Final report
LRI-B4

Integrated Exposure for Risk Assessment in Indoor Environments (INTERA)

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1. PROJECT OVERVIEW

1.1. Introduction

Reducing the risks we suffer in daily life is a great challenge for everyone. Some of these risks are well known and accepted by the majority of the population, like flying in an airplane, cycling to your work or horse riding. Other risks like exposure to environmental pollutants are often poorly understood. For example, houses built with bricks can produce Radon that in combination with poor ventilation may result in lung cancer (Darby et al. 2005). Great uncertainty and variability makes it difficult to characterise the exposure and risk in microenvironments for pollutants. These uncertainties and variability can be explained by variation between and within individuals in behaviour and activities. For an indoor environment three other factors are of great importance, namely toxic dynamics of contaminants (interactions among several contaminants), susceptibility of different populations and cumulative exposure-mixture effects (where contaminants are individually within the proposed safety limits). As a result, making decisions based on epidemiological data and monitored levels for single contaminants to protect the wider (indoor) population may not be appropriate anymore. Overall, a full chain mechanistic approach, i.e. evaluation of exposure by taking into account all steps from emissions to concentration, from concentration to exposure and from exposure to internal dose, is a more adequate approach for an indoor environment.

The Integrated Exposure for Risk Assessment in Indoor Environments (INTERA) project aimed to improve our understanding of human exposure to air pollutants in homes by defining optimal methodologies for predicting indoor exposure to chemical contaminants and their inter-relationships.

The INTERA project developed and applied a full chain mechanistic approach that includes the following elements:

- Sources of contamination (outdoor and indoor), and the relationship between these sources and levels of indoor contamination.
- Air pollution modelling to calculate the spatial and temporal pattern of the indoor concentrations.
- Exposure estimation. Time activity patterns need to be defined in order to link them properly to the spatial and temporal course of indoor contamination. Details of how time-activity patterns and behaviours differ between age groups, family structures and geographical location are vital to understand the variability in personal exposures. Data on product use are also essential. Moreover, the procedure needs to be conducted for the majority of the known contaminants in order to assess the cumulative exposure.
- Internal dose modelling. Physiology Based ToxicoKinetic (PBTK) modelling is necessary to dynamically describe the fate of the contaminant (absorption, distribution, metabolism, excretion) in the human body. Furthermore, considering that for many chemicals, toxicity arises not from the parent compound but from its metabolites, internal dose represents the proper exposure metric to be considered for assessing the health risk for the population. Moreover, possible interactions among the several contaminants (mixture effect) can be implemented, accounting, as much as possible, for accumulation based on the levels and patterns of exposure (single and repeated events, continuous).

The elements above represent a ‘full chain approach’ which the INTERA project implemented within a dynamic simulation environment. The main objective of INTERA was to define optimal methodologies for predicting indoor exposure to chemical contaminants and their inter-relationships. The project design includes the following elements:

- The characterisation and justification of a framework capable of being applied to indoor exposure data/information and covering parameters relevant to their wider interpretation.
- The development/incorporation of appropriate databases of quality assured source data.

- The development/incorporation of suitable models and statistical methodologies for the characterization and treatment of such data.
- The application of suitable models and/or statistical methods that serve to either fill gaps or offer refined exposure assessment where uncertainties are considered unacceptable.
- The ability to display exposure predictions in a number of formats in order that they can be better applied within the context of both research and policy development.

To achieve these outputs the INTERA project team has defined the following sub-objectives:

1) Determine the main parameters influencing exposure.
2) Review and collate existing indoor exposure data, including the most prominent indoor exposure studies in Europe.
3) Collate all the above data and organise them into a comprehensive database/knowledge management system.
4) Develop full chain models using exposure reconstruction algorithms to fill data gaps and support refined exposure assessment.
5) Display exposure predictions at different spatial and temporal scales.
6) Implement the integrated approach in three case studies.
7) Disseminate research findings.

The overall project work was broken down into 6 scientific/technical work packages (WP) as illustrated in Figure 1. WP1 (exposure determinants and modifiers) and WP2 (collation of indoor exposure data and development of knowledge management system) both supply input data to WP3 (full chain model) which provides results to WP4 (exposure displays). The full chain approach developed was then tested in the WP5 by three case studies and the results of the project are disseminated by the WP6.

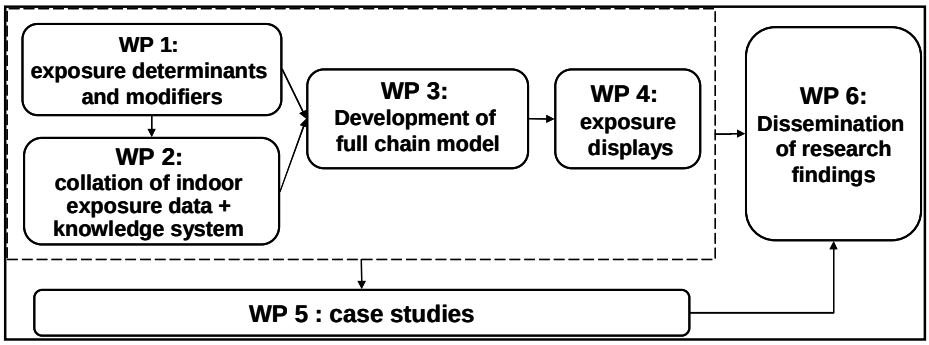

Figure 1: Overview of INTERA work packages (WP)

1.2. Issues to overcome in development of the methodology

It became evident at the early stage of INTERA that the development of a full chain modelling system suitable for exposure assessments in variable situations in indoor environments is a complex task. The creation of a general tool requires flexibility for the input data. Furthermore, aggregate exposure assessment requires taking into account all three (inhalation, dermal, ingestion) exposure routes. In addition the planned linkage of the modelling tool with a comprehensive database storing the input data having variable dimensions was an ambitious objective. The development of the methodology included several issues that we had to overcome and which determined the content and form of the final outputs of the project.

One of the first tasks required was to make a decision on the scope of the case studies. Particulate matter (PM) was included as one of the possibilities based on its evident health effects compared on any other indoor pollutant (Oliveira Fernandes et al. 2009, Jantunen et al. 2011, Arvanitis et al. 2010). However, in non-smoking homes the main source of indoor PM is from ingress of outdoor air,

and we therefore decided to concentrate on pollutants having clear indoor consumer product sources. The recent public interest on di-methyl-fumarate (DMF) and its health effects raised it as one of the selected pollutants for our case studies. Furthermore, we wanted to include a chemical for which the main route of exposure was not inhalation. The other consideration was to get examples on pollutants for which exposure occurs by all three exposure routes (dermal, inhalation, ingestion). Phthalates were identified as a group of pollutants that satisfied these criteria and are commonly used in consumer products. We finally chose four phthalates: DEHP (di(2-ethylhexyl)), BBzP (butylbenzyl phthalate), DINP (diisononyl phthalate) and DIDP (diisodecyl phthalate). This selection was based on the following considerations 1) production volumes, 2) known health effects, 3) molecular weight, covering both low and high molecular weight phthalates, and 4) relative importance of indoor exposure sources, i.e. phthalates for which indoor sources constitute a significant contribution to the overall exposure. The third group of chemicals was selected based on the possibility to evaluate cumulative exposure. BTEX (benzene, toluene, ethylbenzene and xylenes) were selected based on their common usage in consumer products and having linkage to the outdoor sources. Here the main objective was to assess how simultaneous exposure to the four VOC's composing the mixture can modify the biologically effective dose (BED) of each individual chemical. The possible simple additive effect (the so-called 'cocktail effect') through metabolic interactions can alter tissue dosimetry, and thereby the toxicity of mixture components might result lower toxicity (antagonism) or greater toxicity (synergism) of mixtures than would be expected from the individual chemicals.

The framework for the modelling platform was the second issue to overcome. One of the first decisions we took was to develop the platform to run online on a dedicated web server hosted at CERTH. We designed an IT architecture based on a 3-tier structure. The components that constitute the platform are the Graphical User Interface, the Model and the Database. The Graphical User Interface is a client side application, executed inside the web browser's window and it is the means through which the End Users interact with the models and database implemented in the platform.

During the first stage of the project it was discussed if the INTERA methodology should address only inhalation as an exposure route or consider all the exposure routes (inhalation, dermal and oral). The latter was deemed to be more pertinent to the overall scope of the INTERA project which, according to the technical annex, is *to define optimal methodologies for predicting indoor exposure to chemical and non-chemical contaminants* without any limitation on how people can come in contact with the contaminants. This decision was reflected in the computational platform development, which was designed to implement several exposure models for the different exposure routes and providing therefore users with a tool for a true cumulative and aggregated exposure assessment.

A further issue related to the computational, platform was the implementation of the Indoor Air Quality model for assessing the concentrations of contaminants met in the indoor locations. To this aim several modelling tools were reviewed. For the needs of the INTERA full chain assessment, a two-compartment box model based on the Pepper (2009) approach was chosen for the following main reasons:

- The problems that we need to tackle refer to residential exposure. In these types of settings, neither very strong sources, nor very efficient ventilating systems exist (in contrast to the situation found in occupational settings) that may impose the need for a refined spatial and temporal analysis assessment. On the contrary, emissions are usually fairly constant (e.g. building materials, furniture), the air exchange rate is low and most of the effect of the determinants can be easily described by first-order differential equations
- Concentrations in the locations are mostly uniform within the rooms
- The main formula which is very flexible and necessary modifications needed to describe possible additional physicochemical processes can be easily implemented.

More complex models such as the Computational Fluid Dynamics ones (CFD) were briefly considered. However, these models require very detailed information and have a much higher level of mathematical complexity than the 2-box model. It was decided that the benefits of these more complex model did not outweigh these disadvantages to justify their use in the INTERA platform.

During the development phase of the platform it became evident that we needed to incorporate in the IAQ model the mechanism describing partitioning of a chemical between gaseous particle and dust phases. The flexibility of the mathematical formulation of the IAQ box model chosen allows us to easily modify the source code to include the partitioning mechanism in the indoor air modelling.

A confirmation of the fitness-for-purpose of the chosen approach modelling was provided by the comparison of the concentration of DEHP in the dust phase obtained through the application of the modelling platform and the corresponding measured data in the phthalates case study.

2. WP1: EXPOSURE DETERMINANTS AND MODIFIERS

2.1. Objective

Work Package 1 (WP1) of the INTERA project had the following primary aims:

- To identify the main studies describing inhalation, dermal and ingestion exposure to, or determinants of, indoor domestic pollutants published in the past 15 years;
- To identify ongoing studies and indoor exposure models for domestic environments;
- To identify and review existing and developing indoor pollutant modelling approaches;
- To develop a summary matrix of the exposure determinants for various indoor air pollutants used in existing models and previous studies.

2.2. Achievements

Using a systematic approach and the online database Ovid Medline (see figure 2), a total of 57 scientific publications relevant to exposures generated by the use of household consumer products were identified and reviewed. Additional material relevant to mould, biological material and fine particulate matter were also identified although not reviewed for the purposes of the INTERA project. Full copies of these scientific papers were compiled within an online resource and made available to members of the INTERA study team for assimilation in to WP2 and other elements of the full chain modelling process.

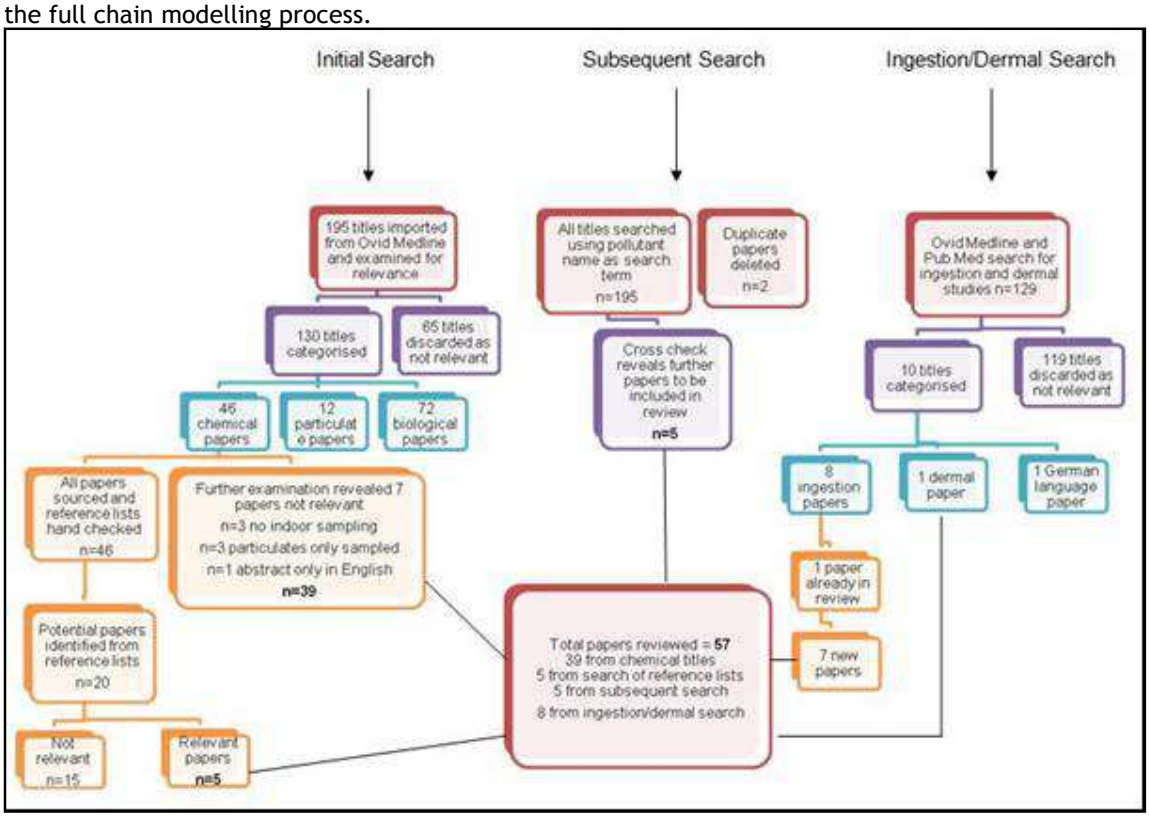

Figure 2. Flowchart of WP1 literature review.

Details of 29 indoor pollutant modelling methods were sourced from both the scientific and grey literature. Several of these are still under development. These models range from broad risk characterisation models through to exposure modelling systems for specific tasks and summary details of these were extracted and presented in the WP1 report. The report provides current web-

based links to all of these models and where possible details of final reports and any peer-reviewed publications arising from these models.

The output of this literature review together with a series of project meetings/expert webinars led to the establishment of an exposure determinant matrix for the main indoor pollutant chemical groups that were to be considered by future work packages in the INTERA project. Factors likely to influence exposure within the home were also rated and incorporated within this matrix (see figure 3). The chemical groups were: radon, carbon monoxide, carbon dioxide, nitric oxides, polycyclic aromatic hydrocarbons (PAHs), aldehydes, polybrominated diphenyl ethers (PBDEs), nicotine and volatile organic compounds (VOCs). The exposure determinant matrix and information on measurements and modelling methods was then utilised in the further development of the knowledge management system (see description under WP2) for the full chain approach that INTERA uses to characterize exposure and risk in indoor environments.

Chemical / Determinants	Outdoor Levels	Ventilation	ETS	Buildings	Household products	Presence of gas appliances	Furnishings	Animals, plants & dampness
Radon		++		++				
Carbon monoxide	+	++	+	+		+++		
Carbon dioxide		++	++			++		+
Nitrogen dioxide	+	++	+			+++		
Aldehydes	+	++	+	+++		+	+++	+
PAHs		++	++	+++				
PBDEs		++		+++	+		+++	
Nicotine		+	+++					
VOCs	++	++	++	+	++		++	

Influence of outdoor levels includes seasonal variation, urban pollution, and proximity to main roads or gasoline stations.
Building parameters such as age, whether the home is a house or a flat, on which level the measurements were taken, such as ground level versus first level, and construction materials used have an impact of the concentrations of certain chemicals. Building characteristics include features such as double glazing and central heating, type of flooring - presence of wall to wall carpets as opposed to smooth floors, recency of ceiling covering and painting or decorating.

Household products include cleaning agents and detergents, air fresheners, do-it-yourself (DIY) products such as solvents, paint remover and latex paints.

Other factors which should be taken into account are time activity patterns: how much time is spent indoors at home differs among individuals, smoking behavior and presence of household pets.

+ Symbols indicate a semi-quantitative assessment of contribution as follows: +some influence; ++considerable determinant of exposure; +++the primary concentration determinant for that pollutant.

Figure 3. The exposure-determinants matrix.

A full report (Appendix 1) was produced in March 2011 and made available on the INTERA project website[1]. It represents a distillation of Work Package 1 (WP1) and presents information on a review of the scientific literature of inhalation, dermal and ingestion exposures to indoor pollutants in domestic environments since 1995. The review additionally identifies existing and developing indoor pollutant modelling methods across all exposure routes.

One component of the WP1 review, relating to airborne chemical pollutant concentrations in domestic premises, was refined for publication in the scientific literature. A manuscript (Integrated Exposure for Risk Assessment in Indoor Environments (INTERA): A review of existing data on airborne chemical pollutant levels in domestic environment) was prepared during late 2011 and submitted for publication.

Details of the WP1 literature review of primary studies of indoor exposures within homes in EU settings together with the compilation of exposure models relevant to inhalation, dermal and ingestion exposure routes for indoor pollutants were also presented at the INTERA stakeholders' workshop held in Brussels on the 18th November 2011.

[1] http://www.intera-home.eu/LinkClick.aspx?fileticket=gAgzRQDZrZs%3d&tabid=201

3. WP2: COLLATION OF INDOOR EXPOSURE DATA AND ORGANISATION OF INDOOR EXPOSURE KNOWLEDGE SYSTEM

3.1. Objective

The purpose of the knowledge management system (KMS) is to host exposure factors for the EU population, including 1) measured indoor (and outdoor) concentrations, 2) release rates of chemicals in consumer products, 3) behaviour (products usage, time-microenvironment-activity patterns, mouthing behaviour, etc.), 4) physiological parameters (inhalation rates, body masses, skin surface areas of body parts. etc.), and 5) housing conditions (house volumes, air exchange rates, etc.). The objective was to compile all this information to a comprehensive on-line system / database having the following features: 1) easy to access, 2) freely available, 3) easy to update and 4) provide technical capability to be linked with the INTERA modelling tool.

This work package included two tasks:

a) Review and collate existing indoor exposure data, including the most prominent indoor exposure studies in Europe, and

b) Collate all the reviewed data and organise them into a comprehensive database/knowledge management system (KMS).

The objective was to develop a web based internet platform, which provides access to all important data that are needed when performing the exposure assessments in indoor environments. Furthermore, the purpose was to store the collected data in such a form that they could be utilized by the modelling tool developed by this project. In addition information and links to available indoor exposure modelling tools were gathered.

3.2. Achievements

The starting point for compiling the content of KMS was the literature review done in the WP1, which identified the main parameters influencing exposure levels in indoor environments and provided data on the measured concentrations. In addition, the content ExpoPlatform[2] was utilized as far as possible and the reports of several previous studies such as EXPOLIS[3], AIRMEX, INDEX (Koistinen et al. 2008), GErES[4] and THADE[5] were reviewed and the suitable data in them were collected. Emission information for indoor sources provided by BUMA[6], EnVIE[7] and HEIMTSA[8] were utilized too.

The technical solution used for the KMS is a Wiki based system, which was built up within a previously developed Open assessment network (OpasNet) maintained by THL. This solution ensures easy maintenance and updating of the data, and the possibility to use and update the system even after the project has ended.

The content of the KMS was divided into three blocks: 1) Data, 2) Modelling tools and 3) Documents. The data and information included in each block is schematically presented in the Figure 4.

[2] http://www.ktl.fi/expoplatform

[3] http://www.ktl.fi/expolis/

[4] http://www.umweltbundesamt.de/gesundheit-e/survey/index.htm

[5] http://www.efanet.org/activities/documents/THADEReport.pdf

[6] http://www.enman.uowm.gr/bumaproject/

[7] http://www.envie-iaq.eu/

[8] http://www.heimtsa.eu/

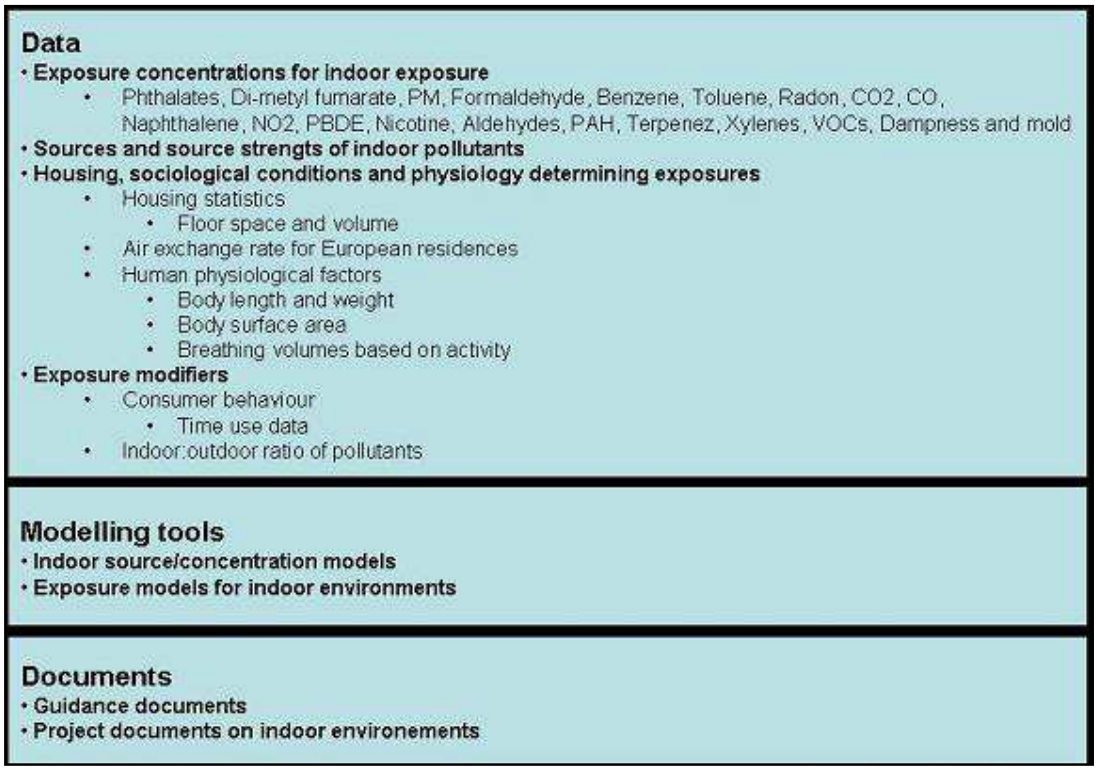

Figure 4. The content of the knowledge management system

The KMS is freely available[9] and can be utilized by any interested people or parties. Furthermore, the data collected to the database (Opasnet Base) can be used by any systems that are capable of retrieving data with SQL queries. This ensures that the collected data are available to and can be updated with new data gathered in any future projects.

The data collected for the KMS and stored to the Opasnet Base are linked automatically to the modelling tool developed in the project and described in the WP3. This allows the user of the modelling tool to get access to the available data automatically. Furthermore, new data can be introduced to the Opasnet Base and they will be readily available to the modelling tool. The system provides simple way to upload new data by using excel files. THL receives automatically a notification when the data related on the INTERA project is updated. THL will check the reliability of the uploaded data, but does not take responsibility on possible mistakes.

[9] http://en.opasnet.org/w/Intera

4. WP3: DEVELOPMENT OF "FULL CHAIN" MODELLING SYSTEM

4.1. Objective

The overall purpose of this work package was the development and implementation of the INTERA computational platform, a web based computer program, which follows the full chain approach from source to dose to support refined exposure assessment in indoor settings.

To this aim the methodology for quantitative aggregate exposure assessment developed in the frame of the project needed to be hosted within a proof-of-concept computational toolbox, the core of which is a synthetic dynamic modelling environment able to track and describe in mathematical terms all the steps of the full chain approach, implementing both mechanistic (e.g. indoor fate modelling, Physiology Based ToxicoKinetic Models) and probabilistic methodologies (Markov Chain Monte Carlo) based on outcome optimization and the current status of knowledge and data availability.

The computational platform was a central element within the project being linked with all the others WP's and in particular with WP2 (KMS) and WP4 (visualization tool): WP2 supplied input data to the platform which, in turn, returned results to WP4.

According with the above the computational platform needed to allow a seamless integration with the others WPs developing common standard protocols to communicate with them in a transparent way for the final user.

To be a real operational and valuable tool to support a refined aggregate and cumulative exposure assessment and according with what was identified in the early stages of the project life, the computational platform includes:

- A user-friendly user interface to facilitate and support users in the exposure scenario development process, easily allowing differentiation in relation to geographical location, age classes and gender.
- An Indoor Air Quality model of chemicals addressing the part of the full chain linking source of chemicals to the immediate indoor environment of their human receptors.
- An exposure modelling tool addressing all the exposure routes to translate indoor concentrations and consumer products use into exposure profiles taking into account time activity patterns and behaviour data and how they affect exposure.
- A PBPK modelling platform to translate chemical exposure into internal dose both systemically and in target tissue for adequate aggregation of exposure routes and in order to allow coupling exposure modelling with exposure biomarker measurements.
- A hierarchical population modelling module (using Markov chain Monte Carlo) to account for probabilistic exposure assessment.

4.2. Achievements

The INTERA computational platform has been finalized and it is currently available on-line[10]. The user guidance manual (Sarigiannis et al. 2012) including descriptions of the mathematics behind the modelling are provided in a file within the tool.

[10] http://www.intera.cperi.certh.gr/modelling/main.php

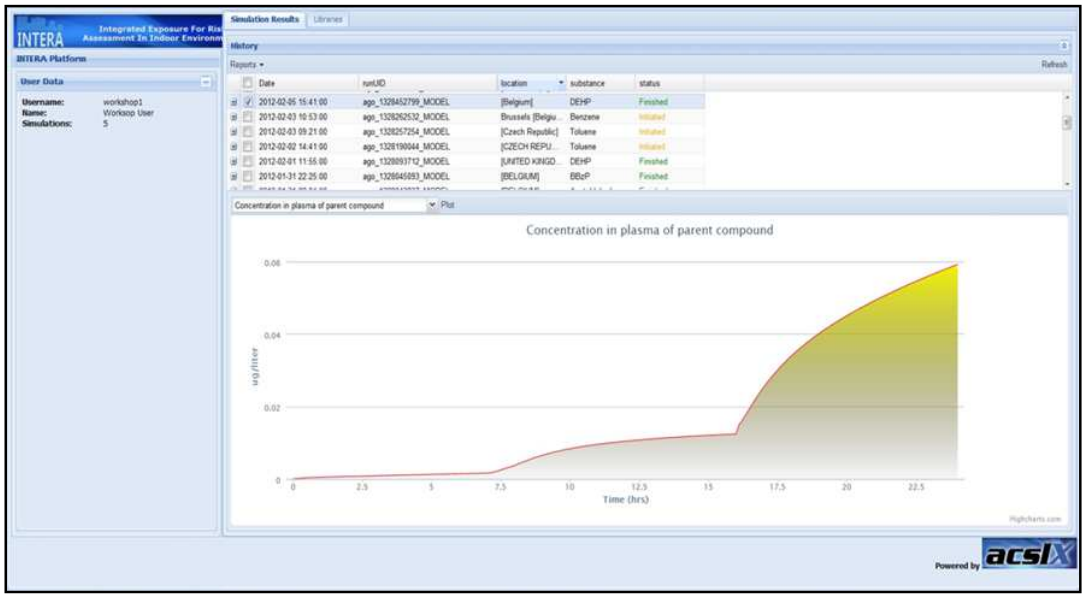

Figure 5. User interface of the INTERA computational platform showing the diurnal variation of the internal dose of an indoor pollutant in the body of the people exposed to it

The program offers a number of generally applicable exposure models for the different exposure routes (inhalation, oral and dermal), a generic Physiology Based ToxicoKinetic Model and a database containing several types of data ranging from human physiological parameters to emission data from consumer products and from indoor concentration levels to building characteristics. Data are stored and retrieved along with their geographical information in order to allow user to build realistic exposure scenarios to represent typical exposure conditions for specific Cities and/or Cities in Europe. Together, database and models provide the tools to assess exposure for a wide range of scenarios, whereby only basic additional information on consumer products use and the physicochemical properties of the compound of interest are needed.

The implemented modelling environment comprises four main vertical modules, as follows:

1. Emissions-concentrations module, linking sources to indoor concentrations, taking into account the physicochemical processes in indoor settings: dispersion, ventilation, gas-particle-dust partitioning, etc.
2. Exposure module including several models for the dermal, inhalation and oral routes, taking into account time-microenvironment-activity patterns and inhalation rates based on activity, gender and body weight.
3. Internal dosimetry module, which computes aggregate exposure by absorption factors for each route, links temporal patterns to internal dose through a generic PBPK model. It estimates the internal doses of contaminants and their metabolites at the target tissue. Quantitative linkage between exposure and internal dose allows for assimilation of biomarker data, which is emerging from national and European biomonitoring programs.
4. Uncertainty and variability of exposure and risk determinants are assessed along the full chain assessment through hierarchical modelling using Markov Chain Monte Carlo.

In addition the INTERA computational platform is linked with the KMS through automatic queries developed to retrieve data needed to configure an exposure scenario in a transparent way for the user. In accordance with the overall “philosophy” of the platform, users have the possibility to directly enter the values of every simulation parameters at every step of the platform.

In the development of the computational platform special efforts have been taken to improve transparency, flexibility and ease of use of the software. According to data availability, the INTERA

computational platform flexibly allows the user to begin from different starting points along the source to dose continuum.

The link with the visualization tool allows the display of results, which are automatically stored in the INTERA Database according to a common standard protocol. Finally, input data used to build an exposure scenario as well as the results obtained can be easily downloaded by the user for further elaborations.

All the above characteristics have been implemented in a web based computational platform providing the following advantages compared to the currently existing indoor air quality modelling software:

- the flexibility of the INTERA platform allows the user to tackle exposures with a wide range of exposure pathways and different exposure route by varying the parameterization and individual model selection;
- the fusion of mechanistic and probabilistic approaches in order to minimize the total boundaries of uncertainty;
- the development of an exposure biology based approach, taking into account inter-individual susceptibility and the different biological response to the same exposure levels;
- indoor exposure and metabolic processes are tackled simultaneously and continuously, describing in a realistic way the interaction among human body and the continuously changing surrounding environment;
- the accessibility and the user-friendliness of the platform which facilitate and support users in the exposure scenario development process.

5. WP4: EXPOSURE DISPLAYS

5.1. Objective

The objective of this working package was to develop tools for visualizing the output of the modelling platform (WP 3) in an attractive and correct way. Adequate visualization tools for presenting results of exposure in the indoor environment are essential for policy-making purposes as well as for communication to the public at large.

The development of Geographical Information System (GIS) over the past few decades has greatly improved spatial visualization and analysis of environmental information and data. Maps also constitute a powerful tool to communicate the outcome of complex environmental risk assessment to stakeholders such as the general public and risk makers. With appropriate cartography one can improve communication and thus bridge the gaps between experts and users. Appropriate risk communication is pivotal to risk management, decision making and implementation and may prevent unnecessary concerns about environmental pollutants. However, at present, few risk maps are specifically tailored to meet the demands of such defined uses (Lahr & Kooistra, 2010).

Whereas outdoor air quality is driven by geographically related driving mechanisms (traffic, meteorological conditions, industrial emissions, etc.), indoor air quality is mainly determined by parameters like presence of indoor sources and ventilation systems with little or no geographical correlation. In order to display influence of these types of modifying factors, a second set of visualization tools, namely charts generation, was developed. This type of tools allows the user to create online graphs (time trends, scatter plots, bar charts).

Whereas the computational platform (WP 3) is featured with tools to generate graphs within one scenario run, the additional value of the visualization platform is that it can present the output of various model runs in one graph or map, thereby allowing comparison of different runs of the computational platform, as function of a user selected parameter (e.g. geographical location, air exchange rate (AER), indoor/outdoor ratio,…).

Thus, the tasks of this work package were:

- Development of database to import, store manipulate and retrieve outputs of the computational platform;
- Development of an online GIS tool to display geographical trends;
- Development of online tool to create charts to display user-selected Y and X variables;
- Development of tools to visualize variability and time trend when using these tools.

5.2. Achievements

The technical solution for the online visualization platform is shown in Figure 6. Firstly, the visualization platform imports the generated output data of the computational platform (WP3). This process happens on the server side, where modelling platform output is imported and structured in a relational database. The import protocol and scripts to select and retrieve data from the SQL databases are written in a PHP-based server-side environment.

The display of maps and charts is situated on the client PC side, and uses libraries and technologies such as ExtJS, OpenFlashChart, KML and OpenLayers. As with the computational platform, the visualization tool runs completely inside the web browser on the client PC (the use of Google Chrome is advised), connecting to the INTERA server in order to run the platform; other specific software is not needed.

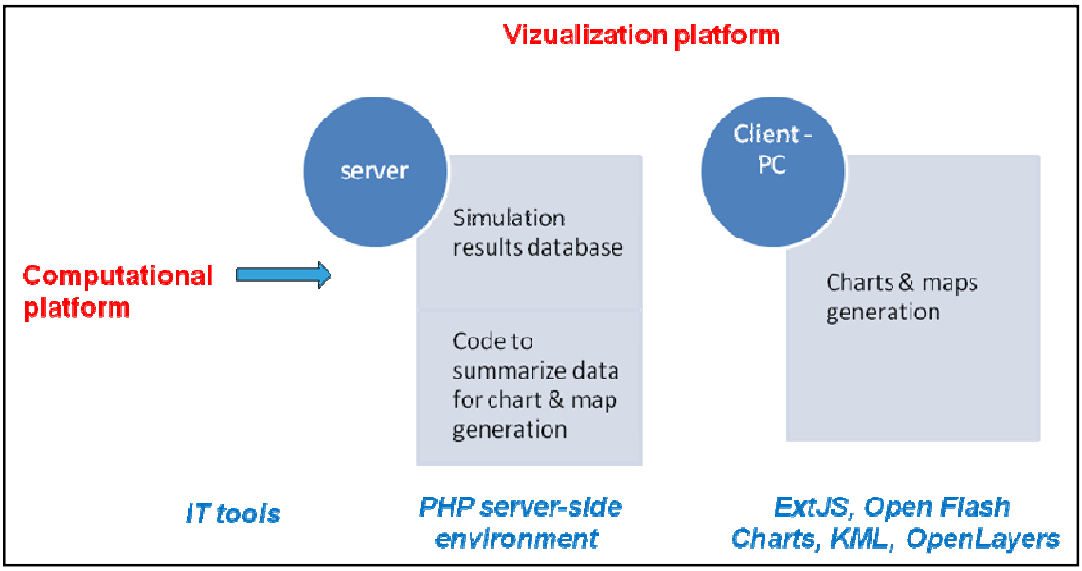

Figure 6: INTERA visualization platform structure

A user friendly Graphical User Interface (GUI) has been developed to guide the user with the selection and generation of the different types of visualizations (maps, charts) of his interest (based on outputs of computational model runs that the user performed in the past; also the ones based on previous login-sessions for that user). Drop-down menus will help the user to select parameters to plot in the Y-axis and X-axis for the generation of charts. The tool is designed in such a way that the user can display the results in an interactive way: by clicking on e.g. a region of map, the appropriate values, including indices for variability, pop up on the map/graph. Tools to export the graphs and charts have been implemented.

The tool and the user manual can be accessed via the same URL as the computational platform[11].

The visualization tools have been applied in the phthalates and DMF case studies (see reports on WP 5).

[11] http://www.intera.cperi.certh.gr/modelling/main.php

6. WP5: IMPLEMENTATION OF THE INTEGRATED APPROACH IN THREE CASE STUDIES

6.1. Objective

The purpose of the case studies is to apply the full chain approach which is developed in an earlier stage of the project. The aims of the case studies are to:

1) Test the developed integrated methodology;
2) Suggest any refining to the data tools;
3) Identify where the data gaps are.

In addition, health endpoint(s) is/are included in the case studies to perform a health impact assessment for Europe in relation to the contaminants.

The outcome of each case study is twofold:

> Firstly, reports *on overall indoor exposure in Europe* for the pollutants dealt with in the case study providing *exposure distributions for households in the EU* and highlighting the characteristics of homes identified as having particularly *high personal exposures* is produced.
>
> Secondly, suggestions regarding the current data gaps, ways to fill them and how to optimize the full chain indoor exposure assessment methodology to become an across-the-board standard for indoor exposure and risk assessment is provided.

The contaminants that the three case studies address are:

- Dimethyl fumarate (DMF) through dermal exposure, led by IOM;
- Phthalates through multi-pathway exposures, led by VITO;
- BTEX (benzene, toluene, ethylbenzene, and xylenes) with mixture effect, led be CERTH.

This report is structured in that the general methods used to run the case studies, the findings and overall conclusions of each are also presented. In addition, suggestions regarding the current data gaps, ways to fill them, and how to optimize the full chain indoor exposure assessment methodology to become an across-the-board standard for indoor exposure and risk assessment will be provided within the last chapter of this report (chapter 7).

6.2. Methodology

6.2.1. The framework

To increase the comparability of the three case studies, the methodologies followed the same framework. This framework contains eight steps which are described below. However, it should be noted that due to the scope of the case studies, not all steps were relevant and these instances are identified.

> **Step 1**: The scope of the case study was defined and, if possible, 1-2 long term health endpoints related to exposure to the contaminant were identified and quantified.
>
> **Step 2:** The main sources of emission (products) in the residential settings were identified for each contaminant. For each of these sources their patterns of use, prevalence and frequency as well as mitigating factors of exposure in the home were indentified.

Step 3a: Emission-indoor air modelling (only for phthalates and BTEX case studies). Data on the following parameters were required and collected:

- Emission rates of the contaminants or releases from consumer products.
- Residence volumes.
- Indoor-outdoor air exchange rates.
- Outdoor concentrations for contaminants present outdoor.

Step 3b: Exposed area; uptake factor and dermal loading mechanism modelling (only for DMF and phthalates case studies). Data on the following parameters were required and collected:

- Instant application (weight fraction of the compound in the total product and the amount of the product applied to the skin).
- Constant rate (contact rate at which the product is applied to the skin and the release duration the compound is applied).
- Migration (leachable fraction that migrates to the skin, the product amount that is in direct contact with the skin and the skin contact factor for partially contact with the product).

Step 3c: Oral exposure (only for phthalates case study). Data on the following parameters were required and collected:

- Exposure time: The amount of time a product is mouthed
- Product amount: the total amount of product that is being mouthed
- Weight fraction compound: the fraction of the compound in the product
- Contact area: the surface area of the product that is being mouthed
- Initial migration rate: The amount of the compound migrating from the product per unit of time
- Uptake fraction

Step 4: Exposure modelling. In the absence of the above information, chain starting from the indoor concentrations was used. Data on the following parameters were required and collected:

- Knowledge on the exposure mechanism
- Time/Activity data
- Use frequencies
- Use patterns

Depending on the data availability, the data collected in the previous steps was used as input or in the first step of modelling chain implemented in the INTERA platform: i.e. the IAQ model to determine the ambient air levels of indoor contaminants and then to the exposure models to determine the actual exposure levels or directly to exposure model, if only concentration data (ambient air levels of indoor air contaminants) were available.

In both cases the outcome of this process had to determine the actual indoor exposure levels for the selected contaminants.

Step 5: Internal dose modelling.

The external exposure levels were the starting point to derive the internal dose in the target tissues through PBPK models. The reason for calculating the internal dose was to use the appropriate exposure metric that would properly support risk assessment (especially relevant when potency of parent compound and metabolites is very different, and when we do not address systemic toxic effects, but rather organ-oriented health effects).

Step 6: Addressing data deficits

It is apparent that there were deficits in the data required to run the computational platform. These were identified to ensure that appropriate action was taken to remedy the deficit.

Step 7: Running the full chain computational platform. The collected data was used as input for the computational platform. Further information on the computational platform is provided in section 3.

Step 8: Interpreting and reporting the computational platform outputs. This included the use of the visualization platform. Further information on this platform is provided in section 4.

6.2.2. Common values

To increase the comparability of the three case studies, it was agreed that common values would be applied for certain key variables, based on mean and standard deviations provided for each EU country (appendix 2):

- Body weight (kg), length (cm), surface area (m^2, for arms, feet, hands, head, legs, trunk and total) for the age categories 0-1, 1-2, 3-8, 9-14 and 15-64 years for both males and females for each EU country.
- Typical time activity patterns for each of the age categories for both weekdays (Monday till Friday) and weekend (Saturday and Sunday).
- Building volume (m^3) and air exchange rates (h^1) for residences' and workplaces for each EU country.

The assigned common values were included in the KMS, along with all other relevant data identified and collected during the case studies.

6.3. Case study findings

A summary of the findings and overall conclusions of each of the three case studies is provided below. A more detailed description of the methodology, results and conclusions from each of the three case studies are provided in Appendices 3, 4, and 5 respectively.

6.3.1. DMF case study

Dimethyl fumarate (DMF) is a fungicide used to prevent mould growth in leather and textiles. It has been applied by spraying of the product or via slow evaporation from sachets inside the product. In 2006 an outbreak of allergic dermatitis was observed in some EU countries, which was later attributed to dermal exposure to DMF in furniture and footwear (Susitaival *et al.*, 2009; Gimenez-Arnau et al. 2009; Lammintausta et al. 2009, Gonzalez- Guzman et al. 2009, Virgan et al. 2009, Hasan et al. 2010, Santiago et al. 2010). This led to a ban of DMF in products at concentrations in excess of 0.1 ppm in 2009, first in France and Belgium and EU wide in 2009.

The INTERA methodology was tested to assess the intake of DMF through dermal exposure. Peer reviewed and grey literature were reviewed to collate the necessary input data for the INTERA modelling platform. Far from complete, the data were particularly lacking on numbers of exposed, exposure conditions and DMF concentrations in the contact materials. We estimated a concentration of DMF in furniture (readily sofas) of the order of 1 ppm and in footwear of 58 ppm.

Clothing thickness of 0.5 mm was assumed to reduce DMF migration to the skin by 10% and 0.1 mm by 1%. Other potentially modifiers affecting the exposure dose (e.g. body temperature and weight) were ignored due to lack of data on how they affected the migration rate of DMF. The dose was calculated from concentration in the skin contact material, exposure time, thickness of clothing, and the exposed skin area. We assumed 100% absorption as recommended by the EC (2004) for substances with MW < 500 and $-1<\log K_{ow}<4$. The largest source of uncertainty is the concentration of DMF in the product.

The available information together with anthropometric data for each EU country was linked to the computational platform.

For an exposure scenario of a woman sitting on a DMF contaminated sofa for 3 h, wearing thick clothes, thin clothes and being exposed to bare skin, results showed intake doses of 0.30 µg/kg bw/day, 0.33 µg/kg bw/day and 0.34 µg/kg bw/day, respectively, which are within the range of doses that results in a reaction in the patch-test allergy studies.

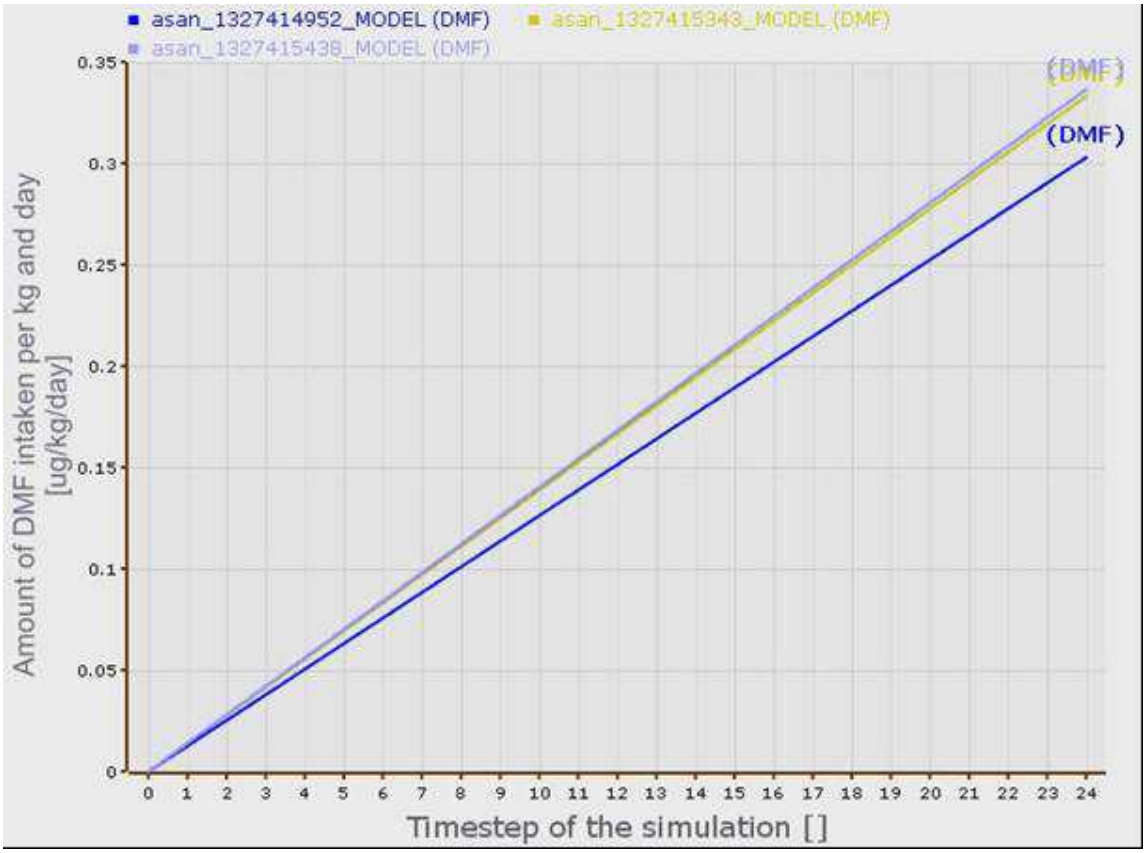

Figure 7. Typical European adult doses from 3 hrs of sitting on a DMF contaminated sofa.

DMF has not been included in the national or European biomonitoring programmes. Internal doses could not be estimated by PBPK modelling. No model validation data were available. Yet, had even the current rough assessment been done proactively, it would have correctly alarmed the industry and authorities, and prevented thousands of cases of serious dermatitis and eczema.

6.3.2. Phthalates case study

Many consumer products used in the indoor environment contain and release phthalates. Several phthalates are known to result in harmful developmental and reproductive effects. This case study describes the exposure caused by indoor sources to four phthalates: bis(2-ethyl hexyl)phthalate (DEHP), benzylbutyl phthalate (BBzP), di-isononylphthalate (DINP) and di-isodecylphthalate(DIDP) among the EU population.

Given the multitude of phthalates originating from sources in the indoor environment, their usage patterns and routes of exposure, an aggregate, multi-pathway exposure approach is needed for the evaluation of systemic health effects.

Indoor exposures to DEHP, BBzP, DINP and DIDP in the EU population, split up into several subpopulations (e.g. infants 0-1 year; toddlers 1-3 year; adults) were modeled using the INTERA methodology and tools. Concentrations and release rates of phthalates in consumer products, as well as behavioural and physiological factors which determine the inhalation exposure, dermal contact and oral exposure to dust via mouthing were fed into the INTERA platform to describe the fate of phthalates in the human body.

The European average aggregate exposure to DEHP in the indoor environment is more than 10-fold higher for infants than for adults (infants: 7.4 µg/kg bw/day; adults: 0.5 µg/kg bw/day). Similar differences in aggregate exposure between these groups were found for BBzP, DIDP and DINP.

Infants' exposure to DEHP in the indoor environment was dominated by oral exposure via mouthing toys and other plastic objects (40 %) and by unintentional ingestion of dust (35 %). Dermal contact contributed to about 24 % of the systemic dose for DEHP, while dermal contact with dust was negligible; inhalation contributed only marginally (0.7 %) to the systemic dose for DEHP.

The theoretical impact of a policy measure such as the Toys Directive (Dir. 2005/84/EC) on body burden and internal doses of phthalate metabolites in children was investigated. Hereto, scenario 1 (before ban in 2007) assumed DEHP content in toys as the ones reported in monitoring surveys before 2007, and, in scenario 2 (since ban in 2007) all toys were assumed to be compliant to the Toys Directive () (< 0.1 % DEHP). Other exposure routes and modifying factors (inhalation of air, dust, etc.) were kept constant across the 2 scenarios. The (theoretical) impact of the restrictions on aggregate exposure (as generated by the computational platform in terms concentrations of the first metabolite of DEHP (i.e. MEHP) in urine is shown in Figure 8.

As a result, concentrations of metabolite MEHP are about factor 4- 6 lower in the scenario where compliance to 0.1% DEHP in toys is assumed versus the scenario before the ban.

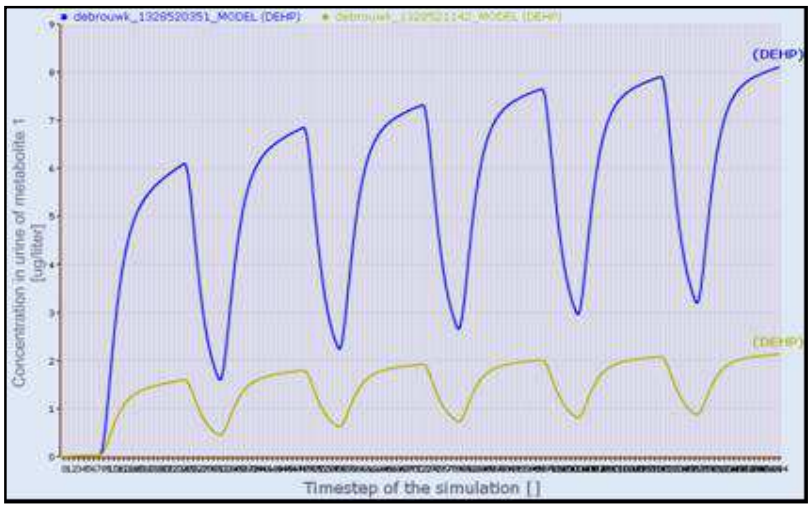

Figure 8. Predicted concentrations of DEHP metabolites in urine of an infant (0-1year) during 1 week (168 h) for 2 contrasting scenario's: 1) scenario 1: exposure before DEHP restrictions in toys and childcare articles (blue line), and 2) scenario 2: exposure of DEHP under the assumption of fully compliance restrictions in toys and childcare articles (green line).

At various stages of the modelling chain the model predictions were validated by means of independent data. There was a good match between predicted concentrations in settled house dust (135, 410 and 4400 mg DEHP/kg dust) and measured data (210 – 1050 mg DEHP/kg dust). In addition, predictions of metabolites of DEHP in urine of 0-1 years old infants (2-8 ng MEHP/ml) fell in the same order of magnitude as reported averages from biomonitoring studies on toddlers (1-3 years) in the literature (mean MEHP in urine: 4.64 ng/ml). The finding that the predictions are a bit above the measured data are not very surprising since the aggregate dose for the infants (0-1 years) are higher than for the age category 1 – 3 years, which is the age category of the children in the study of Brock et al. (2002). However, one should keep in mind that MEHP measured concentrations in urine integrate all exposure sources and routes, while our predictions only account for indoor sources (thus excluding contribution from dietary intake).

The findings from this case study demonstrate the use of the INTERA tools for indoor exposure assessment for chemicals with multiple sources and pathways, and with complex dynamics between gas and settled phase.

6.3.3. BTEX case study

The BTEX case study describes the development of a mechanistic modelling approach implemented in a dynamic simulation environment, for assessing aggregate and cumulative exposure to the quaternary mixture of benzene, toluene, ethylbenzene and xylenes (BTEX) found in door environments.

The case study comprised an extensive review of the peer-reviewed literature (2001-2011) on BTEX concentrations in indoor locations within Europe, clustered by location, i.e. residences, workplace, schools, leisure facilities (bars, restaurants, museums) and transportation (tram, metros, buses). Exposure was estimated based on detailed activity patterns (stratified by age), on the basis of time spent at the respective locations. Uptake was estimated based on diurnal variability of exposure, incorporating the effect of the activity type on inhalation rate. Uptake was used as input to a multi-compartmental Physiology Based PharmacoKinetic (PBPK) model of a quaternary mixture of VOC's (BTEX), which takes into account the interaction (i.e. competitive inhibition of metabolism) among the mixture constituents. The aim was to assess the biologically effective dose (BED) in the target tissue (bone marrow) of the benzene metabolites (benzene oxide, phenol and hydroquinone) which are associated to leukaemia and to validate the estimated dose against human biomonitoring data of occupants exposed to benzene.

The review process revealed large gaps in the concentration/exposure data necessary for a comprehensive Europe-wide exposure assessment study. Additional data problems were revealed regarding the representativeness and quality of the measurements made. The above indicate the need for an indoor air sampling harmonisation protocol, the outline of which will be highlighted.

Large differences were identified within the several indoor locations, the highest concentrations being related to transportation modes. Intra-country variability is larger than inter-country variability, reflecting the significance of local effects (e.g. proximity to heavily traffic roads), as well as indoor sources (e.g. smoking).

Feeding the full distributions of the input parameters into the Monte Carlo module of the INTERA platform we simulated the benzene exposures and uptakes and the respective bone marrow dose distributions of the metabolites in the infant and adult male populations of 19 EU countries. The results demonstrated order of magnitude higher average doses for infants than adult males, large differences between the countries and even larger differences within the countries (Figure 9).

These differences are attributed to the higher bodyweight normalized dose for infants (0 to 2 years old) and children (3 to 9 years old) compared to adults (2.5 μg/kg bw/d vs. 1.8 μg/kg bw/d). These differences were further amplified in terms of BED (0.08 μg/L compared to 0.03 μg/L), indicating the increased risk for infants and children compared to adults for similar levels of environmental exposure. Exposure to toluene, ethylbenzene and xylenes (TEX) was in general lower than benzene, and far below of any toxicological/legislative threshold. Inhibition of benzene metabolism due to TEX co-exposure was initiated in indoor locations associated to elevated BTEX level (cumulative concentrations above 100 $\mu g/m^3$), modifying the overall BED. This is, however, a very rare case in common residential settings.

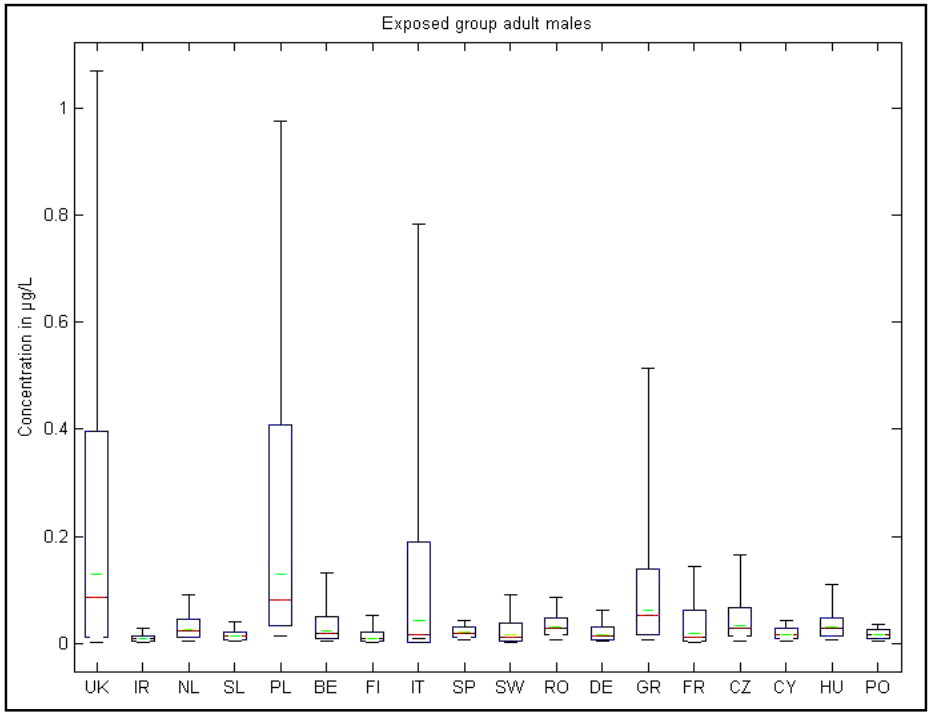

Figure 9. Whisker plot of benzene metabolite (BO, PH, HQ) concentration in bone marrow for adult males (max, min, 95%, 5%, median (red) and mean (green) estimates)

The methodology described above introduces a more biologically based dose response approach for indoor air risk assessment. This approach aims at understanding and describing the modes of toxic action of airborne pollutants. Thus, it links molecular level changes with measured events at the individual or population level.

6.3.4. Overall case study conclusions

The INTERA methodology and computational platform has been implemented in the case studies in a flexible modular environment allowing the user to start either from emission if concentrations or releases from consumer product are available (phthalates) or estimated (DMF) or from chemical concentrations measured indoors (BTEX) if these data are available. To successfully apply the generic PBPK model implemented in the INTERA computational platform, however, validated parameterization schemes must exist for the specific chemicals of concern in each study. When such data exist and consequently a validated PBPK model is available (e.g., DEHP in the Phthalates case study), internal dose of the chemical in the body (total internal dose) or in the target tissue(s) (biologically effective dose at the target tissue) can be estimated, increasing thus the value of the platform. Internal dose modelling when used within a probabilistic approach can capture the impact that inter-individual variability in the biochemical/physiological parameters might have on the overall toxicokinetic behaviour of the indoor chemical. The same intake might correspond to an order of magnitude difference in internal dose, with consequent differences in the phenotypic response to the specified chemical(s).

Throughout the case studies, the INTERA KMS was able to provide generic and region specific data on body weight, skin surface area, volumes of rooms and air exchange rates. On the other hand, at the onset of the case studies, few substance-specific data (e.g. concentrations, emission rates, etc) were available in the KMS. During the execution of the case studies, the data were fed into the KMS. As a learning lesson for future studies for which the INTERA tools might be used, a user should not expect from the KMS a ready for use, up to date database on substance/product specific data. Instead, one should regard the KMS as a starting point, and add new, quality-checked data. The possibility to do that was built into the KMS to make it flexible for the future needs and wider

usage. The strength and completeness of the KMS will depend on these updates (and its quality) from users of the tool.

In addition, the computational tools were experienced as a powerful tool to calculate aggregate exposure to contaminants from indoor sources, especially for complex scenarios and substances with complex interactions with dust, and when one wants to model up to concentrations of metabolites in the human body. As a learning lesson from the phthalate case study, one should always try to verify (intermediate) model predictions by means of measured, independent data. Verification of sub modules of the INTERA computational platform were helpful in giving confidence in the output, or were very helpful in identifying bugs and needs for model corrections or improvement. Especially when running the platform for a substance not previously assessed by means of the computational tool, some verification of predictions would be essential

In summary, the conclusions of the case studies are as follows:

- A web based indoor exposure, uptake and target organ dose modelling platform for cumulative and aggregate exposure, PBPK and Monte Carlo simulation capabilities has been developed and tested in the INTERA project.
- The three case studies successfully demonstrated the INTERA method and platform applicability for chemicals ranging from VVOC to SVOC, for dermal, inhalation and multi-route exposure settings, and for endpoints ranging from exposure to target organ metabolite dose.
- The results, which can be compared to respective measured field or laboratory data, support the validity of the modelling platform.

WP6: DISSEMINATION OF RESEARCH FINDINGS

6.4. Objective

The aim of dissemination work package was to use a multi-faceted approach to disseminate the INTERA project. It was intended that this would include both proactive participation in international fora (scientific and stakeholder conferences, pre-normative committees at the European and international levels), publication of two peer-reviewed journal publications (targeting the appropriate scientific communities) and Internet-based communication with the development of a project web site and a regularly published project newsletter (in conjunction with other communication channels of CEFIC).

6.5. Achievements

6.5.1. Website

A project specific website[12] was developed and went live June 2010. The website is structured to aid usability and access of information to interested viewers and includes the following key section /pages:

- Home page – general introduction to the project, key developments of the project, for example, new news items, events etc, contacts for further information.
- The project – further information on the INTERA project and aims, methods, deliverable and final reports for each of these.
- News and events – includes copies of project newsletters and INTERA workshop.
- As well as pages identifying each of the project partners and links to other relevant indoor air quality and modelling websites.

In addition the website provided a 'members only area', a private working space for members of the project team to access and share project related documents.

The INTERA website will continue to remain live upon completion of the project.

6.5.2. Newsletters

Three newsletters providing details and updates on the INTERA project were produced:

- Newsletter 1: October 2010
- Newsletter 2: February 2011
- Newsletter 3: September 2011

A fourth and final newsletter will be distributed late March 2012 to advise the completion of the project and where copies of project reports and integrated methodology will be made available.

Copies of the newsletters were emailed to a distribution list of stakeholders. This stakeholder list was created using names provided by INTERA team members, and selected stakeholders from the EPHECT project. The stakeholder list has grown since the project began and currently has a circulation list of over 300 names.

[12] http://www.intera-home.eu/Home.aspx

In addition, copies of the INTERA newsletters are available on the INTERA website[13].

6.5.3. Stakeholder involvement

Stakeholder involvement was of paramount importance for the development of INTERA. Since the very beginning of the project, several representatives of relevant stakeholders, including academia, industry, regulatory authority experts and NGOs, were involved in a series of web-based seminars / workshops. In these events, the user requirements for the work done in WP1 (data collection), WP3 (methodology and computational platform development) and WP4 (visualization module development) were identified with the help of the participating experts.

At a later stage, once the computational platform was operational, a free workshop was held at the Radisson Blue hotel, Brussels, 18th November 2011, to provide interested stakeholders with an overview of the INTERA project and an opportunity to try out the indoor exposure assessment tools developed within INTERA. Feedback from delegates was actively encouraged throughout the workshop to allow consideration to be given to the comments and views expressed by stakeholders when finalizing the tools and methodology developed in the INTERA integrated approach.

The workshop was attended by 15 delegates representing a range of research, industry and regulatory organizations from Europe and beyond. Copies of presentations given during the workshop, as well as a short report on the workshop, are available from the INTERA website[14].

Valuable comments were obtained from delegates during and following the hands-on interactive session with the computational platform including recommendations for clarifying the route that users should take to progress through the tool and making this more logical; standardization of button placement and mechanisms for saving/applying/loading and storing changes. The INTERA project team considered carefully consider all comments received during the session when finalizing the INTERA integrated assessment approach and associated tools.

6.5.4. Conference presentations (podium and poster)

The INTERA team has been presented throughout the lifespan of the project at the following scientific conferences and forums.

Podium presentations

- De Brouwere K et al. (2011). The INTERA project: Integrated Exposure for Risk Assessment in Indoor Environments in Europe – full chain modelling from emissions to internal exposure. Methodology and tools. European Workshop Human Biomonitoring and indoor/outdoor air quality, Brussels, December 2011.
- Sarigiannis D et al (2011). A full chain mechanistic approach to assessing health risks from multiple sources in indoor environments. Indoor Air, Austin, Texas, June 2011
- Sarigiannis D et al (2011). Mechanistic Approach for Exposure Assessment from Multiple Sources in Indoor Environments. The International Society of Exposure Science (ISES) – 2011, Baltimore Maryland, 2011
- Sarigiannis D et al (2012). INTERA platform for mechanistic risk assessment of indoor air pollutants – VOCs Europe-wide assessment. Air Quality - 2012, Athens, Greece, March 2012

Poster presentations

- Galea KS et al. Integrated exposure for risk assessment in indoor environments (INTERA): the use of case studies to test INTERA tools. Long range Initiative conference, Brussels 17th November 2011.

[13] http://www.intera-home.eu/NewsEvents.aspx

[14] http://www.intera-home.eu/NewsEvents/Workshop/Presentations.aspx

- Asikainen A et al. INTERA: Integrated exposure for risk assessment in indoor environments. Indoor Air, Austin, Texas, June 2011.
- Asikainen A et al. A full chain mechanistic approach to assessing health risks from multiple sources in indoor environments. Long range Initiative conference, Brussels, 17th November 2010.

The following abstracts have also been accepted at the X2012 conference, Edinburgh, 2-5th July 2012, which will further disseminate the project outputs following completion of the INTERA project:

- Gotti A et al. INTERA computational platform: a web-based tool for mechanistic exposure and risk assessment in indoor settings. (Oral presentation).
- De Brouwere et al. Mechanistic risk assessment of indoor air pollutants: Exposure to phthalates. (Oral presentation).
- Sanchez Jimenez A et al. Mechanistic risk assessment of indoor air pollutants: Exposure to Dimethyl fumarate (DMF). (Oral presentation).
- Sarigiannis D et al. Mechanistic risk assessment of indoor air pollutants: BTEX Europe-wide assessment. (Oral presentation).
- Standaert A et al. INTERA visualisation platform: a web-based tool for visualization of indoor exposure. (Poster presentation).

In addition, abstracts for the following conferences have also been submitted.

- Sanchez Jimenez A et al. Integrated Exposure for Risk Assessment in Indoor Environments, INTERA - Example: The Dimethyl Fumarate (DMF) Case Study. Healthy Buildings 2012, Brisbane, 8-12 July 2012.
- Sarigiannis D et al. INTERA platform: A tool for mechanistic risk assessment of indoor air pollutants. Protection and Restoration of the Environment XI. Aristotle University of Thessaloniki, 3–6 July 2012.

6.5.5. Publications

To date, four publications have been published / drafted from the INTERA project. These are:

1. Garden C, Semple S, De Brouwere K, Galea KS, Asikainen A, Sanchez-Jimenez A, Gotti A, Karakitsios S, Sarigiannis D, Jantunen M. (submitted) Integrated Exposure for Risk Assessment in Indoor Environments (INTERA): A review of existing data on airborne chemical pollutant levels in domestic environments. Draft manuscript. This is an output from WP1, describing the review of existing data on airborne chemical pollutants in the indoor environment.
2. Sanchez Jimenez A, Sarigiannis DA, Asikainen A, De Brouwere K, Galea K, Standaert A, Karakitsios S, Jantunen MJ. Integrated Exposure for Risk Assessment in Indoor Environments, INTERA - Example: The Dimethyl Fumarate (DMF) Case Study. *Healthy Buildings 2012 conference proceedings*.
3. Sarigiannis D, Karakitsios SP, Gotti A, Liakos IL, Katsoyiannis A. (2011) Exposure to major volatile organic compounds and carbonyls in European indoor environments and associated health risk. *Environment International*; 37: 743-765.
4. Sarigiannis DA, Karakitsios SP, Gotti A. (submitted) Exposure and risk characterization in European indoor environments related to benzene and formaldehyde. *Fresenius Environmental Bulletin* (to appear in 2012).

Further submissions for peer-reviewed journals are planned and their scope is currently being discussed. It is anticipated that one will describe the full chain integrated approach to assessing exposure from sources in the indoor environment, with separate publications also being drafted for the various case studies.

7. DISCUSSION AND CONCLUSIONS

7.1. Internal evaluation

In overall the objectives and tasks defined by the project plan were fulfilled. Naturally some practical limitations and new thoughts arising from the discussions in the project group resulted some changes to the work plan. One of the most evident changes compared to the original plan was the exclusion of the biological pollutants from the project. This decision was taken following discussions with CEFIC in the projects infancy on the scope and focus of INTERA. These discussions identified chemical pollutants as being the primary concern and where the project should focus on. The second clear change compared to the original plan was to leave out Geographical Information System (GIS) from the methodology. This decision was based on the fact that the exposure in indoor environments is more related on the factors describing the buildings (such as air exchange rate, building volume) and behaviour of people than on factors related on geo-referenced location. The spatial variance of data and assessments was described in the country level (in some cases in the city level), which seems to be more appropriate for the indoor environments. Furthermore, some of the planned exposure determinants, such as socioeconomic status and climatological factors, were not considered due to lack of data, which prevented us to draw any realistic connections between exposures and these determinants. In addition the copyright restriction limited the use of some of the essential information, such as emission database BUMA and sales data from industry, and this lowered the amount of data to be available for the assessments and to be stored to the on-line database of KMS.

Overall, despite of these rather minor changes experienced, the project group feels that the INTERA methodology is a clear advancement towards refinement of exposure and risk assessment. Although measurements of personal exposure have marked good progress in exposure/risk assessment compared to environmental monitoring, the process is significantly enhanced by translating external exposure to actual uptake and internal dose metrics as developed in the INTERA project.

7.2. Utilization of the project outputs

The on-line tools (KMS and the modelling / visualization platform) are freely available for all interested users as per agreement of CEFIC. The content of KMS will be maintained after the end of the INTERA project and it is anticipated that the content will expand by the future projects. Data collected in the KMS can be accessed and used in stand-alone mode, but they are also automatically used by the modelling platform and provided as input data for the modelling exercises.

The modelling platform will continue to be hosted at CERTH and will be maintained after the project completion. CERTH will assure that the modelling platform will remain available for users as per agreement with CEFIC. Improvements and adaptation to scientific and technical progress will be implemented if necessary to allow the continuous provision of service to the user community for indoor environment exposure and risk assessment. Larger improvements as described in the needs for future research in section 7.4 of this document could be implemented if the necessary financial support can be found. Consideration to a service level agreement and a service charge for the use of the overall INTERA system (the KMS, the computational platform and the visualization module) will be given to explore the financial survival of the scientific and technical legacy of INTERA.

The INTERA website will continue to be live and will represent a portal for interested stakeholders to access information on the INTERA project and the deliverables that the project provides.

7.3. Addressing current data gaps and optimization of the full chain methodology

The INTERA project applies a full chain mechanistic approach for predicting indoor exposure to chemical contaminants and their inter-relationships. This multi-faceted and integrated approach;

- considers the relationships among the sources of contamination (outdoor and indoor), and the levels of indoor contamination;
- includes appropriate modelling of air pollution from sources / emissions strengths to calculate spatial and temporal patterns of indoor concentrations;
- allows the inclusion of time activity patterns, geographical location, age groups and product usage to understand variability in personal exposure
- includes internal dose modelling (PBPK) which is an essential element for describing these dynamic procedures, allowing for possible interactions among several contaminants to be implemented
- supports the development of Biology Based Dose Response (BBDR) functions and allows the commensurate use of human biomonitoring data in order to further enhance the biological robustness of indoor chemical risk assessment.

The 'full chain approach' was implemented within a dynamic simulation environment, which was found to operate very satisfactorily for the case study pollutants. An exposure assessment in INTERA is a step-by-step process, starting with the basic information on chemical, products and the exposed population. The wide variety of exposure determinants is associated with very diverse population groups both from the gender/age class and from geographical point of view. This variety poses a problem for exposure assessors, who often do not have measured exposure data related to these determinants for all conceivable exposure scenarios and all consumer groups. To assist in the risk assessment associated to exposure in indoor settings, INTERA can be used to estimate exposure for different scenarios for which there is paucity of measured data. This is reflected in the overall philosophy of the platform which allows user to load data necessary to configure a simulation: automatic data retrieving from the database (if stored online) or to manually input data to the platform when user has newer or more updated information. Furthermore, the approach followed permits the user to use the platform as a tool to create hypothetical scenarios and investigate how the modified determinants affect the resulting exposure. This could be useful to simulate impact of policy measures.

However, through the lifespan of the project it was evident that a major difficulty in undertaking an EU indoor air exposure assessment for any indoor pollutant arises from the relative paucity of data in many of the EU countries. Even for the countries where data does exist, there are significant problems and inconsistencies in the respective datasets. A major issue is that within the same country no data set exists from a large number of different cities/towns. Yet, large variation in the measured data might be expected due to socio-economical differences, affecting both consumer product use and building materials/emission sources, and/or climatic differences that may affect the indoor/outdoor air exchange. In many studies, the number of samples and/or the combination of the selected dwellings (mixed occupational and non-occupational settings) are not adequate for considering them representative of the entire urban area. Finally, the way that the results are presented lacks consistency with regard to the statistical metrics used, obstructing data interpretation. A realistic and representative view to indoor exposure of the wider population would be greatly facilitated by a sampling harmonization protocol that provides guidance on the number and spatial distribution of samplers (at the country and urban scale), taking into account the arguments discussed above as well as on the way of presenting the results so that they can be easily utilized by other experts and policy makers.

There is a need to consider regulating sources and other indoor air pollution determinants in residential and non-residential environments mostly by emission characterization and labeling schemes, issuing guideline values for major indoor air chemicals at the WHO and European Commission level. Labelling schemes for building materials are common practice in Germany (AgBB scheme[15]) and France (AFFSETT scheme[16]). Efforts at the EU level on harmonization of LCI (Lowest

[15] AgBB Health-related evaluation of emissions of volatile organic compounds (VOC and SVOC) from building products, 2010. Available at: http://www.umweltbundesamt.de/produkte-e/bauprodukte/agbb.htm

[16] AFFSETT: Agence française de sécurité sanitaire de l'environnement et du travail. Available at http://www.anses.fr/

Concentration of Interest) values for setting maximal emissions of VOC from building materials are ongoing in the EU LCI working group led by JRC. In addition, there is a need to consider publicizing good practices in the handling of newly acquired consumer goods (destined for primarily indoor use), maintenance of older products and substitution of toxic chemicals in articles with less toxic ones.

Given the complexity and the differences in the chemical composition of the indoor air chemical mixture in Europe, there would be scope for addressing the combined exposure of the population to airborne chemical mixtures characteristic of specific environmental settings in order to assess the potentially attributable health risk and identify the most appropriate risk management strategies. Considering also the relatively large variance of concentration values for most of the chemicals reviewed herein within the same city (especially for dwellings) it is essential to include in future studies analyses of the socio-economic determinants that may affect population exposure to indoor air chemicals.

From the methodological point of view, the INTERA methodology offers a clear advance towards the further refinement of exposure assessment. Although measurements of personal exposure comprise an advance of exposure/risk assessment compared to environmental monitoring, the process might be further enhanced by translating external exposure to actual uptake and even more to internal dose metrics. This is of particular importance in the case of chemicals with particularly toxic metabolites such as benzene. In this case the appropriate exposure metric is the biologically effective dose of the substance metabolites at the target tissue (in the case of benzene and its carcinogenic potency, the bone marrow) or the total internal dose in the body (in the case of systemic toxicity). The further development of the biologically effective dose-based exposure assessment methodology would have two key positive outcomes:

(a) it will allow the ready integration and use of human biomonitoring data into indoor environmental chemicals risk assessment;

(b) it will help to operationalize the concept of biomonitoring equivalent of toxicological thresholds currently used in chemical safety legislation throughout the world. Biology-based dose-response models could then be developed, enhancing thus the biological basis of chemical risk assessment.

The INTERA method, because of its mechanistic and integrative nature, can be used to analyse the importance of several exposure determinants for realistic exposure assessment in support of EU-wide risk assessment of indoor pollutants. This could include determinants and exposure/risk modifiers such as consumer behaviour, climate, age of exposed population, time window of exposure, dietary habit of exposed individuals among others. Thus, the methodology and the corresponding computational platform are expected to support efficiently exposome studies at the EU and worldwide scales.

Currently, there is no Community or national legislation in Europe that prescribes explicitly, a monitoring and control program for indoor air quality. Consequently, no EU-wide systematic indoor air monitoring data exist. Harmonized criteria on monitoring requirements and the development of harmonized protocols will improve exposure assessment of indoor air pollutants. The harmonized protocols must include pollutants to be measured, standardized analytical techniques to be employed, survey designs (including standardized questionnaires), target locations for measuring exposure (e.g., kindergartens, schools, offices, private dwellings, day care centres, hospitals, transportation vehicles), periods and frequencies of measurements, range and distributions of concentrations, target populations (general public, susceptible groups, etc) and statistical tools for data evaluation. As already mentioned above, one of the major difficulties encountered in the current study for proper data interpretation as well as for exposure assessment was the lack of adequate data and the extent to which these data are representative of the exposure settings they referred to. Thus, in view of optimizing the exposure assessment procedure, while containing the sampling/measurements cost, we suggest the following criteria for a sampling protocol framework towards harmonization in indoor air measurements:

- The number of samples should be representative of the population. A ratio of one sampler per thousand residents should be the minimum in order to effectively support the assessment process with adequate and representative data.
- The distribution of samplers within the city. This is very important since within the limits of a large urban agglomeration, the intra-urban variability of indoor air concentrations is in general seen to be higher compared to inter-urban or, even, inter-country variability for the same climatic zone according to the data collected thus far. Thus, "density" of samples should be higher in more populated areas, so that the mean value represents with less uncertainty the actual exposure of the population. If a sufficiently large sample can be collated, a probability sample randomly drawn from the target population and/or indoor spaces is the ideal choice. It will also cover the monitoring locations listed above in a representative way and allow for generalization of the results.
- Sampling in residential and non-residential locations. Indoor air concentration data are needed from the majority of the locations encountered by the population; thus, besides dwellings, a significant number of samplers (about one third) should be placed in non-residential locations. Special attention should be paid to children, considering that they constitute the most vulnerable group among the members of a population from the point of view of public health. At least half the samples taken from non-residential locations should be devoted to assessing indoor air quality in schools and kindergartens. Overall, the following locations are characteristic for designing a representative indoor air survey:
    - City centre
    - Suburban/residential
    - Urban background
    - Rural background
    - Sites in proximity to major roads/streets
    - Sites in proximity to specific industrial site(s)
    - Specific source/target-oriented (e.g., garages, car parks, tunnels, schools, hospitals, kindergartens, public buildings, etc)
- Sampling distribution within the country. The variation of indoor dwellings concentrations in the cities within a country might vary based on several differences discussed above. However, an overview of the situation in the whole country is necessary and for this reason, considering also the cost of sampling, the cities should be clustered by relevance criteria; one city from each *cluster* should be the field of a measurement campaign as described above. The criteria for clustering the cities refer to either a) strong outdoor sources/ high concentrations, which affect the indoor concentrations by penetration of ambient air indoors; or b) purely indoor emission processes and sources. Thus, possible clustering criteria should comprise:
    - degree of urbanization and population density, which affects traffic volumes and ambient air pollution
    - meteorological conditions and local topography, which affect indoor-to-outdoor air interactions, as well as the use of ventilation, heating or cooling devices etc.
    - existence of industrial sites or power generation plants nearby the urban location
    - socioeconomic status of the urban population, a parameter which affects consumer products choice, use pattern and consequently indoor air emissions
    - information on the specific building materials and consumer products/apparatus used in the indoor environment sampled

- Duration and type of sampling. Careful consideration must be given to the duration and type of sampling (passive vs. active), both of which have their respect advantages and disadvantages. For example, passive sampling data are time-integrated and thus have low temporal resolution, a problem that does not exist when active sampling is used. For some pollutants, peak exposures might be important and a higher temporal analysis is needed. Passive sampling may be used to give an overview at low temporal resolution over wide areas with relatively low cost, whereas active sampling could be applied additionally to target specific activities and microenvironments, elucidating thus their respective role in the definition of the overall exposure profile.
- Repetition of the sampling. Seasonal variation might significantly alter indoor concentrations due to differences in ventilation, indoor/outdoor interaction, use of space heating etc. At least a two-season campaign (winter and summer) is necessary in each sampling location.
- Laboratory analysis. Fully validated and recognised analytical methods should be used for the chemical analysis of indoor pollutants.

It has to be noted at this point that the European Commission's Joint Research Centre (JRC) is leading a European effort towards harmonized criteria for sampling and monitoring selected indoor air pollutants. The results of the corresponding JRC project and expert group are expected to come out later in 2012.

7.4. Implications for future research

7.4.1. Methodology

Three are the main implications for future research with regard to the INTERA methodology development:

(a) To implement a generic PBPK model for chemical mixtures allowing us to model co-exposure to indoor chemicals from within the INTERA platform.

Thus far, the generic PBPK model implemented into the INTERA platform can only handle single chemical compounds, thereby not allowing us to model scenarios comprising co-exposure to several chemicals at a time inside specific indoor settings. Our immediate future developments will pertain to extending this capability of the platform to include a generic PBPK model that can handle exposure to chemical mixtures, taking into account the principal pathways of bio-chemical interaction among mixture components at any exposure level range. This will require enriching our parameter database with many more data and, more importantly, with the necessary QSARs for estimating partitioning and biochemical kinetic parameters that are required to run such a complex model. As this is a non-trivial piece of work, we anticipate that this development will take at least a year to come to fruition, if not longer.

(b) To analyze data to identify determinants of exposure and quantify the respective levels of significance.

The wealth of data collected during the INTERA project would require further in depth analysis in order for us to identify the main determinants of exposure to indoor chemicals and to assess quantitatively how significant each determinant (or modifier of exposure) is in the specific studies. Determinants and modifiers that have not been addressed in the project case studies would have to be explored, such as socio-economic status, age and time window of exposure, the role of gender in determining exposure patterns to specific indoor chemicals would need to be analyzed in this context. Furthermore, incorporation into the KMS of human biomonitoring data that can be related to indoor chemical exposure

would allow us to better validate the internal dosimetry models employed in the platform. Associating biomonitoring data with exposure determinants with the use of the INTERA methodology and platform could result in the determination of easy-to-use transfer functions characterizing exposure to realistic indoor settings and converting the estimated or measured exposure levels into actual biologically effective dose of the toxicants analyzed.

(c) To expand the methodology to include biological contaminants and physical stressors in the indoor environment.

INTERA did not address non-chemical (i.e. biological or physical stressor) exposure in the indoor environment. However, biological contamination of indoor space is a key issue of concern, which can be also associated with parameters such as building age, proper ventilation, climatic conditions, and, most importantly, socio-economic status. Our methodology would still be valid in the case of biological health stressors; however, the definition of the appropriate exposure metric would need revisiting in that case.

Furthermore, the interaction between chemicals and physical stressors such as noise has been reported as having adverse effects on specific health endpoints including both neurological and cardiovascular damage. It would be interesting to include noise exposure assessment in the INTERA methodology and attempt to capture realistically the conditions under which the co-exposure to chemical and noise pollution indoors might have adverse health effects or at least reasons for concern.

7.4.2. The case studies

The case studies also identified areas for further research. For example, for BTEX, a first step will be to enhance and revisit the assessment after introducing newly collected data on emissions from building materials and consumer products in Europe through gaining access to the databases produced (or in the course of being produced) in the frame of the DG SANCO projects BUMA and BUMAC. In this way, the emissions data present in the KMS will be enriched and they will become relevant for Europe. This will allow us to use the full strength of the INTERA method and computational platform, namely by starting the full chain calculation from emissions rather than from measured concentrations. Comparison with the measured concentration data would allow us to reconstruct the relevant exposure scenarios in indoor settings in Europe. The result of this work would permit us to identify the major determinants of exposure to BTEX and, indeed, of the biologically effective dose of the BTEX parent compounds and their metabolites. With this information at hand, we would be then in a position to suggest risk management measures if needed, both related to controlling the indoor climate and aeration conditions in different types of indoor settings and to controlling the emission rates of the BTEX compounds from consumer products and building materials. The benefit from applying the INTERA integrated methodology is that in addressing risk management measures, realistic estimates of BTEX toxicity based on actual co-exposure patterns would be taken into account instead of single substance measurements. Thus, risk management could be associated to the type of the indoor environment considered each time, as opposed to taking control measures tackling each VOC separately no matter what the plausible exposure scenario would be.

A second step will be to expand the geographical scope of the assessment by collecting data from other world regions, including the Americas and South-East Asia. Preliminary contacts with academic institutions in the USA, the Korean Institute for Public Health and academic institutions in China have been undertaken to move in this direction. This would be particularly useful given the large imports of building materials and other consumer products and fabrication material from Asia into Europe. Being able to compare the respective exposure datasets and exposure scenarios would

(a) widen the applicability and user acceptance of the INTERA methodology and tools; and

(b) provide useful information for further refining the assessment of indoor exposure to BTEX (and, as a follow up to this, to other VOCs) taking into account consumer product imports when constructing the respective exposure scenarios.

A number of the points highlighted above are also relevant to the phthalates and DMF case study.

7.4.3. Data gaps

Two are the main research actions that would continue and expand on the work done in INTERA and its findings with relevance to addressing the currently observed data gaps in Europe:

(a) Work towards Community-wide acceptance of harmonization schemes for sampling and monitoring indoor air quality and release of chemicals from products. Suggestions towards this goal have been articulated in the frame of INTERA, starting from the VOCs case study and extending them to cover other types of indoor chemicals. In parallel, activities in this direction continue at the European Commission's Joint Research Centre through the coordination of a European expert group on the establishment of sampling and monitoring harmonization criteria and on control and labeling schemes for releases from consumer products and building materials. An EU-funded research project, EPHECT, looks at the same issue from the point of view of public health protection. Integrating these efforts towards a harmonized scheme would undoubtedly set the premise for gradually filling the current data gaps with regard to chemical releases in the indoor environment with measurements that would follow a widely accepted protocol. Organization of a workshop along these lines would be a first action in this direction. This could very well be organized in the context of international exposure assessment meetings, such as the forthcoming ISES conferences in 2012 and 2013. Alternatively, a specific purpose meeting could be set up with the involvement of all relevant stakeholders. The network of stakeholders developed within INTERA would a valuable asset in this regard. The assistance and support of CEFIC for such as development would be essential to ensure the necessary industry buy-in.

(b) A related and not insignificant point that would require further study is the development of robust and widely applicable techniques for filling the currently observed data gaps in several of the full chain methodology steps. Of particular importance in this context is the completion of datasets related to exposure determinants and modifiers across Europe. Surrogate data and data mining and data fusion techniques have so far been used as needed in the case studies of the project. The procedures developed in this context would have to be formalized, documented, and generalized so as to render them usable in other cases as well. This would be a great aid towards addressing data paucity, which hampers our capacity to make realistic exposure assessments and makes regulators take decisions on the basis of precaution using incomplete information.

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LIST OF APPENDICES

Submitted as separate files

Appendix 1: WP1 report. A review of existing indoor air pollutant exposure data and model

Appendix 2: Tables of the common values for case studies

Appendix 3: DMF case study report

Appendix 4: Phthalates case study report

Appendix 5: BTEX case study report