputs from/to

- ✓*water*
- ✓*sediments*
- ✓*preys*

Processes

- ✓*Respiratory uptake and excretion*
- ✓*Uptake via food and egestion*
- ✓*Growth*
- ✓*Metabolism*

Allometric relationships



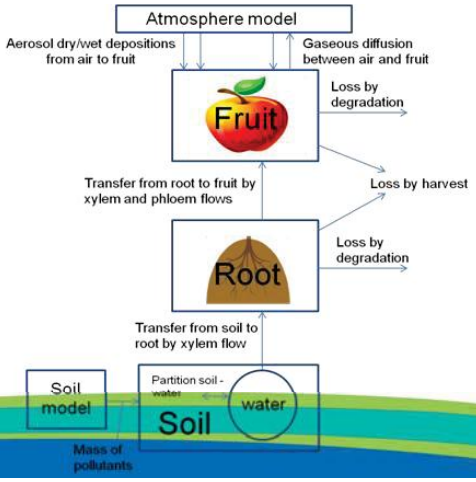
Fruit tree model

Inputs/outputs from/to

- ✓*soil*
- ✓*atmosphere*

Processes

- ✓*Soil-to-root uptake*
- ✓*Root-to-above ground plant by xylem + phloem*
- ✓*Dry/Wet interception of atmospheric deposits*
- ✓*Diffusion air-fruit*
- ✓*Degradation*



MERLIN-Expo: library of models

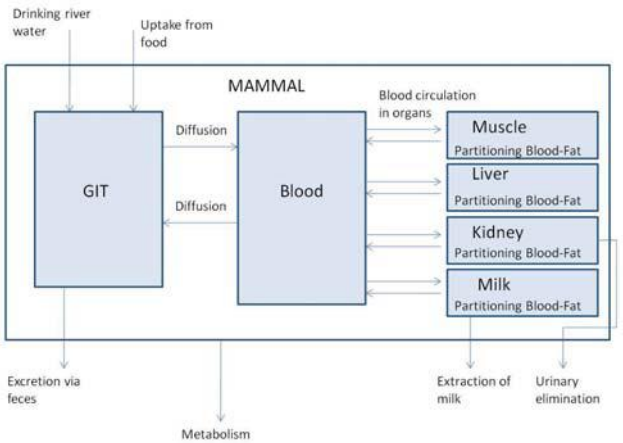
Mammals model

Inputs/outputs from/to

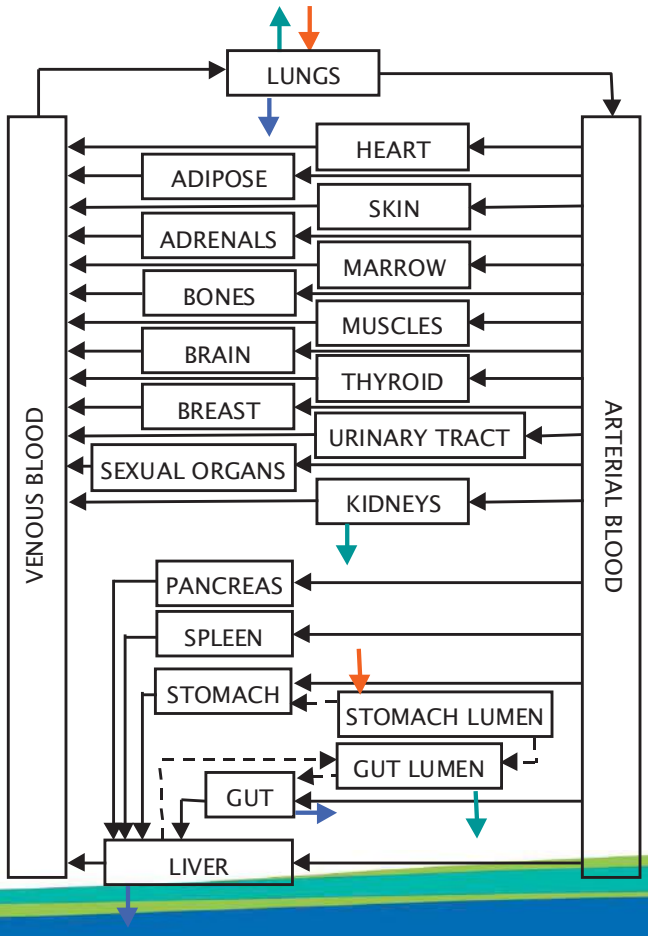
- ✓*drinking water,*
- ✓*food*

Processes

- ✓ *Digestion in GIT and excretion,*
- ✓*Diffusion GIT-Blood,*
- ✓*Blood circulation in muscle, liver, kidney and milk,*
- ✓ *Partioning Blood-Fat,*
- ✓*Urinary elimination,*
- ✓*Excretion of milk*



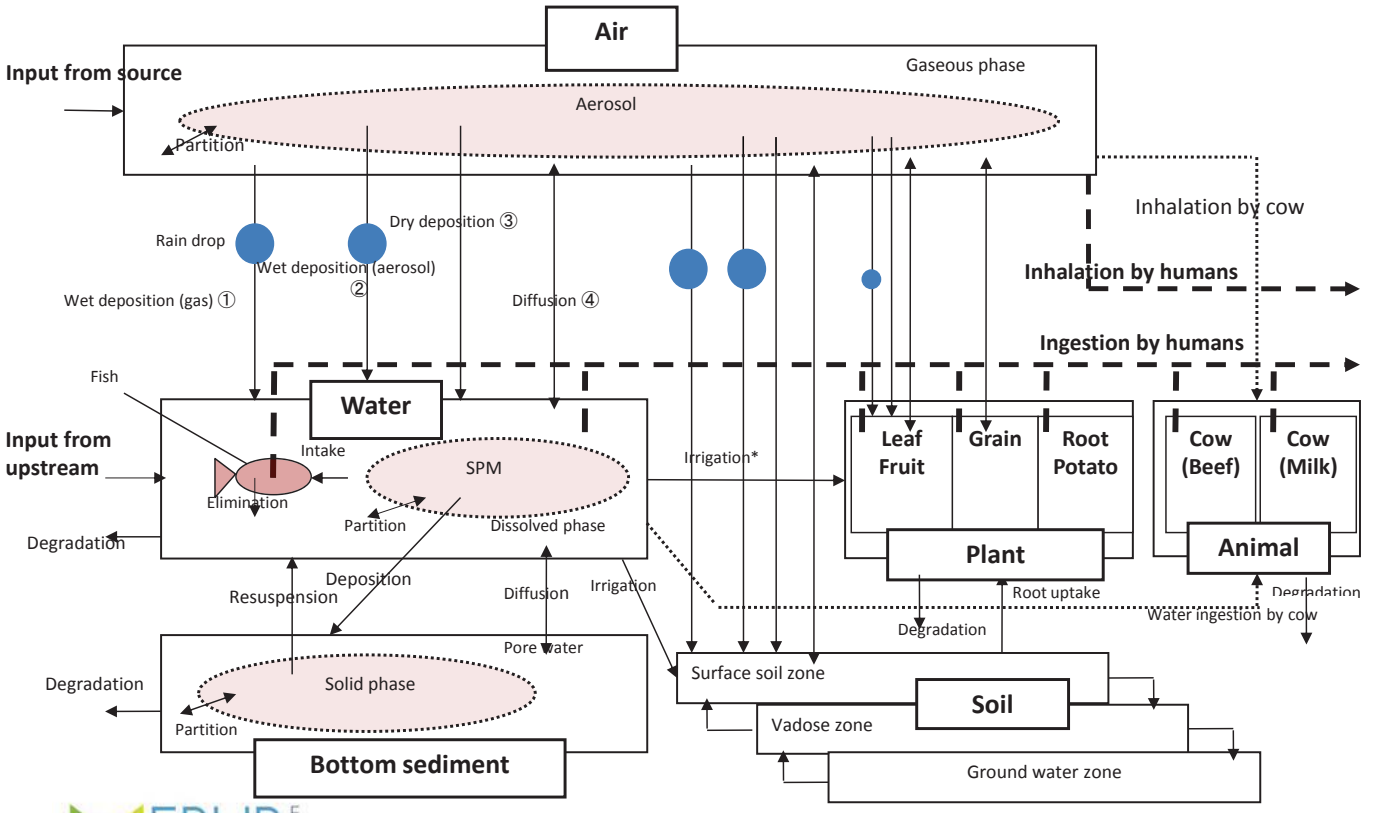
MERLIN-Expo: library of models



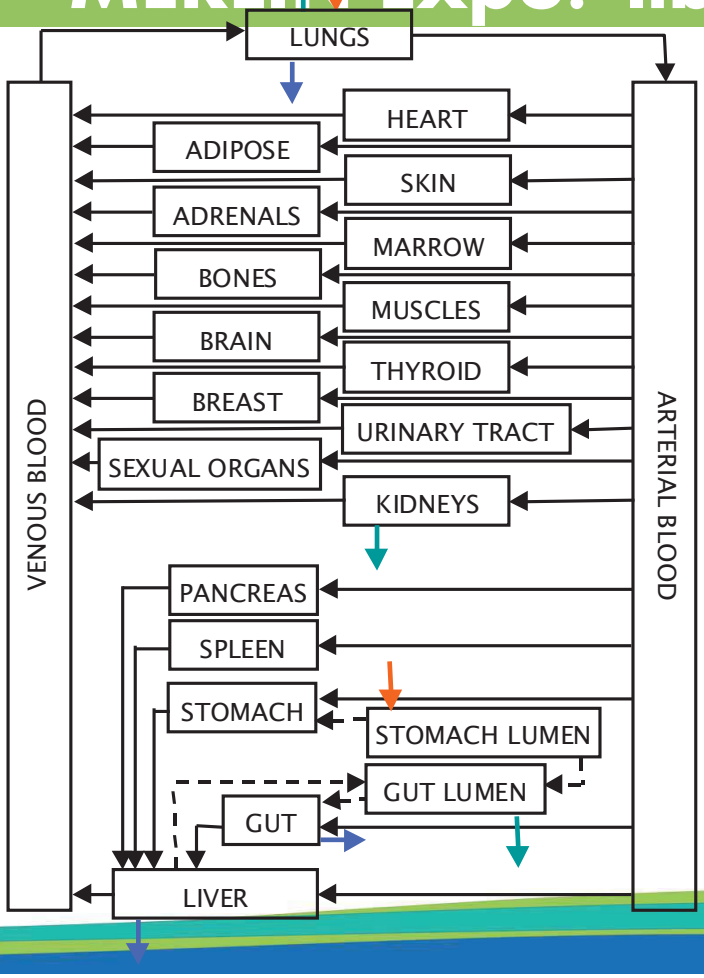
Describe the human body in detail and the redistribution processes of a substance:

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

MERLIN-Expo: library of models



MERLIN-Expo: library of models



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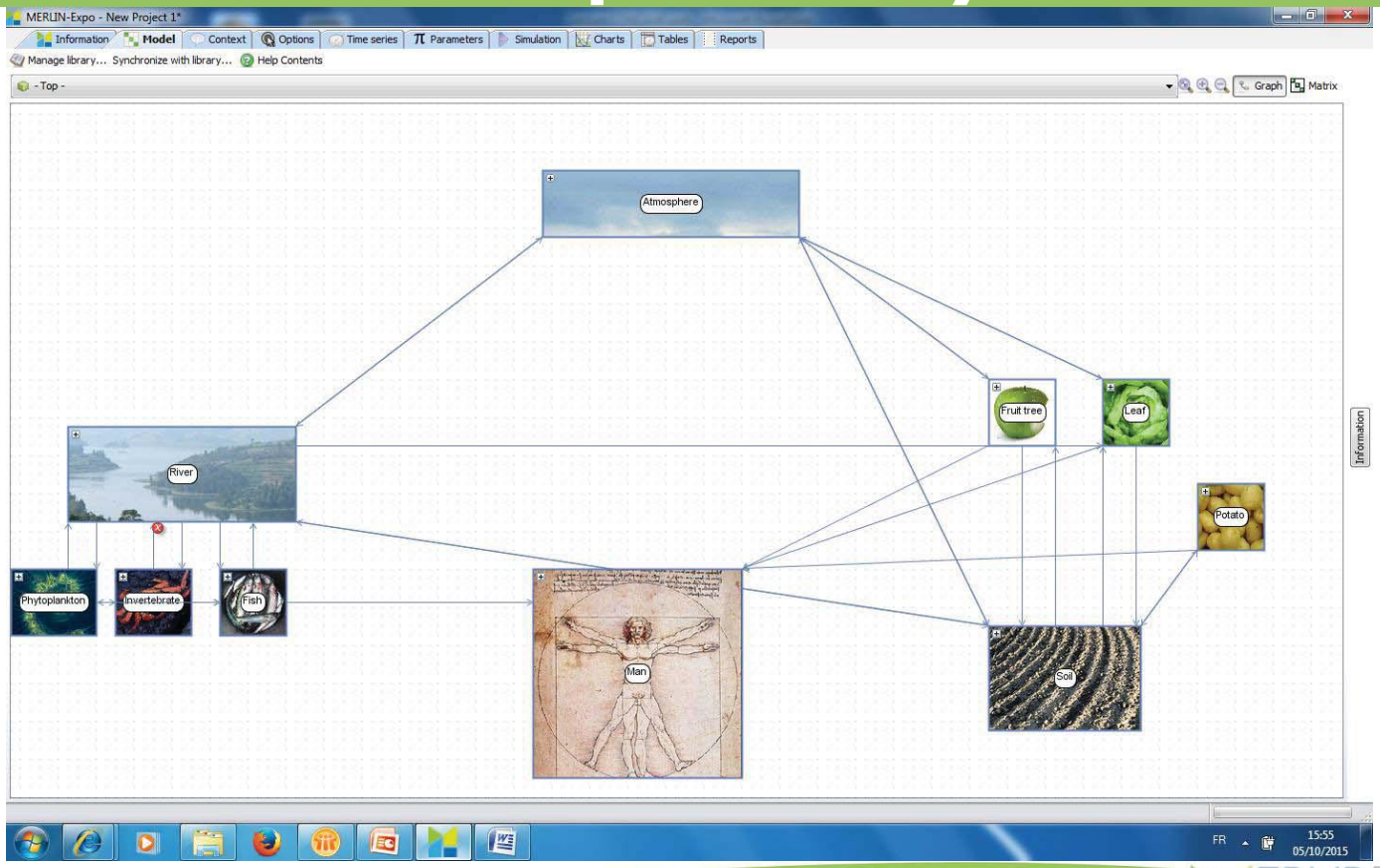
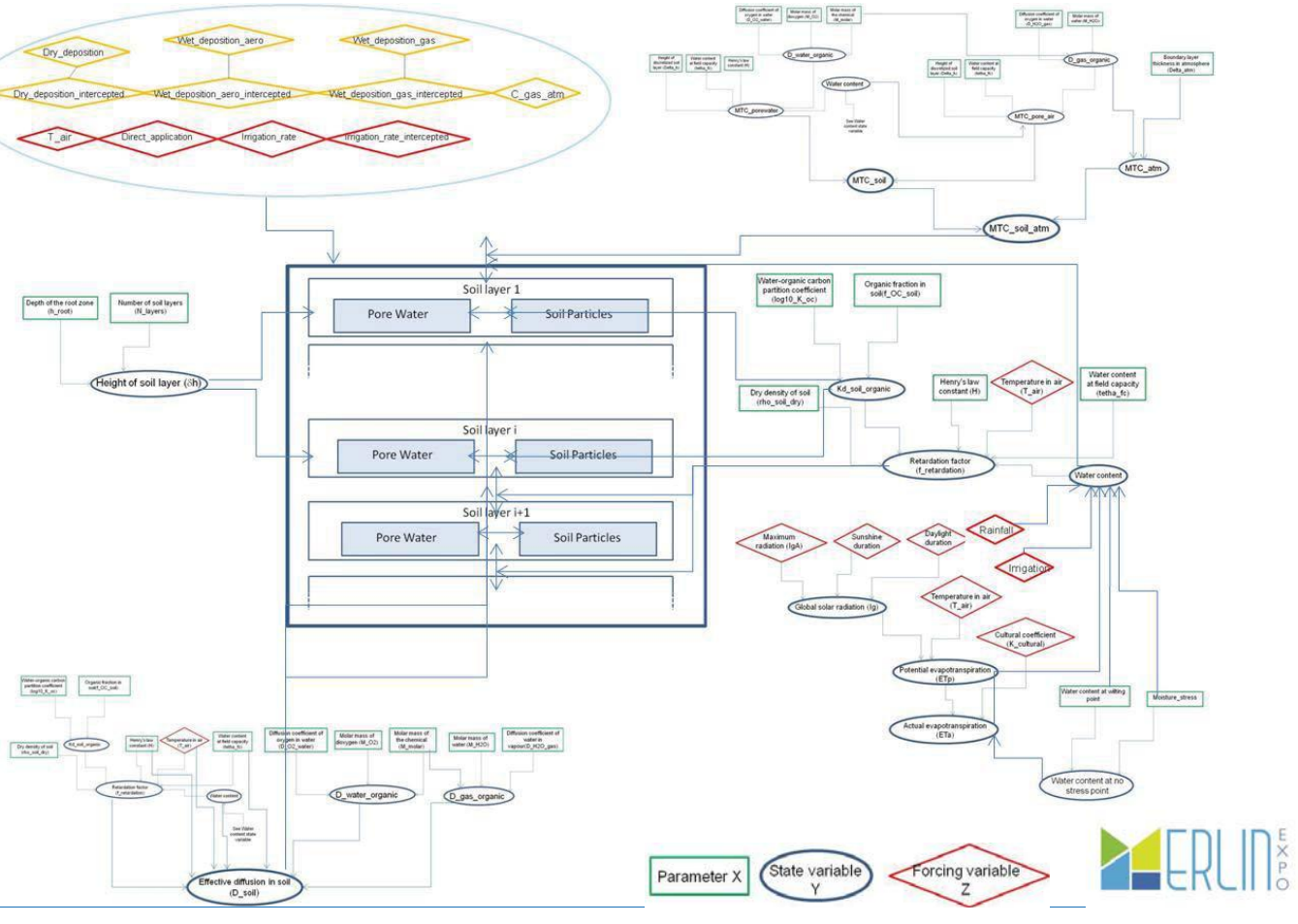
MERLIN-Expo: library of models



Content of the presentation

1. The MERLIN-Expo tool: general purpose and scope
2. Model structure
3. **Model documentation and parameterization**
4. Model scenarios

THE CHALLENGE: HOW TO COMMUNICATE A COMPLEX MODEL?



THE CHALLENGE: HOW TO COMMUNICATE A COMPLEX MODEL?

1. The models contain a large number of 'entities' (parameters, compartments, state variables, forcing variables, equations, etc)

2. The models are based on scientific background

3. The models require 'numbers' (parameter values, forcing variables values)

4. Different end-users are interested by the models (regulators, expert scientists)

ACTION PLAN FOR DISSEMINATION/COMMUNICATION

1. On line training

- Tutorials on models for 'beginners' (videos 10')
- Tutorials on software for 'beginners' (videos 10')

2. Documentation

3. Training courses

DOCUMENTATION

Model documentation must be:

1. **<u>comprehensive</u>, i.e. containing all the information needed for end-users**

2. **<u>transparent</u>, i.e. sources of information (e.g. Scientific background, parameter values, etc) must be accessible to end-users**

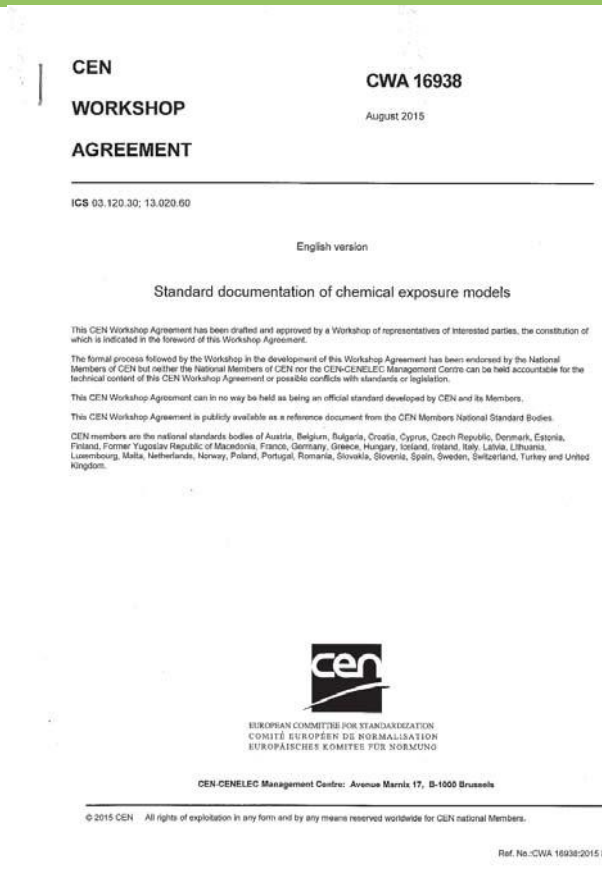
3. **<u>unambiguous</u>, i.e. 'variability' in interpretation among different end-users must be minimum (risk of poor reproducibility)**

4. **<u>structured</u>, i.e. to avoid a 'mixture' of general considerations, lengthy verbal descriptions, lengthy justifications, complex mathematics, etc (risk of inefficient and 'boring')**

5. **<u>adapted</u> for a targeted end-user, i.e. some of them want to read the entire model description in every detail while others only want to have a general idea of model's purpose, structure and/or processes.**

→ **Working group CEN (with contributions from JRC, IRSN, TNO, UBA, etc)**

DOCUMENTATION



CEN

WORKSHOP

AGREEMENT

CWA 16938

August 2015

ICS 03.120.30; 13.020.60

English version

Standard documentation of chemical exposure models

This CEN Workshop Agreement has been drafted and approved by a Workshop of representatives of interested parties, the constitution of which is indicated in the foreword of this Workshop Agreement.

The formal process followed by the Workshop in the development of this Workshop Agreement has been endorsed by the National Members of CEN but neither the National Members of CEN nor the CEN-CENELEC Management Centre can be held accountable for the technical content of this CEN Workshop Agreement or possible conflicts with standards or legislation.

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EUROPEAN COMMITTEE FOR STANDARDIZATION
COMITÉ EUROPÉEN DE NORMALISATION
EUROPÄISCHES KOMITEE FÜR NORMUNG

CEN-CENELEC Management Centre: Avenue Marnix 17, B-1000 Brussels

Ref. No.:CWA 16938:2015 E

CEN standard is based on:

1. **a clear terminology**

2 Definitions and abbreviations

2.1 Definitions

For the purposes of the present document, the following terms and definitions apply.

2.1.1
accuracy
closeness of a measured or computed value to its "true" value, where the "true" value is obtained with perfec information

NOTE Due to the natural heterogeneity and stochasticity of many environmental systems, the "true" value generally derives from spatial and temporal aggregation.

2. **a comprehensive review of required information (model applicability domain, model components, scientific background, numerical data, mathematics, etc)**

3. **a proposal for a structured documentation framework: four levels**

Level 1: Basic knowledge

Elements	Items
3.2 Model purpose	3.2.a Purpose
	3.2 b Potential decision and regulatory framework
	3.2.c Chemicals
	3.2.d Target model users (optional)
3.3 Model components	3.3.a Compartments
	3.3.b Input data (including loadings) – list and describe
	3.3.c Loss processes – list and describe
	3.3.d Exposure routes and/or exchanges between model media – list and describe
	3.3.e Coupled models (if applicable)
	3.3.f Forcing variables – list and describe along with units
	3.3.g Parameters – list and describe along with units
	3.3.h State variables – list and describe along with units
	3.3.i Constants
3.4 Model mode and type	3.4.a Model Mode
3.5 Model applicability	3.5.a Spatial scale and resolution
	3.5.b Temporal scale and resolution
	3.5.c Human population

Level 2: Process knowledge (Scientific background)

Process	Aspect
Process n°1	Rationale, e.g. importance of taking into account the process and its role in the model
	Selected model and underlying assumptions
	Model type (choose in chapter 3.4 the features of the model used for representing the process)
	Alternative models and limits
Process n°2	Etc.

Level 3: Input data

Section	Item
State variable n°1	Initial and/or boundary conditions
State variable n°2	Etc.
Parameter n°1	Physical/chemical/biological/empirical meaning (e.g. description of the parameter)
	Factors influencing parameter value (e.g. explaining why the parameter value can be variable or uncertain)
	Role in the model (e.g. explaining where, why and how is the parameter used in the model)
	Database used for parameter estimation (referring sources in the literature or elsewhere used for proposing/deriving parameter value(s))
	Parameter estimation type (explain if the parameter value(s) were estimated by calibration, statistical analysis of large database(s), extrapolation, expert elicitation, QSAR model, mechanistic approach, etc.)
	Parameter default value and/or probability density function (clearly present the parameter values proposed in the model based on the previous analysis)

Level 4: Mathematical knowledge (equations)

Section	Item
State variable n°1	Parameters required for calculating State variable 1
	Forcing variables required for calculating State variable 1
	Other state variables required for calculating State variable 1
	Description of the equation used for calculating State variable 1
State variable n°2	Etc.

Level 5: Model evaluation (optional)

Section	Item
Input data for evaluation	3.6.a Source and type of data used for evaluation, including information on accuracy, variability and precision (if applicable)
	3.6.a Dataset used for calibrating the model (training dataset)
	3.6.a Dataset used for verifying the model (validation dataset)
Model verification	3.6.b Results of model calibration
	3.6.c Results of model accuracy
Uncertainty and sensitivity analysis	3.6.d Uncertainty related to framework and structure of the model (qualitative uncertainty)
	3.6.e Method(s) used for quantitative uncertainty/sensitivity analysis
	3.6.d Results of model uncertainty analysis
	3.6.e Results of model sensitivity analysis

All the models included in the MERLIN-Expo library are documented according to this CEN framework

1. On line training

- **Tutorials on models for 'beginners'**
- **Tutorials on software for 'beginners'**

2. Documentation

3. Training courses

Regulators training course – France – February 2015

Belgrade training course – May 2015

SETAC – Barcelona – May 2015

Informa conf – Barcelona – September 2015

Summer school – Italy – June 2015

Some examples of parameterization

- **Use of QSAR models (from ChemProp or VEGA)**

Several QSAR models were tested for parameterizing Koc e.g.

1. **Sablić et al (1995; 1996):** hierarchical decision tree, with 20 different equations in total according to chemical class
2. **Schüürmann et al (2006):** QSAR model based on 29 parameters (molecular weight, bond connectivity, molecular E-state, fragment correction factors);calibrated on 457 substances; validated on 114 substances
3. **Tao et al (1999) :** QSAR model based on 98 parameters (fragment constants, structural factors);calibrated on 430 substances; validated on 162 substances
4. **Huuskonen (1999) :** QSAR model based on 12 database with organic pesticides
5. **Franco et al (2008, 2009):** QSAR model for ionizable compounds (monovalent organic acids and bases) - Neutral and ionic fractions are calculated from the substance pKa and the surrounding pH

➡ Selection according to applicability domain

- **Uncertainty of QSAR models**

$$LogK_{oc,p} \sim \overline{LogK_{oc,p}} + t_{n-k-1}.SE(\overline{LogK_{oc,p}})$$

Standard error of the model

Number of data in the training set

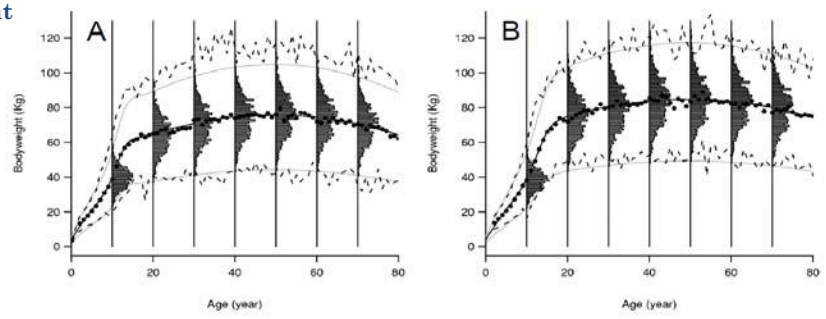
Number of descriptors in the model

Some examples of parameterization

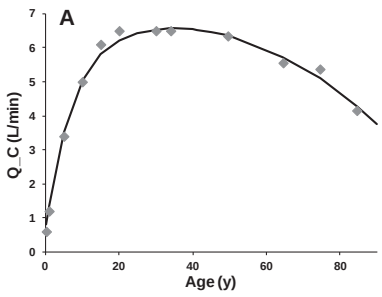
- **Physiological parameters for PBPK modeling**

Inter-individual variability

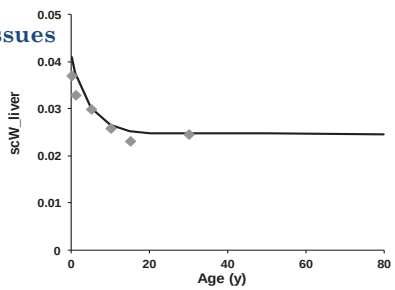
Bodyweight



Cardiac output



Relative weight of tissues



etc...

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1. The MERLIN-Expo tool: general purpose and scope
2. Model structure
3. Model documentation and parameterization
4. **Model scenarios**
   - ✓ **Internal exposure**
   - ✓ Full-chain assessment for biota exposure
   - ✓ Reconstruction of past exposures
   - ✓ Investigation of mechanistic processes

Internal exposure (to PAHs) (1)

Environ Geochem Health (2011) 33:371–387
DOI 10.1007/s10653-011-9382-6

ORIGINAL PAPER

Linking fate model in freshwater and PBPK model to assess human internal dosimetry of B(a)P associated with drinking water

Philippe Ciffroy · T. Tanaka · E. Johansson · C. Brochot

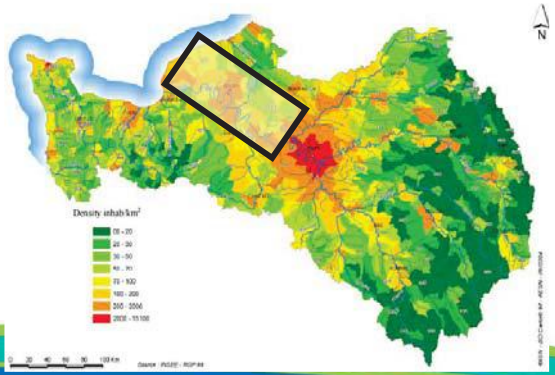
Atmospheric Environment 44 (2010) 958–967
Contents lists available at ScienceDirect
Atmospheric Environment
journal homepage: www.elsevier.com/locate/atmosenv

Contribution of atmospheric emissions to the contamination of leaf vegetables by persistent organic pollutants (POPs): Application to Southeastern France

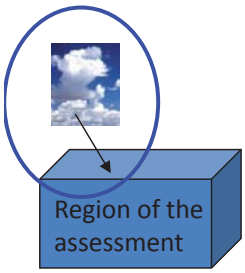
Solen Quéguiner[a], Luc Musson Genon[a,*], Yelva Roustan[a], Philippe Ciffroy[b]
[a] Cerea, Joint laboratory École des Ponts ParisTech/EDF R&D, Université Paris-Est, 6-8 avenue Blaise Pascal, 77455 Marne la Vallée Cedex 2, France
[b] Laboratoire National d'Hydraulique et Environnement, EDF R&D, 6 quai Watier 78401 Chatou Cedex, France

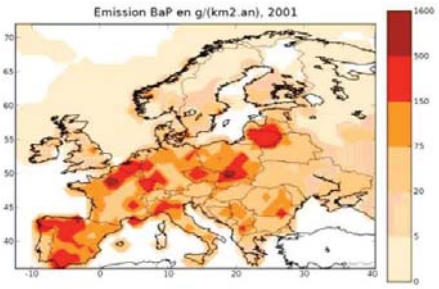
Target region: A region situated on **the Seine river watershed**, just downstream of Paris, France

Target substance: **Benzo (a) Pyrene**



Internal exposure (to PAHs) (1)





Advection/dispersion of aerosols

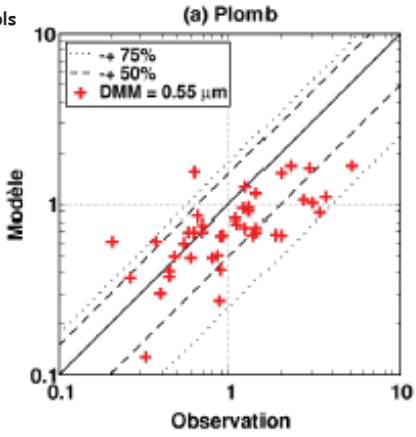
Dry deposition = f(particles diameters, LUC, meteo fields)

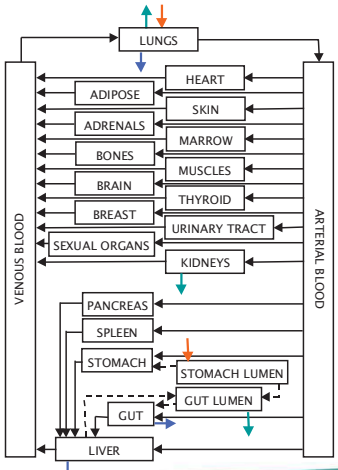
Wet deposition (in-cloud and below-cloud washout)

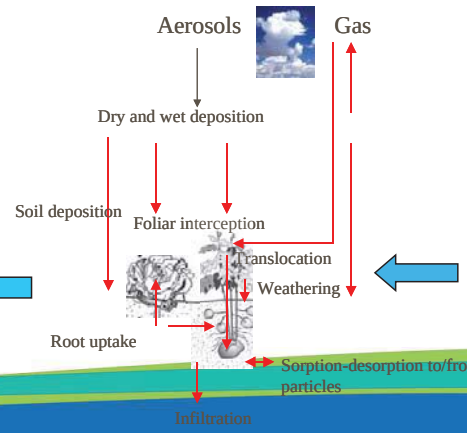
Polair3D

vs

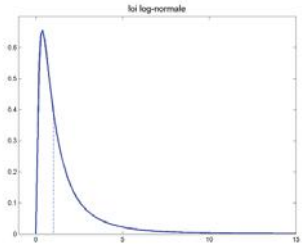
Monitoring







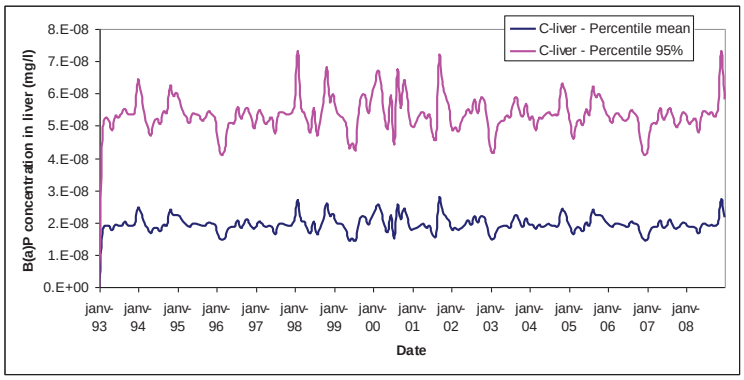
Accuracy function ε



Internal exposure (to PAHs) (1)

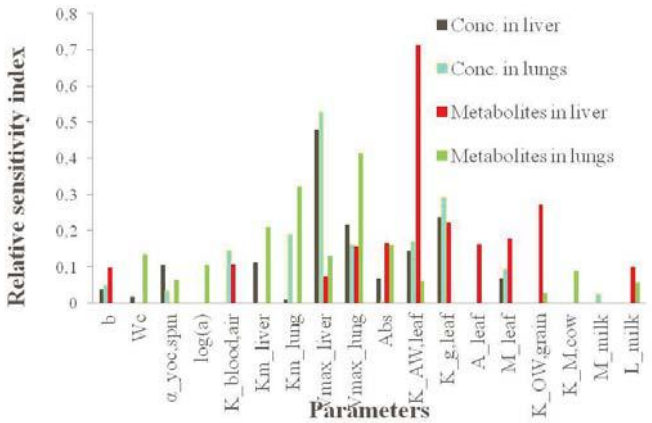
B(a)P in liver

(mean and pessimistic scenario)



Sensitivity analysis

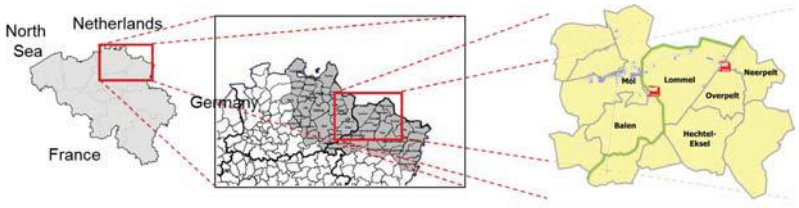
(identification of the most sensitive parameters of the full chain modeling on several outputs)



Internal exposure (2)

Context

- Northern Campine region of Belgium
- Past: presence of zinc smelters → historical contamination with heavy metals



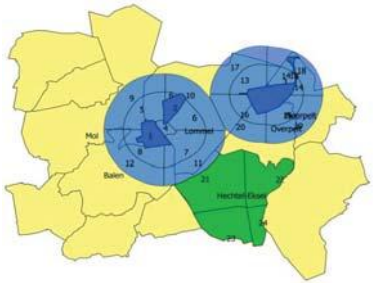
- 2 subpopulations – case studies

	Children	Adults
N° of participants	334	1214
Age	2-6 yr.	19-79 yr.
Chemical	Lead	Arsenic
Human matrix	Blood	Urine

Internal exposure (2)

Study area

- Children & adults living/spending time in 4 main areas
  - Industrial area (deep blue)
  - Surrounding area (pale blue)
  - Reference area (green)
  - Background/external area (yellow)



Available Pb & As data

- Environment → soil, outdoor air, indoor air & dust
- Foods & drinks
- Human matrices → blood & urine

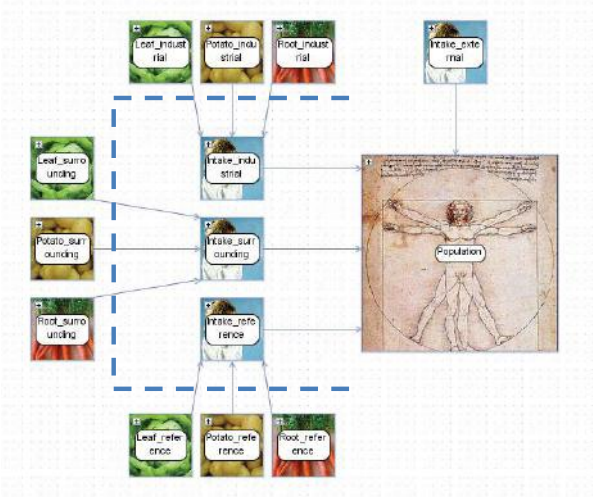
	Children	Adults
N° of participants	334	1214
Age	2-6 yr.	19-79 yr.
Chemical	Lead	Arsenic
Human matrix	Blood	Urine

Other available data

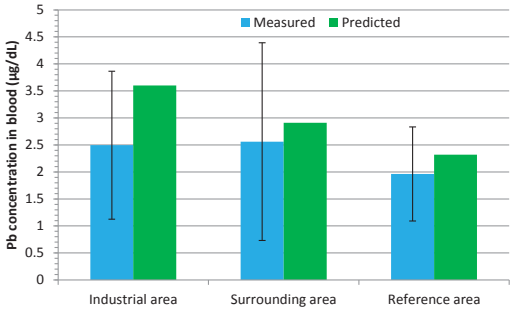
- Food frequency questionnaires → local & shop
- Time activity patterns → hours/year spent in 4 main areas (indoor & outdoor)

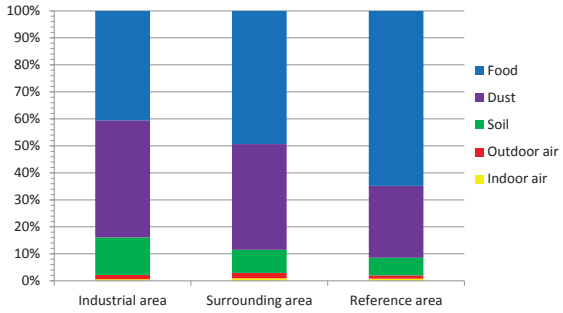
Internal exposure (2)

Model implementation



Some results





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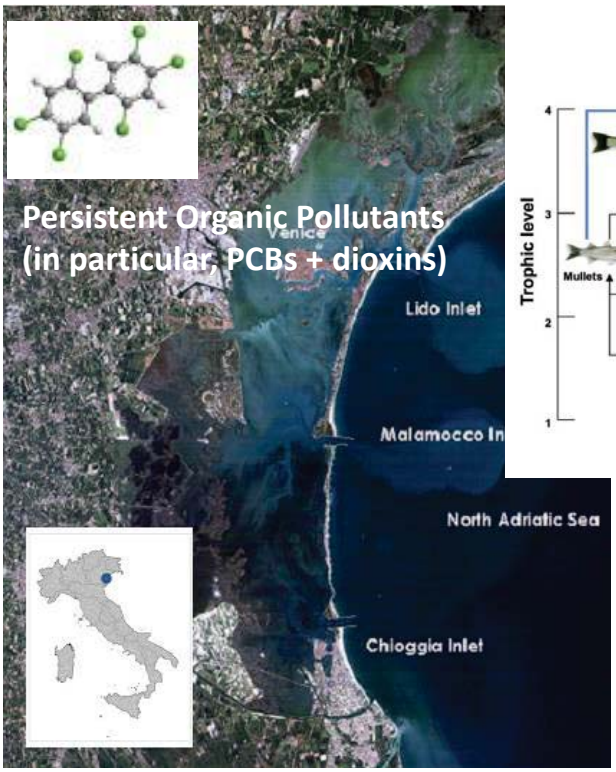
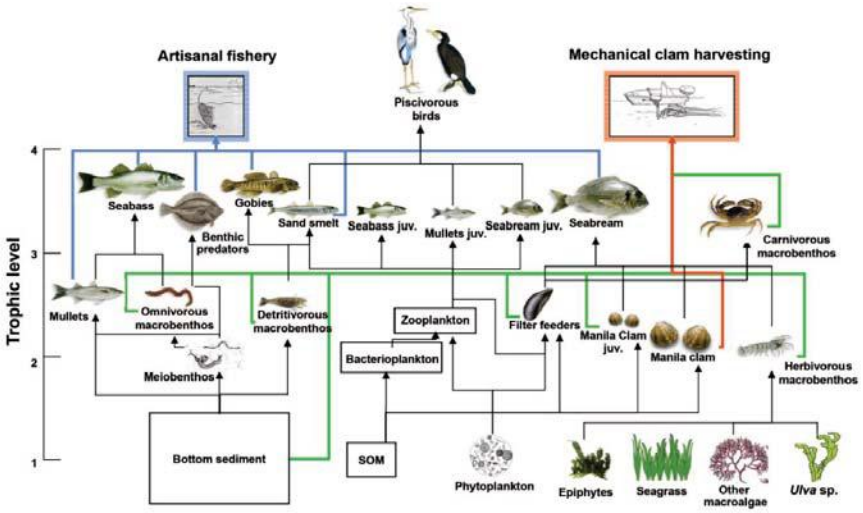
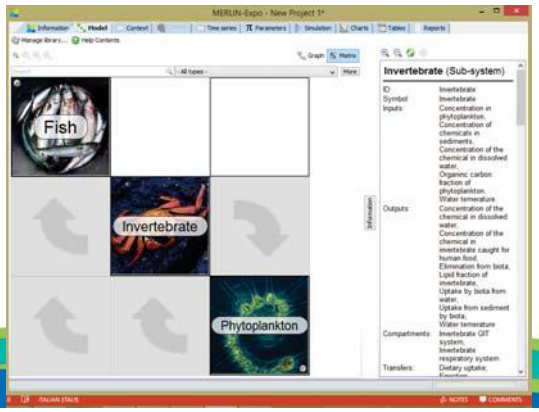
   - ✓ Reconstruction of past exposures
   - ✓ Investigation of mechanistic processes

Full-chain assessment for biota exposure

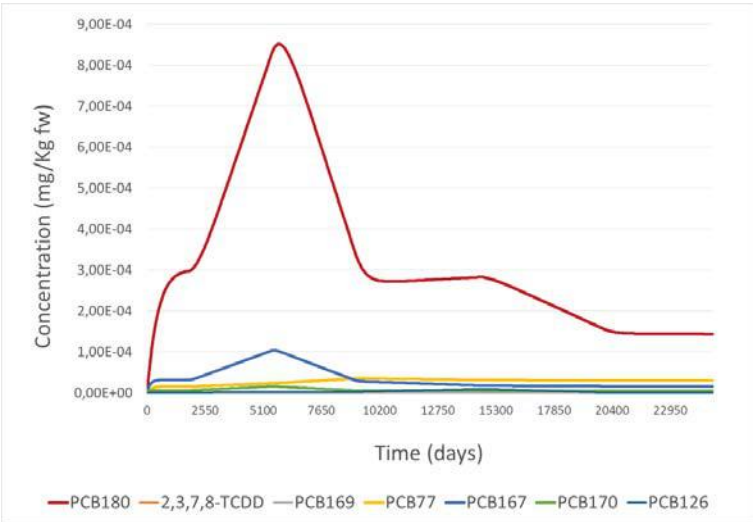






Full-chain assessment for biota exposure

Chemical concentrations in fish *Zosterissessor ophiocephalus* (Goby)



CHEMICAL	SIMULATION mg Kg^{-1} fw	MEASURED mg Kg^{-1} fw
2,3,7,8-TCDD	8,62E-10	9,31E-10
PCB77	2,84E-05	3,06E-05
PCB126	5,40E-07	5,90E-07
PCB167	1,51E-05	1,61E-05
PCB169	4,86E-07	5,36E-07
PCB170	4,34E-06	4,45E-06
PCB180	[illegible]	1,43E-04

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Reconstruction of past exposures

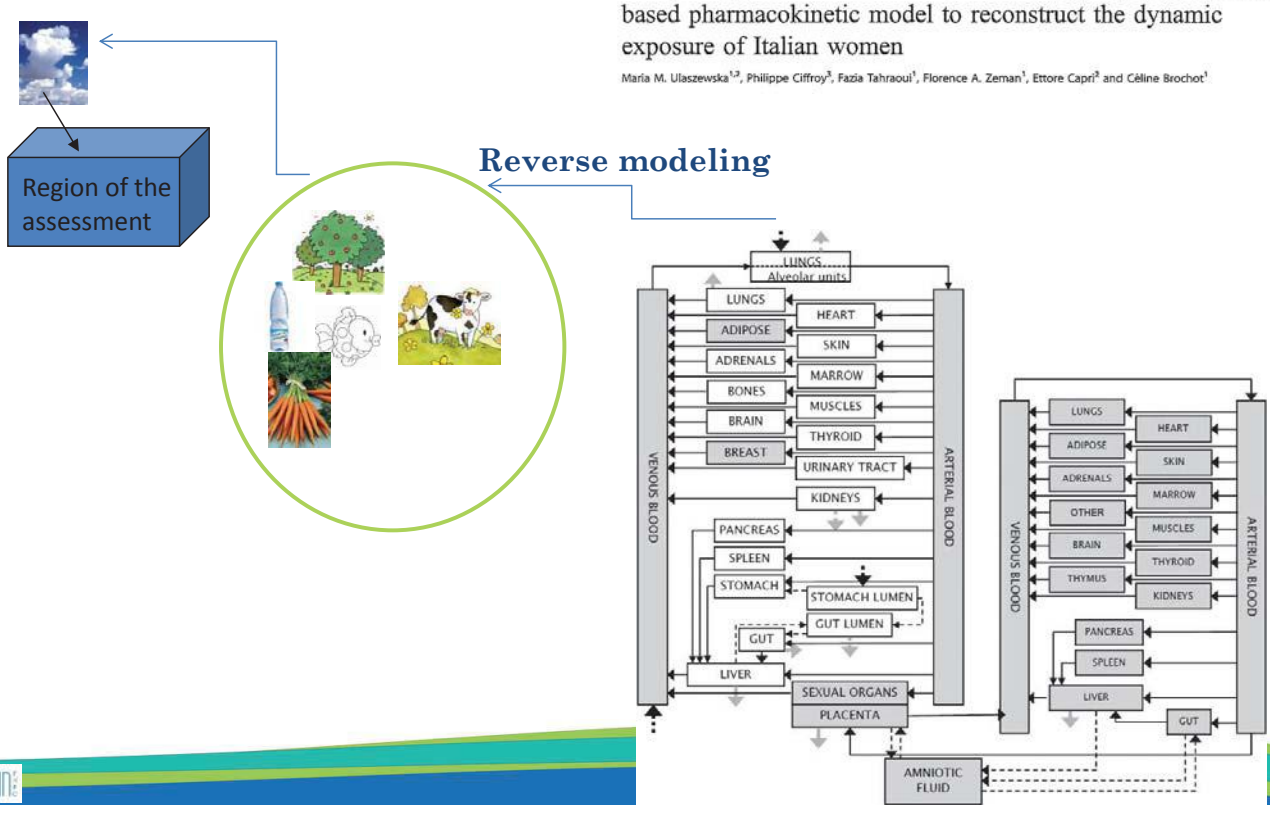
Journal of Exposure Science and Environmental Epidemiology (2012) 1–9

www.nature.com/jes

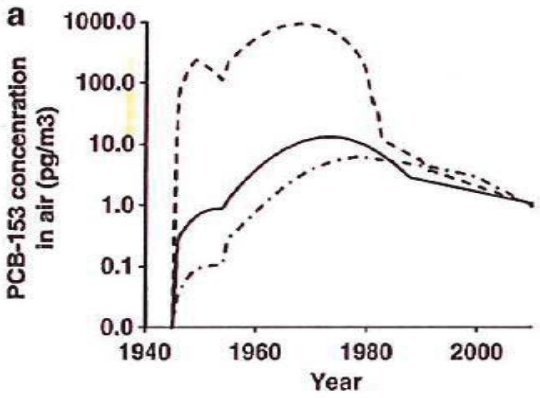
ORIGINAL ARTICLE

Interpreting PCB levels in breast milk using a physiologically based pharmacokinetic model to reconstruct the dynamic exposure of Italian women

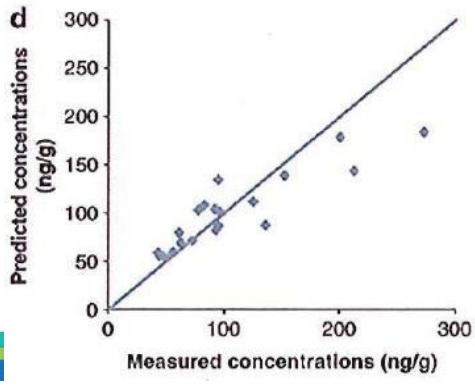
Maria M. Ulaszewska[1,2], Philippe Ciffroy[3], Fazia Tahraoui[1], Florence A. Zeman[1], Ettore Capri[3] and Céline Brochot[1]



Reconstruction of past exposures



Several potential scenarii (according to economic data, etc)



Selection of the most probable historical scenario

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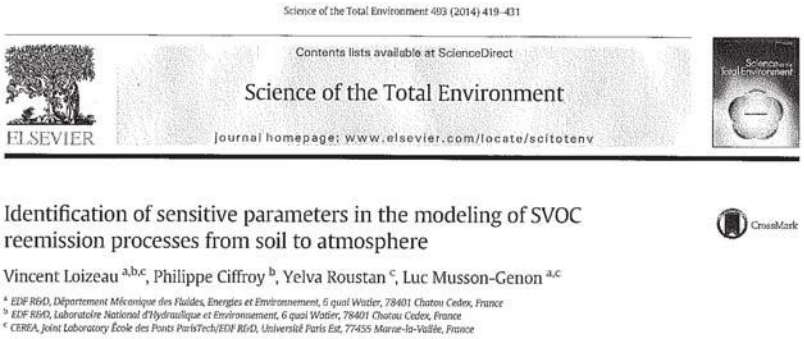
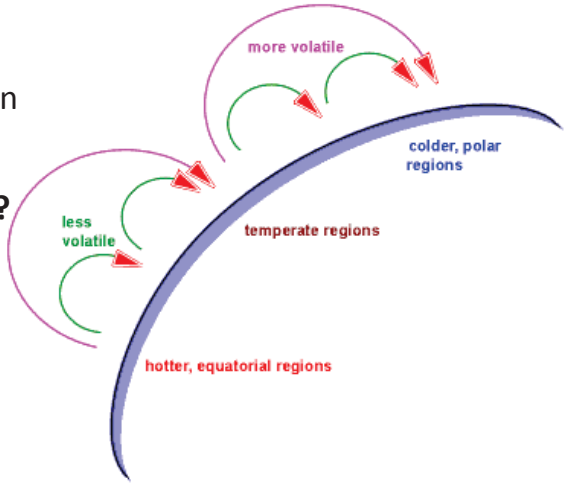
   - ✓ **Investigation of mechanistic processes**

Investigation of mechanistic processes

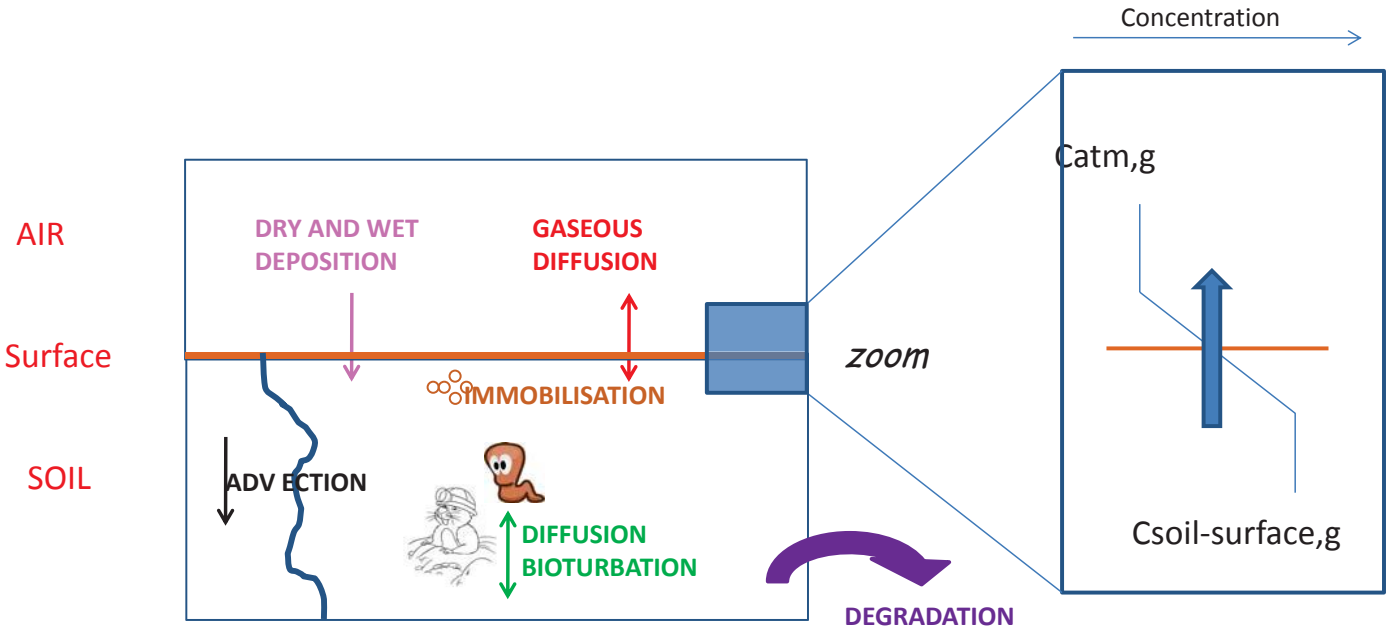


- Grasshopper effect : Succession of several processes
  - Dispersion in atmosphere
  - Dry and wet deposits onto soil
  - Reemission through evaporation or volatilization

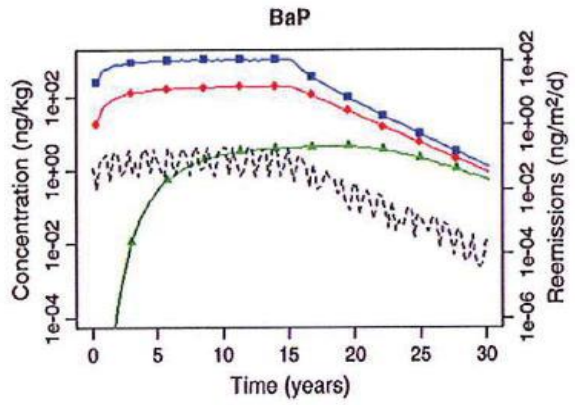


- **How to simulate reemission process? (which processes are preponderant, which are the most sensitive environmental variables, etc?)**

Investigation of mechanistic processes



Investigation of mechanistic processes



Dynamics of chemicals in soils and dynamics of reemission before/after ban regulation

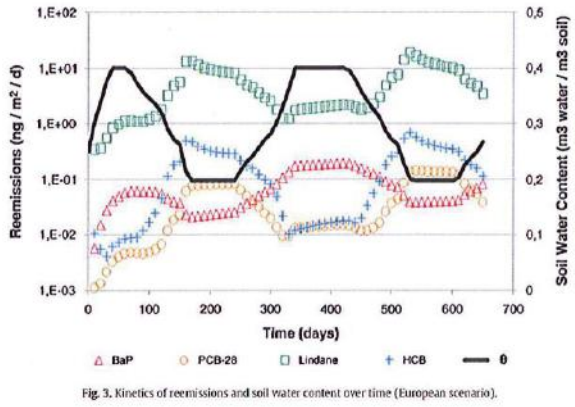
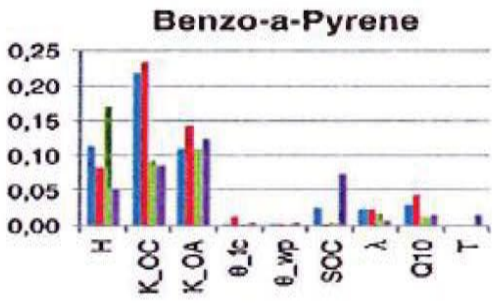


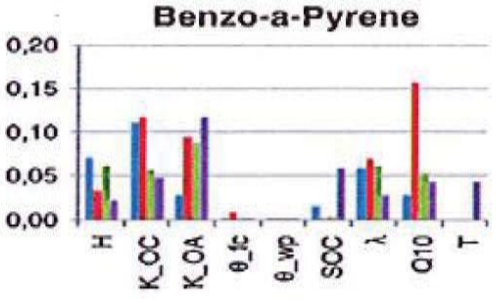
Fig. 3. Kinetics of reemissions and soil water content over time (European scenario).

Seasonal dynamics of chemicals in soils

Investigation of mechanistic processes



Sensitivity analysis EFAST → identification of the most sensitive parameters



How to improve description occurring at the soil-atmosphere interface

4FUN project has received funding from the European Union's Seventh Programme for research, technological development and demonstration under grant agreement N° 308440.

Modeling from external exposure dose down to internal doses – INTEGRA model

Denis Sarigiannis[1,2,3], Spyros Karakitsios[1,2], Alberto Gotti[1,2]

[1]Environmental Engineering Laboratory (EnvE-Lab), Department of Chemical Engineering, Aristotle University of Thessaloniki GR-54124, Thessaloniki, Greece

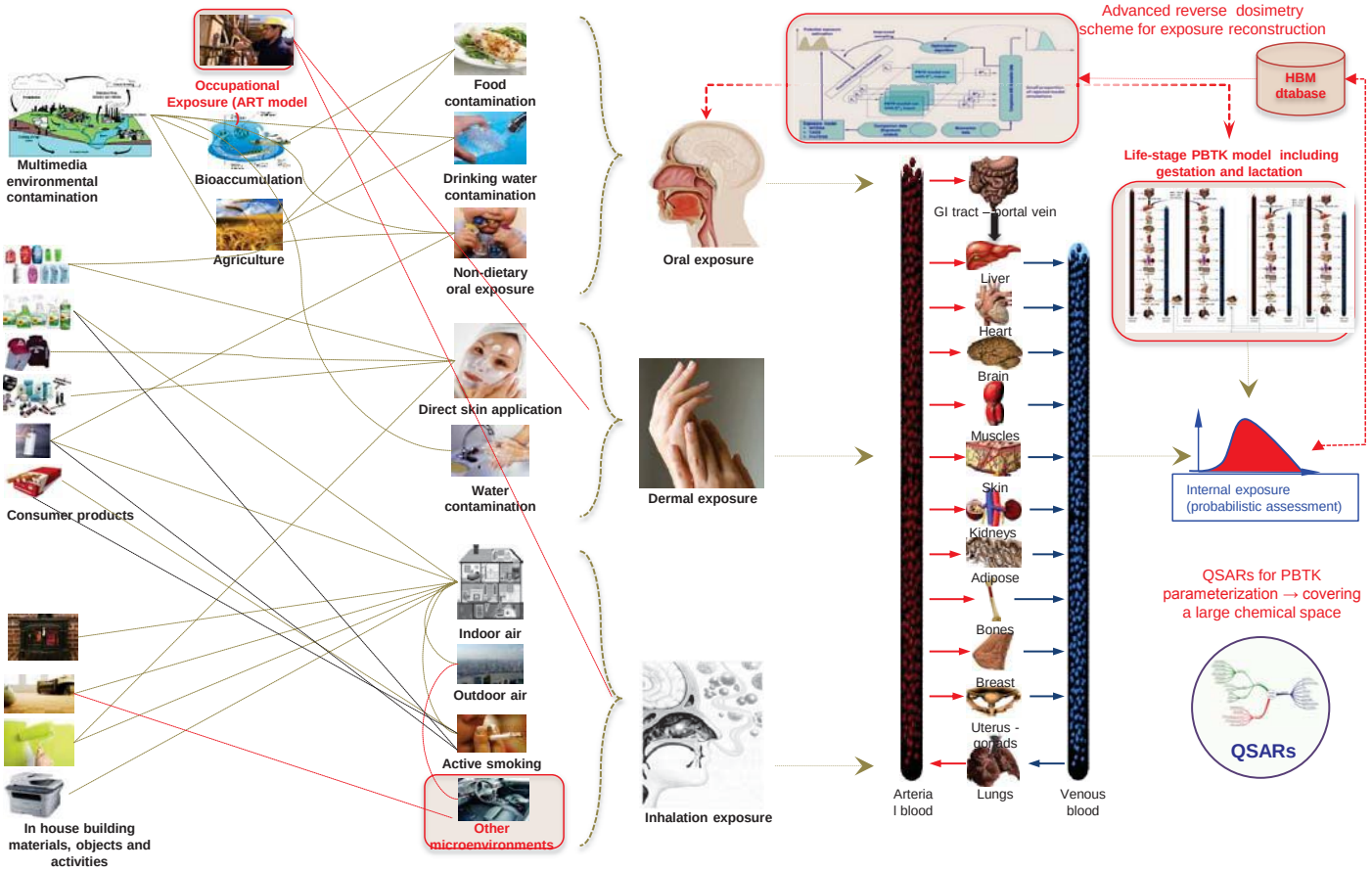
[2]Centre for Research and Technology Hellas (CE.R.T.H.), Thessaloniki, 57001, Greece

[3]Chair of Environmental Health Engineering, Advanced Study Institute, Pavia, Italy

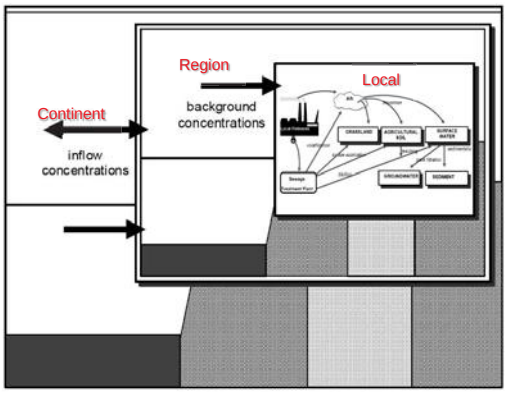
Purpose and scope of INTEGRA

- The INTEGRA computational platform has been developed in the frame of several CEFIC LRI-funded projects (INTERA, TAGS and INTEGRA) and it is currently used extensively (especially INTERA)
- In the context of REACH, INTEGRA can be used for integrated exposure modeling, bringing together external and internal exposure.
- INTEGRA uses REACH use descriptors to identify pathways of exposure
- INTEGRA output can be used to fill refined exposure estimates across the value chain of chemicals in a REACH dossier
- It can also support refined exposure-based risk assessment and use of human biomonitoring data since it unites external and internal exposure estimates
- A key feature is the estimation of external and internal exposure for specific target groups (age, gender, etc.) making thus the exposure assessment more targeted and the corresponding risk management cost-effective

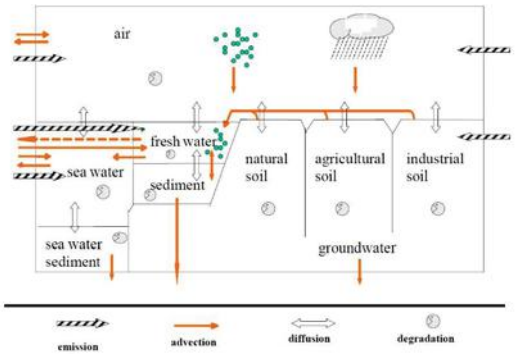
INTEGRA methodological concept

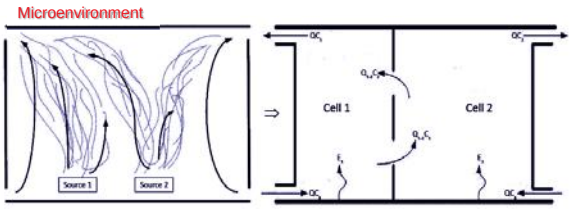


Multi-scale environmental exposure model



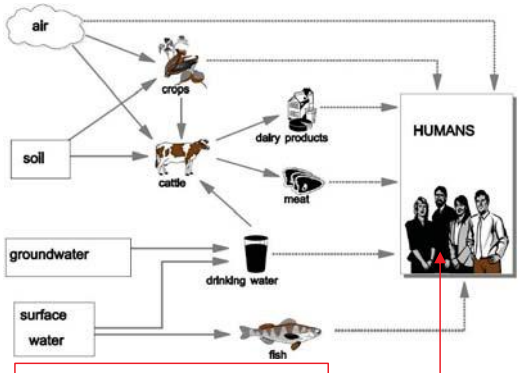
Multimedia environmental modelling, taking into account mass transfer and transformation across different scales and media, following ECHA recommendations





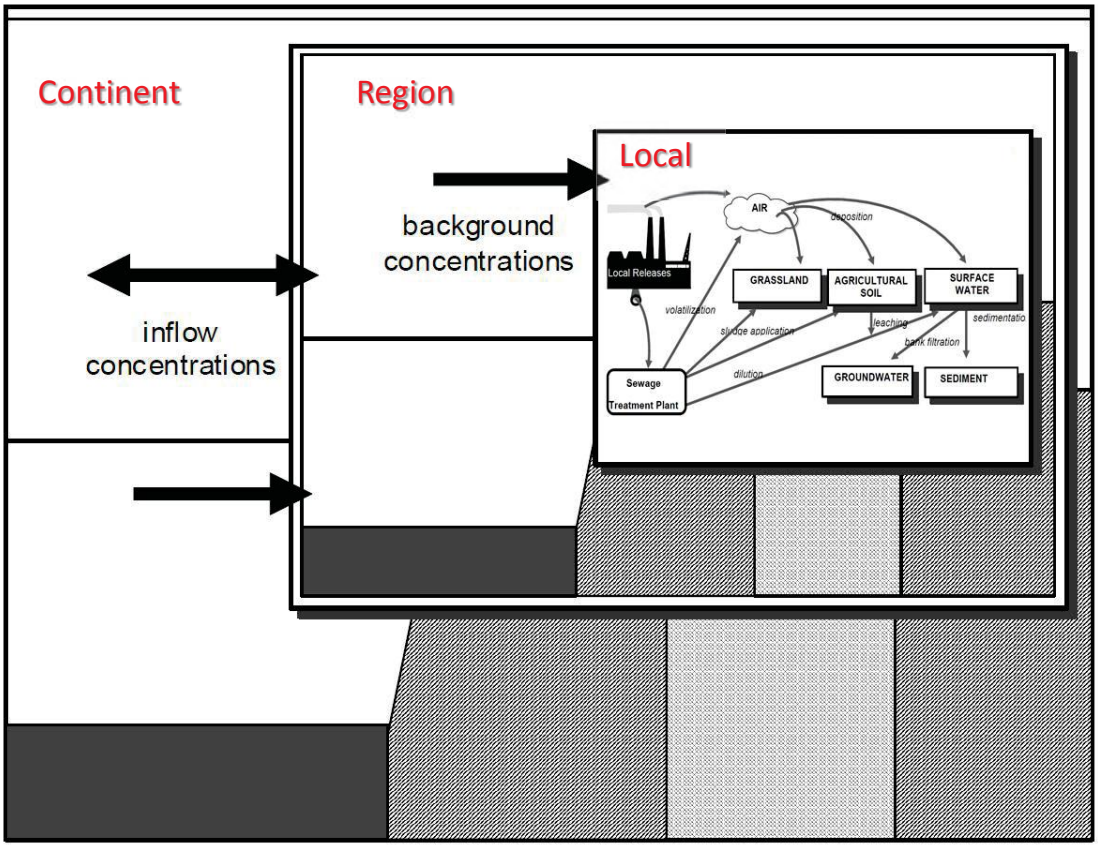
Detailed micro-environmental concentrations taking into account interactions among different media (gas, particles and dust)

Detailed exposure modelling taking into account multiple pathways and routes of exposure

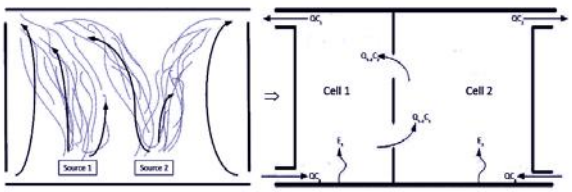


Consumer products

Multimedia environmental modelling



Micro-environmental / indoor air modelling



Gas phase mass equilibrium

$$V\frac{dC_{chem\_gas}}{dt} = E_{chem\_gas} - Q_{ind\_out}\cdot\left(C_{chem\_gas} - C_{chem\_gas\_out}\right)\cdot V$$
$$-k\cdot C_{chem\_gas}\cdot V - r_p\cdot\left(C_{chem\_gas} - \frac{C_{chem\_PM}}{K_p\cdot C_{PM}}\right)\cdot V$$
$$-r_d\cdot\left(\left(C_{chem\_gas} + C_{chem\_PM}\right)\cdot V - \frac{C_{chem\_dust}\cdot m_{\_dust}}{K_{\_dust}}\right)$$

Particles phase mass equilibrium

$$V\frac{dC_{chem\_PM}}{dt} = r_p\cdot\left(C_{chem\_gas} - \frac{C_{chem\_PM}}{K_p\cdot C_{PM}}\right)\cdot V$$
$$-Q_{ind\_out}\cdot\left(C_{PM} - C_{PM\_out}\right)\cdot\frac{C_{chem\_PM}}{C_{PM}}\cdot V$$

Dust phase mass equilibrium

$$V\frac{dC_{chem\_dust}}{dt} = r_d\cdot\left(\left(C_{chem\_gas} + C_{chem\_PM}\right)\cdot V - \frac{C_{chem\_dust}\cdot m_{\_dust}}{K_{\_dust}}\right)$$

E_{chem_gas} : chemical emission rate

Q_{int_out} : Indoor/outdoor air exchange rate

K : chemical decay coefficient

K_P : gas/particles partition coefficient

K_{dust} : gas/dust partitioning coefficient

r_P, r_d : partitioning kinetics

V : location volume

C_{PM} : PM concentration indoors

C_{PM_out} : PM concentration outdoors

C_{chem_gas} : chemical concentration in gas phase

C_{chem_PM} : chemical concentration in PM phase

C_{chem_dusts} : chemical concentration in dust phase

$m_{\_dust}$: mass of dust in the location

Oral exposure – Non Dietary

Soil ingestion uptake model

m – amount of chemical taken up by the body (ug)
C_{soil} - Concentration of the chemical in soil (ug/mg)
q_{soil} - Amount of soil ingested (mg)
$delt_{exposure}$ - Duration of exposure event (h)
$abs_{fraction}$ – absorbed fraction from the ingested quantity

$$\frac{dm}{dt} = \frac{C_{soil} \cdot q_{soil\_ingested} \cdot abs_{fraction}}{delt_{\text{exposure}}}$$

Dust ingestion uptake model

m – amount of chemical taken up by the body (ug)
C_{dust} - Concentration of the chemical in dust (ug/mg)
q_{dust} - Amount of dust ingested (mg)
$delt_{exposure}$ - Duration of exposure event (h)
$abs_{fraction}$ – absorbed fraction from the ingested quantity

$$\frac{dm}{dt} = \frac{C_{dust} \cdot q_{dust\_ingested} \cdot abs_{fraction}}{delt_{\text{exposure}}}$$

Object-to-mouth uptake model ingestion uptake model

m – amount of chemical taken up by the body (ug)
C_{dust} - Concentration of the chemical in dust (ug/mg)
q_{dust} - Amount of dust ingested (mg)
$delt_{exposure}$ - Duration of exposure event (h)
$abs_{fraction}$ – absorbed fraction from the ingested quantity

$$\frac{dm}{dt} = \frac{release_{rate} \cdot surface \cdot mouth_{duration} \cdot duration_{\text{exposure}} \cdot abs_{fraction}}{delt_{\text{exposure}}}$$

Personal Care Products ingestion uptake model

m – amount of chemical taken up by the body (ug)
$C_{PCP\ -\ Concentration}$ of the chemical in the Personal Care Product (ug/mg)
$q_{PCP\_ingested}$ - Amount of Personal Care Product ingested (mg)
deltexposure - Duration of exposure event (h)
absfraction – absorbed fraction from the ingested quantity

$$\frac{dm}{dt} = \frac{C_{PCP} \cdot q_{PCP\_ingested} \cdot abs_{fraction}}{delt_{\text{exposure}}}$$

Oral exposure
Dietary and through FCM

Dietary ingestion uptake model

C_i *is the chemical concentration of food category **i** in µg/g and **FC_{ijk}** is the daily average consumption in g/d of food category **i**, age category **j** and gender category **k** and **BWjk** is the Body Weight in kg of age category **j** and gender category **k***

$$DI_{ijk} = \frac{C_i \cdot FC_{ijk}}{BW_{jk}}$$

Food uptake / food contact materials migration

$$\frac{\partial C}{\partial t} = D_p \frac{\partial^2 C}{\partial x^2}$$

Food	Infants (0-12 months)	Toddlers (1-3 years)	Children (4-10 years)	Teens (11-18 years)	Adults
	Food consumption (g/d)				
Pasta, rice	17.0	25.0	24.2	64.1	74.6
Cereals	52.0	21.7	18.1	21.9	29.3
Breakfast cereals					74.6
Bread	30.4	39.6	41.8	123.7	130.3
Biscuits, crispy bread	5.0	15.2			21.3
Cakes, buns, puddings	21.5	10.0	25.9	55.4	45.9
Bakeries, snacks	2.2	7.7	9.1	102.7	10.6
Milk, milk beverages	386.3	307.3	276.5	212.6	188.3
Cream			2.5	4.1	4.8
Ice cream	17.0	18.3	17.8	25.8	15.2
Yogurt	38.0	43.1	26.3	39.2	36.0
Cheese	7.5	5.6	7.6	77.6	34.1
Eggs	6.3	6.3	9.4	15.4	31.1
Spreads	3.0				35.4
Animal fats	3.0	2.2	2.3	3.8	16.5
Vegetable oils	3.0	7.1	10.3	26.5	17.6
Meat, meat products	21.5	27.3	28.8	76.4	117.1
Sausage	26.0	9.5	9.0	29.4	42.7
Poultry	14.7	4.5	8.2	23.6	59.5
Fish	5.2	10.0	5.1	30.8	55.5
Vegetables	35.8	56.1	72.0	137.0	198.2
Potatoes	21.9	54.8	53.4	66.7	122.5
Fruits	117.3	91.6	113.2	103.4	220.5
Nuts, nut spreads	1.5		1.5		6.1
Preserves, sugar	3.0	6.8	7.6	8.8	14.8
Confectionery	6.0	13.3	30.9	22.2	29.3
Spices			5.1	7.8	31.6
Soups, sauces			1.7	2.7	41.3
Juices	72.0	64.2	59.2	78.0	101.9
Tea, coffee	3.3	1.4	2.1	4.7	
Or coffee					17.2
Or tea					3.9
Soft drinks	16.7	450.0	416.1	384.0	518.4
Beer			1.9	267.7	280.4
Wine			1.0	14.0	281.4
Spirits			0.0	10.0	10.3
Tap water			255.4	346.4	428.9
Bottled water			194.3	272.2	270.8
Commercial infant food	85.5				
Infant formulas	485	53	13.6		
Breast milk	336.0				

Inhalation exposure

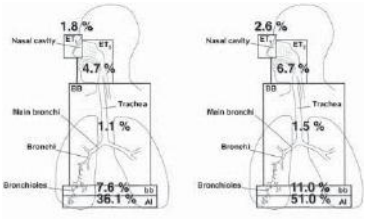
Personal exposure is equal to the average concentration of a pollutant that a person is exposed to over a given period of time. If over the given period of time, ***T***, the person passes through n locations, spending a fraction f_n of the period ***T*** in location n where the concentration of the pollutant under consideration is C_n, then the personal exposure for this period ***T***, represented by the concentration C_T, is given by:

$$E_T = \sum_n f_n \cdot C_n$$

Inhalation intake was estimated by the area under the curve of exposure ***E*** multiplied by the inhalation rate inh_n for each type of microenvironment ***n*** encountered, divided by the bodyweight ***BW*** and for the desired simulation time.

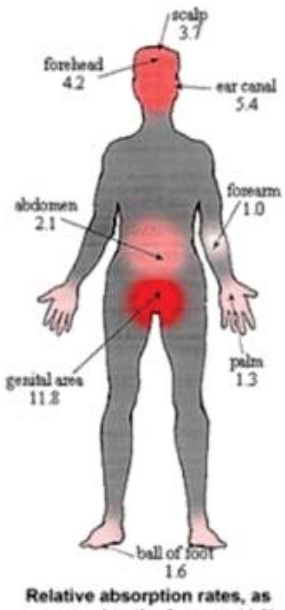
$$Intake_{inh} = \frac{\sum_n E_n \cdot ihn_n}{BW}$$

For **particles** and **adsorbed compounds**, deposition across the HRT is considered



	Inhalation rate correction coefficient			
Age	Resting/sleeping	Light	Moderate	Heavy exercise
3 months	0.56	0.63	1.19	2.50
1 year	0.43	0.63	0.99	1.99
5 years	0.47	0.63	1.11	2.15
10 years	0.51	0.63	1.81	3.29
15 years				
Male	0.55	0.63	1.82	3.78
Female	0.55	0.63	2.03	4.06
Adult				
Male	0.52	0.63	1.74	3.47
Female	0.51	0.63	2.08	4.33
	0.56	0.63	1.19	2.50

Skin exposure



Relative absorption rates, as compared to the forearm (1.0)

Instant application uptake model

m – amount of chemical taken up by the body (ug)
$C_{product}$ - Concentration of the chemical in product (ug/ml)
$area_{exp}$ - Skin area where the product is applied (cm^2)
permeability – the permeability of the skin (cm/h)

$$\frac{dm}{dt} = permeability \cdot C_{product} \cdot area_{\exp}$$

Migration uptake model

m – amount of chemical taken up by the body (ug)
$migration_{rate}$ - Rate of migration from the product (ug /cm^2/h)
$uptake_{factor}$ – uptake factor
$area_{exp}$ - Skin area where the product is applied (cm^2)

$$\frac{dm}{dt} = migration_{rate} \cdot uptake_{factor} \cdot area_{\exp}$$

Rubbing off model

w_f - the weight fraction of the compound in the product (fraction)
$F_{dislodge}$ - the dislodgeable amount of product or used formulation that can be rubbed off per unit surface area (kg/ m^2)
S_{exp} - the surface area of the exposed skin (m^2)
R_{trans} - area rubbed per unit time (m^2/s)

$$\frac{dm}{dt} = R_{trans} \cdot F_{dislodge} \cdot \frac{w_f}{S_{exp}}$$

PBTK model

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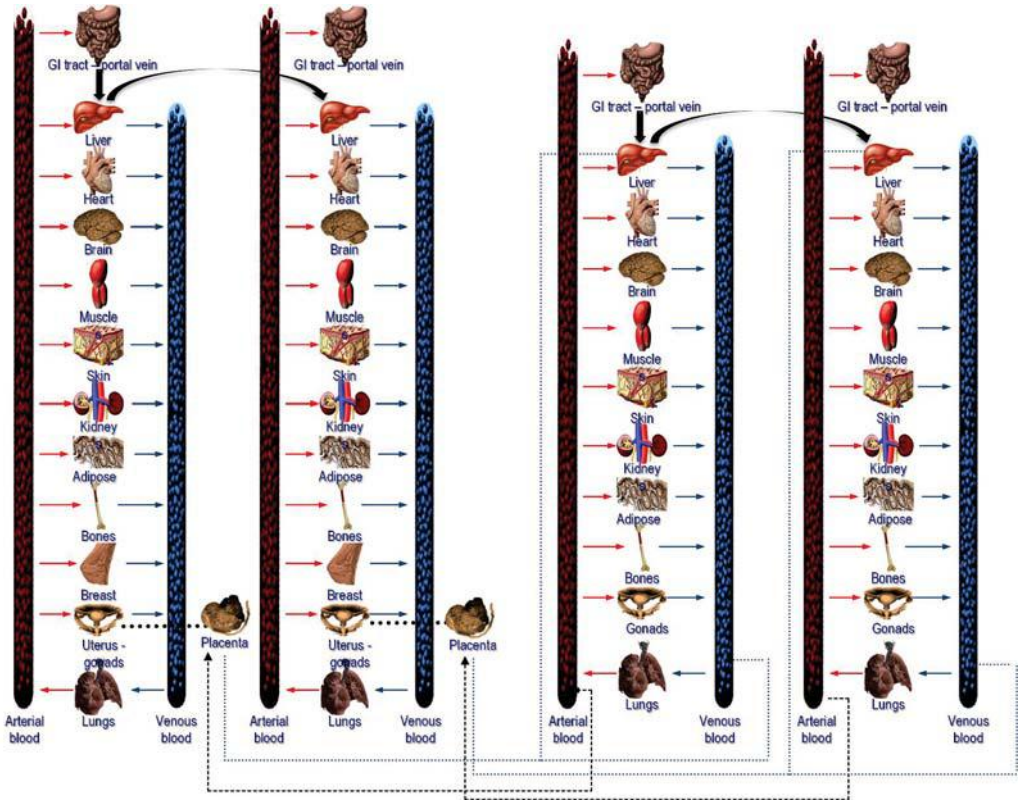

Lifetime evolving parameters

- Organ volumes
- Blood flows
- Age-dependent clearance

Mother – Fetus interaction

Breast feeding

Skin Structure and PBPK modelling

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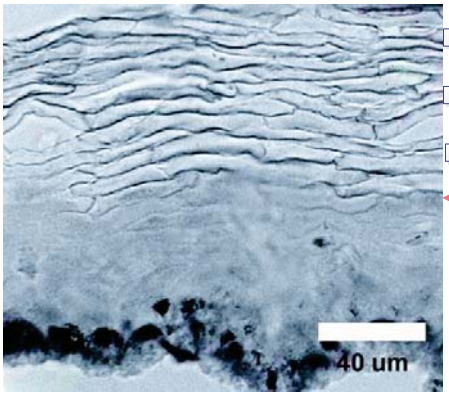
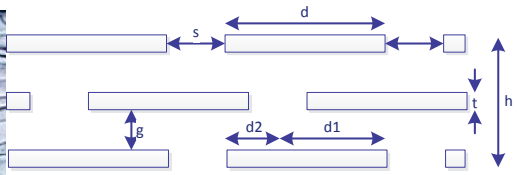
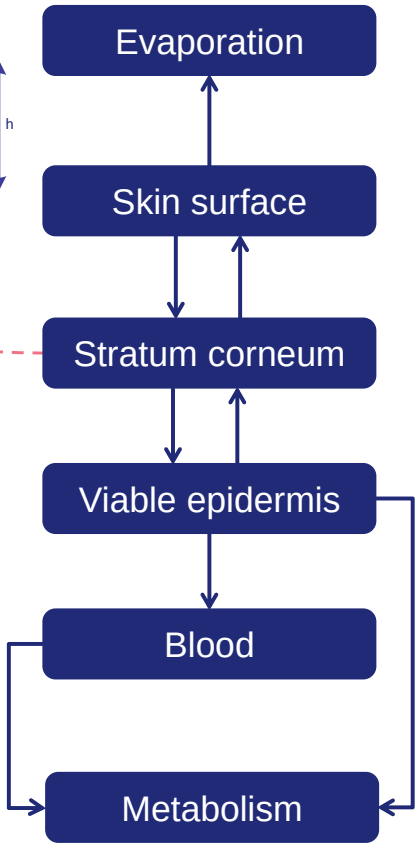




$$t = 1 + \frac{2g}{h}\ln\left(\frac{d}{2s}\right) + \frac{N \cdot d \cdot t}{s \cdot h} + \left(\frac{d}{1+\omega}\right)^2 \frac{\omega \cdot (N-1)}{h \cdot g}$$

Description	Symbol	Value	Unit
Number of layer	N	15	-
Length of corneocyte	d	30	um
Thickness of corneocyte	t	10	um
Length of path 1	d_1	20	um
Length of path 2	d_2	10	um
Vertical gaps	s	0,03	um
Horizontal gaps	g	0,03	um
corneocyte edge angle	φ	90º	degrees
Effective Diffusivity f(φ)	D_{ef}	0.002	cm^2/m



Additional considerations

Model parameters (e.g. bodyweight, inhalation rates, intake rates for food, time activity patterns, body parts surfaces, amount of soil and dust eaten in a day, etc.) are stored in the INTEGRA Db according with

- geographical location,
- gender and
- age group

These are automatically retrieved according with the initial simulation setup.

Variability and **uncertainty** are incorporated across all full chain assessment calculation through the MCMC approach. The most important model parameters (~ 100) determined after global sensitivity analysis can be entered as probability distribution functions of several types (e.g. normal, log-normal, uniform, etc.).

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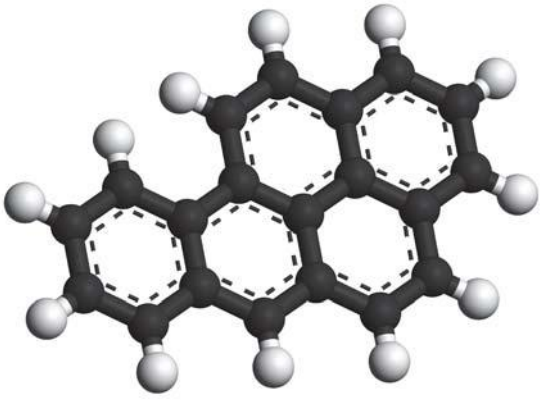
Applying the INTEGRA methodology in PAHs



Scenario 1 /

human internal exposure to PAHs from all sources

- which (minimal) input data (types) are required?
  - Food residues
  - Consumer products concentrations and use data
  - Air pollution data (PM and gaseous)
  - Dust contamination
    - ***All of the above can be estimated starting from environmental releases as well***
- which population groups are addressed?
  - neonates
  - children
  - adults
  - elderly
- How is the 'internal exposure' expressed? (external dose equivalent, levels of metabolites in urine, blood?)
  - external dose equivalent / intake / uptake
  - levels of parent compound and metabolites in urine, blood
- How is variability and uncertainty addressed
  - variability and uncertainty are incorporated across all full chain assessment calculation through MCMC approach

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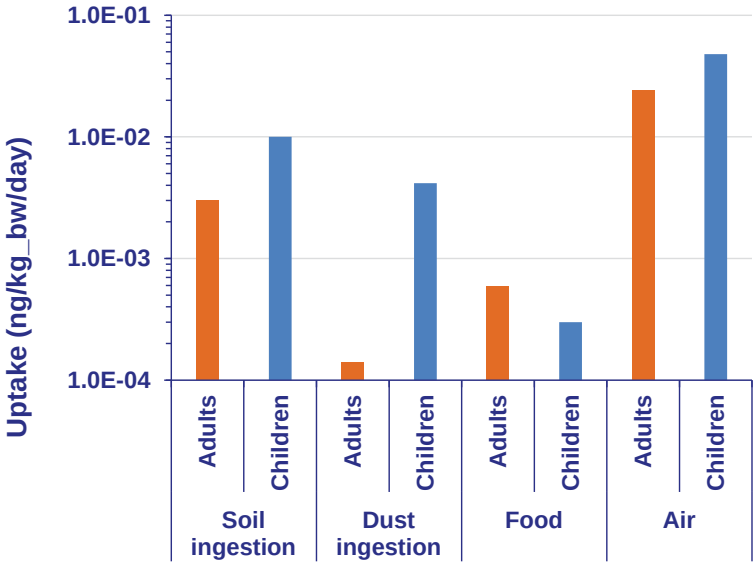
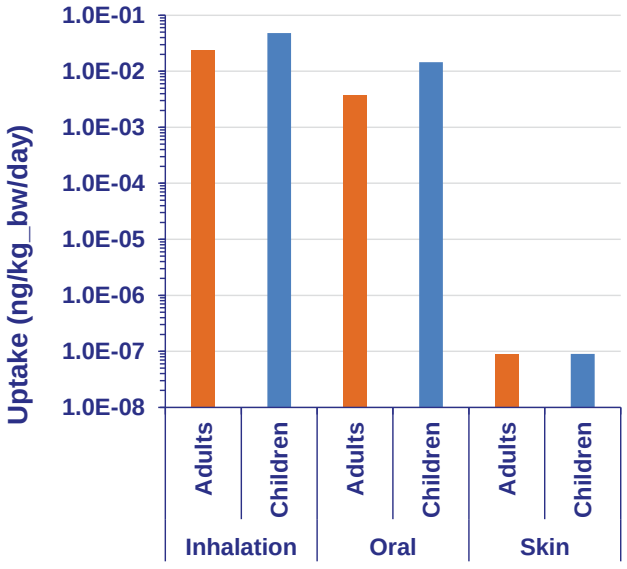
Scenario 1 /

human internal exposure to PAHs from all sources (B[a]P case)

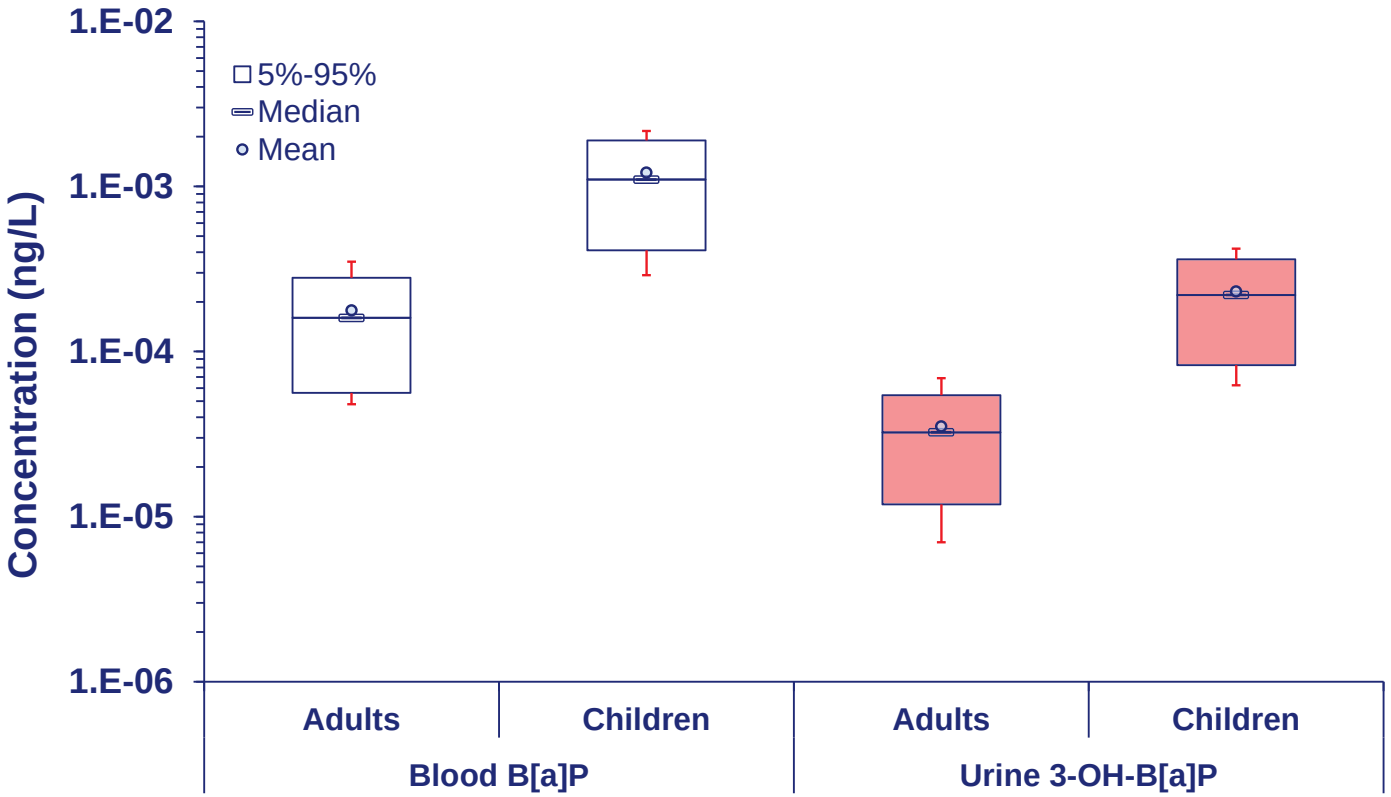
- Starting from annual emissions of 400 tones B[a]P in air within EU, and for regional emissions of 15 tons
- Distribution across different environmental media is estimated
- Contribution of different pathways and routes is estimated
- Internal exposure to B[a]P and urinary concentration of 3-OH-B[a]P is estimated





Scenario 1 /

human internal exposure to PAHs from all sources (B[a]P case)

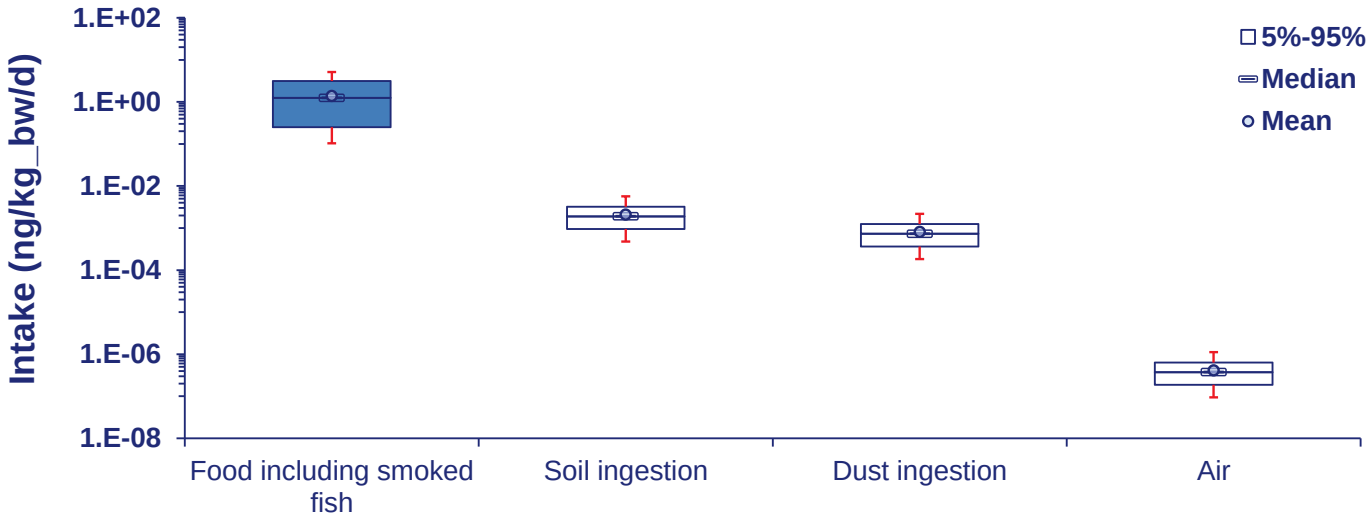


Scenario 2 /

human internal exposure to PAHs arising from specific use(s)/source(s)

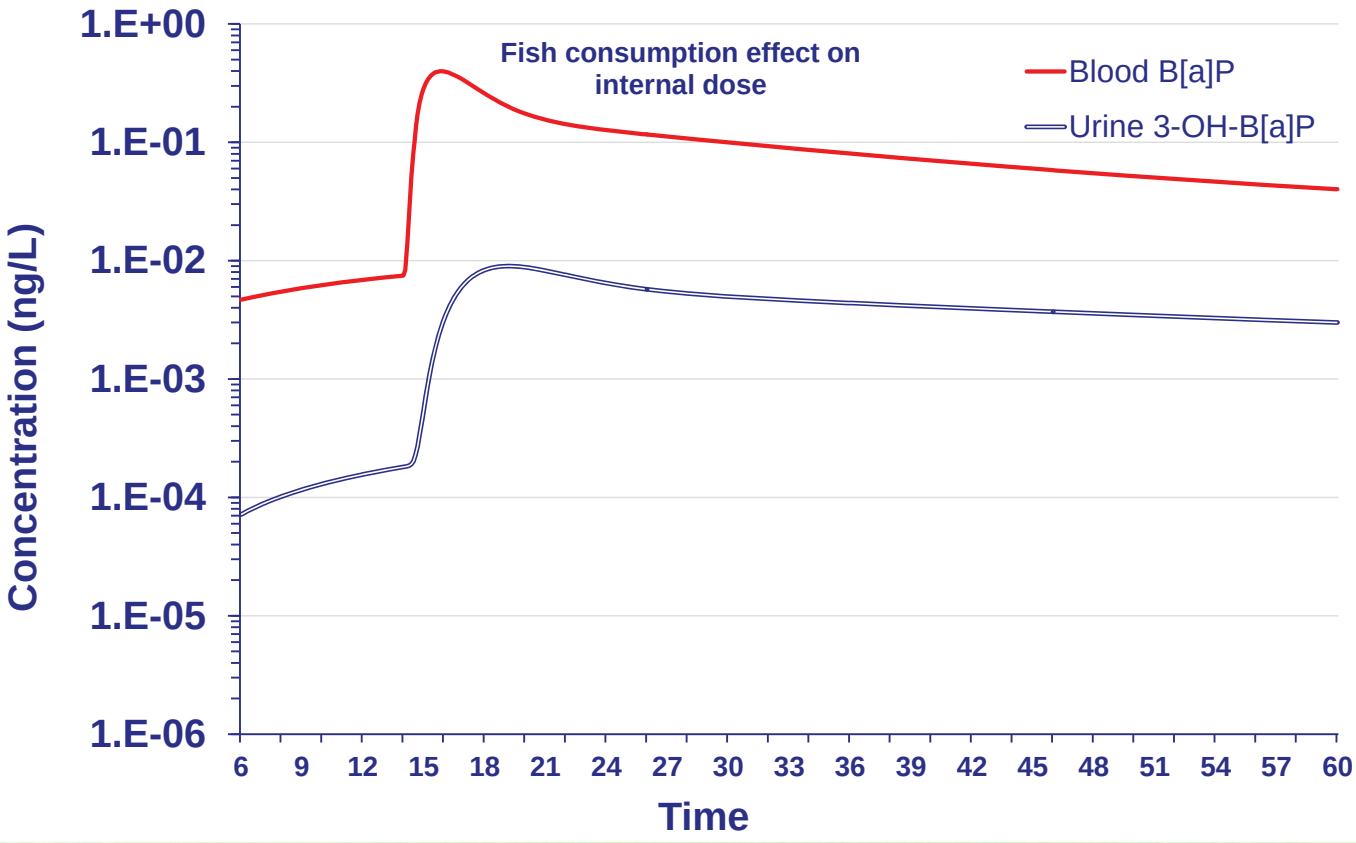
Scenario 2A “smoked fish”

- Concentration in fish is estimated by the multimedia model 10^{-7} μg/kg
- This concentration is compared to the ones identified in the literature from smoked fish analysis / B[a]P levels in smoked fish range from 0.08 to 4.1 μg/kg (median of 1μg/kg and consumption of 110 grams of fish)
- Intake due to smoked fish consumption dominates among other pathways



Scenario 2 /

human internal exposure to PAHs arising from specific use(s)/source(s)



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Scenario 2 /

human internal exposure to PAHs arising from specific use(s)/source(s)

Scenario 2B: contribution of petroleum products to integrated PAH exposure

Is it possible to calculate the contribution of a category of petroleum products (e.g. RAE Residual Aromatic Extracts/ OLBO – other lubricants based oils) to the integrated PAH exposure of EU population?

- Contribution via: release of PAHs to the environment (production and downstream use sites of a category of petroleum products) - indirect human exposure
  - In the vicinity of an industrial plant of petroleum products (production or downstream user site - local scenario under REACH)
  - In general in Europe – regional scenario under REACH
- Contribution via consumer use of a category of petroleum products (e.g. lubricants, certain coatings)

Scenario 2 /

human internal exposure to PAHs arising from specific use(s)/source(s)

Scenario 2B: contribution of petroleum products to integrated PAH exposure

What is the required input?

- Tonnages of production, use, PAH release factors?
- Composition, PAHs levels in petroleum products?
- REACH: sector of use, process category (PROC), (specific) Environmental Release category [(sp)ERC]?
- Specific Consumer Exposure Determinants (SCEDs)?
- Other data needed?

Is it possible to split out the uses consumer exposures that are covered under REACH for the ones out of scope of REACH (e.g. foodstuffs, medicines, combustion derived PAHs)

✓ *Contribution from different sources could be assigned in the setup of the run*

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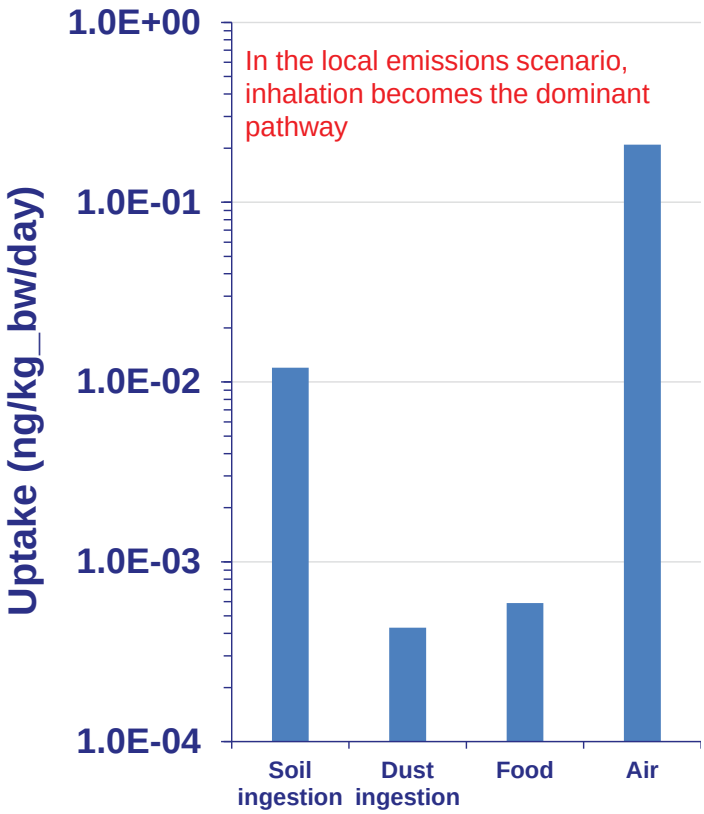
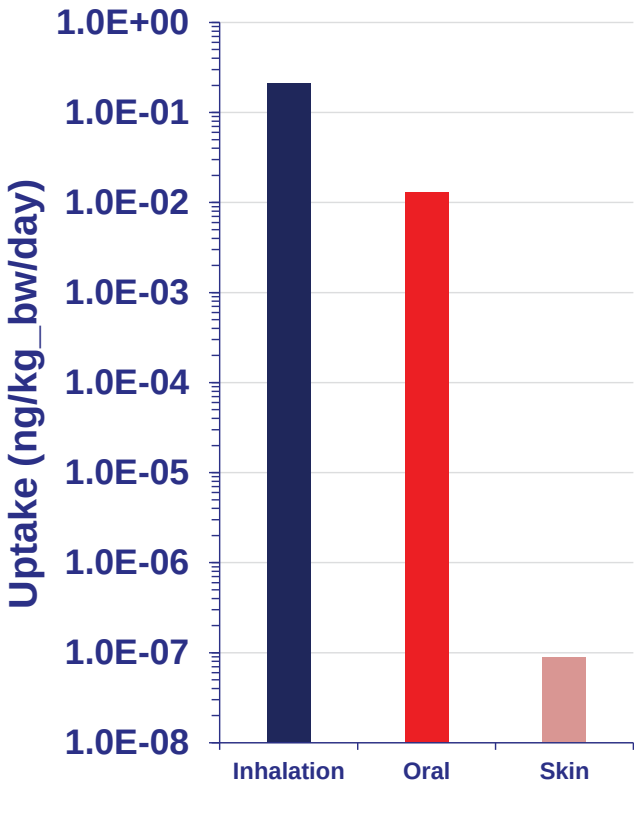
Scenario 2 /

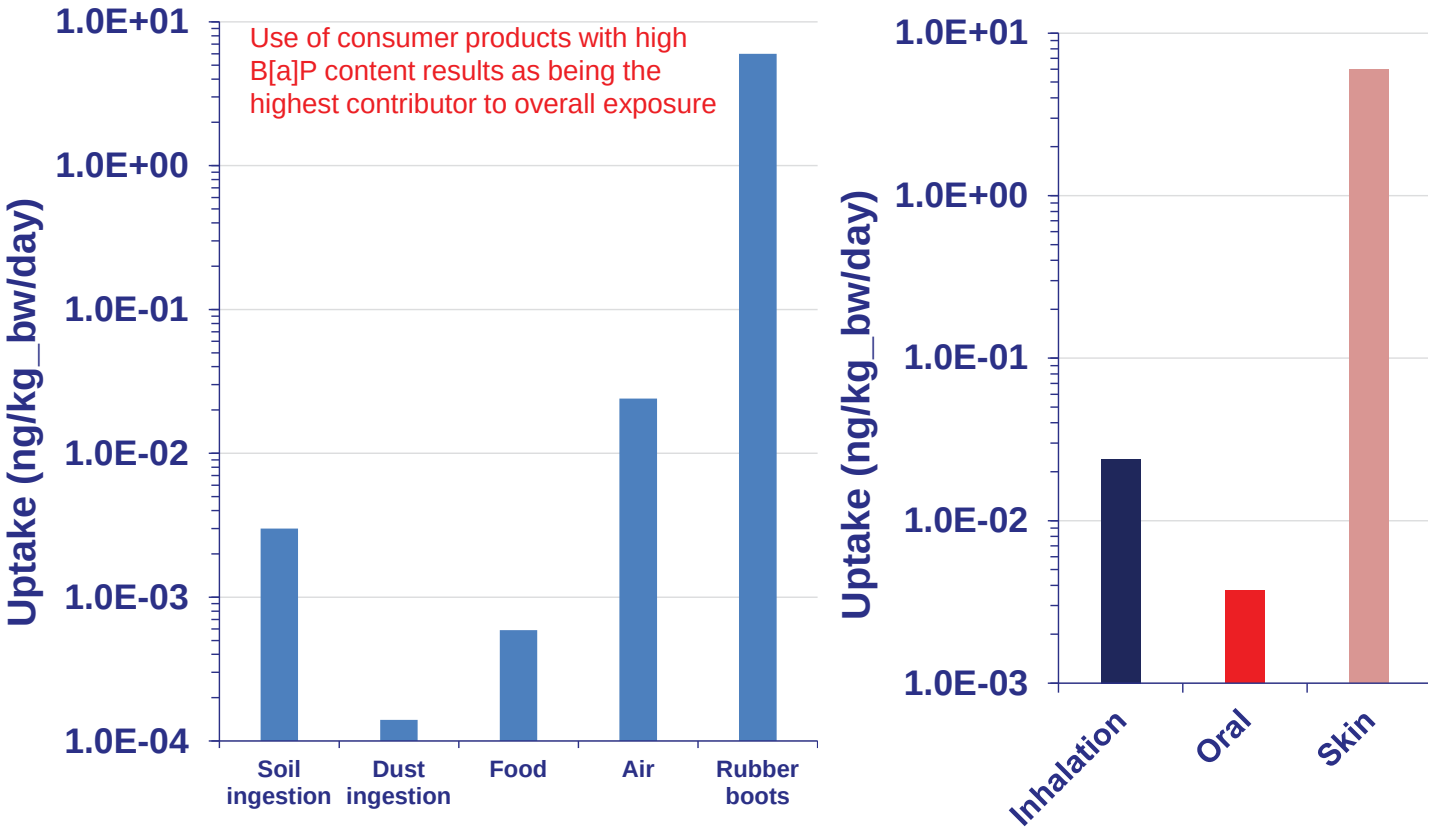
Continental / Regional + Local exposure scenario





Scenario 2 /

Continental / regional emissions scenario + Consumer exposure



Scenario 3 /

complex combustion exposure scenario / differences in internal dosimetry

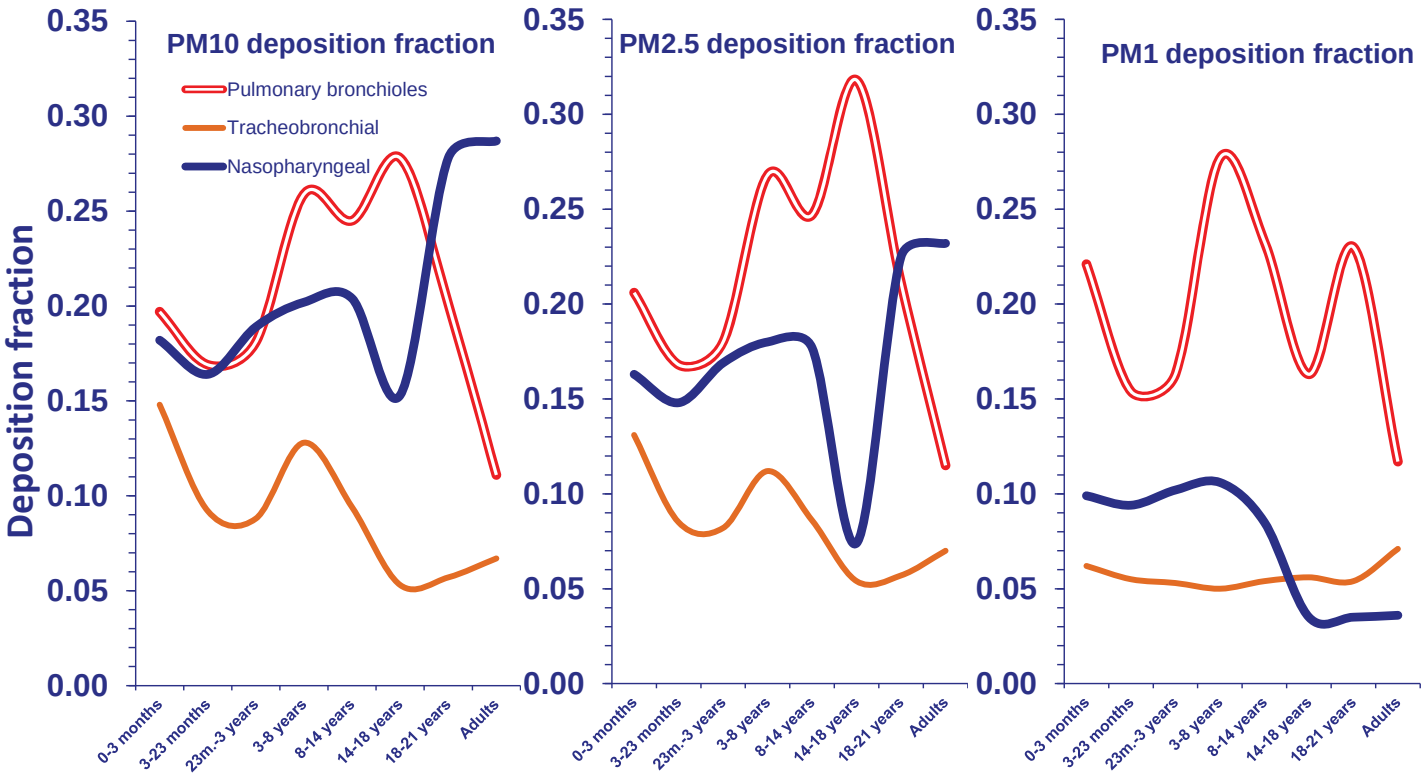
Different combustion sources contribute differently to PAHs exposure

- Differences in emitted particles size; biomass combustion results in the formation of lower particles than traffic
- Differences in PAHs content; biomass emitted particles have larger active surface and higher content of PAHs per mass of PM

To better describe the PAHs absorption process through combustion sources PM, HRT tract deposition modelling is incorporated in the INTEGRA platform.

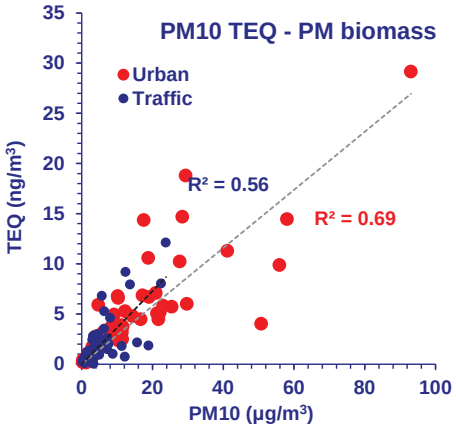
- The actual amount of PM reaching tracheobronchial and pulmonary regions is taken into account, which is actually a fraction of the ambient air PM
- The concentration of PAHs on the PM finally deposited on tracheobronchial and pulmonary regions is estimated

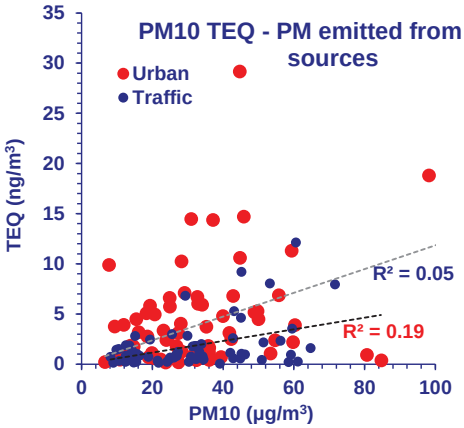
PM deposition across the HRT



PAHs content

biomass burning vs other sources





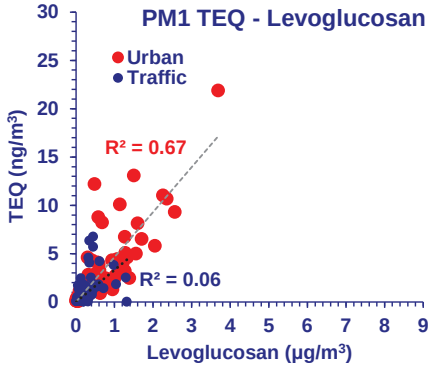
Biomass emitted particles
- *Lower aerodynamic diameter, hence penetrate deeper across HRT*
- *Higher PAHs content per mass of PM* (more toxic)

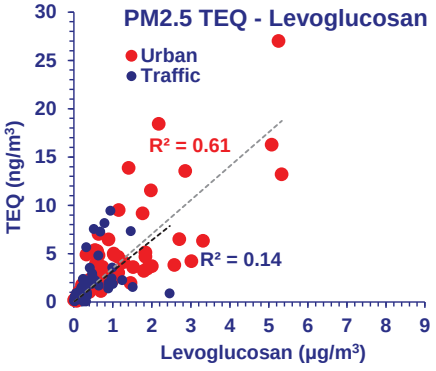
↓

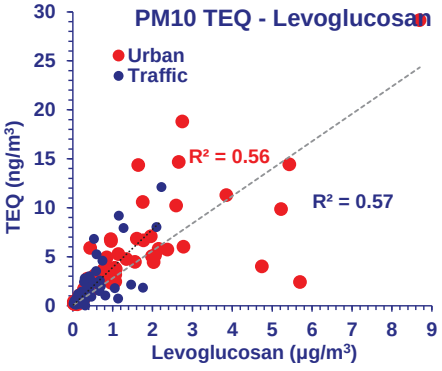
Significantly higher amount of PAHs reaches alveoli

↓

Highly **spatially** and **age** stratified differentiated internal dosimetry







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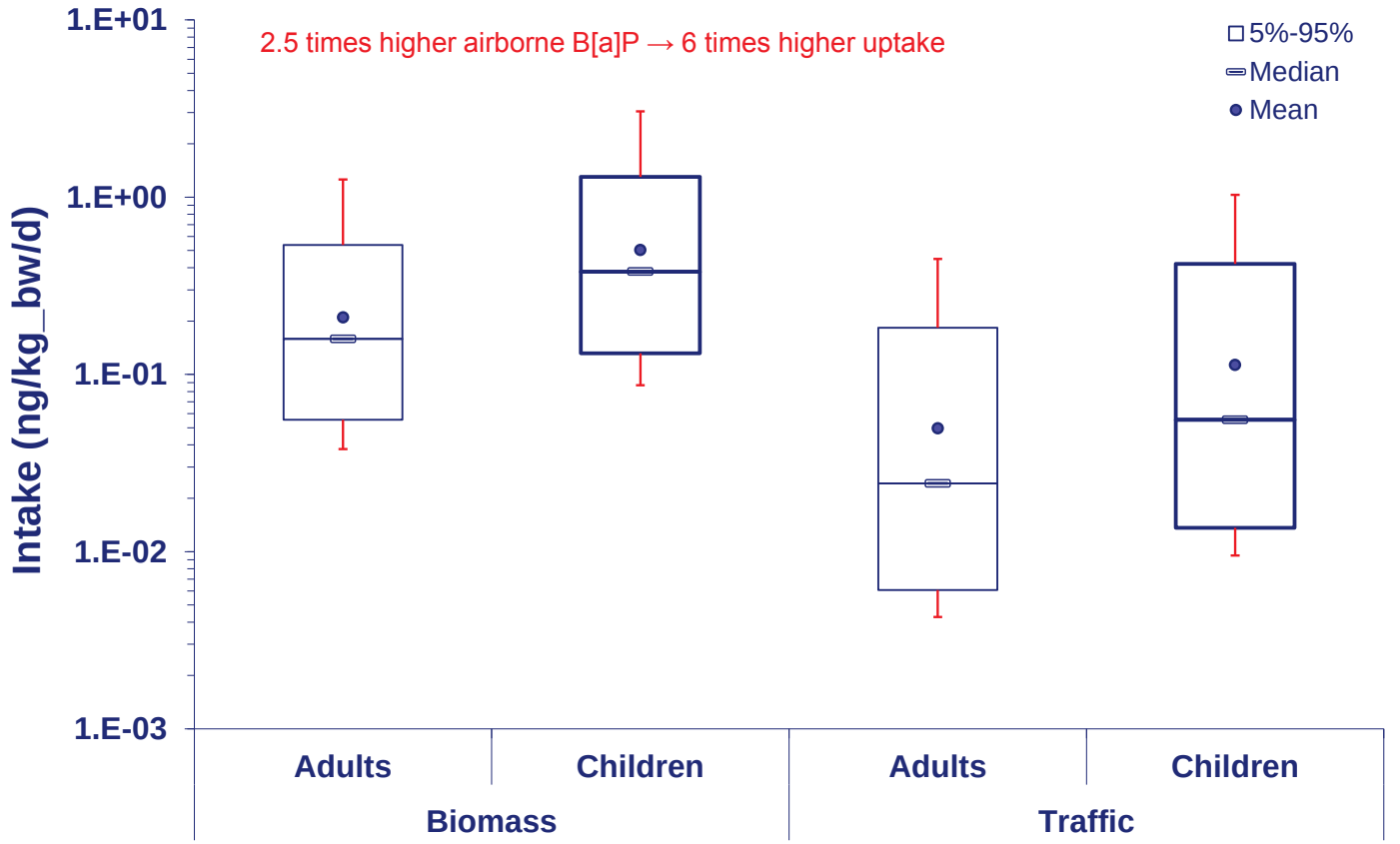
Uptake variability

(accounting for PM deposition across HRT)



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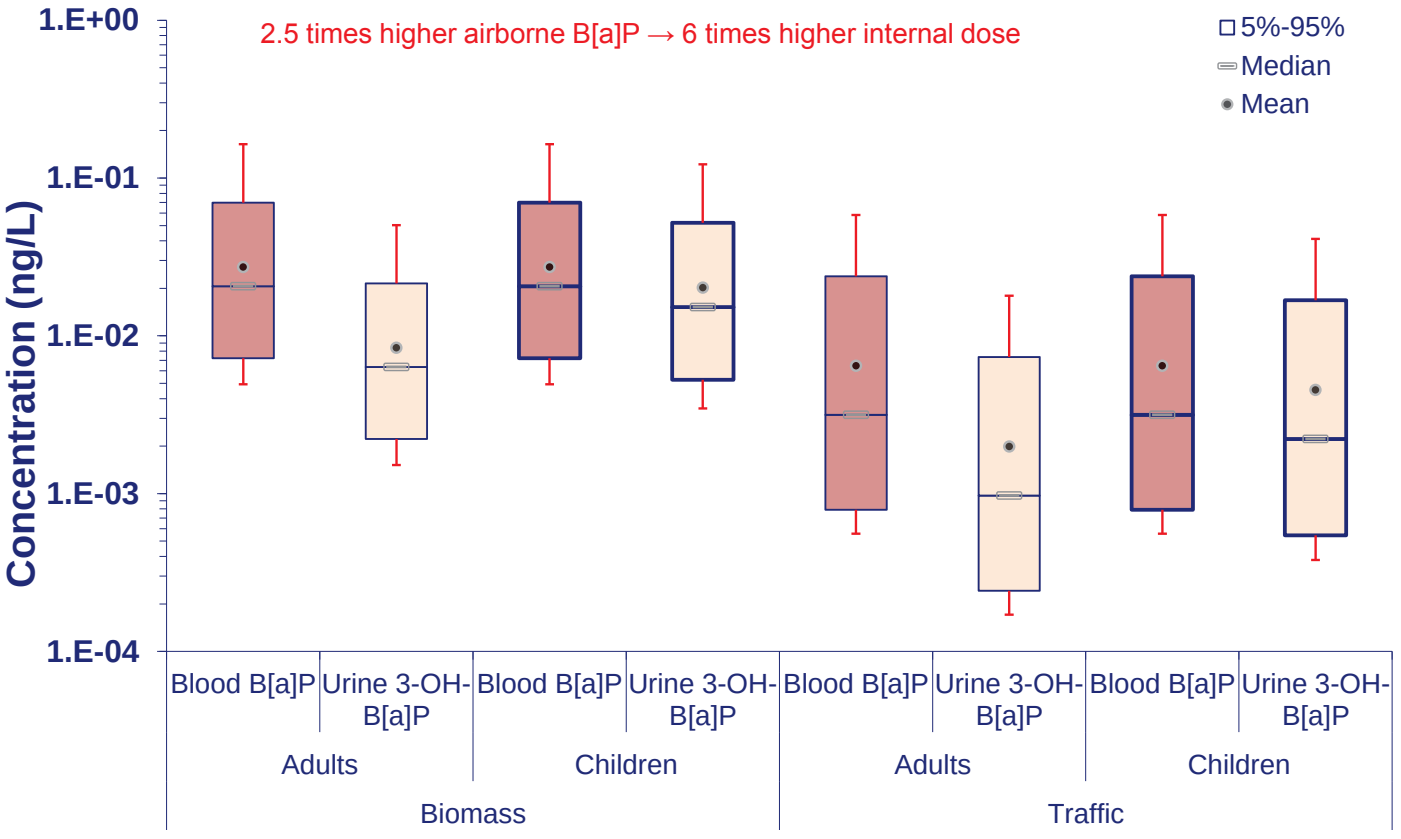
Department of Chemical Engineering
School of Engineering
Aristotle University of Thessaloniki

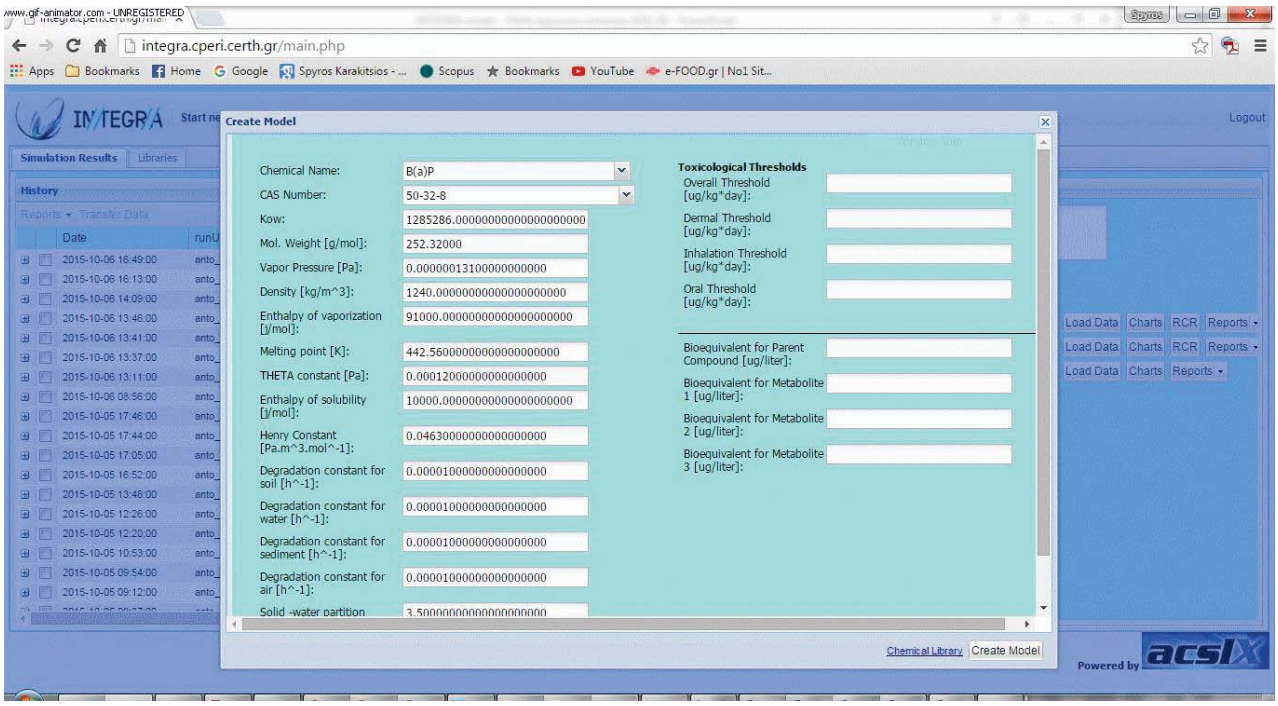
Internal exposure variability



Conclusions

- Linking Emissions, Concentrations, Exposure and Internal dose in a “continuous” mathematical framework allows us to couple environmental and biological processes efficiently, validating each step of the way.
- Contribution from different pathways and routes can be explicitly calculated. The latter can be also aggregated to derive cumulative exposure.
- Integration of toxicokinetics allows:
  - the evaluation of exposure estimates against biomonitoring data
  - the incorporation of internal dosimetry metrics for risk characterization
- Specific consumer exposure scenarios may dominate over other pathways.
- With regard to combustion-related exposure, modelling PM deposition across the HRT allows to differentiate actual uptake and internal dosimetry among different combustion sources.

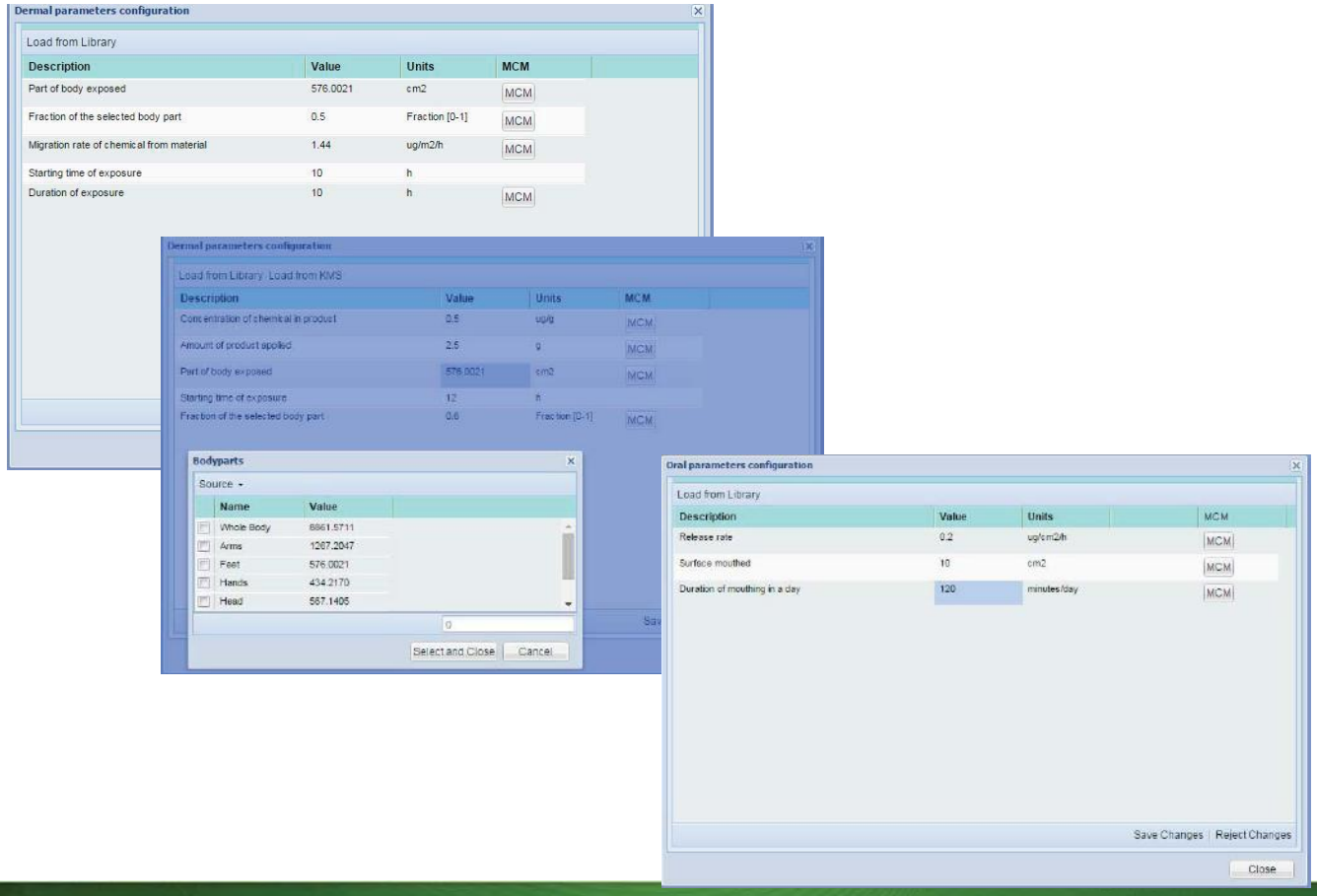
Thank you for your kind attention



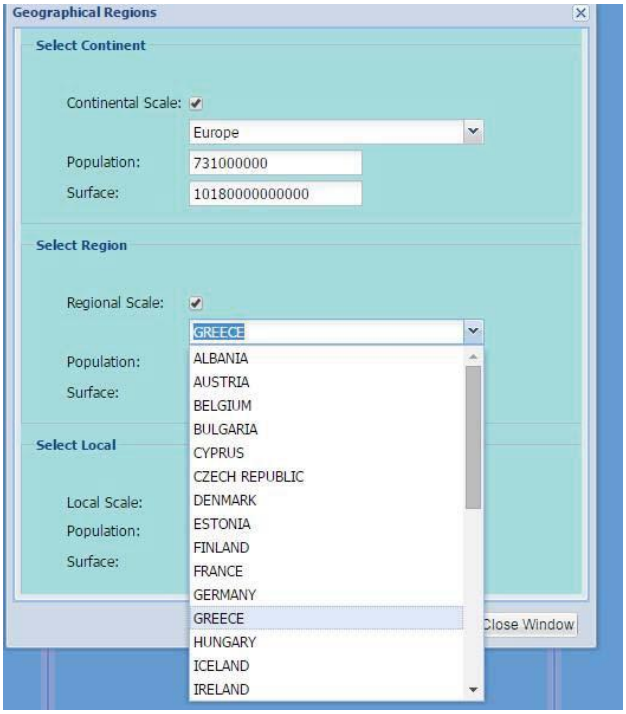
www.enve-lab.eu

A connectivity perspective to environmental health

Consumer uses included - examples



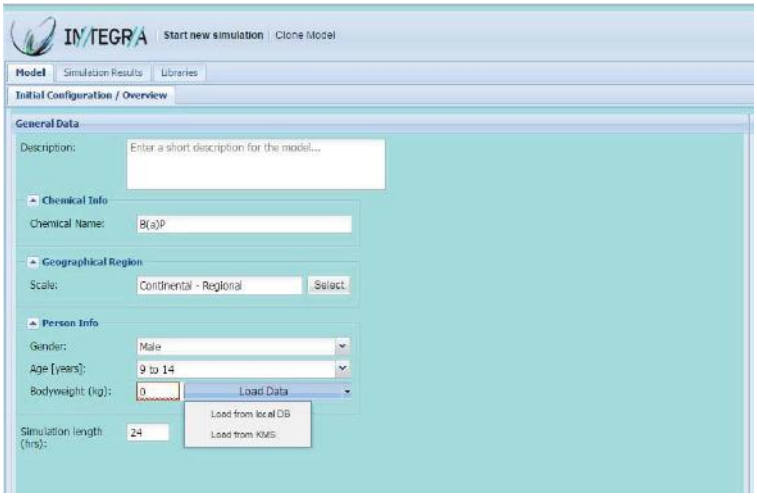
Model parametrization



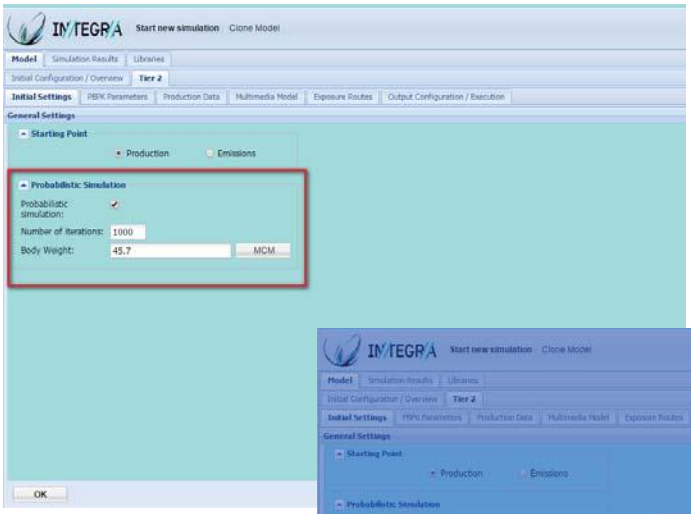
Model parameters (e.g. bodyweight, inhalation rates, intake rates for food, time activity patterns, amount of soil and dust eaten in a day, etc.) are stored in the INTEGRA Db according with

- geographical location,
- gender and
- age group

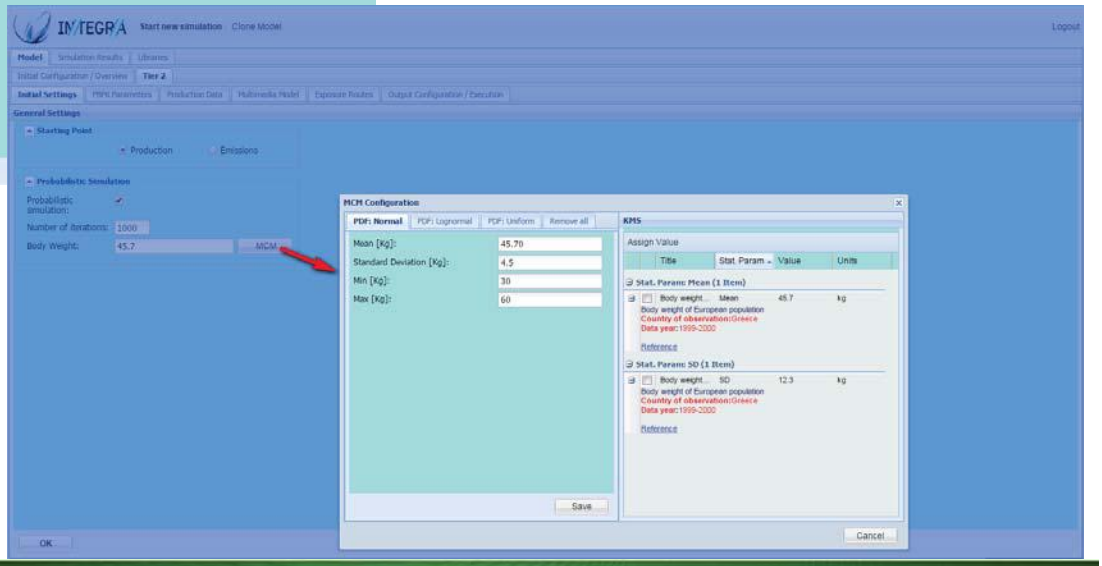
Automatically retrieved according to the initial simulation setup



Variability and uncertainty



Variability and uncertainty are incorporated across all full chain assessment calculation through MCMC approach. The most important model parameters (~ 100) determined after global sensitivity analysis can be entered as probability distribution functions



Expanding the chemical space - Use of QSARs - Artificial Neural Networks

According to Abraham's solvation equation, a biological property SP can be described by the following equation

$$\log SP = c + r \cdot R_2 + s \cdot \pi_2^H + a \cdot \Sigma\alpha_2^H + b \cdot \Sigma\beta_2^H + v \cdot \log V_x$$

Where:

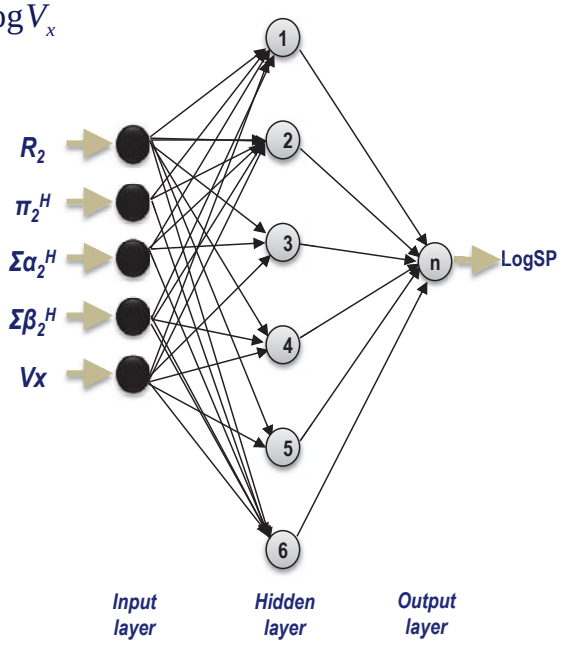
R_2 is an excess molar refraction that can be determined simply from a knowledge of the compound refractive index

π_2^H is the compound dipolarity/polarizability

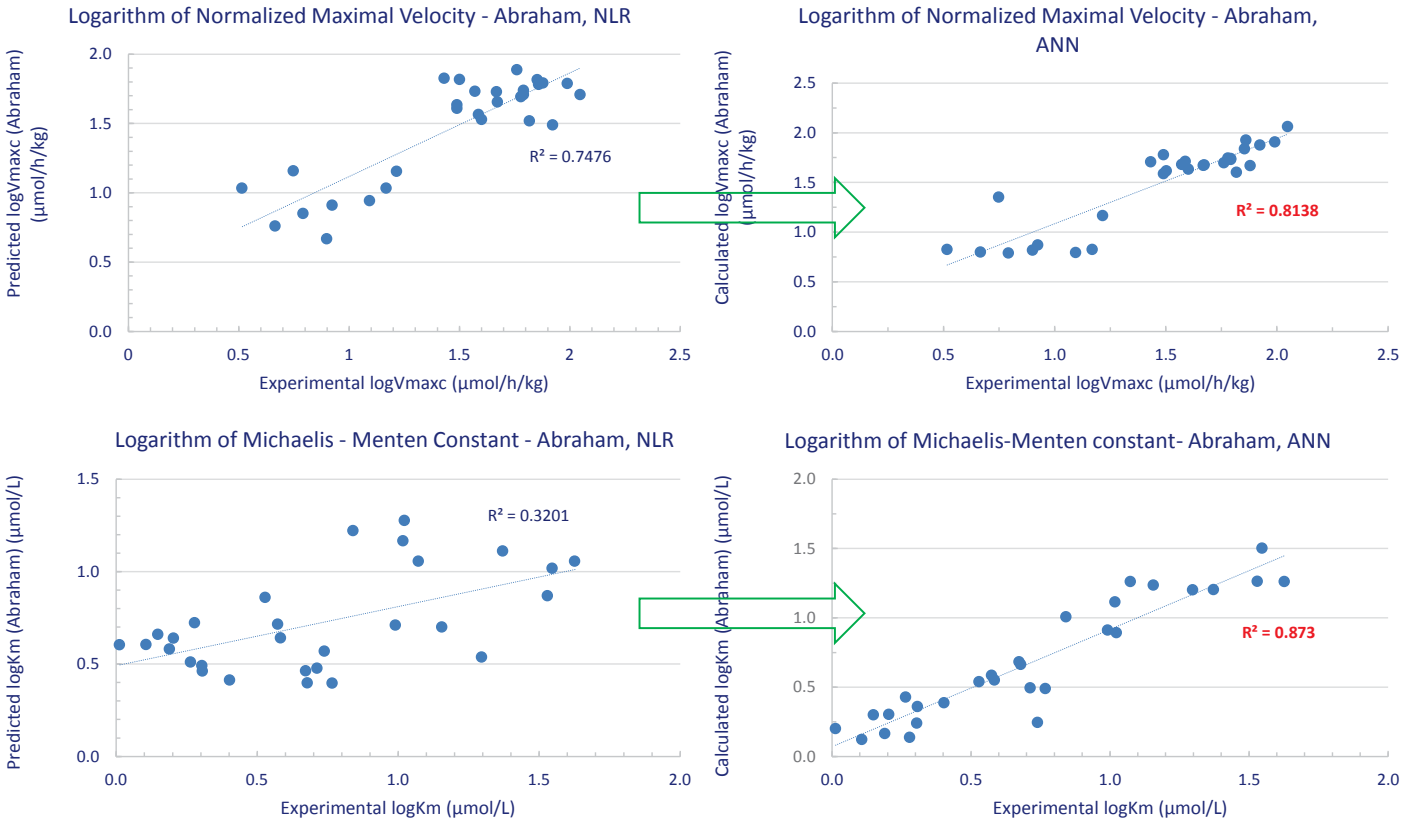
$\Sigma\alpha_2^H$ is the solute effective or summation hydrogen-bond acidity

$\Sigma\beta_2^H$ is the solute effective or summation hydrogen-bond basicity

V_x is the McGowan characteristic volume

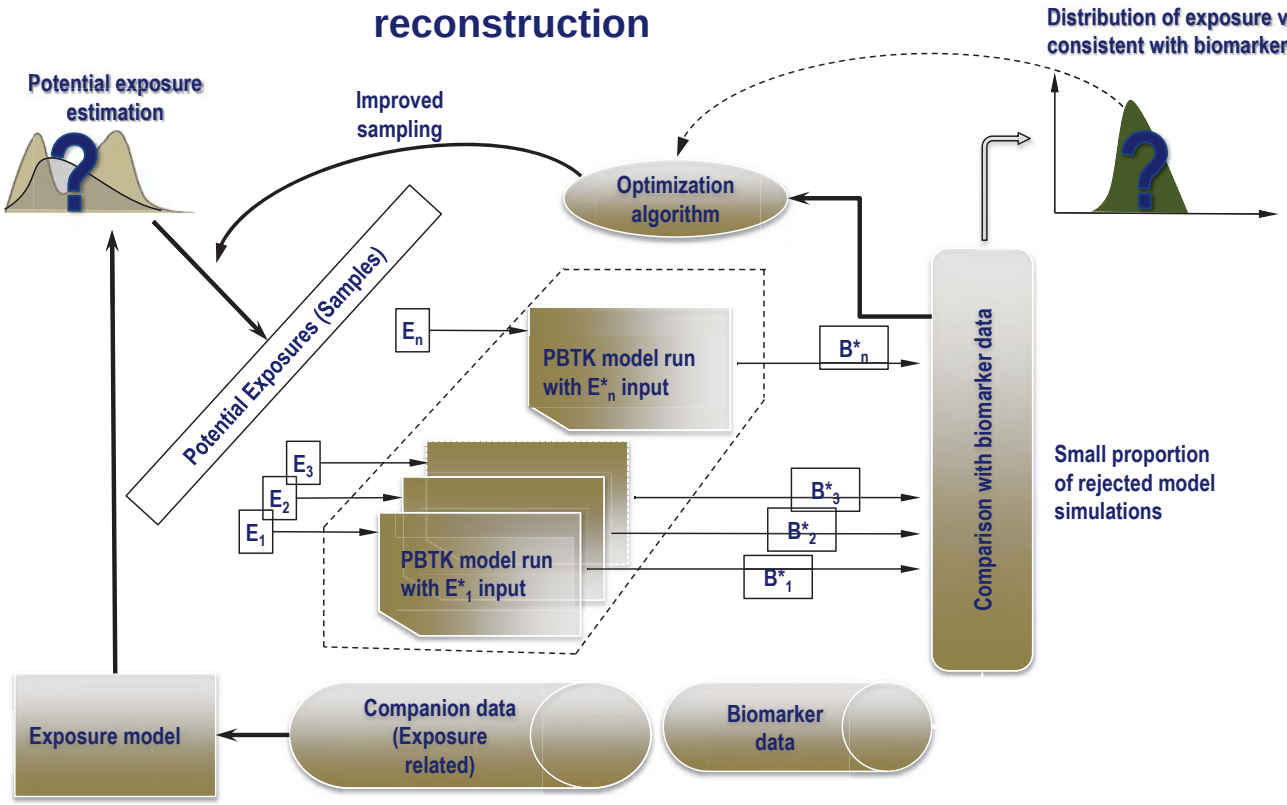


Expanding the chemical space: QSARs - Artificial Neural Networks



HBM data assimilation

Optimal methodological scheme for exposure reconstruction



Reconstructing exposure from time-dynamic data

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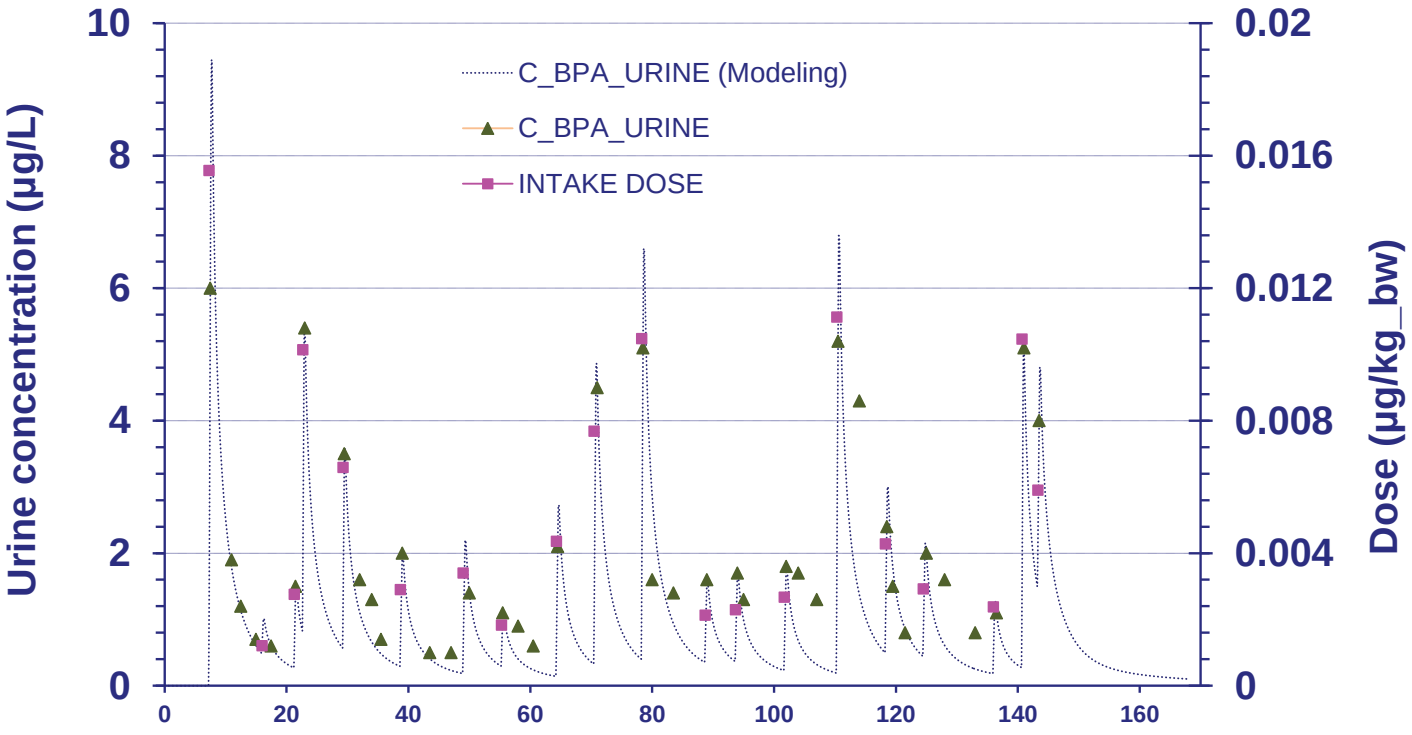


ExxonMobil

Exposure Risk Assessment Tools Environment

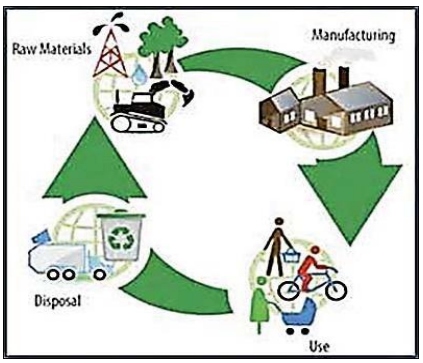
Carol Lee

Energy lives here

ENVIRONMENTAL EXPOSURE ASSESSMENT

Principle: Characterizing Environmental Risk

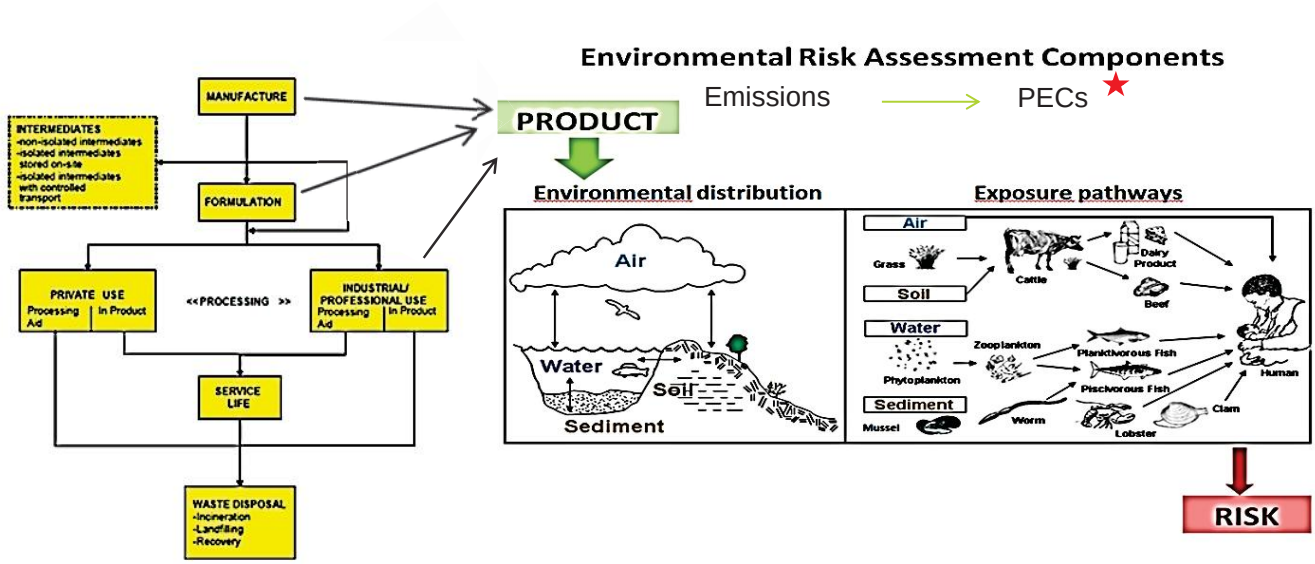
- Derive a quantitative /qualitative estimate of substance concentration to which the population and the environment may be exposed; compare to ‘safe level’
- Risk characterization ratio = predicted environmental concentration/predicted no effect concentration;
- RCR= PEC/PNEC;DNEL
- Consider all stages of a substance’s life cycle: production, uses and waste to estimate emissions and environmental concentrations.



Compliance Requirements:

- EU REACH enforces a strict process for all marketed substances to be evaluated throughout the supply chain
- (reported in CSR of registration dossier) and communicated to the downstream user (E-SDS).
- USEPA TSCA recent initiative more generic
- PMN (US), (NSN) Canada, AP registrations also require some level of environmental exposure assessment

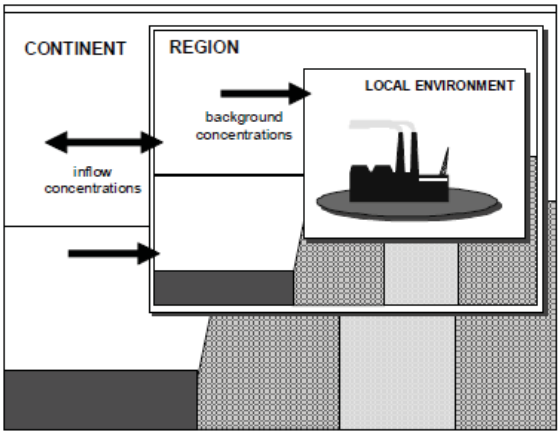
Elements of Environmental Exposure – Life Stage of Use and Emissions

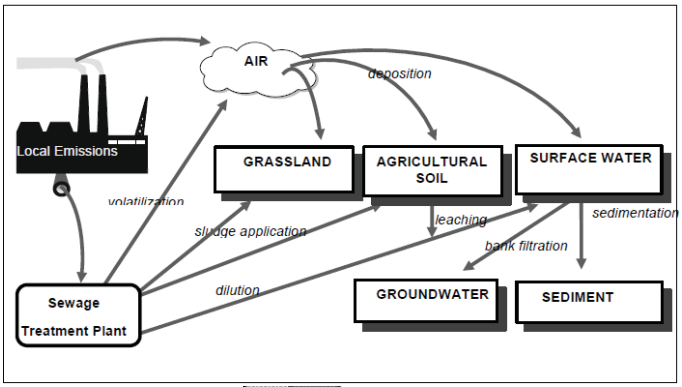


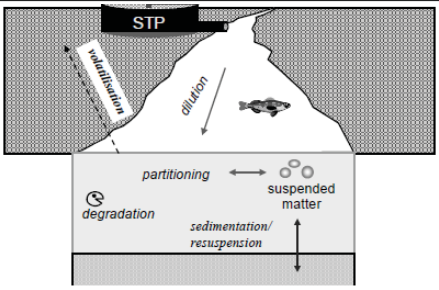
★ Environment emissions of a substance quantified for each use per life cycle stage based on tonnage via the release pathway to the receiving environmental (air, soil, water, sediment);

Predicted environmental concentrations (PECs) are calculated for each environmental compartment potentially exposed, based on distribution and fate processes.

Environmental Exposure Spatial Scale Distribution







Environment emissions of a substance quantified for each use per life cycle stage based on tonnage via the release pathway to the receiving environmental (air, soil, water, sediment);

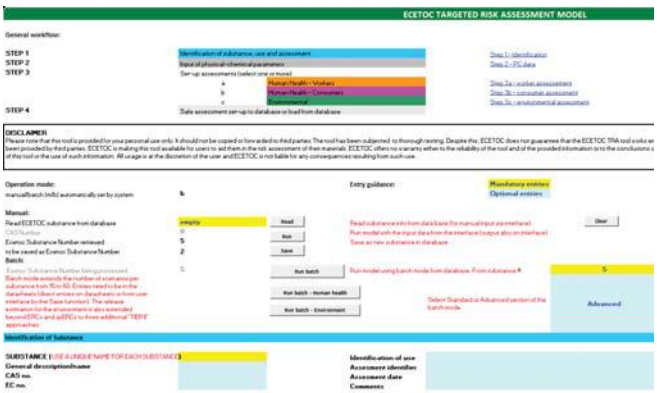
Predicted environmental concentrations (PECs) are calculated for each environmental compartment potentially exposed, based on distribution and fate processes.

Environmental Exposure Tools: EUSES, ECETOC-TRA

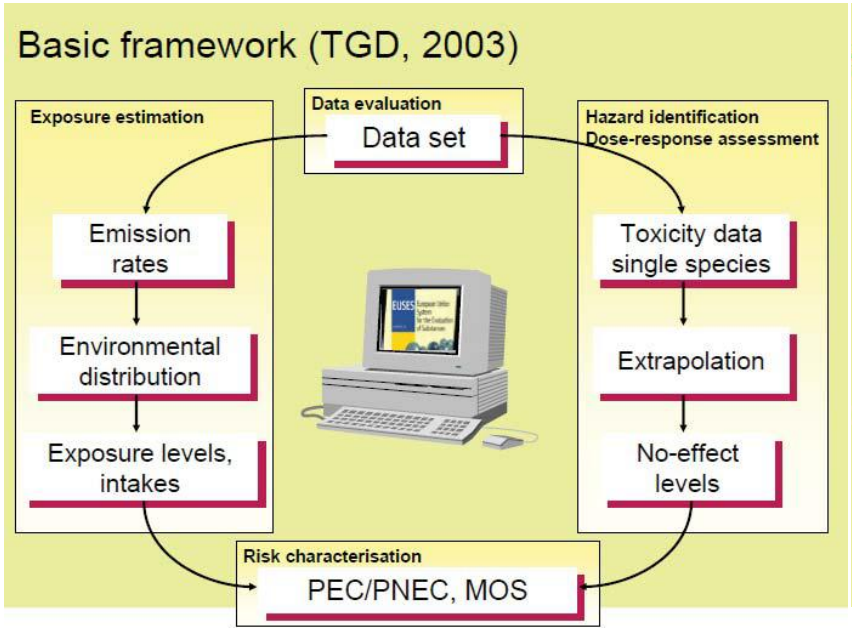
1) EUSES: The European Union System for the Evaluation of Substances model was developed by RIVM for quantitative assessment of the risks posed by new and existing chemical substances and biocides to man and the environment. Hard coded software lacks transparency, suited for single (pure) substances, only one substance assessment per 'run', structured report output (not aligned with CSR or SDS formats).

EUSES European Union System for the Evaluation of Substances

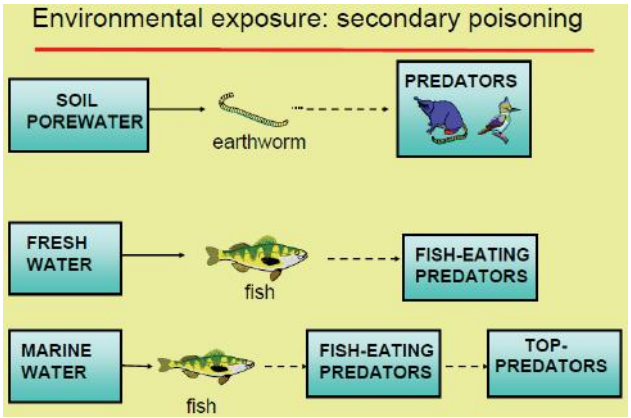
2) ECOTOC-TRA v3.1: ECETOC model based on EUSES equations, calculates risk assessments for man, environment using 'GES' based determinants and transparent code. Suitable for single (pure) substances, supports multiple substances /batch assessments, very limited structured report output (not aligned with CSR or SDS formats), includes scaling tool.

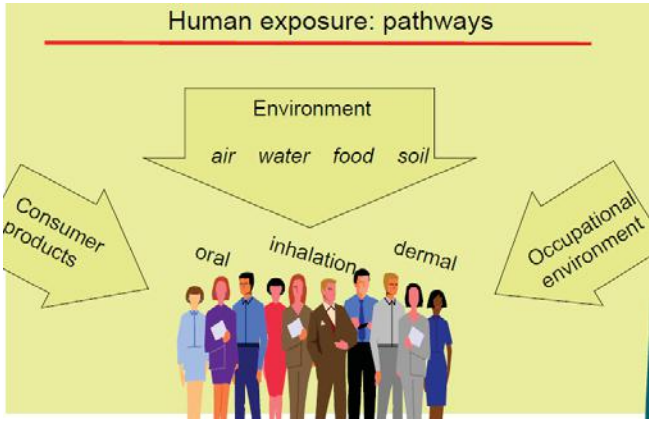


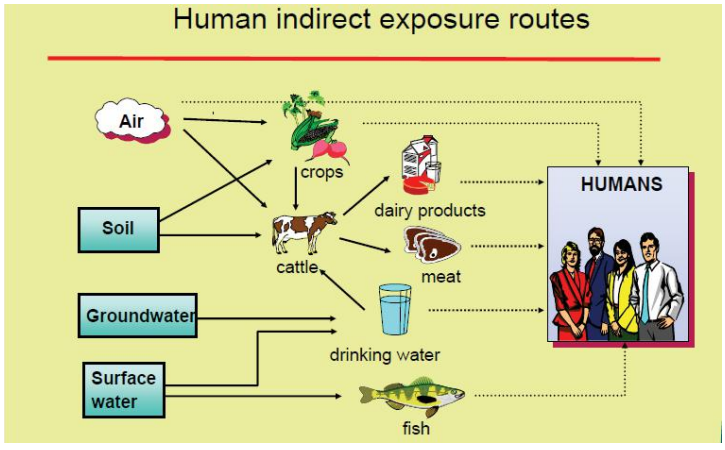
Environmental Exposure Tools: EUSES



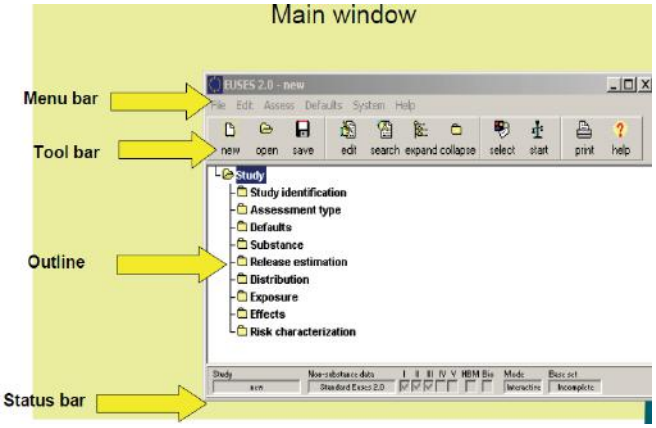
Environmental Exposure Tools: EUSES

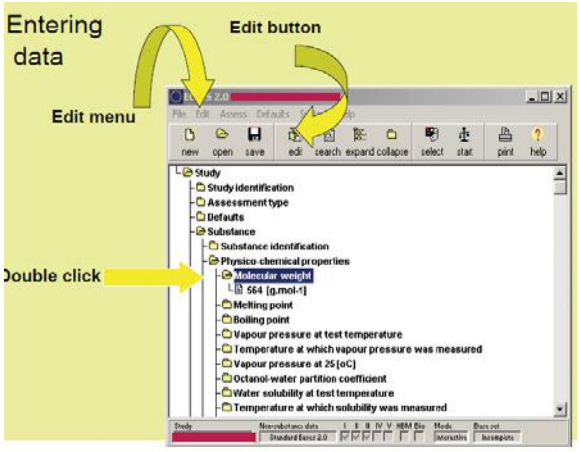


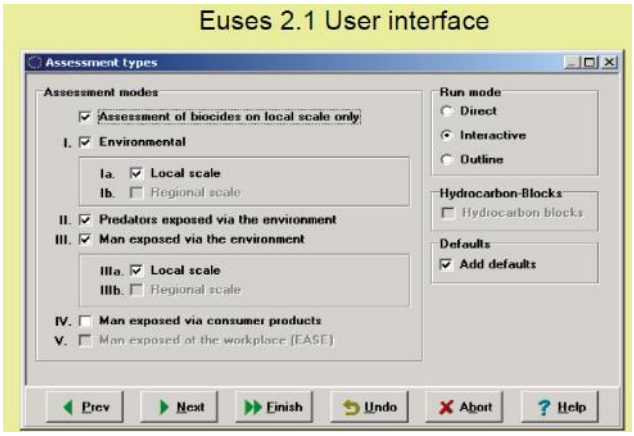




Environmental Exposure Tools: EUSES



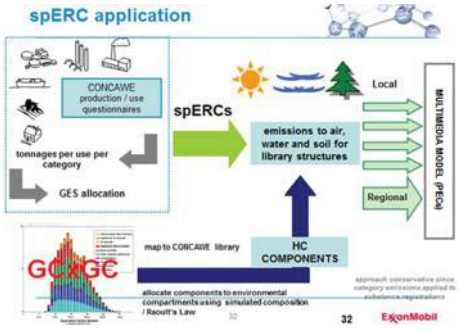




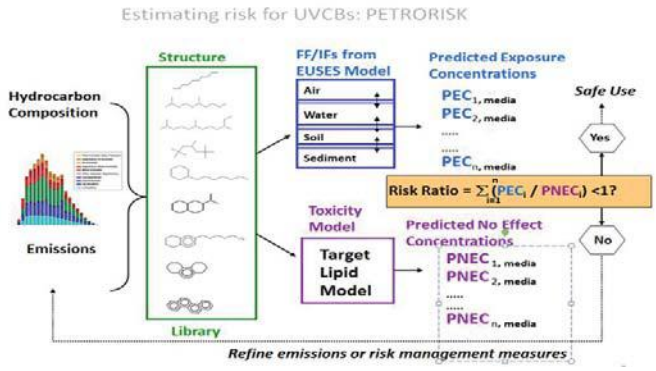
ExxonMobil

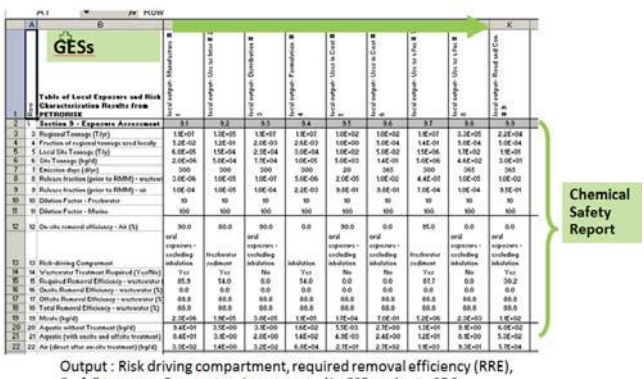
Environmental Exposure Tools: PETRORISK

Excel Macro tool (EUSES based) for exposure assessment of HC UVCBs: petroleum streams, solvents, LOA



PETRORISK Output Worksheet





Output : Risk driving compartment, required removal efficiency (RRE), "safe" tonnage. Parameters incorporated in CSR and ext –SDS

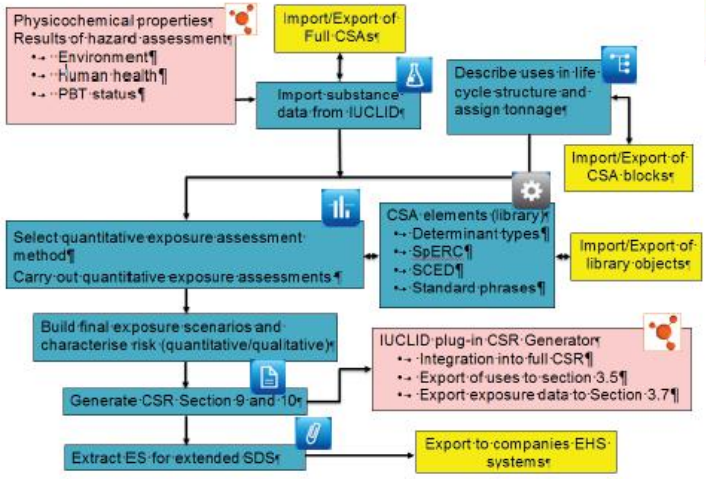
Section 2.2 Control of environmental exposure	
Product characteristics	
Substance is complex UVCB [PrC3]. Predominantly hydrophobic [PrC4a].	
Amounts used	
Fraction of EU tonnage used in region	0.1
Regional use tonnage (tonnes/year)	2.5E+1
Fraction of Regional tonnage used locally	1
Annual site tonnage (tonnes/year)	2.5E+1
Maximum daily site tonnage (kg/day)	1.3E+3
Frequency and duration of use	
Continuous release [FD2].	
Emission days (days/year)	20
Environmental factors not influenced by risk management	
Local freshwater dilution factor	10
Local marine water dilution factor	100
Other given operational conditions affecting environmental exposure	
Release fraction to air from process (initial release prior to RMM)	1.0E-3
Release fraction to wastewater from process (initial release prior to RMM)	1.0E-6
Release fraction to soil from process (initial release prior to RMM)	0.001
Technical conditions and measures at process level (source) to prevent release	
Common practices vary across sites thus conservative process release estimates used [TCS1].	
Technical onsite conditions and measures to reduce or limit discharges, air emissions and releases to soil	
Risk from environmental exposure is driven by Freshwater [TCR1a]	
Prevent discharge of undissolved substance to or recover from onsite wastewater [TCR14].	
No wastewater treatment required [TCR6].	
Treat air emission to provide a typical removal efficiency of (%)	70
Treat onsite wastewater (prior to receiving water discharge) to provide the required removal efficiency ≥ (%)	0.0
If discharging to domestic sewage treatment plant, provide the required onsite wastewater removal efficiency of ≥ (%)	0.0
Organisation measures to prevent/limit release from site	
Do not apply industrial sludge to natural soils [OMS2]. Sludge should be incinerated, contained or reclaimed [OMS3].	

ExxonMobil

Environmental Exposure Tools: Chesar

3) Chesar : ECHA model based on EUSES equations, calculates risk assessments for man, environment using ECHA defaults, 'GES' based determinants (SpERCs), and/or measured/monitoring data. Suitable for single (pure) substances, supports one substance / assessment, no scaling allowed, very structured report output, aligned with both CSR or SDS formats. Data transfer from/to IUCLID dossier required.

Figure 1: Chesar Assessment Workflow



An icon is associated to each Box. All the icons form the main toolbar:

	Box 1	Manage substance
	Box 2	Use management
	Box 3	Exposure assessment management
	Box 4	CSR management
	Box 5	SDS ES management
	Box 6	Library management
	Box 7	User management

Chesar: Chemical Safety Report Exposure Assessment

Pros:

- Worker, consumer and environmental exposure assessed by one tool
- Assessment output transferred to Chemical Safety report and E-SDS
- Distributed version accessible for all exposure assessors

Cons:

- Single chemical assessment only
- D/U info incomplete (Msafe)
- Limits on RMM application

Improvements:

- Chemical entities allow isomeric assessment
- Incorporate Msafe in output
- Will populate IUCLID data fields (use, emissions, PECs)
- Increase SpERC XML availability

9.1.1. Environmental contributing scenario 1: Manufacture [edit]

9.1.1.1. Conditions of use

Amount used, frequency and duration of use (or from service life)
• Daily use at site: <= 1.5E3 tonnes/day *Maximum site tonnage based on sector knowledge (Msperc): maximum amount of substance that is manufactured and transported from a site in one day based on typical site capacity (e.g., 80 trucks, each with a volume of 25 tonnes) Default number of emission days: 300 emission days/year (base on tonnage > 10000 tonnes/year - ECHA Guidance R16.3.2.1)*
• Annual use at a site: <= 2.36E4 tonnes/year
• Percentage of EU tonnage used at regional scale: = 100 %
Technical and organisational conditions and measures
• Indoor/Outdoor use: Indoor use
• Process efficiency: Process optimized for highly efficient use of raw materials (very minimal environmental release)
• Equipment cleaning: No release to wastewater from process as such, wastewater emissions limited to release generated from final equipment cleaning step using water
• On-site treatment of off-air: Typical measures to maintain workplace concentrations or airborne VOCs and particulates below respective OELS (e.g. thermal wet scrubber - gas removal and/or air filtration - particle removal and/or thermal oxidation and/or vapour recovery - adsorption)
• On-site treament of wastewater: Acclimated biological treatment [Effectiveness Water: 90%]
• On-site treatment of off-air: Vapor recovery (adsorption ...) [Effectiveness Air: 90%]
Conditions and measures related to sewage treatment plant
• Municipal STP: Yes [Effectiveness Water: 91.29%]
• Discharge rate of STP: >= 2E3 m3/d
• Application of the STP sludge on agricultural soil: No

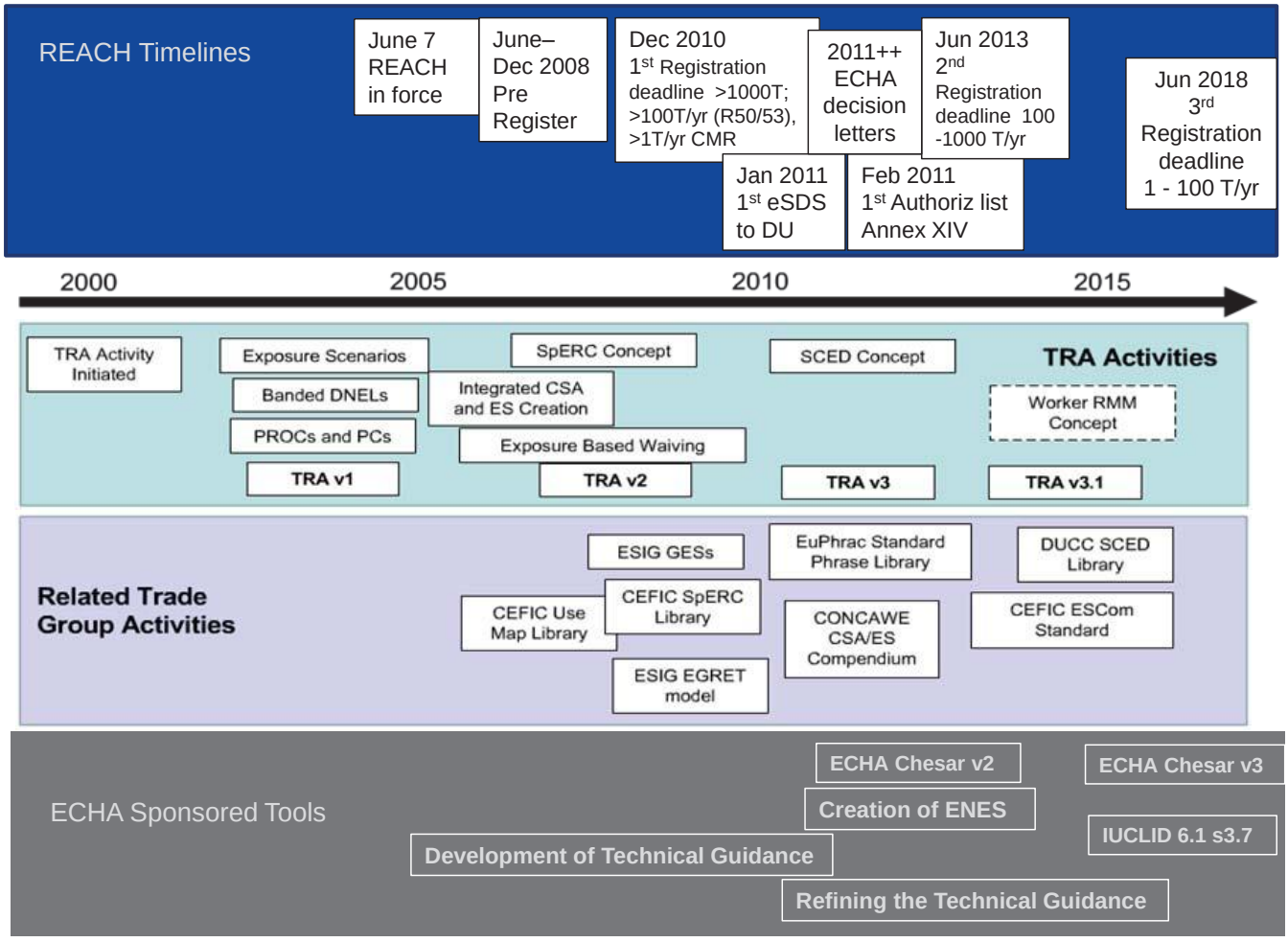
9.1.1.3. Exposure and risks for the environment and man via the environment

The exposure concentrations and risk characterisation ratios (RCR) are reported in the following table.

Table 7. Exposure concentrations and risks for the environment

Protection target	Exposure concentration	Risk characterisation
Freshwater	**Local PEC:** 0.02 mg/L	RCR = 0.664
Sediment (freshwater)	**Local PEC:** 13.47 mg/kg dw	RCR = 0.116
Marine water	**Local PEC:** 0.002 mg/L	RCR = 6.609 >>>**CAUTION:** Risk not controlled <<<
Sediment (marine water)	**Local PEC:** 1.341 mg/kg dw	RCR = 1.16 >>>**CAUTION:** Risk not controlled <<<

Back Up


REACH Timelines
June 7 REACH in force
June–Dec 2008 Pre Register
Dec 2010 1st Registration deadline >1000T; >100T/yr (R50/53), >1T/yr CMR
2011++ ECHA decision letters
Jun 2013 2nd Registration deadline 100 -1000 T/yr
Jun 2018 3rd Registration deadline 1 - 100 T/yr
Jan 2011 1st eSDS to DU
Feb 2011 1st Authoriz list Annex XIV
2000
2005
2010
2015
TRA Activity Initiated
Exposure Scenarios
Banded DNELs
PROCs and PCs
TRA v1
SpERC Concept
Integrated CSA and ES Creation
Exposure Based Waiving
TRA v2
SCED Concept
TRA v3
TRA Activities
Worker RMM Concept
TRA v3.1
Related Trade Group Activities
ESIG GESs
CEFIC Use Map Library
CEFIC SpERC Library
ESIG EGRET model
EuPhrac Standard Phrase Library
CONCAWE CSA/ES Compendium
DUCC SCED Library
CEFIC ESCom Standard
ECHA Sponsored Tools
ECHA Chesar v2
Creation of ENES
Development of Technical Guidance
Refining the Technical Guidance
ECHA Chesar v3
IUCLID 6.1 s3.7

EPA's SHEDS-Multimedia Model & Its Potential Application for PAHs

Valerie Zartarian, Ph.D., Jianping Xue, M.D., M.S.

U.S. Environmental Protection Agency
Office of Research and Development
National Exposure Research Laboratory

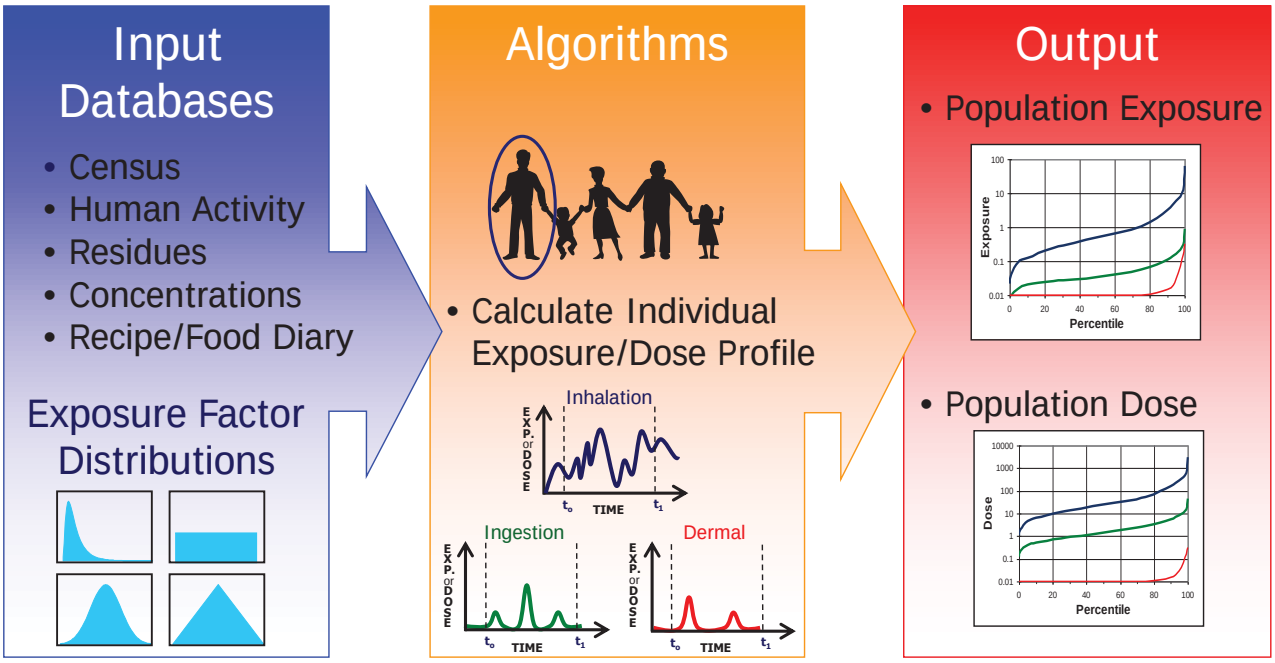
Concawe Integrated PAH Modeling Workshop
Brussels, Belgium
October 8, 2015

SHEDS-Multimedia is a physically-based, probabilistic model…

…that can simulate aggregate or cumulative exposures over time via dietary…

… and residential routes of exposure for a variety of multimedia, multipathway environmental chemicals.

General SHEDS Model Structure



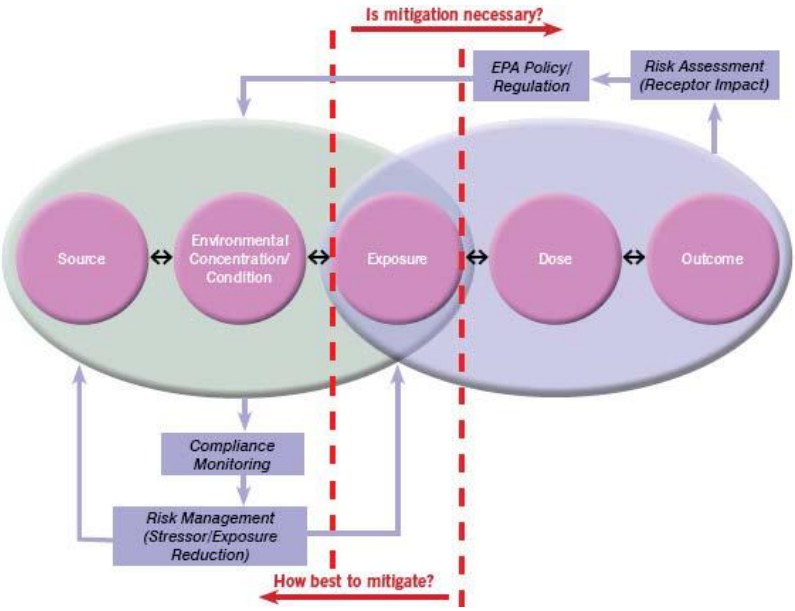
Goals of EPA/ORD/NERL's SHEDS-Multimedia Model

- To improve estimates of human exposure to multimedia, multipathway chemicals
  - Exposure is defined in SHEDS as the contact between a chemical agent and a simulated human target at the external surface
  - Dose is defined as the amount of chemical that enters the target after crossing the exposure surfaces

- To help answer key questions
  - What is population distribution of exposure (variability/uncertainty)?
  - What is intensity, duration, frequency, route, timing of exposures?
  - How to effectively reduce exposure (media, pathways, factors)?
  - How to identify and address greatest uncertainties (->risk)?
  - How do modeled estimates compare with measurements data?

What is the context for this science?

- U.S. Food Quality Protection Act of 1996
- SHEDS-Multimedia is EPA/ORD's probabilistic model for improving estimates of aggregate and cumulative human exposure and dose.
- Reliable human exposure models are critical for improving health risk assessments for pesticides.



- EPA developed and applied SHEDS-Multimedia to support its cumulative and aggregate assessments for multiple chemicals

International Use of SHEDS-Multimedia to Date

- >20 peer-reviewed journal publications on SHEDS-Multimedia methods, model applications, evaluation
- SHEDS-Multimedia registered users in 26 countries and U.S. for different chemicals and applications (from accessing EPA website)
  - Academia
  - Industry
  - Consultants
  - Individual Citizens
- Part of 1st and 2nd International Conference on Risk Assessment of the Global Risk Dialogue (2008, 2011) which included REACH

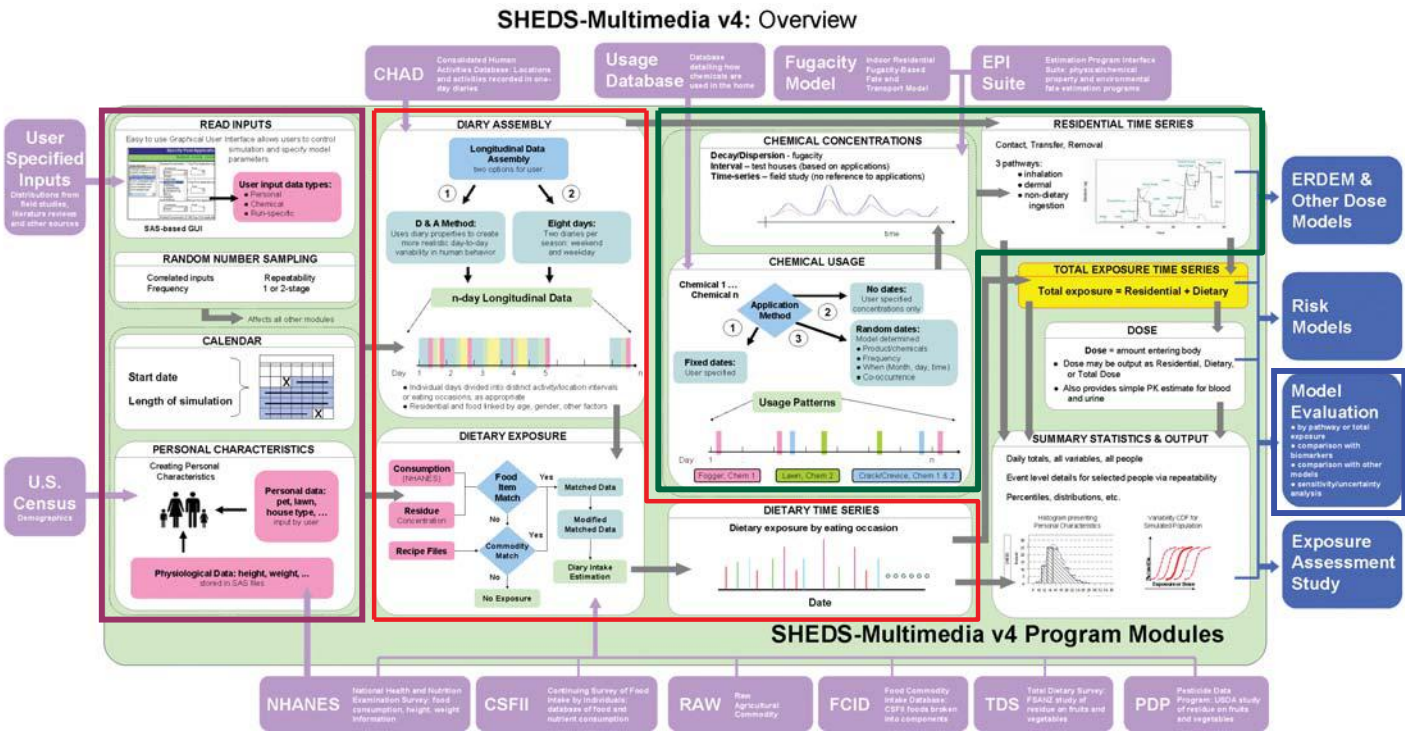
Examples of SHEDS-Multimedia Applications to Date

- CCA-treated wood exposure assessment for U.S. children
- MeHg dietary exposures
- Arsenic exposure for drinking water and dietary exposures
- PCBs dietary exposure and multi-media exposure of school children
- Chlorpyrifos exposure assessment
- Organophosphates cumulative risk assessment
- Aldicarb exposure assessment
- Carbaryl exposure assessment
- N-methyl carbamates cumulative risk assessment
- Permethrin exposure assessment
- Pyrethroids cumulative exposure assessment
- Diazinon exposures to residents from pet dogs following lawn applications

SHEDS-Multimedia Key Features

- ✓ Produces population percentiles of dietary exposure by source and age-gender group
- ✓ Flexible, transparent code, input (including input data) and code are separate
- ✓ Multi-chemical capability with integrated and cumulative exposures
- ✓ Can link to PBPK models for estimating dose
- ✓ Modularized code to accommodate new chemicals, scenarios and population
- ✓ Can be used to conduct sensitivity and uncertainty analyses for key factors
- ✓ Well evaluated with other exposure models and measured data

SHEDS-Multimedia Overview



Overview of Residential Methodology

1) Read in user-specified information
2) Create a simulated individual
3) Generate individual's longitudinal activity pattern
4) Generate usage patterns & conc. time series for each medium
5) Simulate contacts between the individual and affected media
6) Calculate individual's pathway-specific exposure time series
7) Generate individual's dose time series (if applicable)
8) Extract daily statistics from exposure or dose time series
9) Repeat steps 2-8 with Monte Carlo sampling to construct population variability estimates
10) Conduct sensitivity and uncertainty analyses if desired

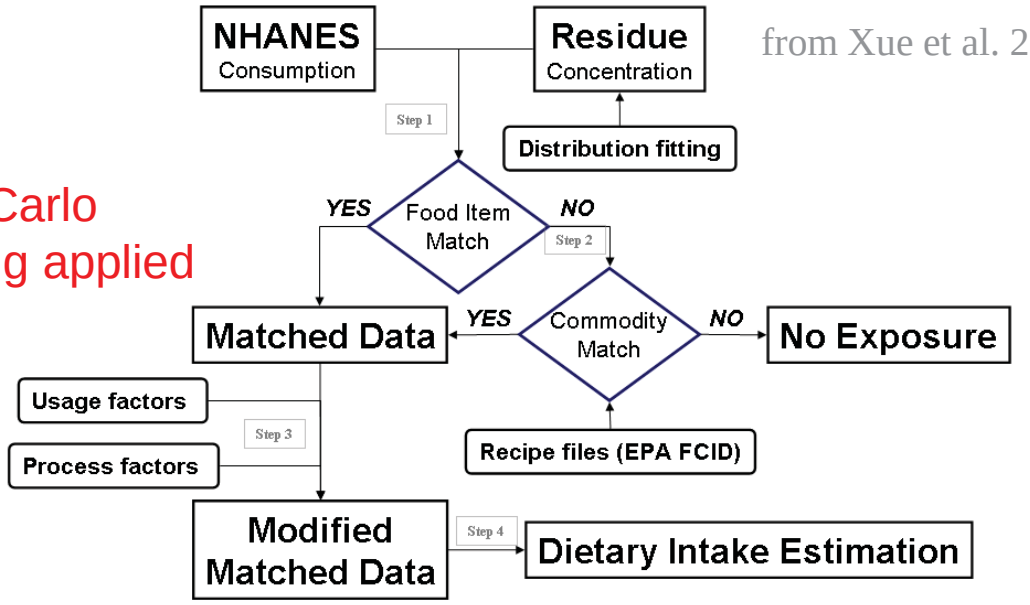
Residential Module Inputs

- User-specified inputs
  - Application/population-specific inputs
  - Chemical usage-related inputs
  - Co-occurrence factors (Variable Dates option)
  - Contact-related
  - Concentration-related
  - Exposure and dose factors
  - Inputs related to handlers
- Default inputs
  - CHAD database, U.S. Census (population statistics), NHANES (height and weight), list of application scenarios and contact media, standard age groupings
- Minimal values embedded in code

Residential Module Outputs

- Population Outputs for Exposure or Dose Metrics
- Individual Outputs for Exposure or Dose Metrics
- Sensitivity Analyses
  - ranked input table
- Uncertainty Analyses
  - ranked input table
  - 2 types of graphs

Figure 1 SHEDS Dietary Module Overview



from Xue et al. 2010, *EHP*

Monte Carlo sampling applied

NHANES Consumption:	Food consumption data from NHANES
Residue Concentration:	Residue concentration data by food item or commodity from TDS
Distribution fitting:	Fitting of residue data into suitable statistical distribution
Food Item:	Food products people in the survey consumed such as pizza, raw apple
Commodity:	Raw agriculture commodity (RAC)
Usage factors:	Pesticide usage percentages by RAC from USDA
Process factors:	Concentration or dilution factors due to processes of food from RAC into food products
Recipe files (EPA FCID):	Data base for percents of various RACs for the food products

EPA United States Environmental Protection Agency

Dietary Module Inputs

- Food and Indirect Water Consumption
  - USDA CSFII 1994-96, 1998 *OR*
  - NHANES/WWEIA 1999-2006
- Direct Water Consumption Data
  - SHEDS currently distributes total direct water consumption in 6 equal amounts at 6 fixed times (6 am, 9, 12, 3, 6, 9)
- Food Residues & Drinking Water Concentrations
  - Point estimate or empirical distributions
  - Field Trials, USDA/PDP, FDA/TDS; PRZM-EXAMS, etc.

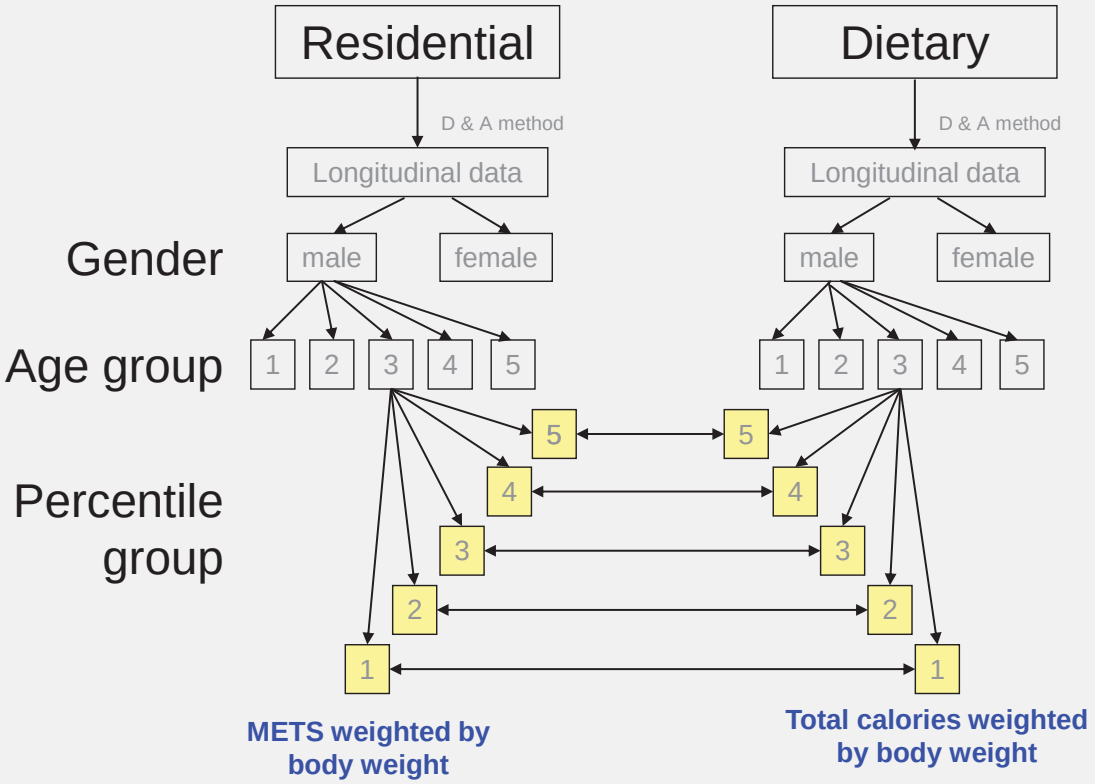
Dietary Module Inputs (cont'd)

- Recipe Files
  - EPA Food Commodity Intake Database (FCID) contain recipes for each food item recorded in the CSFII diaries
  - Recipes are being developed by OPP for new NHANES/WWEIA food items
- Pesticide Use (Percent of Crop Treated)
  - USDA National Agricultural Statistics Service
- Processing Factors (concentration or dilution factors due to cooking, food processing, etc.)
  - Registrant submission
  - Peer reviewed literature

Dietary Module Outputs

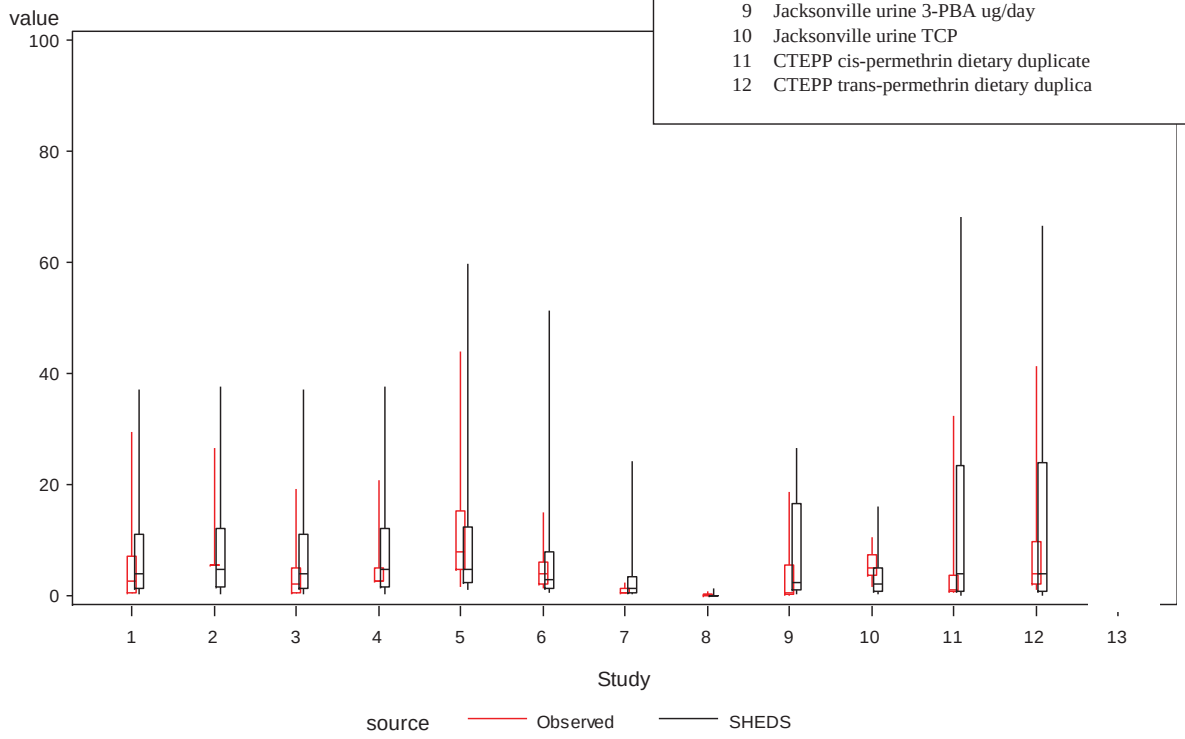
- Total dietary exposure at different percentiles, by source (food, water, food+water), age-gender group
  - CDFs of dietary exposures for populations of interests
- Pie/bar charts showing contribution to total exposure in upper %iles (e.g., 99.9-100th), by food, commodity, commodity-chemical (multi-chemicals)
- Sensitivity analyses
  - NHANES/WWEIA (1999-2006) vs. CSFII (1994-1996, 1998)
  - impact on exposure of removing commodities
  - half-life analyses
  - eating occasion analyses
- Uncertainty analyses
  - assess impact of residues, consumption, and sample sizes

Linkage of Dietary & Residential Modules



SHEDS-Multimedia Evaluation with Different Chemicals

study	study label
1	3-PBA 2007-2008 NHANE
2	DCCA 2007-2008 NHANE
3	3-PBA 1999-2002 NHANE
4	DCCA 1999-2002 NHANE
5	2003-2004 NHANE total As in Urine
6	2003-2004 NHANE DMA in Urine
7	2003-2004 NHANE MMA in Urine
8	As NEXUS dietary duplicate study
9	Jacksonville urine 3-PBA ug/day
10	Jacksonville urine TCP
11	CTEPP cis-permethrin dietary duplicate
12	CTEPP trans-permethrin dietary duplica



Peer Review & Quality Assurance

- External peer reviews by EPA FIFRA SAP (Scientific Advisory Panel) and scientific journals
- Followed modeling Quality Assurance Project Plan for all aspects of SHEDS development
- Placed emphasis on QA by EPA and contractors for algorithms, code, GUI
- Cross-checked all components
- Conducted 1-person, event-by-event simulation for residential code verification
- Conducted model-to-model and model-to-data comparisons
- Addressed comments of non-developers in EPA and contractors who reviewed the models and documentation, and tested the GUIs

Pyrethroids Example: Approach applies to proposed PAH Application

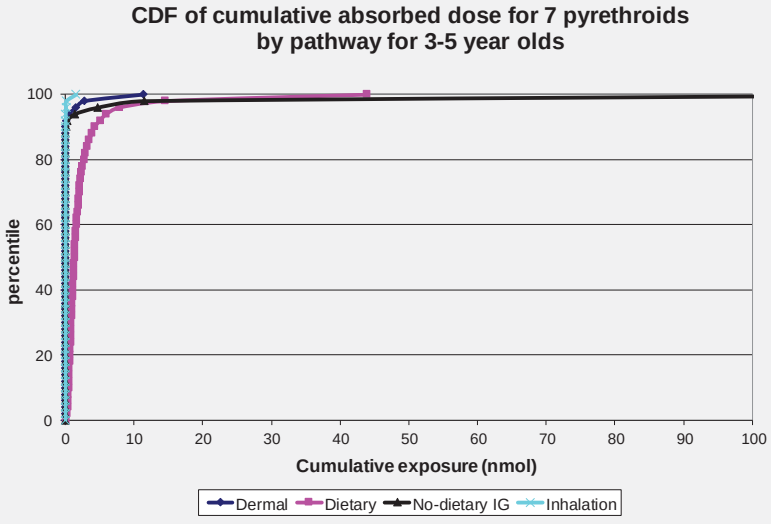
- ❑ Select population(s) & exposure scenarios for chemical(s) of interest
- ❑ Assess Census time/activity & dietary consumption data
- ❑ Fit input distributions to available concentration data in multiple media
- ❑ Verify non-chemical-specific inputs & modify chemical- specific input files
- ❑ Apply SHEDS to estimate aggregate or cumulative exposures
- ❑ Use SHEDS pharmacokinetic model to estimate dose and/or export exposure profiles for PBPK model
- ❑ Conduct chemical contribution/pathway, sensitivity & uncertainty analyses
- ❑ Evaluate SHEDS estimates vs. biomarker data and other measured data

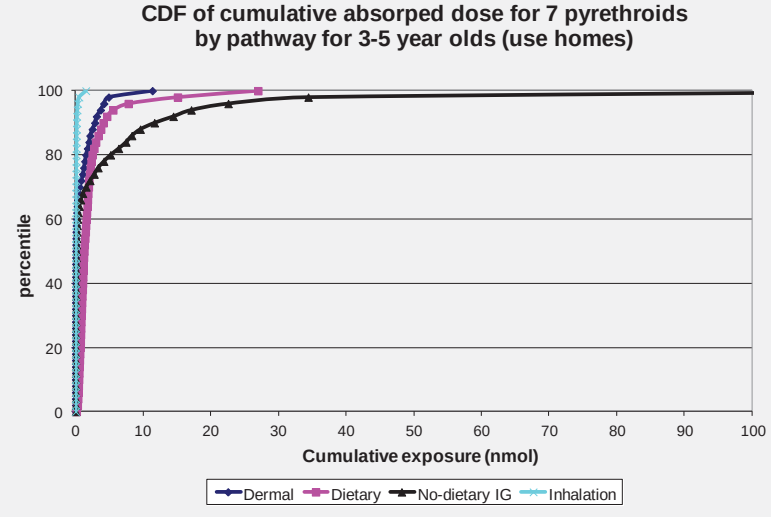
Pyrethroids Example for Illustrating Potential Use of SHEDS for PAHs

Cumulative annual absorbed dose of 7 pyrethroids from residential & dietary sources (nmol)

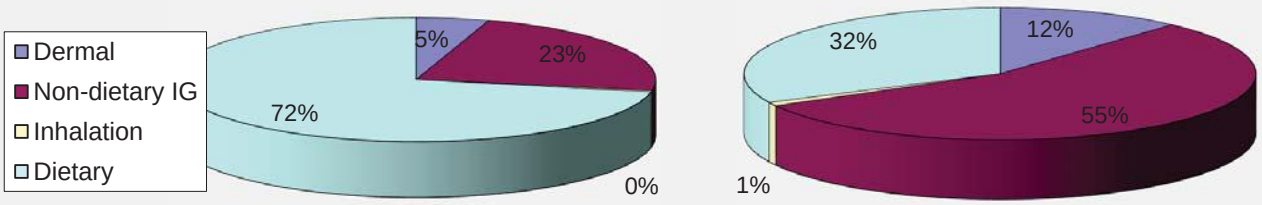
age group	use population	n	mean	std	p5	p25	p50	p75	p95	p99
Adult	general population	4143	8.4	9.6	1.0	2.9	5.7	10.4	24.7	47.0
	residential use	815	10.5	11.5	1.3	4.0	7.2	12.7	31.3	60.1
3-5 years old	general population	5733	3.1	5.8	0.4	0.8	1.4	2.8	12.4	27.0
	residential use	1101	6.7	10.8	0.5	1.1	2.3	7.7	26.4	46.3

Pyrethroids Example for Illustrating Potential Use of SHEDS for PAHs



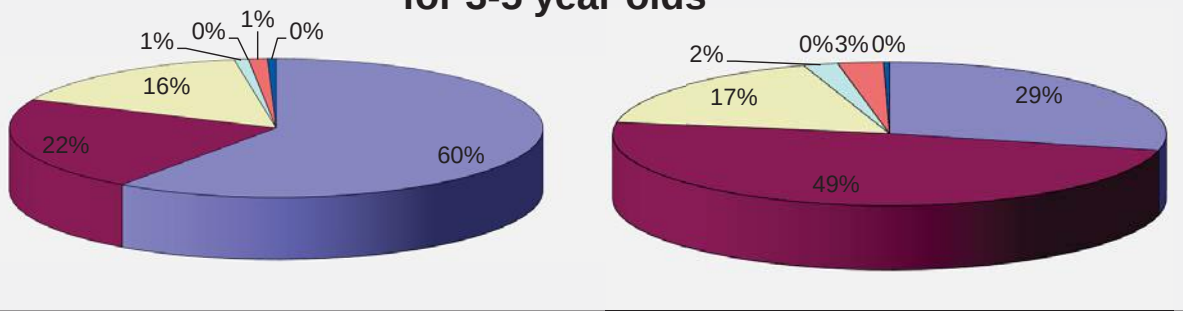


Contribution of 7 cumulative pyrethroids absorbed dose by pathway for 3-5 year olds



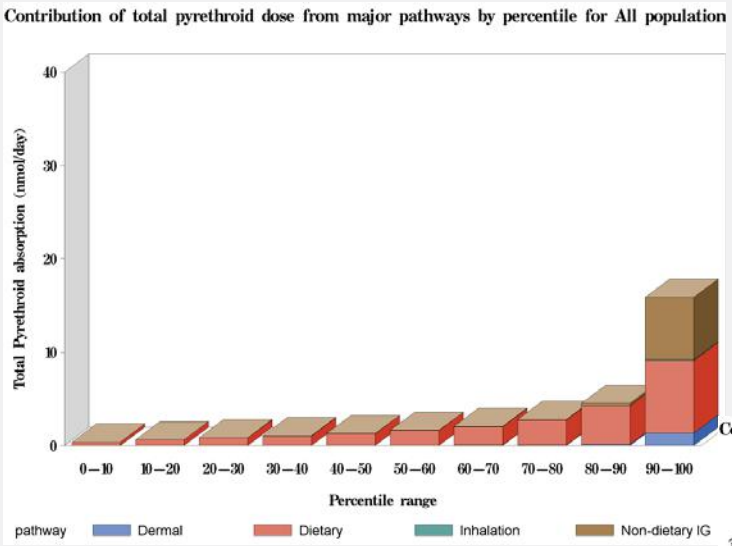
Residential Use and Non-use Homes **Use Homes**

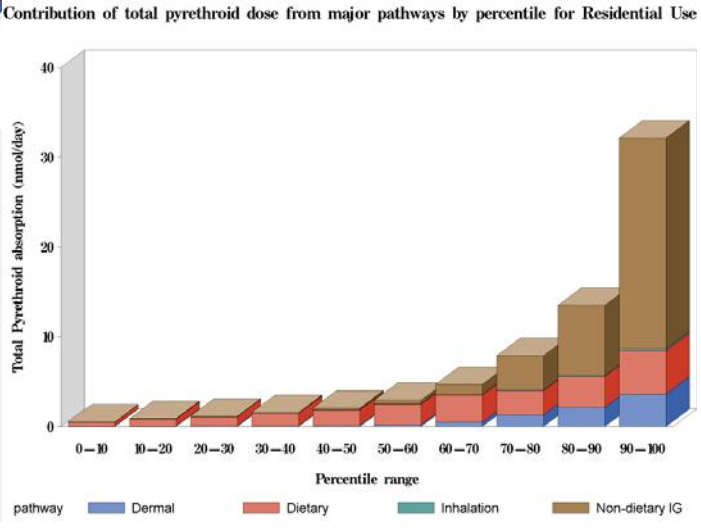
Contribution of cumulative absorbed dose by 7 major pyrethroids for 3-5 year olds



Permethrin Cypermethrin Cyfluthrin Allethrin Resmethrin Deltamethrin Esfenvalerate

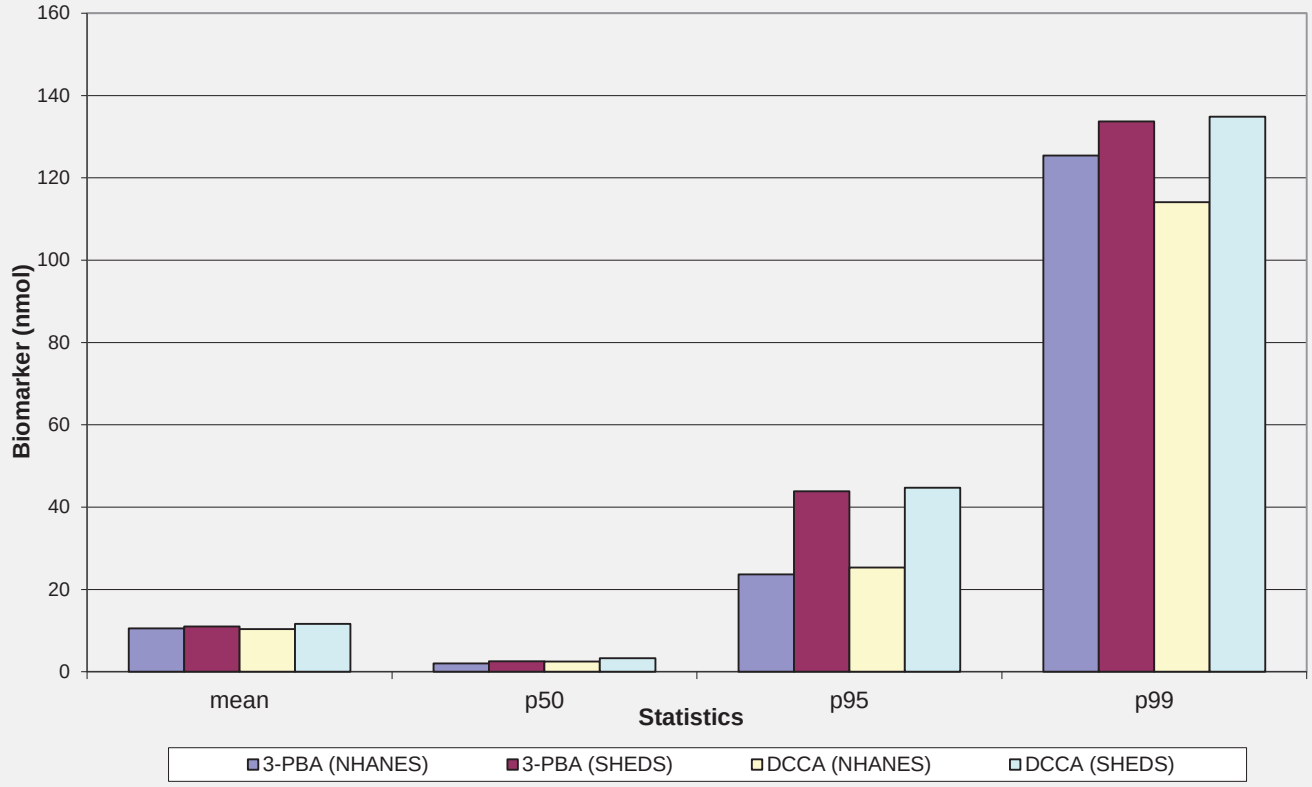
Contribution of pyrethroids dose by pathway & percentile for 3-5 year olds





EPA United States Environmental Protection Agency

Comparison of urinary biomarkers from '99-'02 NHANES vs. SHEDS results



EPA United States Environmental Protection Agency

Summary of SHEDS-Multimedia Pyrethroids Example Illustrating Potential for PAHs

- Cumulative averaged absorbed dose of 7 pyrethroids:
  - *9 and 4 nmol/day for adult and child, respectively, with residential use population higher than general population*
- Contributions to cumulative exposure by chemical:
  - *General pop'n: permethrin (60%), cypermethrin (22%), cyfluthrin (16%)*
  - *residential use: cypermethrin (40%), permethrin (29%), cyfluthrin (17%)*
- Primary exposure route for 3-5 year-olds:
  - *non-dietary ingestion in residential use households*
  - *dietary exposure including use and non-use households*
- Sensitivity of dermal absorption methodology:
  - *new method considering SL issues has some impact, but does not change order of pathways*
- Evaluation:
  - *SHEDS compares well versus NHANES biomarkers*

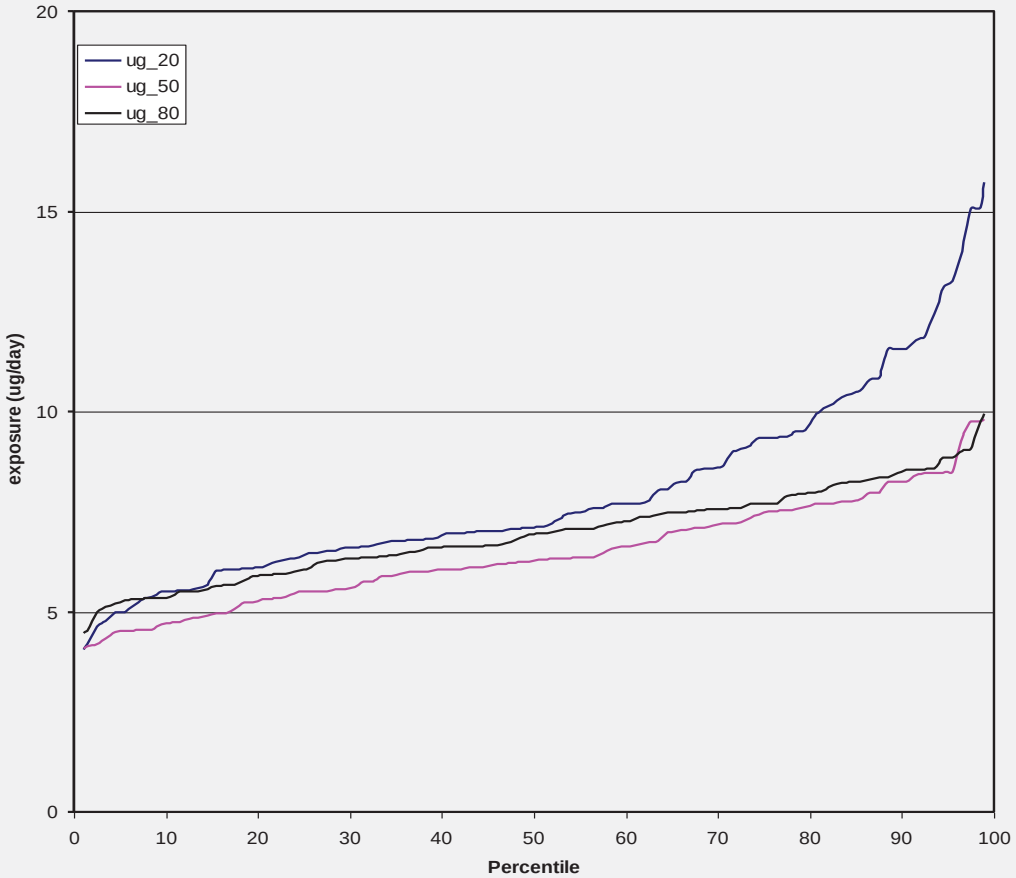
Example SHEDS Sensitivity Analyses

Sobol Sensitivity Analyses for Modeled Residential Exposure Inputs

Input variable	Main effect	Total Effect	Percent contribution
Usage frequency for CC_Aerosol	0.245	0.529	32.8
Surface-to-skin transfer efficiency	0.012	0.244	15.1
Usage frequency for CC_Liquid	0.124	0.204	12.6
Usage frequency for Ind_Fogger	0.092	0.193	12.0
Hand-mouthing events per hour	0.013	0.121	7.5
Rank	0.004	0.091	5.6
Fraction of house treated	0.004	0.078	4.8
Usage frequency for Ind_FIK	0.031	0.039	2.4
Personal mean for DiaryKey ranking	0.002	0.029	1.8
Maximum Dermal Loading	0	0.018	1.1
Fraction lost per day indoors	0.001	0.017	1.1
Object-to-floor concentration ratio	0.001	0.015	0.9
Object-mouthing events per hour,Pool selections for one-day diaries	0.001	0.011	0.7
Mean # of hand washings per day	0	0.01	0.6
Physiology (weight, height, BMR, age, gender…)	0.001	0.008	0.5
Object-to-mouth transfer efficiency	0.001	0.008	0.5

Example SHEDS Uncertainty Analyses

99th percentile uncertainty profiles by bootstrap 50% dietary consumption data and 20%,50%,80% dietary sampling rates for cis-permethrin



Key Considerations for Potential Application of SHEDS-Multimedia to PAHs

- Approach used in pyrethroids example could apply
- May need to switch embedded input data depending on population for simulation
- Modification of code needed for scenarios of consumer products such as petroleum products
- SHEDS-Multimedia was developed in SAS v.8

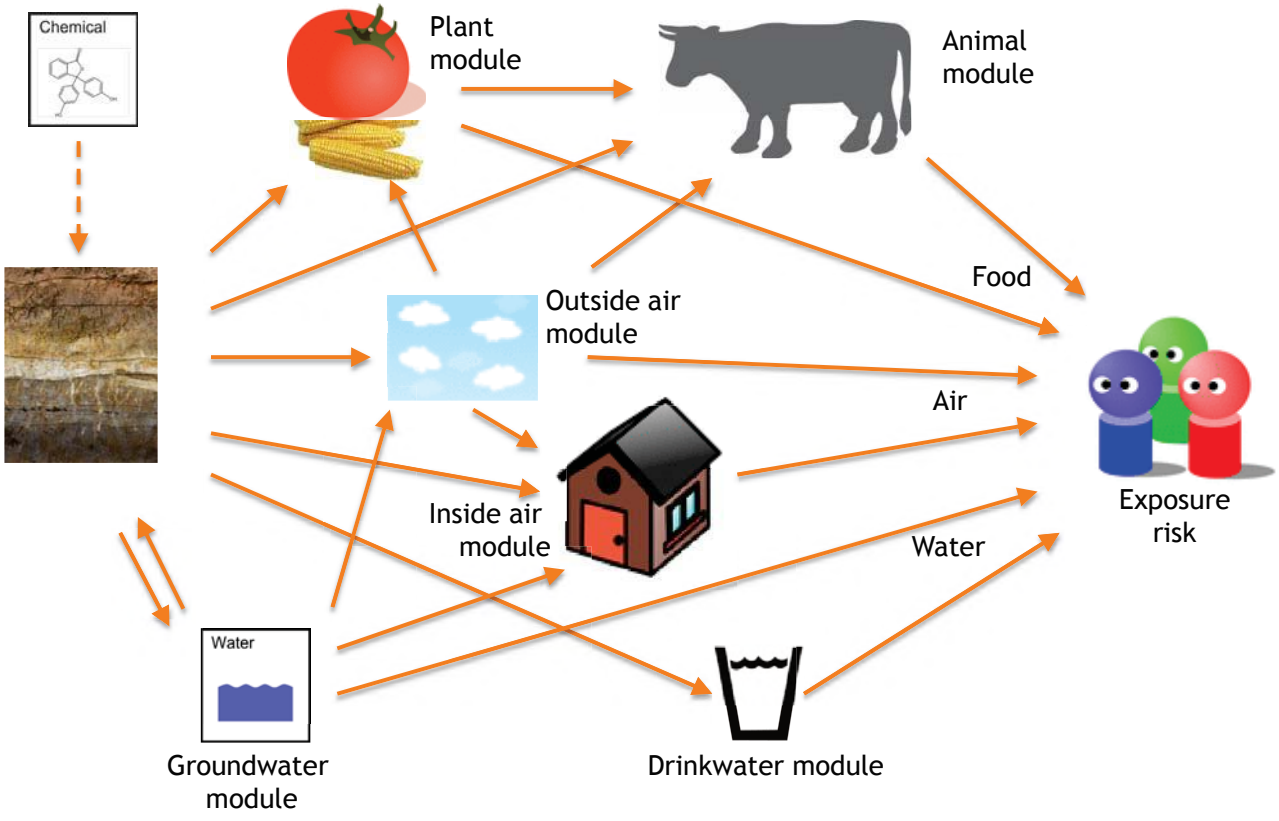
vito

concawe

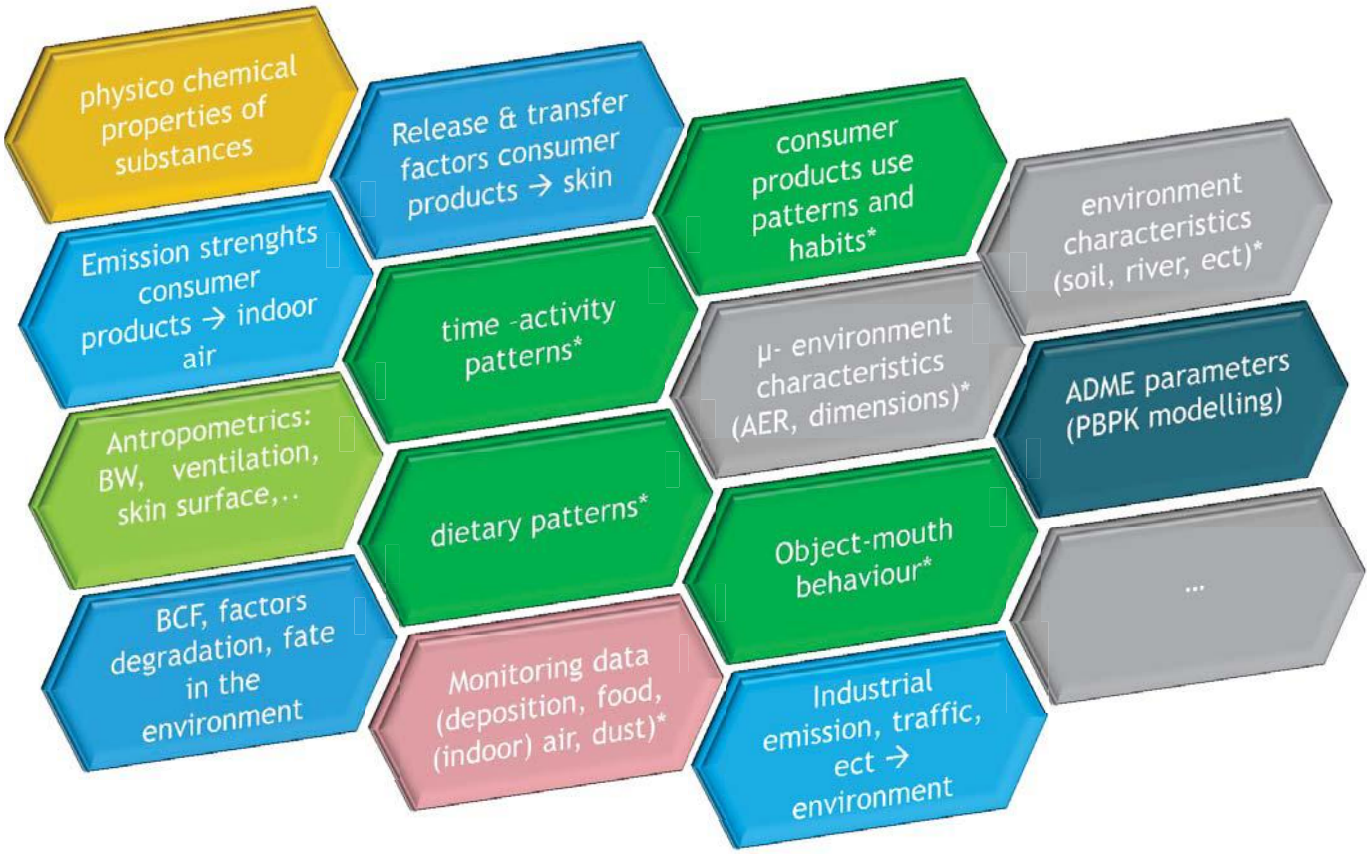
ENVIRONMENTAL SCIENCE FOR THE EUROPEAN REFINING INDUSTRY

EXPOSURE DATA SOURCES

CONCEPTUAL MODEL | SOFTWARE | EXPOSURE DATA



EXPOSURE DATA



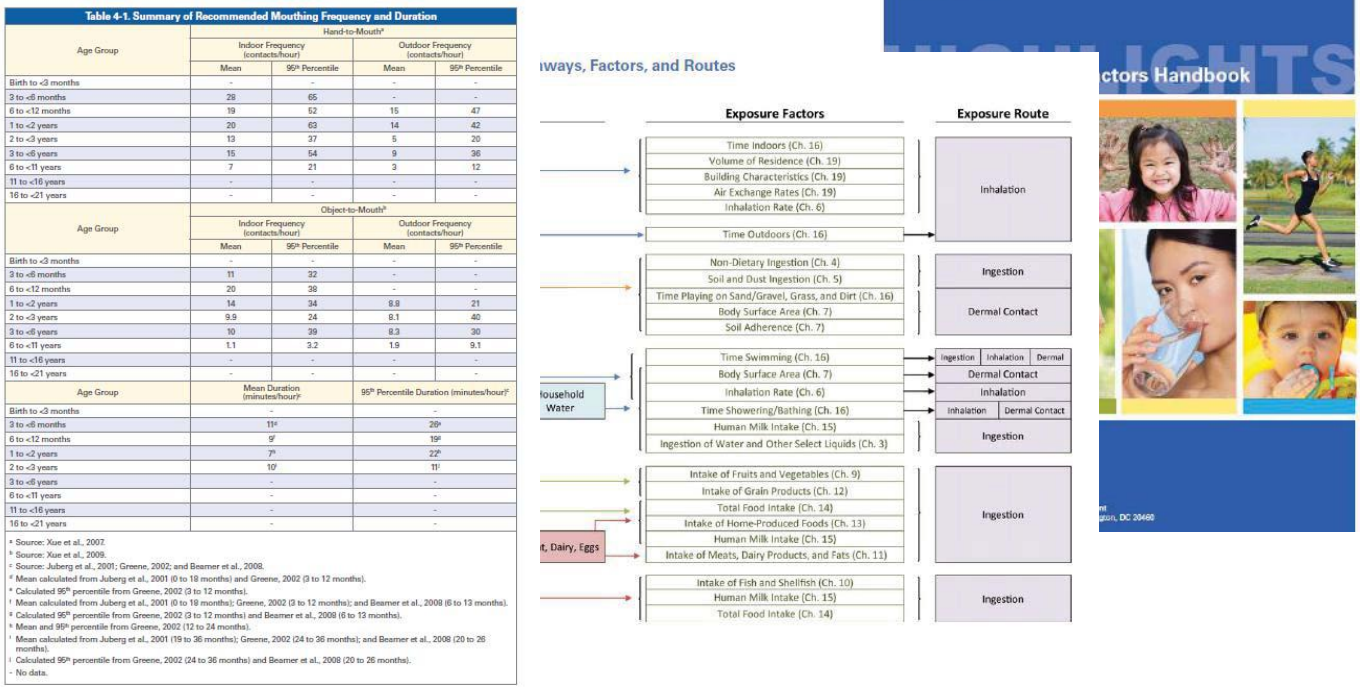
Sources for generic exposure factors

KEY SOURCES FOR EXPOSURE FACTORS

Expofacts database (JRC): http://expofacts.jrc.ec.europa.eu/

KEY SOURCES FOR EXPOSURE FACTORS

» US EPA exposure factors handbook (2011)



» US EPA Child specific exposure factor handbook (2002)

DIETARY PATTERNS

Tiered level

EUSES defaults:

Table R.16-16: Human daily intake of food and water (from EUSES)

Food	Intake
Drinking water	2 l/d
Fish	0.115 kg/d
Leaf crops (incl. Fruit and cereals)	1.2 kg/d
Root crops	0.384 kg/d
Meat	0.301 kg/d
Dairy products	0.561 kg/d

No differentiation age groups

No variability

No contribution from non-environmental sources

Imported food commodities not considered

Simple food Baskets

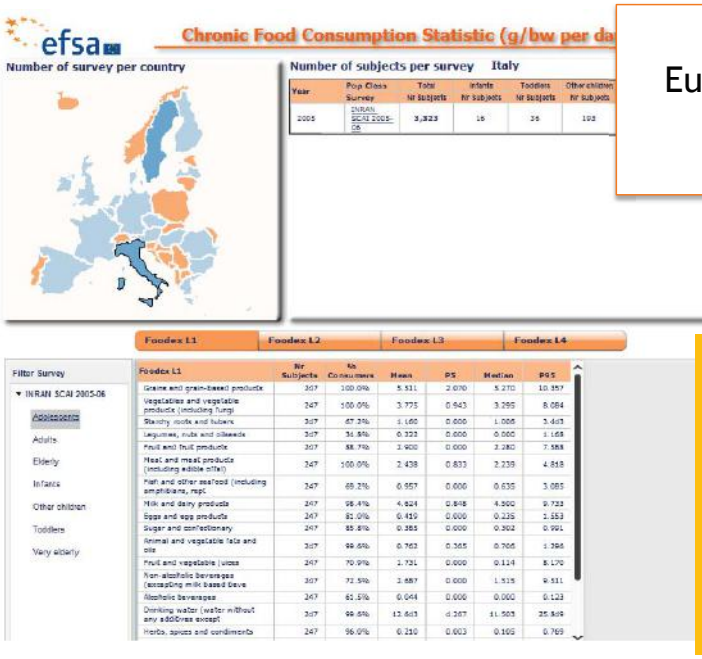
Table 3.
Daily consumption data for Danish consumers of the age 4-5 years and 14-75 years (females), mean and 95th percentile for both groups, and consumption data suggested in the TGD.

	4–5		14–75 (♀)		
Food type	Mean	95th	Mean	95th	TGD
Root vegetables (g/d)	30	54	43	89	384[c]
Potatoes (g/d)	56	137	90	198	
Lettuce (g/d)	6	11	9	18	1200[d]
Other leafy veg. (g/d)	7	13	10	21	
Tree fruits (g/d)	111	235	137	318	
Cereal products (g/d)	185	269	195	309	
Milk (g/d)	448	796	303	754	561
Meat (non-poultry) (g/d)	76	138	89	166	301

Legind et al. 2009
Modeling the exposure of children and adults via diet to chemicals in the
environment with crop-specific models (Env. Pollution)

DIETARY PATTERNS

Tiered level



EFSA comprehensive European Food Consumption Database In Exposure Assessment

EFSA database:
national surveys harmonized in the same food classes
considering different age groups, and variability
flexibility of Food Class levels (FoodEx1, FoodEx2,…)
freely downloadable database (excel)

DIETARY PATTERNS

Tiered level

EUSES defaults:

1.2 kg/day leaf crops
0.38 kg/day root crop

Simple food Baskets

EFSA comprehensive Food database

Individual food patterns

efsa
European Food Safety Authority

Level needs to be aligned with the level of environmental & consumers exposure model

TIME ACTIVITY PATTERNS

» ROLE of time activity patterns:

» time - µ-environment:

$$Inh\ Exp_{personal} = \sum_{i=1}^{n} Inh\ Exp\ \mu\ env_i = \sum_{i=1}^{n} C_i \times t_i$$

monitoring or modelling air quality indoor & outdoor µ-environments

time activity records

» time - physical activity level → inhalation rates

TIME ACTIVITY PATTERNS

EXPOLIS (2003)

CAR/TAXI

INDOOR HOME

OUTDOOR HOME

WALK/BIKE

BUS/TRAM

OTHER INDOOR

OTHER OUTDOOR

Table 1. Time spent in various indoor locations among people reporting time (habitués).

	n	Min	Median	Max	Mean[a]	SD
Home indoors						
Helsinki	430	3.81	13.15	24.00	13.73	3.01
Athens	98	4.19	15.30	24.00	15.44	4.08
Basel	320	0.94	13.02	22.48	13.53	3.34
Grenoble	100	3.88	14.13	23.63	14.67	4.14
Milan	298	8.13	13.09	22.50	13.48	2.60
Prague	81	7.63	13.23	23.50	13.92	3.50
Oxford	100	2.75	15.19	24.00	15.76	3.17
All cities	1427	0.94	13.31	24.00	13.95	3.29
Work indoors						
Helsinki	370	0.07	7.48	11.04	6.83	2.15
Athens	67	1.19	6.13	13.06	5.90	2.34
Basel	266	0.13	7.38	13.31	6.67	2.50
Grenoble	79	0.38	7.00	13.25	6.73	2.62
Milan	267	0.25	7.50	12.19	7.09	2.14
Prague	71	0.75	7.50	10.50	6.52	2.68
Oxford	77	1.00	6.25	17.25	5.90	2.81
All cities	1197	0.07	7.29	16.63	6.71	2.37
Other indoors						
Helsinki	349	0.04	1.00	10.70	1.53	1.58
Athens	69	0.06	1.44	7.75	1.76	1.50
Basel	293	0.04	1.50	10.69	1.84	1.57
Grenoble	74	0.13	1.19	16.88	2.22	2.94
Milan	272	0.06	1.23	10.56	1.58	1.32
Prague	56	0.08	1.16	8.58	1.69	1.81
Oxford	69	0.13	0.81	6.25	1.30	1.31
All cities	1181	0.04	1.25	16.88	1.67	1.64

HUMAN (BEHAVIOUR) EXPOSURE DATA

Numerous scientific publications; some examples:

Brochu, P., Brodeur, J., Krishnan, K. (2011). Derivation of physiological inhalation rates in children, adults, and elderly based on nighttime and daytime respiratory parameters. *Inhalation Toxicology, 23* (2), 74-94.

Moya J., Phillips L. (2014). A review of soil and dust ingestion studies for children. *Journal of Exposure Science and Environmental Epidemiology, 24*, 545–554

Minnen, J., I. Glorieux, T.P. van Tienoven (2015): Transportation habits: Evidence from time-use data. *Transportation Research* , Part A, 76: 25-37 - TOR 2015/1.

Etc…

Sources for PAH specific exposure factors

CONSUMER PRODUCTS: USE, EMISSIONS AND RELEASE

» PAHs are not intentionally manufactured and added but they enter the products if softener oils or carbon black are used.

» The European Commission has published the Regulation (EU) No.1272/2013 to amend Entry 50 of Annex XVII to REACH Regulation (EC) No.1907/2006 on the restrictions of polycyclic aromatic hydrocarbons (PAH) in consumer goods. The new requirements shall apply from 27 December 2015.

Article	Limit of PAH
• Toys (including activity toys) • Child care articles	0.5 mg/kg each
All other articles supplied to the general public, for example: • Sports equipment such as bicycles, golf clubs, racquets • Household utensils, trolleys, walking frames • Tools for domestic use • Clothing, footwear, gloves and sportswear • Watch-straps, wrist-bands, masks, head-bands	1.0 mg/kg each

CONSUMER PRODUCTS: USE, EMISSIONS AND RELEASE

- Majority of public data on consumer use and release: personal care products, household products and construction articles (e.g BUMAC database) → no data for PAHs
- Important sources of PAH in indoor environments: combustion
  - Tobacco smoking (in smokers homes: 90 % PAHs from ETS)
  - Developing countries: unvented burning of solid fuels (wood, coal, agricultural residues)

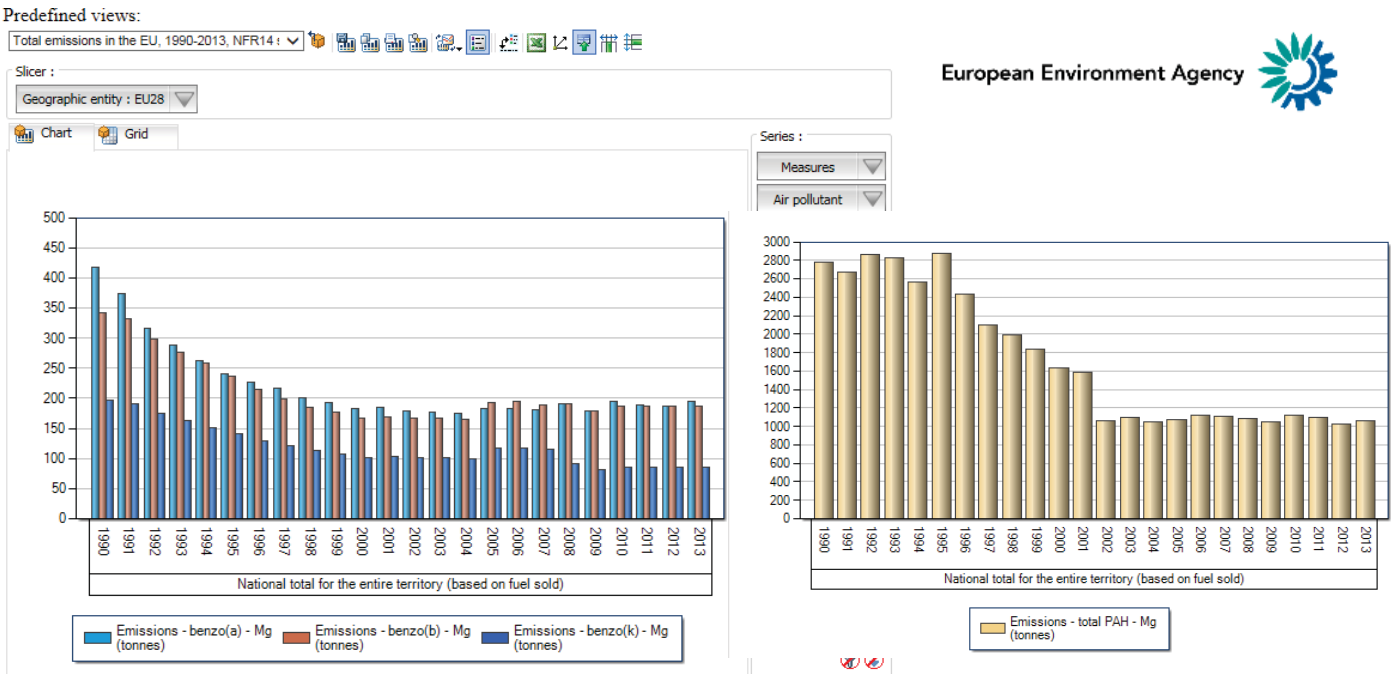
Table 6.1 Benzo[*a*]pyrene emission factors

Source	Emission factor	Unit	Comment	Reference
Cigarettes	35	ng/cigarette	Average content in mainstream smoke before 1960	WHO (23)
	18	ng/cigarette	Average content in mainstream smoke, 1978–1979	WHO (23)
Fuel	0.8	mg/kg	Peat briquettes	Kakareka et al. (26)
	1.6–8.2	mg/kg	Wood	Kakareka et al. (26)
	5.3–13.2	mg/kg	Mixture of wood and root-fuel	Gupta et al. (27); Venkataraman et al. (28)
Candles	n.d.–0.13[a]	ng/g of wax burned	Candles	Lau et al. (16)
Creosote	58–749	µg/g	Creosote-impregnated wood products	Ikarashi et al. (29)

WHO, 2010

EMISSIONS INVENTORY

- European Environment Agency: emissions inventory **Long-range Transboundary Air Pollution** Convention (LRTAP)

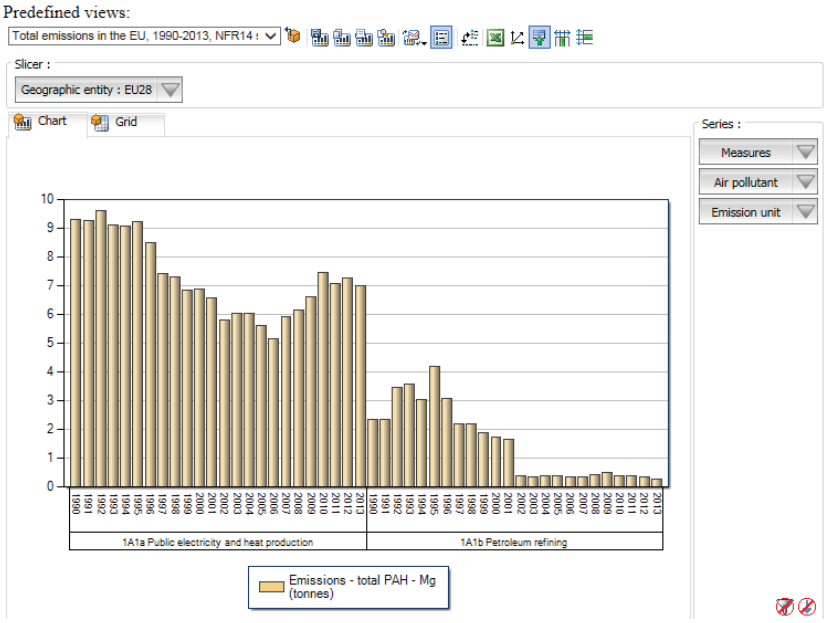


EMISSIONS INVENTORY

» European Environment Agency: emissions inventory **Long-range Transboundary Air Pollution** Convention (LRTAP)

http://www.eea.europa.eu/themes/air

»



Monitoring data of PAHs in the environment

MONITORING DATA IN EXPOSURE MODELLING

VERIFICATION of (intermediate) model predictions

model input (optional)

→ Refined exposure estimates

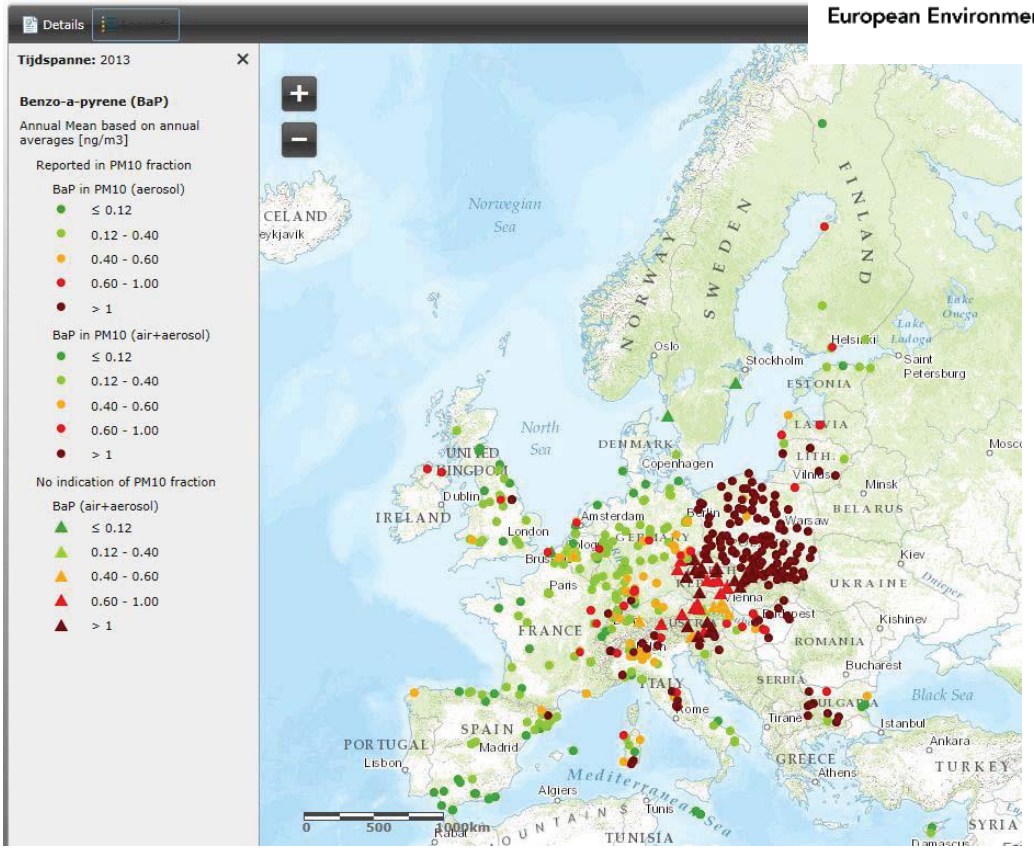
large number of concentration measurements are carried out for various purposes at local, national and international levels (monitoring, surveillance, research)

PAHs: plenty of monitoring data – non-exhaustive overview

AMBIENT AIR

Benzo-a-Pyrene (BaP) in Europe

European Environment Agency



AMBIENT AIR

Tabel 8.1.: PAK-jaargemiddelden in 2013 (ng/m³)						
PAK (ng/m³)	Borgerhout	Gent	Houtem	Steenokkerzeel	Zelzate	gemiddelde
fluorantheen	0,65	0,84	0,29	0,61	0,76	0,63
pyreen	0,43	0,57	0,19	0,47	0,49	0,43
benzo(a)anthraceen	0,23	0,24	0,10	0,27	0,38	0,24
chryseen	0,29	0,37	0,19	0,39	0,40	0,33
benzo(b)fluorantheen	0,21	0,25	0,18	0,32	0,34	0,26
benzo(k)fluorantheen	0,11	0,13	0,08	0,17	0,19	0,14
benzo(a)pyreen	**0,19**	**0,22**	**0,11**	**0,31**	**0,32**	**0,23**
benzo(g,h,i)peryleen	0,14	0,17	0,10	0,18	0,22	0,16
indeno(1,2,3-cd)pyreen	0,21	0,25	0,17	0,42	0,28	0,27
Totaal	**2,46**	**3,03**	**1,41**	**3,14**	**3,39**	**2,68**
aantal meetdagen	102	101	100	77	106	

(VMM jaarrapport, 2013)

INDOOR AIR

- » No systematically monitoring and reporting PAHs in the Indoor Environment in the EU
- » Information in scientific review papers and national agencies;
- » some examples:

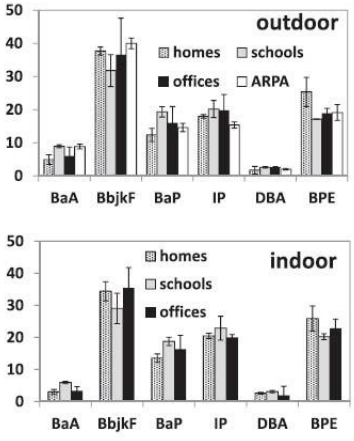


Fig. 2. Mean percent distributions of PAH compounds at homes, schools and offices in the winter season. For comparison, the mean PAH compositions at ARPA Lazio stations (outdoors) are also provided. Error bars represent ±1 standard deviation.

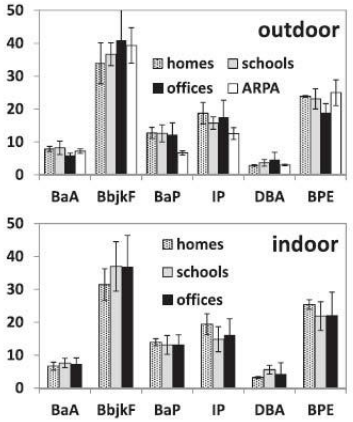


Fig. 3. Mean percent distributions of PAH compounds at homes, schools and offices in the warm seasons. For comparison, the mean PAH compositions at ARPA Lazio stations (outdoors) are also provided. Error bars represent ±1 standard deviation.

(Romagnoli et al, 2014)

FOOD

European Food Safety Authority

The EFSA Journal (2008) 724, 1-114

Polycyclic Aromatic Hydrocarbons in Food[1]

Scientific Opinion of the Panel on Contaminants in the Food Chain

(Question N° EFSA-Q-2007-136)

Adopted on 9 June 2008

- Data from 18 EU MS
- 9700 PAH analytes
- 33 food (sub)categories

- 50 % samples: Benzo(a)pyrene
- 30 % samples neg BaP: other PAHs detected
- Cereals & cereal products Sea food (products)

FOOD

Accessibility of EFSA data ?

- retrieve statistics from EFSA report (pdf) level of details?

Table 7: Descriptive statistics for the concentration in µg/kg for 1,375 food products analysed for all of the 15 SCF priority PAHs.

PAH	N	>LOD	Concentration in µg/kg									
			P05		Median		Mean		P95		Maximum	
			LB	UB	LB	UB	LB	UB	LB	UB	LB	UB
BaP	1375	54.9%	0	0.01	0.04	0.07	0.79	0.81	3.23	3.23	67	67
BaA	1375	70.3%	0	0.01	0.08	0.09	1.33	1.35	4.59	4.59	147	147
BbFA	1375	63.1%	0	0.01	0.05	0.08	1.40	1.42	6.43	6.43	116	116
BkFA	1375	52.7%	0	0.01	0.01	0.05	0.60	0.62	2.90	2.90	52	52
BghiP	1375	56.4%	0	0.01	0.02	0.05	0.63	0.65	2.82	2.82	38	38
CHR	1375	77.8%	0	0.01	0.17	0.19	2.79	2.81	7.90	7.90	353	353
DBahA	1375	18.3%	0	0.01	0	0.03	0.15	0.18	0.72	0.72	10	10
IP	1375	36.7%	0	0.01	0	0.05	0.57	0.59	2.40	2.40	45	45
BjFA	1375	51.9%	0	0.01	0.01	0.05	0.70	0.72	2.74	2.74	57	57
CPP	1375	39.3%	0	0.01	0	0.05	0.68	1.01	1.10	2.95	112	112
DBaeP	1375	12.2%	0	0.03	0	0.10	0.11	0.20	0.78	0.78	6	6
DBahP	1375	3.6%	0	0.01	0	0.10	0.03	0.12	0	0.20	3	3
DBaiP	1375	7.6%	0	0.03	0	0.10	0.06	0.15	0.24	0.35	3	3
DBalP	1375	10.3%	0	0.01	0	0.10	0.08	0.16	0.57	0.57	14	14
MCH	1375	4.0%	0	0.01	0	0.01	0.04	0.07	0	0.15	17	17
Total			0	0.19	0.38	1.12	9.96	10.86	36.42	38.73	1040	1040

N: Number of samples, LOD: Limit of detection

- Database available at EFSA: Food Ex classes, monitoring data EU MS
- Database is not publically accessible
- Request may be sent to EFSA request for parts of database

FOOD

WEB OF SCIENCE™

Search

Results: 385
(from All Databases)

You searched for: TOPIC: (PAH)
AND **TOPIC:** (food)
Timespan: 2008-2015.
Search language=Auto
...Less

Food and Chemical Toxicology 78 (2015) 1–9

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Investigation into the formation of PAHs in foods prepared in the home to determine the effects of frying, grilling, barbecuing, toasting and roasting

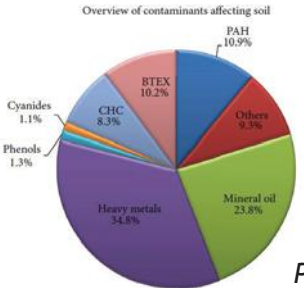
Martin Rose [a,*], Joe Holland [a], Alan Dowding [b], Steve (R.G.) Petch [a], Shaun White [a], Alwyn Fernandes [a], David Mortimer [b]

[a] The Food and Environment Research Agency, Sand Hutton, York YO41 1LZ, UK
[b] Food Standards Agency, Aviation House, 125 Kingsway, London WC2B 6NH, UK

ARTICLE INFO ABSTRACT

SOIL

- EIONET-SOIL (JRC): data collection on contaminated sites from national institutions in Europe using the European Environment Information and Observation Network for soil (EIONET-SOIL)



Paganos et al., 2013

- 'background' levels not included in EIONET-SOIL
- EU wide database GEMAS and LUCAS: soil properties, metals, not PAHs
- Scientific papers, e.g. Nam et al. (2008): PAHs in background soils from W Europe: influence of atmospheric deposition and soil organic matter

SOIL

Table 1
Geometric means of PAH concentrations with range in the UK and Norwegian soils (μg kg^{-1} soil, dry weight soil)*

	UK			Norway		
	Woodland	Grassland	All	Woodland	Grassland	All
Naphthalene	14 (2.5–300)	12 (3.7–27)	13 (2.5–300)	14 (2.2–45)	5.2 (2.9–9.2)	11 (2.2–45)
Acenaphthene	3.4 (0.7–74)	3.9 (1.3–28)	3.7 (0.7–74)	4.6 (1.0–11)	2.3 (1.1–4.2)	3.2 (1.0–11)
Fluorene	5.9 (1.3–15)	4.5 (1.9–20)	5.1 (1.3–20)	8.8 (1.4–22)	6.4 (3.8–11)	6.8 (1.4–22)
Phenanthrene	54 (4.6–350)	54 (13–330)	54 (4.6–350)	42 (6.7–110)	42 (32–50)	40 (6.7–110)
Anthracene	5.4 (0.7–32)	8.1 (1.1–65)	6.8 (0.7–65)	4.0 (1.8–7.4)	4.2 (3.1–5.8)	3.4 (1.8–7.4)
Fluoranthene	102 (6.8–890)	120 (9.8–1770)	110 (6.8–1770)	24 (1.6–91)	8.0 (1.0–110)	14 (1.0–110)
Pyrene	73 (4.4–860)	100 (8.4–1420)	87 (4.4–1420)	21 (3.3–68)	7.3 (0.7–120)	13 (0.7–120)
Benzanthracene	37 (2.2–470)	52 (4.9–1160)	44 (2.2–1160)	6.5 (0.8–37)	2.4 (0.4–77)	4.5 (0.4–77)
Chrysene	64 (4.3–560)	72 (5.4–1100)	68 (4.3–1100)	22 (2.6–110)	5.8 (0.8–120)	14 (0.8–120)
Benzo(*b*)fluoranthene	73 (5.9–480)	83 (7.9–1380)	78 (5.9–1380)	34 (3.2–180)	7.7 (1.2–210)	16 (1.2–210)
Benzo(*k*)fluoranthene	25 (1.6–250)	36 (3.1–740)	30 (1.6–740)	6.0 (0.4–43)	1.6 (0.3–36)	3.1 (0.3–43)
Benzo(*a*)pyrene	35 (1.8–470)	60 (6.0–1600)	46 (1.8–1600)	9.3 (1.0–36)	3.0 (0.5–86)	5.3 (0.5–86)
Dibenzo(*a,h*)anthracene	5.7 (0.4–35)	6.5 (0.8–42)	6.0 (0.4–42)	2.0 (0.2–12)	0.6 (0.1–16)	1.2 (0.1–16)
Benzo(*ghi*)perylene	43 (2.8–340)	61 (5.6–1200)	51 (2.8–1200)	17 (2.4–78)	4.5 (0.9–110)	9.3 (0.9–110)
Coronene	28 (2.1–170)	34 (4.0–540)	31 (2.1–540)	14 (2.1–80)	5.2 (1.1–94)	9.2 (1.1–94)
Sum	580 (42–4850)	700 (56–11 200)	641 (42–11200)	243 (42–750)	63 (8.6–1050)	154 (8.6–1100)
TOC	250 (79–450)	93 (55–18)	183 (55–450)	350 (86–460)	110 (24–200)	287 (24–460)
BC	1.3 (0.5–2.0)	1.0 (0.6–1.6)	1.2 (0.5–2.0)	1.5 (0.5–3.1)	1.1 (0.3–2.2)	1.4 (0.3–3.1)

* The summary data was derived on the basis of the values over the detection limit. The number of samples used were 53; UK (27): woodland (15), grassland (12); Norway (26): woodland (17), grassland (6), not classified (3). TOC and BC are in mg/g soil.

J.J. Nam et al. / Chemosphere 70 (2008) 1596–1602

Nam et al., 2008

- Soil organic matter: retention of PAHs
- Long range atmospheric transport and deposition: heavier PAHs (high log Kow) remained closer to source, lighter PAHs reached remote areas

Summary

SUMMARY

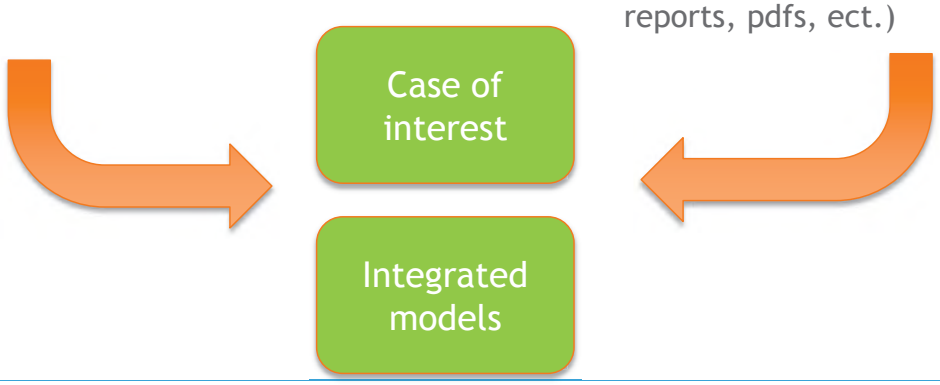
Exposure factors

- From defaults to individual oriented records
- varying degree of standardized data type

Monitoring data

- PAHs: a group of most studied and monitored substances in EU environments
- Plenty of data; mostly in 'patchwork' format (enclosed in reports, pdfs, ect.)

Challenge



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Thank you

GUDRUN KOPPEN

Biomonitoring of PAHs

Polyaromatic Hydrocarbons - PAH




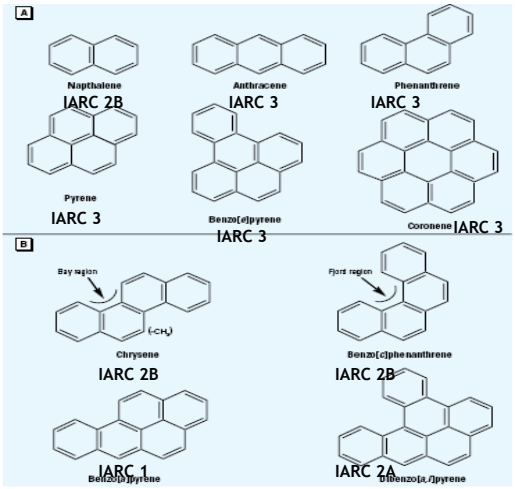

Figure 7. Examples of nontumorigenic (A) and documented tumorigenic (B) PAHs. The bay and fjord regions are indicated by arrows.

BENZENE RINGS (100s of compounds)

2-3	vapour phase
4	mostly particle-bound
5-6	particle-bound

UPTAKE

Inhalation	constant low-level inhalation
Ingestion	food
Dermal	fuels, oils, lumbricants

METABOLISATION to electrophylic compounds

DNA, RNA, protein adducts
Oxidative damage

HEALTH EFFECTS

- Carcinogenic: BaP, coal tar pitch, coke production, and chimney sweep soot -> classified as Group 1 human carcinogens by International Agency for Research on Cancer (IARC)
- Teratogenic, endocrine disrupters, immunotoxic

TYPES OF PAHS

Pyrogenic

- **incomplete combustion of organic materials**
- fossil fuel, biomass burning
- high temperature: pyrosynthesis: compounds cracked into radicals, forming stable PAHs with relatively large amount (unsubstituted) **multiple aromatic rings**
- low temperature (<700°C): larger amount of **alkyl PAHs** (e.g. methyl derivatives)

Petrogenic

- **unburned petroleum products**
- oil spills, leaks and road oil drip evaporation
- contain **more alkylated PAHs** than pyrogenic sources

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EXPLORATION OF PAH SOURCE - DIAGNOSTIC RATIOS

- PAHs always emitted as **mixture**
- **Relative molecular concentration ratios** (diagnostic ratios) characteristic for certain emission source
- PAHs with same molar mass and physicochemical properties, i.e. similar environmental fate processes

Diagnostic ratios	Interpretation
ΣLMW/ ΣHMW	<1 pyrogenic, >1 petrogenic
FL/FL+PYR	>0.5 diesel emissions
ANT/ANT+PHE	>0.1 pyrogenic
FLA/FLA+PYR	<0.4 petrogenic, 0.4-0.5 fossil fuel combustion, >0.5 grass, wood, coal combustion
BaA/BaA+CHR	>0.35 vehicular emissions, <0.2 petrogenic
IcdP/IcdP+BghiP	<0.2 petrogenic, 0.2-0.5 petroleum combustion, >0.5 grass, wood, coal combustion
2MeNAP/PHE	<1 combustion, 2-6 fossil fuels
ΣMePHE/PHE	<1 petrol combustion, >1 diesel combustion <1 pyrogenic, >1 petrogenic (Lian et al.2008)

Tobiszewski & Namieśnik, 2012

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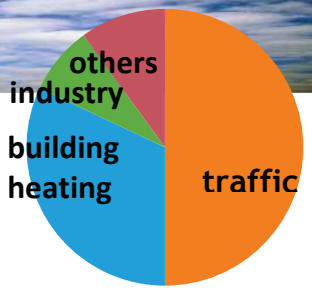
PAH IN INDOOR & OUTDOOR AIR

OUTDOUR



AIR POLLUTANTS

- Particulate Matter (PM)
- Gases: CO, SO_2, NO_x
- Metals: Fe, Ni, V, Cu, Mn,…
- Organic compounds
  - **Polyaromatic Hydrocarbons (PAHs)**
  - Other organic compounds (PCB, phtalates,…)
  - Endotoxins

INDOOR

smoking
heating, cooking
burning candles,
incense, flooring
dyes, adhesives

INDOOR AIR EXPOSURE - EXAMPLE OF FLEMISH STUDY

Indoor B[a]P in 25 Flemish residences

Season	Min	P25	Median	P75	Max	< DL	% of 16 EPA
winter	0.09	0.40	0.58	0.88	9.20	28%	0.2
summer	0.04	0.22	0.24	0.38	0.90	83%	0.05

Residences with B[a]P >= guideline
winter: N=8
summer: N=1

Outdoor
1.18 (winter),
0.14 (summer)
ng/m³

EU_{2012} air quality guideline
1 ng/m³
$1x10^{-4}$ cancer risk (WHO)

1 ng/m³ x 20 m³/d

= 20 ng B(a)P/d
= 10% of total daily intake

Koppen et al. (VITO report 2010)

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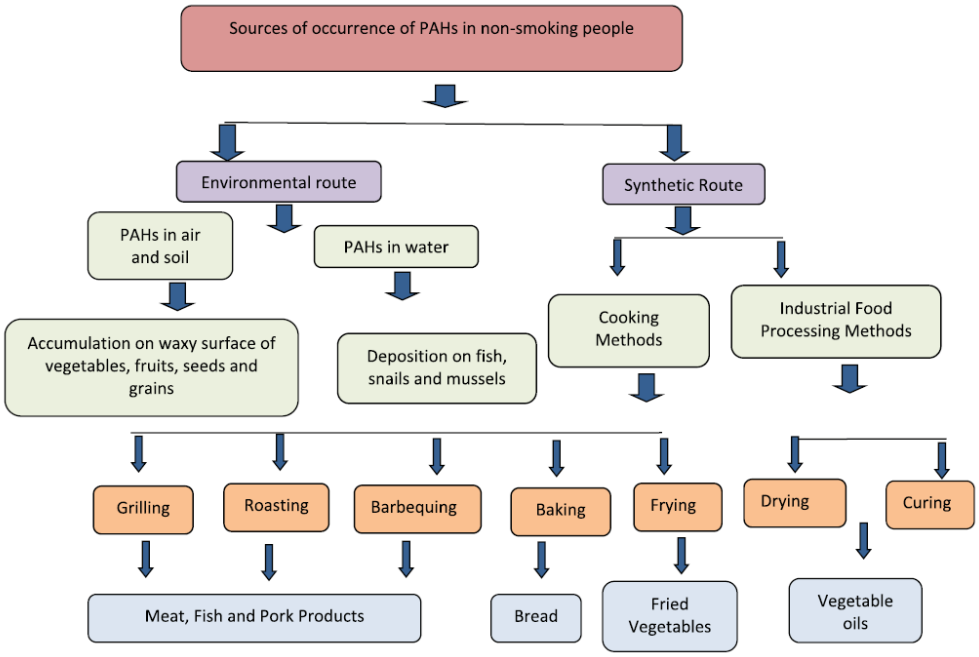
PAHS IN FOOD



Calculated intake via food (EFSA, 2008)

B[a]P: 235-389 ng/day

Bansal & Kim, 2015

PAHS IN CONSUMER GOODS

Consumer goods

- toys, baby items, mouse pads, tool and bicycle handles, bathing shoes or plastic rubber sports gear, wristle bands
- Important for consumers when more than 30 sec skin contact

Sources

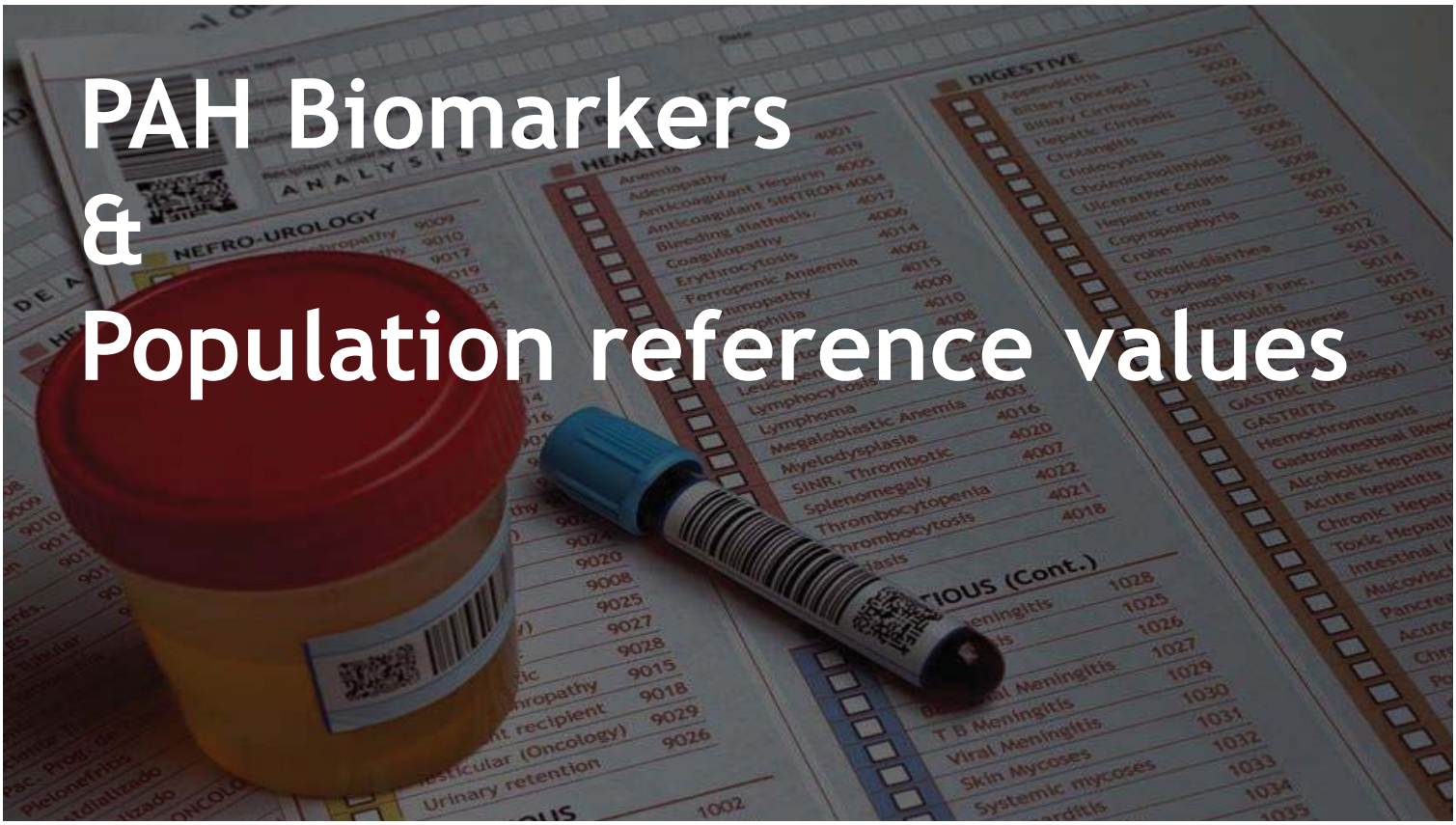
- Extender **oils** added to rubber materials; **soot** added to elastomers to achieve flexibility, damping, solubility in the polymer matrix

Regulation (EU 1272/2013 - REACH)

After 2015: max. carcinogenic PAH content consumer goods: **1 mg/kg** (**0.5 mg/kg**, toys & baby items)

Exposure

E.g.: tool handles: 1 mg B[a]P/kg = 0.20 mg per 200g handle -> 1% migration per hour = 0.02 mg B[a]P exposure per hour -> high, but: no exposure on daily basis, less absorption compared to inhalation (BfR, 2009)



PAH Biomarkers & Population reference values

WHAT & WHERE TO MEASURE THEM IN THE BODY?

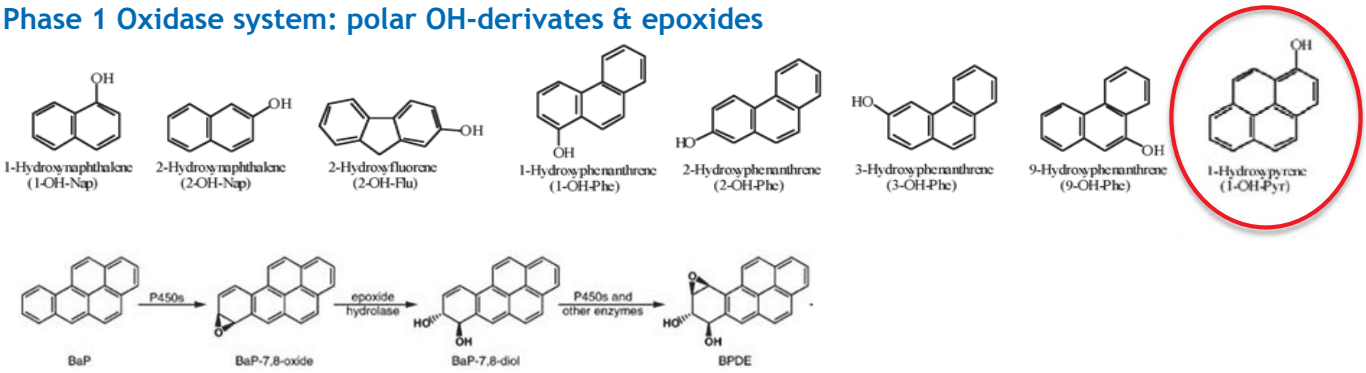
» **Parent compounds**
Urine: only small % excreted unchanged
Blood: 5- and 6-rings often below LOD

» **Metabolites**
Urine: < 4-rings (e.g. pyrene)
Faeces: > 4-rings

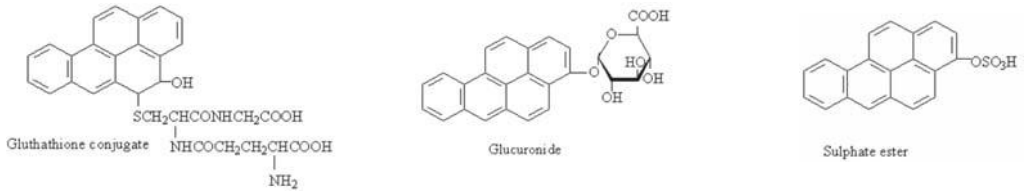
» **Adducts**
Blood: problem of non-detects for PAH-DNA adducts

PAH BIOMARKERS - METABOLITES

Phase 1 Oxidase system: polar OH-derivates & epoxides



Phase 2 Conjugation with glutathion, glucuronic or sulfuric acid

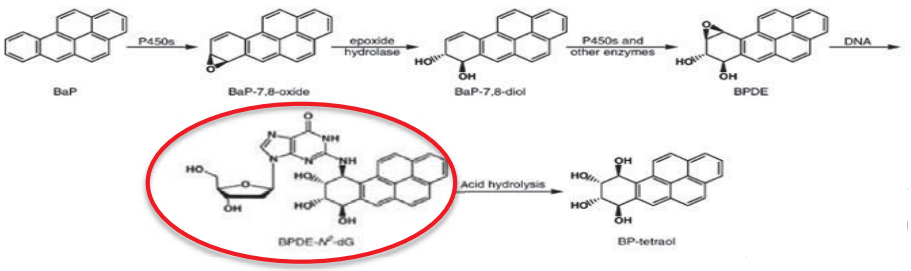


PAH BIOMARKERS - ADDUCTS

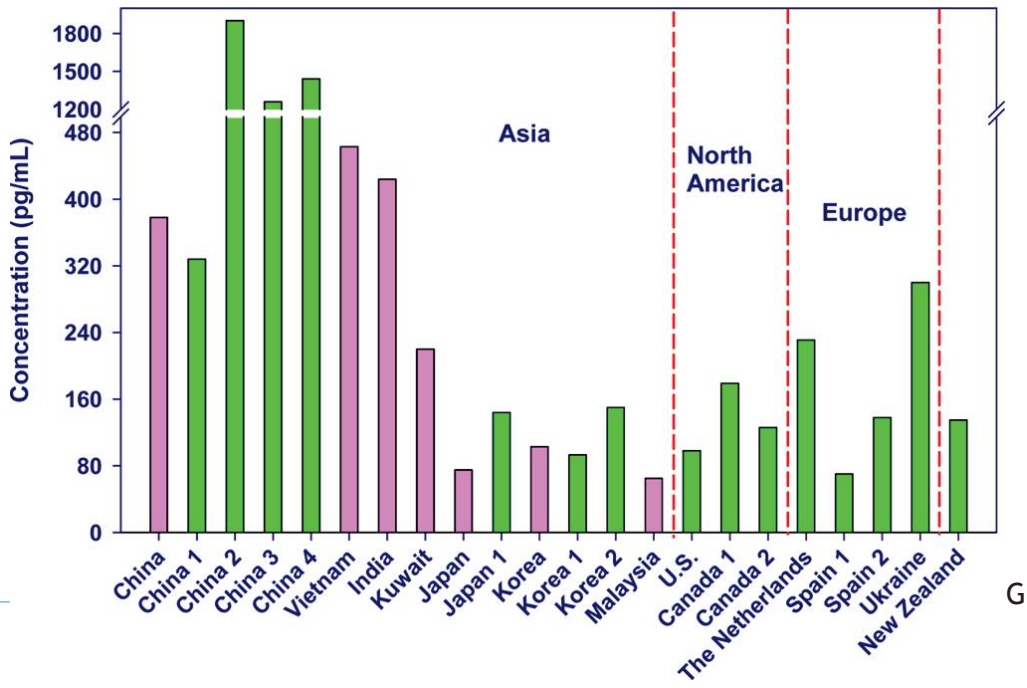
- **Markers of potential risk**
- Epoxides, diol-epoxides and quinones can bind covalently to DNA or proteins (hemoglobin and serum albumin)
- T1/2 weeks-months
- **Protein adducts:** not much used
- **DNA-adducts**

  Unspecific: ^{32}P post-labelling

  Specific
  - 1-100/10^8 nucleotides (**low**) -> e.g. ca. 25% below LOD (Jedrychowski et al. 2013)
  - antibodies against PAH-DNA adducts in serum (Pauk et al. 2013)



1-OH PYRENE LEVELS IN DIFFERENT COUNTRIES



Guo et al., 2013

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GERMANY – GERES- REFERENCE VALUES: URINARY OH-METABOLITES

Table 2. Metabolites of PAH in urine (µg/l) of non-smoking children aged 3 to 14 in Germany – GerES IV (Becker et al., 2008) and reference values derived by the Human Biomonitoring Commission.

Metabolite/Population	N	% ≥LOQ	P50	P95	CI-PP95[1,2]	Reference value[3]
1-hydroxypyrene (LOQ: 0.012)						
Non-smokers	566	99	0.12	0.43	0.40-0.48	**0.5**
Place of residence*						
western Germany	492	99	0.12	0.41	0.37-0.46	
eastern Germany	74	100	0.16	0.65	0.48-0.87	
1-hydroxyphenanthrene (LOQ: 0.016)						
Non-smokers	566	100	0.19	0.59	0.54-0.64	**0.6**
Place of residence***						
western Germany	492	100	0.17	0.54	0.50-0.60	
eastern Germany	74	100	0.26	0.91	0.66-1.09	
2/9-hydroxyphenanthren (LOQ: 0.004)						
Non-smokers	566	100	0.12	0.37	0.32-0.37	**0.4**
Place of residence**						
western Germany	492	100	0.12	0.32	0.30-0.35	
eastern Germany	74	100	0.14	0.48	0.37-0.61	
3-hydroxyphenanthrene (LOQ: 0.004)						
Non-smokers	566	100	0.16	0.52	0.44-0.52	**0.5**
Place of residence***						
western Germany	492	100	0.15	0.46	0.40-0.48	
eastern Germany	74	100	0.22	0.79	0.62-1.06	
4-hydroxyphenanthrene (LOQ: 0.008)						
Non-smokers	566	82	0.02	0.25	0.16-0.23	**0.2**
Place of residence						
western Germany	492	82	0.02	0.22	0.15-0.21	
eastern Germany	74	83	0.03	0.52	0.19-0.49	
∑ hydroxyphenanthrene (1, 2/9, 3, 4)						
Non-smokers	566	/	0.52	1.53	1.39-1.63	**1.5**
Place of residence***						
western Germany	492	/	0.50	1.48	1.28-1.51	
eastern Germany	74	/	0.70	2.13	1.79-2.94	

GerES II (‘90-’92)
higher values in Eastern Germany

GerES III (‘97-’99)
Smoking, decentral heating, Eastern Germany values decreasing

GerES IV (‘03-’06)
Eastern Germany slightly higher due to higher air pollution: **emission rates from domestic fuel & industry**

GerES V (‘14-’17)

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USA – NHANES – REFERENCE VALUES: URINARY METABOLITES

Survey year	ΣNAP	ΣFLU	ΣPHE	1-OH pyrene
2003-2004	7232.2	782.6	356.6	79.6
2005-2006	9045.5	900.8	359.9	95.6
2007-2008	7996.1	846.0	334.7	106.8
Gender				
Males	7468.9	1054.2	346.1	111.2
Females	8623.5	669.9	350.2	79.9
Race/Ethnicity				
Non-Hispanic white	7477.8	831.5	348.7	88.1
Non-Hispanic black	11229.3	1231.4	431.6	115.6
Mexican Americans	6930.4	623.4	285.9	88.9
All others	7222.8	693.0	307.7	95.1

2003-2008: N= 4747 (>=20y)

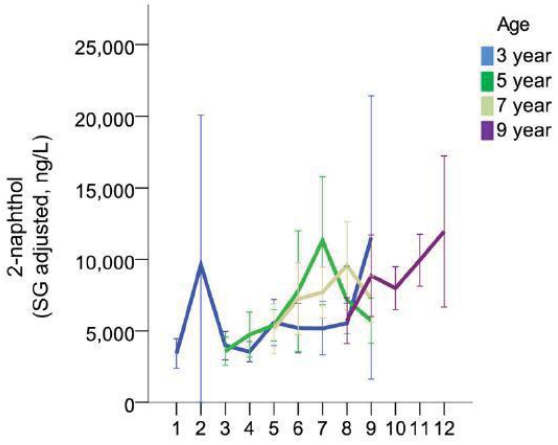
Detects %
100% for naphthalene, fluorene, phenanthrene, pyrene

Trend (2003-2008) - increase (p<0.001) for:
- ΣNAP
- ΣFLU
- 1-OH pyrene

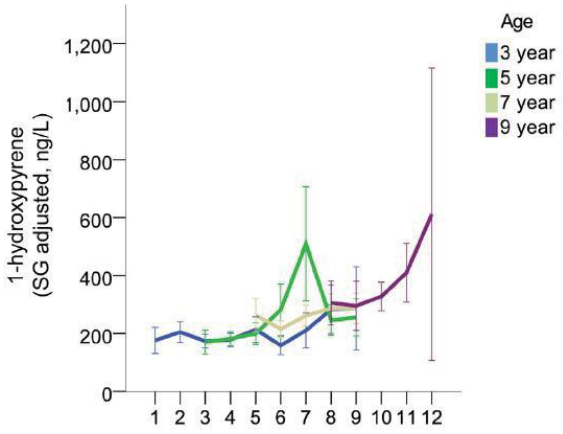
Factors of influence
(passive) smoking
Etnicity
Sex

Jain et al. 2015

USA – NHANES – TRENDS (2001-2012)



Increasing indoor sources: cooking, eating, naphthalene repelllents, petrochemicals (ATSDR 2005)



Increase in diet sources?

Jung et al. 2014

NB: 1-OH naphthalene: indicator for naphthalene and insecticide carbaryl(1-naphyl-N-mehtylcarbamate)

BELGIUM - FLEHS SURVEYS: URINARY METABOLITE

Tabel 37: Vlaamse referentiewaarden (gemiddelde en 90e percentiel) voor 1-hydroxypyreen in urine

Leeftijdsgroep	Biomerker	Eenheid	N	% >LOD/LOQ	Confounders	Geom. gemiddelde (95% BI)	90e percentiel (95%BI)
1-hydroxypyreen (PAK-merker)							
jongeren	1-hydroxypyreen in urine	ng/L	202	100%	leeftijd, geslacht, roken, creatinine	137 (127 – 149)	281 (216 – 347)
jongeren	1-hydroxypyreen in urine	ng/g creatinine	202	100%	leeftijd, geslacht, roker	104 (97 – 113)	224 (170 – 279)
volwassenen	1-hydroxypyreen in urine	ng/L	191	100%	leeftijd, geslacht, roken, creatinine	101 (91 – 111)	281 (223 – 338)
volwassenen	1-hydroxypyreen in urine	ng/g creatinine	191	100%	leeftijd, geslacht, roken	93 (85 – 102)	227 (180 – 274)

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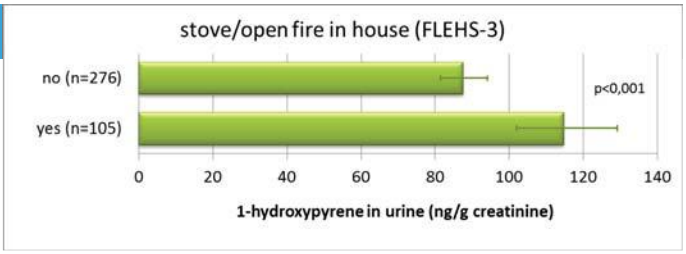
FLEHS: 1-OH PYRENE LEVELS



Study	Year	Age (y)	N	ng/L	ng/g CRT	Factors of influence
FLEHS-1	'02-'06	14-15	1598	122	72	Smoking, Minutes in traffic, Exercise last 3d, Stove, Area of living, Sex, Age
		50-65	1529	79	147	Smoking, Sex, Stove, Area of living, BMI, age
FLEHS-2	'07-'11	14-15	202	137	104	Smoking, Passive smoking
		20-40	191	101	93	Smoking (last 3d), Lower education, Higher in autumn/winter, BBQ last 3d
FLEHS-3	'12-'15	14-15	200	126	92	Smoking, Passive smoking, Lower education level, Stove or open wood fire
		50-65	200	Not yet available		

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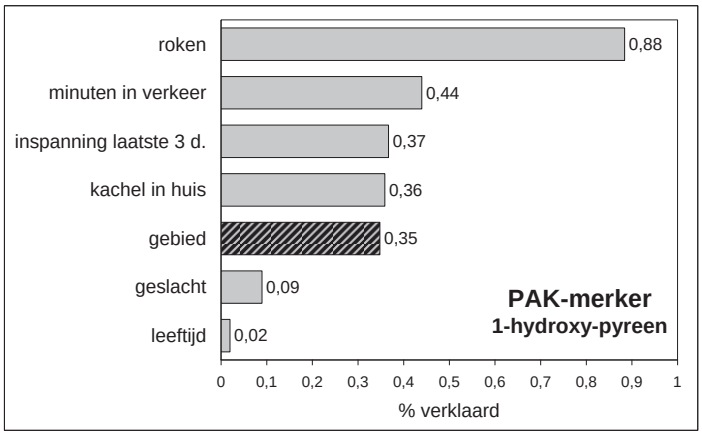
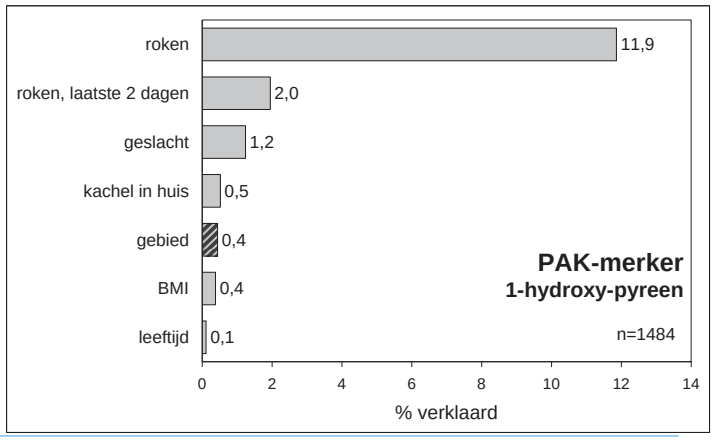
FLEHS reports, 2006, 2011, 2014

FLEHS STUDIES: FACTORS OF INFLUENCE

Adolescents (14-15y, N=1598)



Adults (50-65y, N=1482)



FLEHS-1 report, 2006

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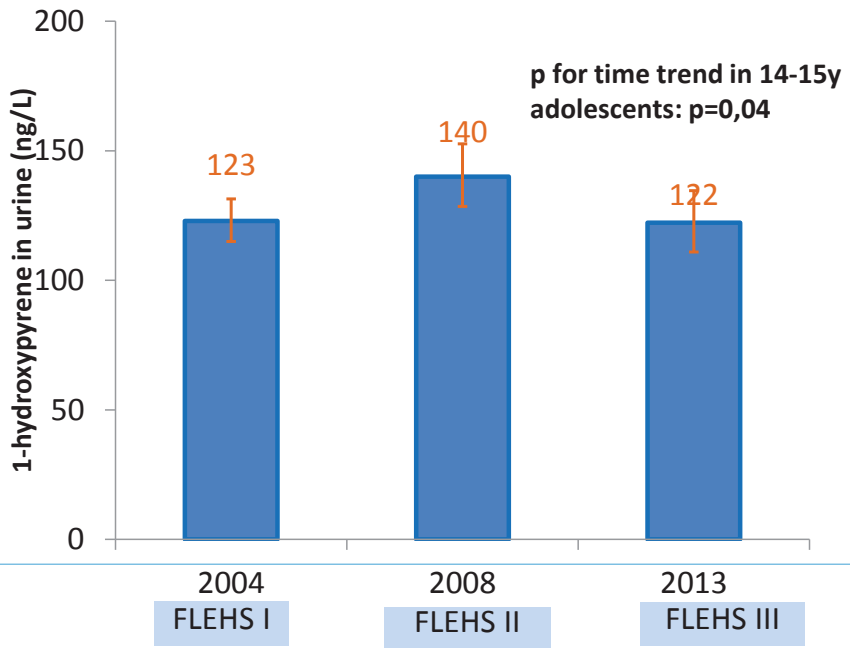
FLEHS STUDIES: 1-OH PYRENE TRENDS



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FLEHS: ASSOCIATIONS WITH EFFECT MARKERS

PAH in urine associated with genotoxicity markers (N=200 adolescents)

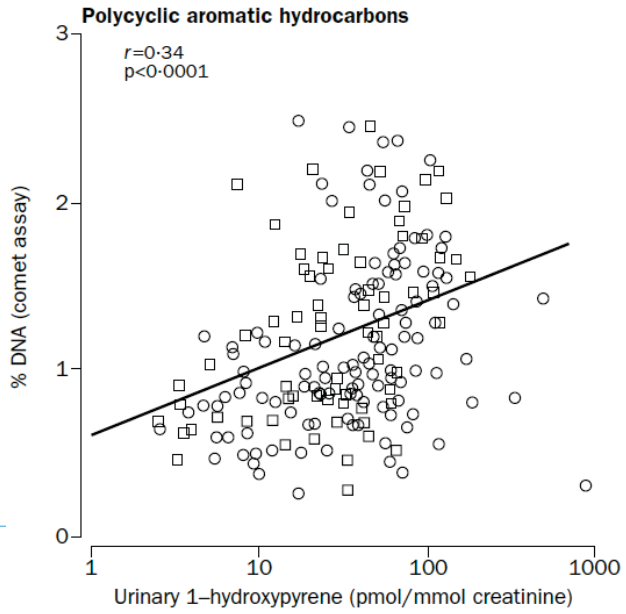
Biomarkers of effect	Related biomarker of exposure	Effect type	Effect size* (95% CI)	p
Renal effects				
Cystatin-C in serum	Lead in blood	% increase	3·6 (1·5 to 5·7)	<0·0001
β_2 microglobulin in urine	Lead in blood	% increase	16·0 (2·7 to 31)	0·02
Cytogenetic effects				
8-hydroxy-deoxyguanosine in urine	Orthocresol in urine	% increase	6·8 (2·3 to 11·5)	0·003
Comet assay (percentage DNA in the tail)	t,t'-muconic acid in urine	% increase	4·3 (−0·70 to 9·3)	0·09
	Orthocresol in urine	% increase	5·3 (1·1 to 9·5)	0·01
	1-hydroxypyrene in urine	% increase	7·0 (3·1 to 10·9)	0·0005
Chromatid breaks	t,t'-muconic acid in urine	Odds ratio	1·74 (1·13 to 2·66)	0·01
	1-hydroxypyrene in urine	Odds ratio	1·58 (1·10 to 2·26)	0·01
Chromosome aberrations	1-hydroxypyrene in urine	Odds ratio	1·56 (1·07 to 2·27)	0·02
Effects on sexual development				
Genital stage G3–G4 in boys	Sum of marker PCBs in serum	Odds ratio	3·80 (0·94 to 8·00)	0·06
Breast stage B3–B4 in girls	Dioxin-like compounds in serum†	Odds ratio	2·26 (1·15 to 4·46)	0·02

For number of participants and factors for which the relations were adjusted, see table 3. *Effect sizes were calculated for a two-fold increase in the biomarker of exposure.
†Calux assay.[23]

21 Staessen et al. The lancet, 2001

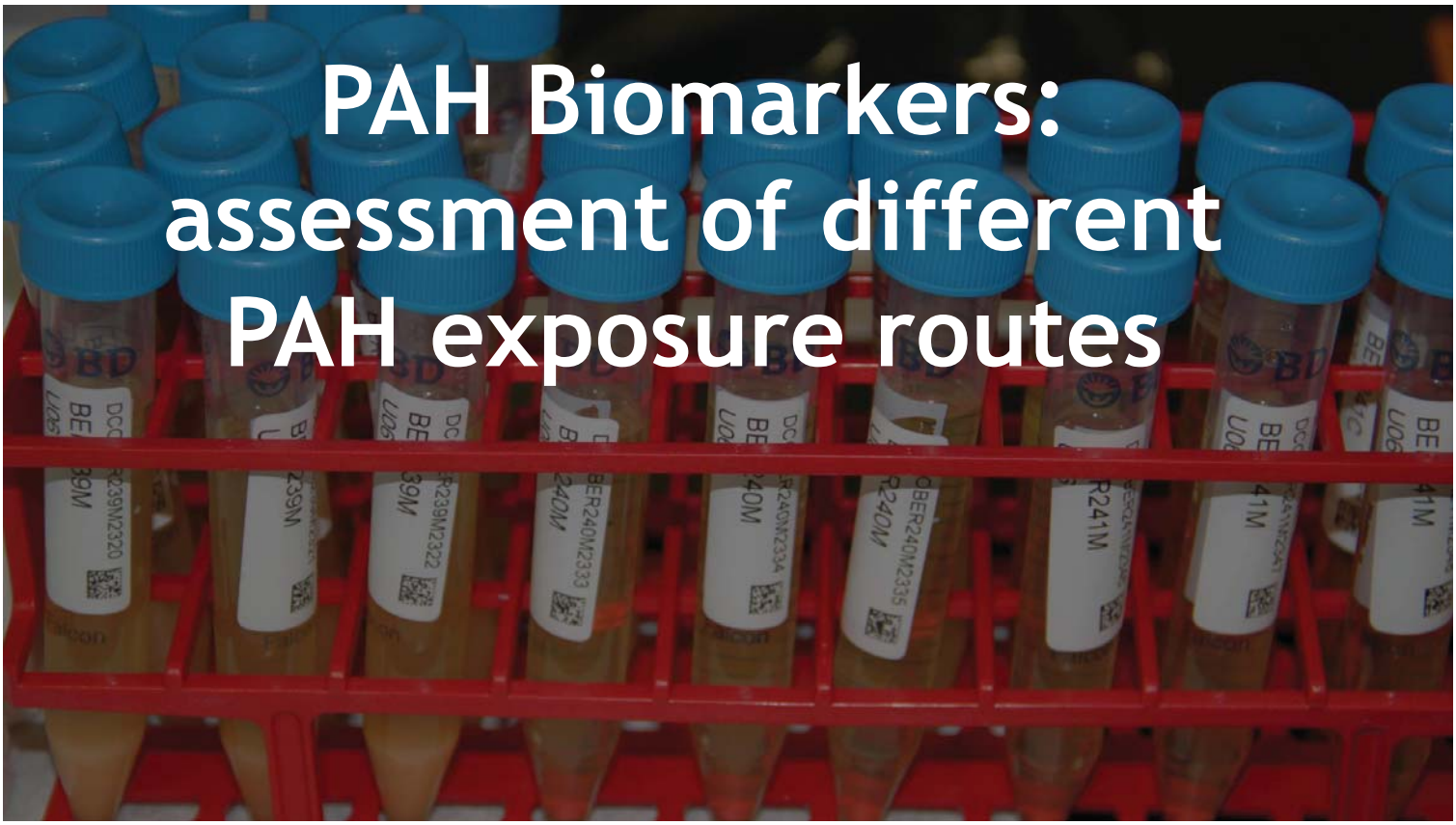
FLEMISH ENVIRONMENT & HEALTH SURVEYS (FLEHS)

PAH in urine associated with breaks and repair sites in blood DNA



Staessen et al. The lancet, 2001

22



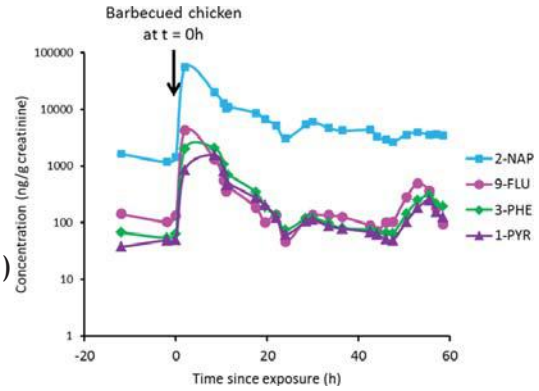
PAH Biomarkers: assessment of different PAH exposure routes

PAH BIOMARKERS: FOOD IMPORTANT FACTOR OF INFLUENCE?

For benzo[a]pyrene, not for naphthalene, fluorene, phenanthrene, pyrene (Shin et al. 2013)

Grilled/BBQ food, but excreted within 12h after exposure
Li et al. (2012)

Chargrilled food: ↑1-OH phenanthrene (Alghmadi et al. 2015)



Diet is negligible when exposure from other sources is important (Hansen et al., 2008)

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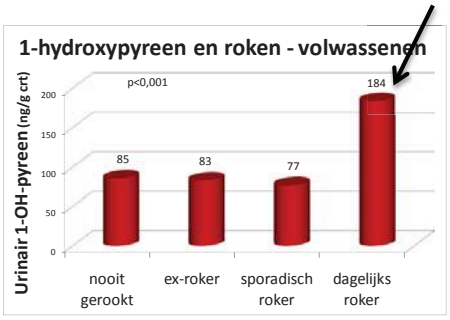
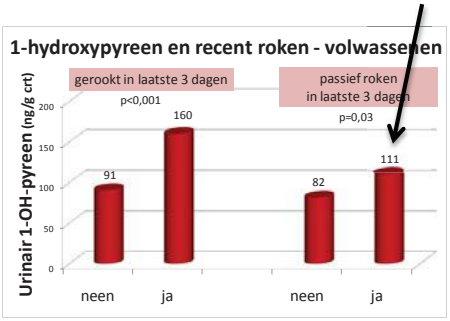
PAH BIOMARKERS – (PASSIVE) SMOKING

FLEHS-2: 20-40y adults





In some studies no effect of passive smoking: e.g. in 10-12y old children (Alghamdi et al 2015)

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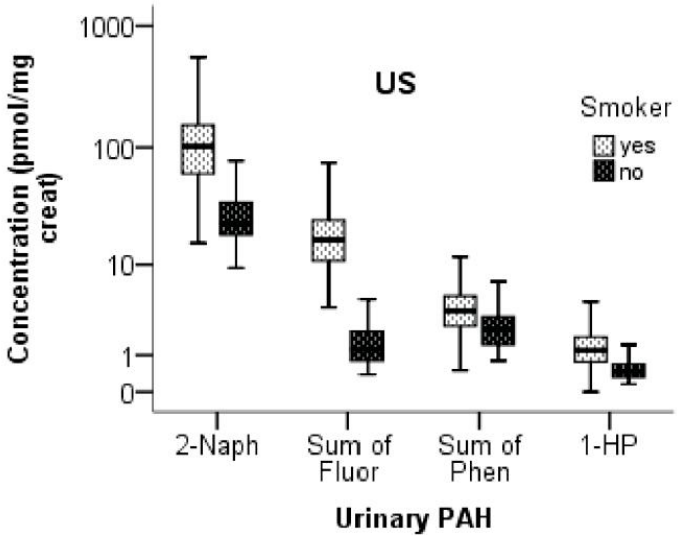
PAH BIOMARKERS - SMOKING

2-OH fluorene and **2-OH naphthalene** most highly discriminative for smokers vs. non-smokers better than 1-OH pyrene and OH-phenanthrenes (Helen et al. 2012)



Helen et al. 2012

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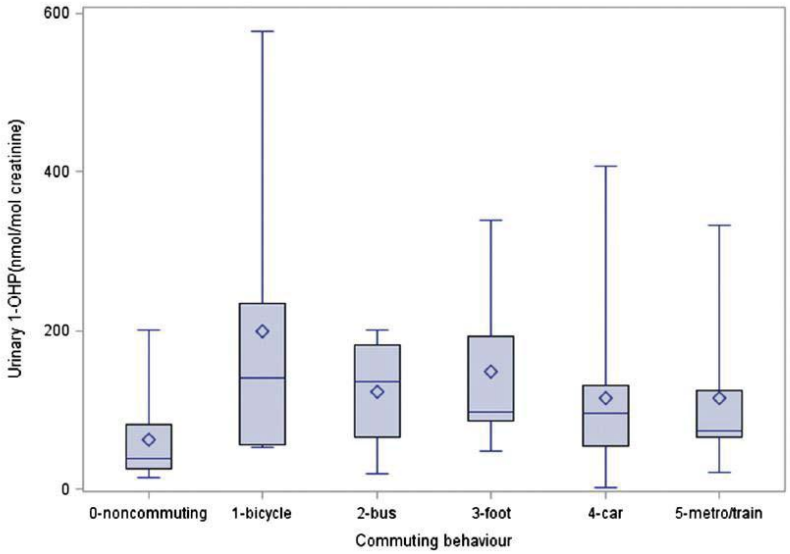
BIOMARKERS: TRAFFIC EXPOSURE

Commuters higher levels of 1-OH pyrene: Miao et al.(2015) – Montreal (Canada)



Miao et al., 2015

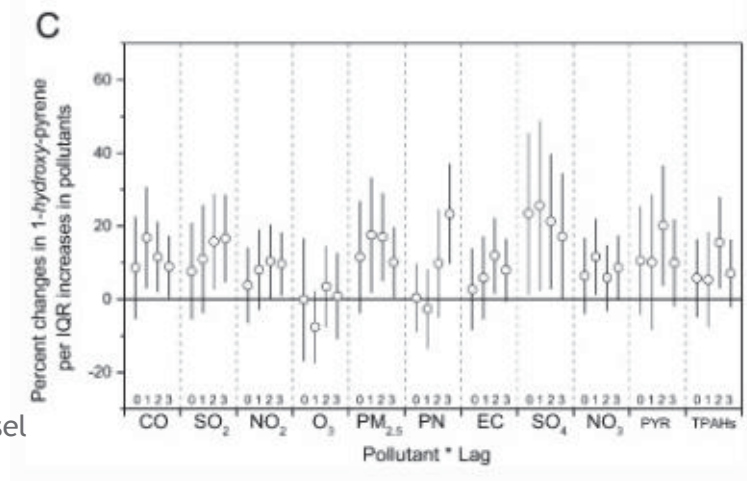
TRAFFIC EXPOSURE

Gong et al. 2015

Decrease in general vehicle- emitted pollutants pre- vs. during-Olympic period (N=111 adults):

1&2-*amino*naphthalene: 32% ↓
1-OH pyrene: 16% ↓

1&2-*amino*-naphthalene and 1-*hydroxy*-pyrene associated with traffic related pollutants
1-*amino*-pyrene associated more strongly with diesel combustion products (e.g. PN & elemental carbon)



Gong et al. 2015

BIOMARKERS: OUTDOOR AIR EXPOSURE - GENERAL

1-OH pyrene levels in a family moving between Brisbane (Australia) and Hanoi (Vietnam)

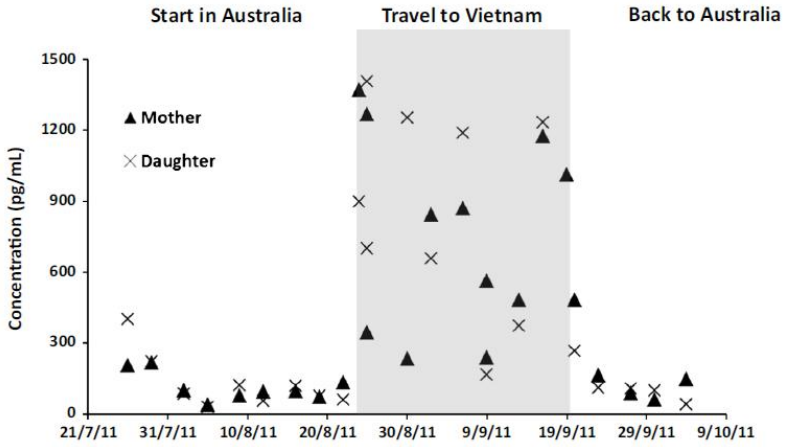


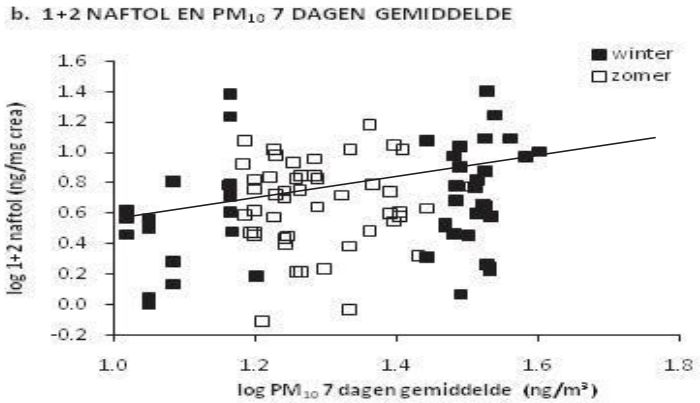
Fig. 1. The concentrations of urinary 1-hydroxypyrene in a family who travelled between Brisbane, Australia and Hanoi, Vietnam.

29 Thai et al., 2015

BIOMARKERS: OUTDOOR AIR EXPOSURE - GENERAL

- Danmark: children in **urban residences** more exposed than in rural (Hansen et al. 2005)
- Flanders: adults PAH metabolite levels related to outdoor PM_{10} in home environment

1+2OH naphthalene



PM_{10}

Koppen et al., VITO report 2010

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PAH BIOMARKERS: INHABITANTS AROUND PETROCHEMICAL SITES

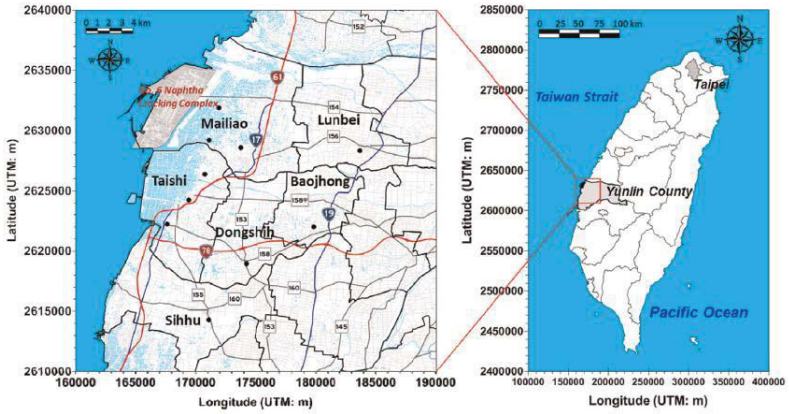
Largest PAH sources in petroleum refinery processes: Process heaters, catalytic cracking (IARC,2005; USEPA,1998)
Coal-fired power plants for electricity generation

Taiwan (Yuan et al. 2015)

N=781 adults living at least 5y within 20 km of large Naphtha Cracking complex

Urinary 1-OH pyrene

- 2x higher levels when living in vicinity compared to 10 km away
- urinary 1-OH pyrene 20% elevated with 0.01ng/m^3 increase of benzo[a] anthracene, benzo[k]fluoranthene, fluoranthene, pyrene, dibenzo[a,h] anthracene ($PM_{2.5}$)



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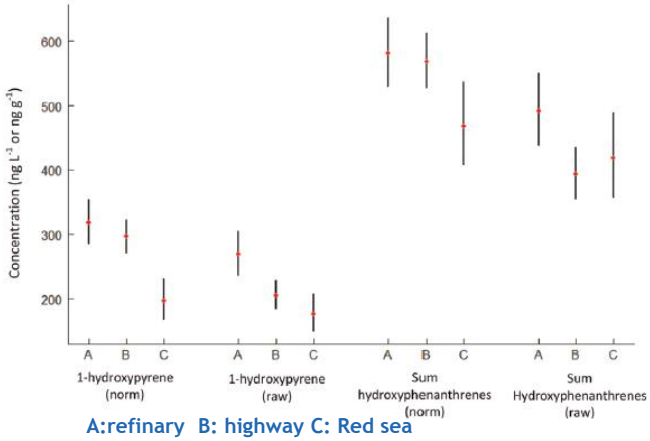
PAH BIOMARKERS: INHABITANTS AROUND PETROCHEMICAL SITES

Saoudi Arabia (Alghamdi et al. 2015)

- 204 children (10-12y)
- 1-OH pyrene: 26% ↑ in refinary site
- OH-phenanthrenes 30% ↑ in refinary site



A:refinary B: highway C: Red sea

Gulf of Mexico (Sanchez-Guerra 2012)

- Coatacoalcos County (280 000 inhabitants)
- 82 children (6-10y)
- 3 schools less than 5 km away from main petrochemical complexes in the region
- High 1-OH pyrene levels: 13% of children values above NOAEL for workers (1.4 µmol/mol CRT)

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CONCLUSIONS - PAHS IN HUMAN BIOMONITORING

- PAHs: everybody continuously exposed
- PAH biomarker studies to assess influence of: smoking, food (mainly grilled, barbecued), traffic, outdoor pollutants, petrochemical activities
- Large amount PAH biomarker data available: children - adults
- Urinary markers
  - easy to monitor
  - relative short half-life -> can be advantage when searching for exposure route
  - not very specific for source, but useful for screening
- How to increase specificity?
  - **Petrogenic PAHs**: urinary methyl-OH-naphthalenes: metabolites of 1- and 2-methylnaphthalenes (Li et al. 2014)
  - **Diesel - nitro-PAHs**: urinary 2-aminopyrene, 6-OH-N-acetyl-1-aminopyrene, 8-OH-N-acetyl-1-aminopyrene, 6-OH-1-nitropyrene, 8-OH-1-nitropyrene in urine (Toriba et al. 2007)

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  - University Hasselt
  - University Brussels
  - University Ghent

Milieu en Gezondheid

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