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Multimedia & PBPK modelling with MERLIN-Expo versus biomonitoring for assessing Pb exposure of pre-school children in a residential setting

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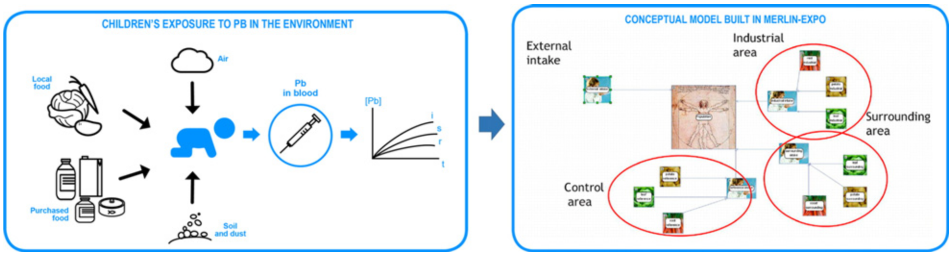
HIGHLIGHTS

- Lead exposure of pre-school children has been simulated using MERLIN-Expo.
- Flexible scenarios were built using sub-models from the MERLIN-Expo model library.
- Predicted blood Pb levels overpredict biomonitoring data by a factor 2.
- Sensitivity analysis indicated age as an important parameter determining exposure.

GRAPHICAL ABSTRACT



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ABSTRACT

This paper reports on a case study – conducted within the European FP7 project "4FUN" – focusing on exposure of pre-school children to lead resulting from past emissions by non-ferrous smelters in Belgium (Northern Campine area). Exposure scenarios were constructed and simulated with the MERLIN-Expo tool to estimate external Pb exposure as well as the Pb body burden in children living in the vicinity of the former industrial sites as compared to children living in adjacent areas and a reference area.

Simulations were run for several scenarios ranging from very simple to rather complex in order to study the effect of different simulation approaches (e.g., deterministic vs. probabilistic, individual vs. aggregated population exposure) and different exposure scenarios (e.g., with vs. without considering local food consumption or time activity patterns) on the model outcomes (predicted concentrations of Pb in environmental and human matrices). This paper discusses the two most complex scenarios, namely exposure at the aggregated population level and at the individual level for a random sub-sample of subjects, respectively.

In the final and most realistic exposure scenario, simulating individual lead exposure, model predictions were shown to be higher than the biomonitoring data. Blood Pb levels in children, irrespective of the area they lived in, were overpredicted by MERLIN-Expo with a factor of about 2 on average. The model predictions for individual

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Abbreviations: 2-FUN, EU project (Full-chain and UNcertainty approaches for assessing health risks in FUture eNvironmental scenarios); 4FUN, EU project (The FUture of FUlly integrated human exposure assessment of chemicals: Ensuring the long-term viability and technology transfer of the EU-FUNded 2-FUN tools as standardised solution); BDW, body weight; CEN, European Committee for Standardisation; EASI, Effective Algorithm for computing global Sensitivity Indices; EFAST, Extended Fourier Amplitude Sensitivity Testing; HBM, human biomonitoring; PDF, probability density function; Pb, lead; PBPK model, physiologically based pharmaco-kinetic model; OAT SA, one-factor-at-a-time (OAT) screening design used for sensitivity analysis; QSAR, quantitative structure activity relationship; SA, sensitivity analysis.

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children overlap with the prediction interval calculated by MERLIN-Expo based on population averages, demonstrating the use of probabilistic approaches in risk assessment. While these results constitute a first verification of the model performance of MERLIN-Expo dealing with inorganic pollutants in a complex real-world exposure scenario and a demonstration of the robustness of the modelling tool, further validation and benchmarking efforts are required for a larger number of inorganic pollutants and different exposure settings.

1. Introduction

MERLIN-Expo is an exposure simulation tool that has been developed during two successive EU funded projects, 2-FUN and 4FUN. MERLIN-Expo has been extensively reviewed by Ciffroy et al. (2016a–in this issue). MERLIN-expo is a standardised software tool for human and environmental exposure assessment to chemicals. The tool can be used to create dynamic exposure models and perform both deterministic and probabilistic simulations. It can be used to conduct exposure assessments of complex dynamic systems evolving over time, integrating multimedia, bioaccumulation and PBPK models in the same platform. MERLIN-Expo covers the entire exposure assessment chain from pollutant levels in environmental matrices to internal doses in man and biota. The structure and technical specifications of the models included in the MERLIN-Expo library are fully documented according to the CEN (European Committee for Standardisation) workshop agreement “CWA16938”.

Case studies on actual data sets for both organic and inorganic pollutants were performed as a way to verify MERLIN-Expo's model predictions, comparing them to real-world measurement data (apart from this case study, also see Van Holderbeke et al., 2016–in this issue; Radomyski et al., in progress; Banjac et al., in progress). More particularly, in trying to simulate real-world case studies, the aim of the project was to (i) parameterise and extend the exposure and PBPK models included in the library, in order to facilitate the shift from a generic to a site-specific assessment; (ii) verify the reliability of model calculations through a systematic comparison with actual measurements; (iii) demonstrate how uncertainty margins can improve risk governance, and; (iv) demonstrate the feasibility of building complex realistic scenarios satisfying the needs of stakeholders.

The focus of this study is on pre-school children exposed to historical contamination to lead (Pb) – a neurotoxic compound affecting intellectual development in children (ENHIS, 2009; Landrigan et al., 2006) – in a former industrial area and its surroundings in the North-Eastern part of Belgium. Exposure scenarios were constructed to estimate external Pb exposure as well as Pb body burden in children living in the vicinity of the former industrial sites as compared to children living in adjacent areas and a reference area. Data sets from a previous biomonitoring study conducted in this region were available to verify the model predictions (Van Deun et al., 2008a, 2008b; Van Holderbeke et al., 2008a; Flemish Government, 2008). Simulations were run with MERLIN-Expo for a range of scenarios using different simulation approaches (e.g., deterministic vs. probabilistic, individual vs. aggregated population exposure) and considering different exposure pathways (e.g., with vs. without considering local food consumption or time activity patterns). Probabilistic analyses were conducted to study the impact of uncertainty and variability in parameter values on the variability of the final model outputs, i.e., blood Pb levels in pre-school children. Sensitivity analyses were run to identify and rank the key input parameters determining exposure, and to assess the relative contribution of the different sources, pathways, and routes of exposure to the overall modelled exposure.

2. Materials and methods

2.1. Case study area

The considered area of this study is located in the North-Eastern part of the Campine region in Belgium, known for its long history harbouring zinc smelting industry (Fig. 1). Although most of the smelters located here have closed down over the last decades and the few remaining factories have modernised their production processes resulting in a significant reduction of heavy metal emissions, exposure of the current inhabitants continues as the soil and dust is still contaminated with heavy metals such as Pb. Moreover, residues (ashes, slags and muffles) from the smelting operations were used for the hardening of roads and industrial terrains, and the discharge of waste water into surface water has led to the contamination of groundwater as well (Van Holderbeke et al., 2009). Based on the distance and wind direction from the former locations of the zinc smelters, the investigated region was divided into the three areas: industrial, surrounding and reference area. The polluted industrial and surrounding areas consists of districts of the municipalities of Mol, Balen, Lommel, Overpelt and Neerpelt whereas the low exposure, reference area is situated more than 10 km south-east of the smelters and includes districts of the municipalities of Hechtel and Eksel (Fig. 1).

2.2. MERLIN-Expo tool and conceptual model

Structure and features of MERLIN-Expo have been extensively reviewed by Ciffroy et al., 2016a–in this issue). In short, the MERLIN-Expo tool is built on the Ecolego platform (http://ecolego.facilia.se). Ecolego is a software for developing and simulating dynamic (compartment) models. It allows the user to create libraries of model components which can later be combined to form larger models. Ecolego has a wide range of numerical solvers as well as support for running Monte Carlo simulations and for performing sensitivity analysis. The MERLIN-Expo library contains a range of environmental multimedia and human exposure models and data for a large set of inorganic and organic substances (Ciffroy et al., 2016a–in this issue). Its modular design allows to conduct exposure assessments of complex dynamic systems evolving over time (Avila et al., 2003). The tool integrates, in the same platform, multimedia models (atmosphere, water, soil), bioaccumulation models for a variety of biota (e.g., vascular plants, fish, cow, etc.), and human PBPK models, allowing to cover the entire exposure assessment chain from concentrations in environmental media and biota via external exposure to internal doses in man. This way, it is possible to carry out lifetime risk assessments for different human populations, including exposure through multiple pathways, both in a deterministic and a probabilistic way. A module including an array of methods to perform sensitivity analyses enables the risk assessor to identify critical model input parameters contributing most to the model predictions, allowing for further refinement of the model if required (Ciffroy et al., 2016a–in this issue).

Human exposure in MERLIN-Expo can be modelled either at population or at individual level. Whereas the “Human Intake” and “Population intake” models assemble the total external exposure of one or multiple person(s) from different sources, respectively, the “Man” and “Population” models calculate the final internal concentrations in the human body, using the total quantity ingested (mg/d) and total concentration inhaled (mg/l) from the Human (Population) intake model as an input. Details on the different multimedia and exposure models included in the MERLIN-Expo model library are provided by Ciffroy et al. (2016a–in this issue) and are also available on the MERLIN-Expo website (http://merlin-expo.eu/).

One of the challenges at the start of the 4FUN project was to translate the considered complex real-world case study into a transparent

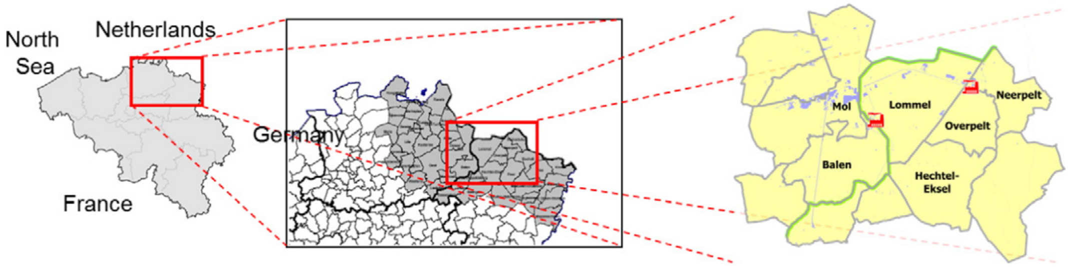

Fig. 1. The Northern Campine region in Belgium and the municipalities considered in this study.

conceptual model, thereby demonstrating the flexibility of the MERLIN-Expo tool. In order to build the conceptual model, all exposure sources, routes and receptors for Pb needed to be considered. The sources of Pb in the considered area are soil, dust, indoor air, outdoor air, groundwater, drinking water, locally produced vegetables and purchased foodstuffs. The major exposure routes were ingestion (for soil, dust, groundwater, drinking water, locally produced vegetables and purchased foodstuffs) and inhalation (for in- and outdoor air). Children are identified as the most sensitive population as they are most vulnerable to the neurological effects induced by Pb. Integration of all these sources and exposure routes, using available models from the MERLIN-expo library yields the conceptual model shown in Fig. 2. In this figure, the leaf, potato and root models account for exposure via the consumption of locally consumed leafy, bulbous and root vegetables. The consumption of purchased foodstuffs on the other hand, is assigned to an additional, "external" area as the concentrations in these foodstuffs derive from literature and national food surveys, i.e., non-local sources (see also Section 2.4.1).

2.3. Model simulations

A gradual approach adopting increasing model complexity was followed in order to fully understand the consequences of the different modelling approaches and of the introduction of new models, parameters, or time-dependent variables to the exposure scenario. Two of the simulations performed are discussed in detail in this paper: a simulation studying exposure at the aggregated population level and one studying exposure at the individual level for a random sub-sample of 30 subjects (i.e. ten in each of the three respective areas; see also Section 2.4.2). These two simulations only differ in the type of human related input data (i.e., time activity data, ingestion rates and initial age) that were used, namely averages (including probability density functions (PDFs) for some parameters) in the simulation at population level and

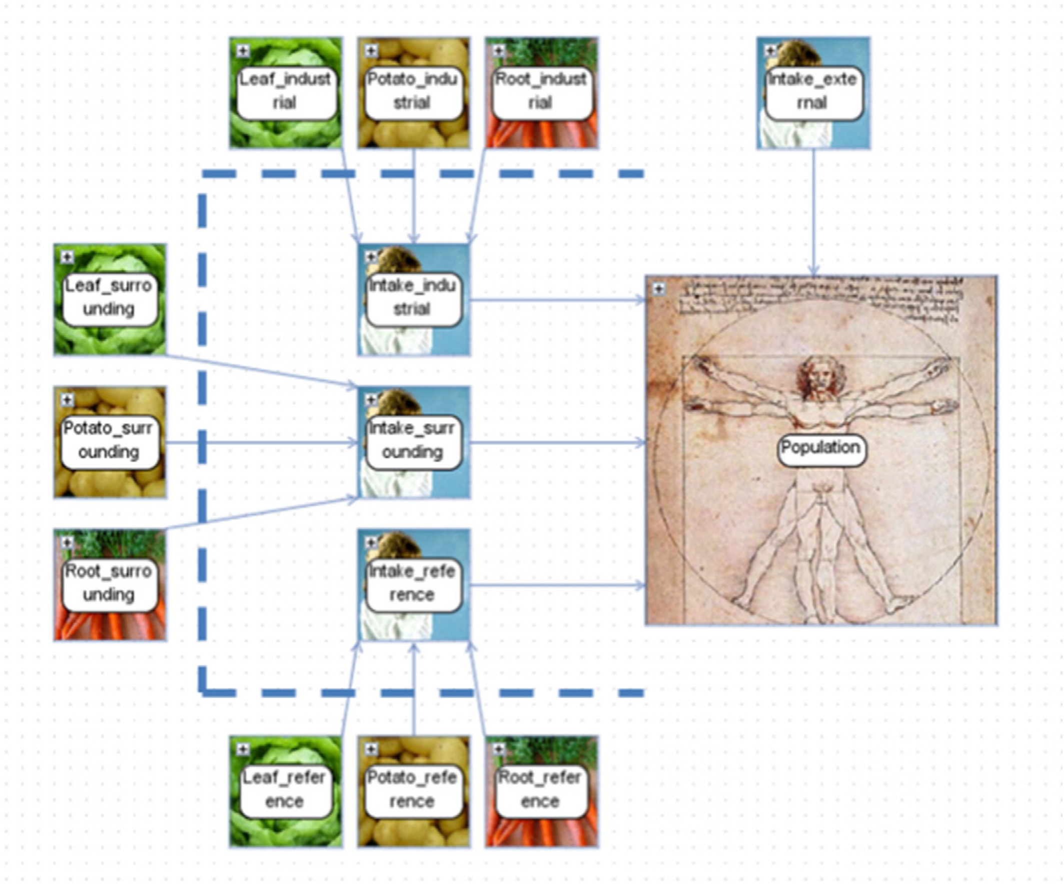

Fig. 2. Conceptual model, built in MERLIN-Expo, linking the different fate and exposure modules used to simulate internal Pb exposure in pre-school children. The leaf, potato and root models are only included in scenarios where local vegetable consumption is considered (indicated with dotted lines).

subject-specific values in the simulation at individual level (for more details, see Section 2.4.1 and the Supplementary information (SI) to this paper). Probabilistic simulations were performed on both scenarios by running Monte Carlo simulations with 1000 iterations. Interaction between soil and dust ingestion was accounted for by applying a correlation coefficient R^2 of 1 (Van Holderbeke et al., 2008a). The simulations of this case study were performed with version 2.0.3 of MERLIN-Expo (i.e., the most recent version available at the start of this study). The simulated time periods amounted to 1 year (i.e. starting from day 0 till day 365). The relative contributions of the considered exposure pathways to the total internal Pb exposures were additionally calculated with Microsoft® Excel version 2010 (Microsoft Corporation, Redmond, Washington, United States) using the internal ingestion and inhalation rates as predicted by MERLIN-Expo.

Sensitivity analyses were performed on the simulation dealing with aggregated population exposure. This type of analyses may allow the end user to (i) identify critical input parameters, i.e., parameters that influence the uncertainty of model outputs to a large extent; (ii) simplify the exposure model by excluding non-influential parameters from the uncertainty analysis; and to (iii) establish research priorities or to fine-tune the model. A two-step approach was followed in this case study, namely the Morris method followed by the EFAST method.

The SA method proposed by Morris (1991) is a one-factor-at-a-time (OAT) screening design. The main features of the method are discussed in Campolongo et al. (2007) and Ciffroy et al., 2016a–in this issue. The Morris method is qualitative, as it only provides a ranking of input parameters in order of importance. For each parameter (factor), the method computes two sensitivity measures: μ^*, which assesses the overall influence of the factor on the output, and σ, which estimates the nonlinear effect and/or the interaction effect with other factors.

The EFAST (Extended Fourier Amplitude Sensitivity Testing) method was proposed by Saltelli et al. (1999). EFAST is a variance-based method that computes the Total Sensitivity Indices (TSi) of the model inputs (Ciric et al., 2012; Ciffroy et al., 2016a–in this issue). The TSi measure the main (first order) effect of each individual or a group of inputs on the model output, as well as all higher order effects (i.e., considering interactions) that can be attributed to that parameter.

2.4. Input and verification data sets

The input and verification data sets used for this study can be divided into two types of data sets: environmental and human related. The majority of the data used derive from a large-scale environmental and biomonitoring campaign (hereafter referred to as “monitoring campaign”) that was conducted previously in 2006 in the considered case study area (Van Deun et al., 2008a, 2008b; Van Holderbeke et al. 2008a). The remaining data, mainly on concentrations in external food stuff, were obtained from literature (EFSA, 2012; FAVV, 2009; Leblanc et al., 2005; Bierkens et al., 2010).

2.4.1. Environmental data sets

During the monitoring campaign, measurements of Pb in soil (top and 30 cm below surface), dust and air particles (both indoors and outdoors) were carried out at 114 locations spread over the case study area (Van Deun et al., 2008a, 2008b). Descriptive statistics (averages, medians, minima and maxima, etc.) of these measurement data were calculated for the considered areas (i.e., industrial, surrounding and reference area and for dust also external area). Measurement data for Pb in soil and air particles for the external area were taken from literature (Bierkens et al., 2010; Cornelis et al., 2013). The average concentrations in soil, dust, indoor- and outdoor air together with the PDFs used for the probabilistic calculations, are listed in Table 4 of the Supplementary information to this paper.

Concentrations in locally produced vegetables were predicted by MERLIN-Expo using soil-plant specific bioconcentration factors. For the prediction of contaminant concentrations in this type of food products, MERLIN-Expo makes a distinction between root crops, leafy vegetables and potatoes (Ciffroy et al., 2016a–in this issue). Besides, Pb exposure via the consumption of 38 purchased food products was also considered in this study (EFSA, 2012; FAVV, 2009; Leblanc et al., 2005; Bierkens et al., 2010; see also Section 2.4.2). Concentrations of Pb in these food items as well as all the area, plant and/or chemical specific parameters required by the plant modules to calculate Pb concentrations in locally produced vegetables (e.g., air temperature, relative humidity, actual evapo-transpiration and transfer factors from soil to leaf, potato, and root) were taken from previous surveys or literature (Allen et al., 1998; ClimaTemps, 2015; Cornelis et al., 2013; Fierens et al., 2014; WeatherOnline Ltd, 2015). All these values are also included in the Supplementary information.

2.4.2. Human related data sets

All participants from the monitoring campaign, i.e., 334 pre-school children between 2 and 6 years old, were asked to fill out a questionnaire inquiring about current and past home locations, food consumption patterns, time activity, birth date, and so on (Van Holderbeke et al., 2008a and confidential, unpublished results). With respect to the food consumption survey, information was available on the number of glasses, table spoons, slices, etc. of 38 food products the participants consume during an average week. In order to be able to calculate oral exposure from these values, the reported cooking units were converted to kilograms or litres per day by using the report of the Belgian Superior Health Council (2005). Since the participants had also reported whether the vegetables they consumed were purchased, locally produced or both (if so, the relative contribution of each was registered), it was possible to make a distinction between exposure via locally produced and external/purchased vegetable consumption in the scenario investigated in this study. To do this, the ingestion rates of the consumed “local” vegetables were summed as they had to be distributed among the three plant types considered by MERLIN-Expo. The time activity data from the questionnaires were used to assign time fractions spent yearly in- and outdoors and the time spent in- and outside the different study areas (e.g., children living in the reference area attending school in the industrial area). Age dependent dust and soil ingestion figures were determined for every participant as previously described (Bierkens et al., 2011b; Van Holderbeke et al., 2008b). Just as for the environmental data described in Section 2.4.1, descriptive statistics (including PDFs for some parameters) on the human related data were calculated for the different case study areas. Lastly, the Pb concentrations determined in the blood of the 334 pre-school children from the monitoring campaign were used to verify the Pb levels in blood as predicted by MERLIN-Expo (Van Holderbeke et al., 2008a and confidential, unpublished results).

3. Results and discussion

We mainly describe and discuss the modelling results of the two simulations performed with MERLIN-Expo as mentioned in Section 2.3 of this paper (i.e., one at population and one at individual level). Where appropriate, results and conclusions of the other simulations performed at population level within the project are included as well. A full report of the all results obtained is available at the 4FUN webpage (http://4funproject.eu/en/home/).

3.1. Simulation based on average population exposure levels

In a first approach, Pb exposure of pre-school children was studied at the population level, i.e., simulation results were compared to measured average blood Pb concentrations in children living in the three different areas (industrial, surrounding and reference area) and their corresponding data in environmental matrices. Also, local food consumption (predicted by using site-specific parameter values for the plant models) as well as complex time-activity patterns obtained from questionnaires were considered in this scenario.

The predicted concentrations of Pb in blood are contrasted with the measured values from the monitoring campaign in Fig. 3. Average predicted blood Pb concentrations range from (4.55 ± 2.67) μg/dL (average ± standard deviation) for children living in the industrial area, over (3.68 ± 1.80) μg/dL in the surrounding area to (2.93 ± 1.02) μg/dL in the reference area. When compared to the actual measurement data, the predicted average concentrations are about 1.5 times higher than the corresponding monitoring data. For the industrial area, this factor is 1.8. Minimum predicted values are nearly identical to the measurement data and the maxima overpredict measurement data with a factor 2.4 (data not shown).

The contribution of the different pathways to the overall internal exposure of pre-school children living in the three considered areas is shown in Fig. 4. Depicted are the relative average, minimum, median and maximum predicted contributions of the different exposure pathways to the internal Pb exposure in children. Dust ingestion and the consumption of external/purchased food products are the two main exposure routes in all areas. Depending on the area (and as a result, on the level of environmental Pb contamination) and on the statistic considered (average, minimum, median or maximum), the contribution of dust ingestion to the total exposure varies between 24% in the reference and 72% in the industrial area, whereas the contribution for external food consumption ranges between 12% in the industrial and 73% in the reference area. Also, the contribution of local food consumption to the overall exposure of Pb in children seems to be area dependent: the maximum relative contribution of local food consumption to internal Pb exposure amounts to 30% in the reference area, 15% in the surrounding area and 7.9% in the industrial area. This is in accordance with the local food consumption values reported by the participants from the monitoring campaign (Bruckers, 2008). In absolute terms (mg/d) however, there is no difference between the exposure rates of locally consumed produce in the three considered areas, i.e., maxima of 1.19×10^{-3}, 2.01×10^{-3} and 1.9×10^{-3} mg/d were predicted for children living in the industrial, surrounding and reference area, respectively.

In this simulation, the contribution of local food to the overall Pb exposure was calculated using site-specific instead of default plant uptake parameters (Cornelis et al., 2013; Fierens et al., 2014; Meneses et al., 2002; WeatherOnline Ltd, 2015). The concentrations of Pb in leafy vegetables, potatoes and root crops predicted by MERLIN-Expo were significantly lower when site-specific instead of default parameter values were applied in the calculations (data not shown). Unfortunately, insufficient actual monitoring data on Pb levels in cultivated vegetables are available to accurately validate the Pb levels predicted in these crops. Still, the ability to run simulations using site-specific parameters is an important feature of MERLIN-Expo, as was also illustrated when customised time-activity patterns obtained from questionnaires were used for the simulations. For instance, when two scenarios were compared, with the first scenario assuming the time spent in- and outdoors only to be in the living area and to be equal (i.e., 50% each) and the second one considering the actual reported times spent in- and outdoors in all the considered areas, the contribution of soil and dust ingestion to the overall exposure shifted from 45% to 59% for dust and from 13% to 4% for soil ingestion as more time is allocated to indoor activities explaining a larger exposure to dust (data not shown).

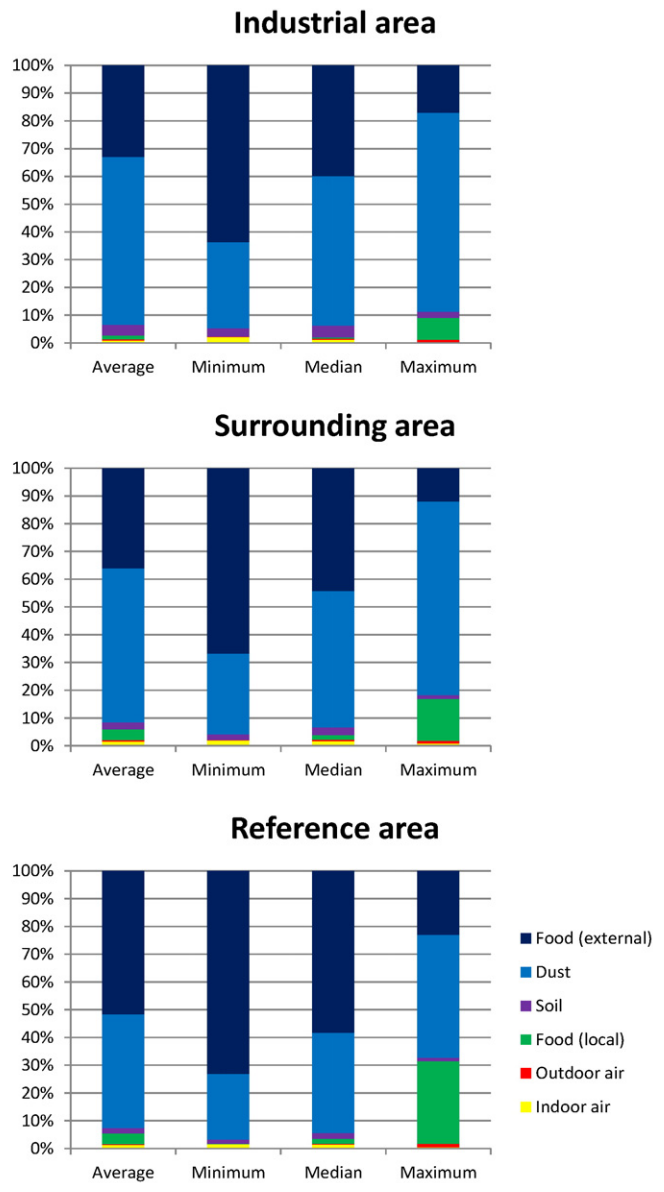

Fig. 4. Average, minimum, median and maximum contribution (in %) of the different exposure pathways to internal Pb exposure in children living in the industrial, surrounding and reference area.

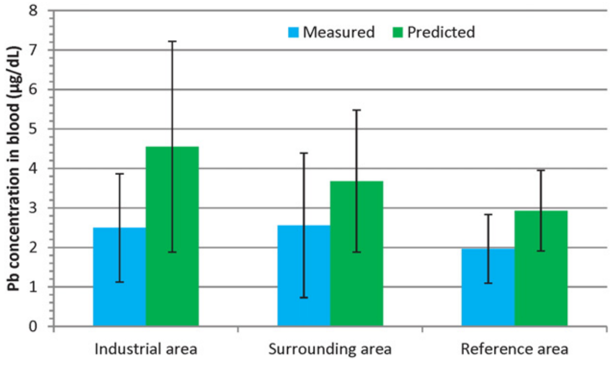

Fig. 3. Measured versus predicted concentrations of Pb in blood (average ± standard deviation; in μg/dL) of children living in the three areas considered.

In general, most of the results of the model simulations at population level reflect the observations made in literature discussing Pb exposure in varying exposure settings. In urban or rural contaminated areas, lead contaminated house dust and soil are often the major sources for blood lead levels in children (Bierkens et al., 2011a; Lanphear et al., 2002; Van den Hazel and Zuurbier, 2005). Lead levels in dust depend on factors such as the age and condition of the housing, the use of lead-based paints or plumbing, lead in petrol and urban density and the (historical) presence of lead-emitting industry (Nielsen et al., 2001). For non-contaminated areas, these figures may differ entirely because of, e.g., another activity pattern of the residents (the time spent on gardening may be larger in non-contaminated areas as compared to contaminated areas). Consequently, other primary exposure sources are of relevance here, such as the consumption of tap water and food products contaminated with lead (Van den Hazel and Zuurbier, 2005). The occurrence of lead in tap water largely derives from household plumbing systems. Non-compliance of lead levels in drinking water with drinking water limits still occurs in EU countries with intake through drinking water being a significant exposure source as a consequence. Food consumption is especially a dominant route of exposure for adults, although it can be significant for children as well. At a local scale, deposition of atmospheric lead in particular and to a lesser extent also root uptake from soil, may contribute to the enhanced lead levels in locally produced food products (Van den Hazel and Zuurbier, 2005).

3.2. Simulation based on individual exposure levels

Next to the simulation based on population averages, model verifications were also performed using individual exposure data, i.e., individually predicted blood Pb levels matched to the corresponding age-related physiological and ingestion parameters as well as the corresponding time-activity and consumption patterns derived from the questionnaires of the participants. To do this, a data subset of ten randomly selected children in each of the areas was used for the simulation. The results of the verification are shown in Fig. 5. Although the simulated values still overpredict the measurement data of the subset, the average overprediction factor for all individuals is slightly reduced to 1.3. More importantly, they do not differ from the model predictions based on average population data for the respective areas discussed in paragraph 3.1 and shown in Fig. 3. So, at least for the current case, similar conclusions as drawn for the predictions based on average population exposure levels can be made. Because individual exposure data are missing very often, this implies that probabilistic simulations using population data may provide sufficiently and reliable prediction margins allowing risk assessors to undertake appropriate actions given the site-specific exposure settings considered.

3.3. Sensitivity analysis

A two step sensitivity analysis was performed on the simulation at population level to evaluate the modelling results in some more detail, i.e., to identify its most influential input parameters which is information that could be used in a further re-design or fine-tuning of the MERLIN-Expo tool.

In first instance, the Morris method was performed on the entire set of input parameters in order to produce a preliminary, qualitative ranking of the influence of the input parameters on the final model outputs, i.e., blood Pb concentrations in pre-school children in each of the considered areas. As an example, the mean of Absolute Elementary Effects for all model parameters determining the blood Pb concentrations in children living in the industrial area as calculated by the Morris method is shown in Fig. 6. In this graph, the non-influential model parameters are characterised by low values for μ^* and σ and are depicted in the central bottom part of the graph. Influential input parameters on the other hand, having linear effects and no interaction (i.e., for which μ^* is high and σ is low) or nonlinear effects and/or interactions (i.e., for which σ is high regardless of the value of μ^*), show up in the upper part and right hand upper corner of the graph. Fig. 6 shows that a body weight related parameter *BDW_variability* is identified as the single most influential parameter, which in itself is positively correlated to the initial age of the children (also characterised by higher σ and μ^* values). Age was previously observed to be of high influence in exposure assessments of children as it determines the motor skill activities, including the hand-mouth behaviour of children and as a result the amount of soil or dust ingested (Bierkens et al., 2011b). Besides, the time fractions spent outdoors (i.e., the various *intake_xx_outdoor_constant* values in the graph, with "xx" denoting the area considered) show up as influential factors as well.

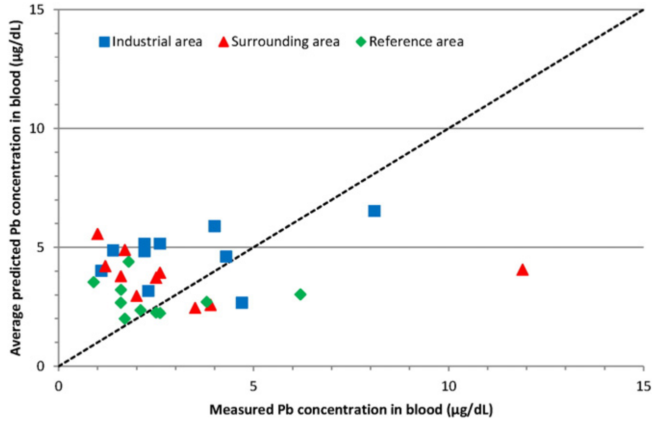

Fig. 5. Comparison of predicted and measured Pb exposure in pre-school children living in the three different areas based on a subset of biomonitoring data.

The results from the Morris methods were further used to reduce the dimensionality of the exposure model. This means that the initial number of input parameters was reduced to only those parameters having a significant impact on the model outcome. This reduced set of input parameters – comprising only Pb concentrations in environmental matrices, ingestion rates constants for soil/dust and food, the variability in BDW and other age related factors – was further analysed with the EFAST method. The results from this analysis are shown in Fig. 7. Three of the influential parameters identified by the Morris method also seem to show up in the EFAST results, i.e., BDW variability, population initial age and time spent outdoors. The concentration in dust in one of the areas and several ingestion rates for food products are identified as additional sensitive factors. Whereas BDW and initial age clearly relate to the natural variability of the data set, other influential factors such as ingestion rates of dust and food products probably relate both to natural variability and lack of knowledge on the input data (results from questionnaires only approximate reality).

The results from the Morris and EFAST methods should not necessarily be identical, because - although both methods rank the model parameters according to their influence on the outputs - in the Morris approach, the factors only vary around their nominal (local) values and one-at-a-time. Therefore, it is a priori more sensitive to sampling design (i.e., the choice of sampling number and level) and the time point of evaluation (Ciric et al., 2012). More scrutiny of the results and optimisation of the methods are required to fully benefit from the sensitivity analyses, but is outside the scope of the current paper. Also, the results shown for children living in the industrial area cannot be generalised for all other areas, as children living in these areas are characterised by exposure to different levels of Pb contamination in their environments and display different time-activity and consumption patterns as extracted from the individual questionnaires.

4. Conclusions

In this study, exposure of Belgian pre-school children to lead has been studied in a site-specific residential setting and related to the levels of Pb in the environment. Both direct exposure through ingestion and/or inhalation of soil, dust, and air particulate matter and indirect exposure via consumption of locally produced vegetables as well as purchased foodstuffs, were included in the scenario and the associated conceptual exposure model. Simulations were performed with MERLIN-Expo at both population and individual level. An important conclusion was that the predicted Pb levels in blood in Belgian pre-school children deviated from related biomonitoring data by an order of 2, on average. Such an agreement between predictions and measurements is generally judged as acceptable in a purely predictive framework, i.e., the MERLIN-

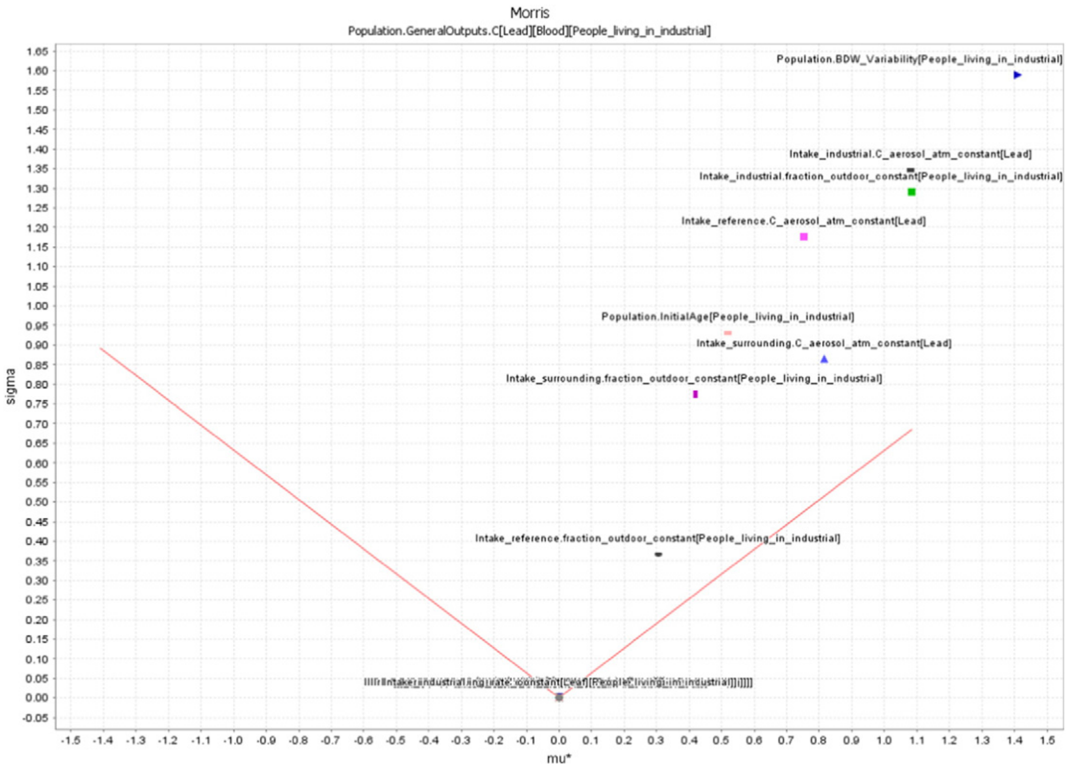

Fig. 6. Mean of Absolute Elementary Effects for all model parameters in the exposure model determining the blood Pb levels in children living in the industrial area, as calculated by the Morris method.

Expo tool seems sufficiently generic to be applied for lead contamination under specified exposure conditions, even when the measurement data were not used to calibrate the models beforehand.

The current case study offered the opportunity to explore the applicability of the MERLIN-Expo tool at several levels of complexity, ranging from very simple to rather complex scenarios in a residential setting.

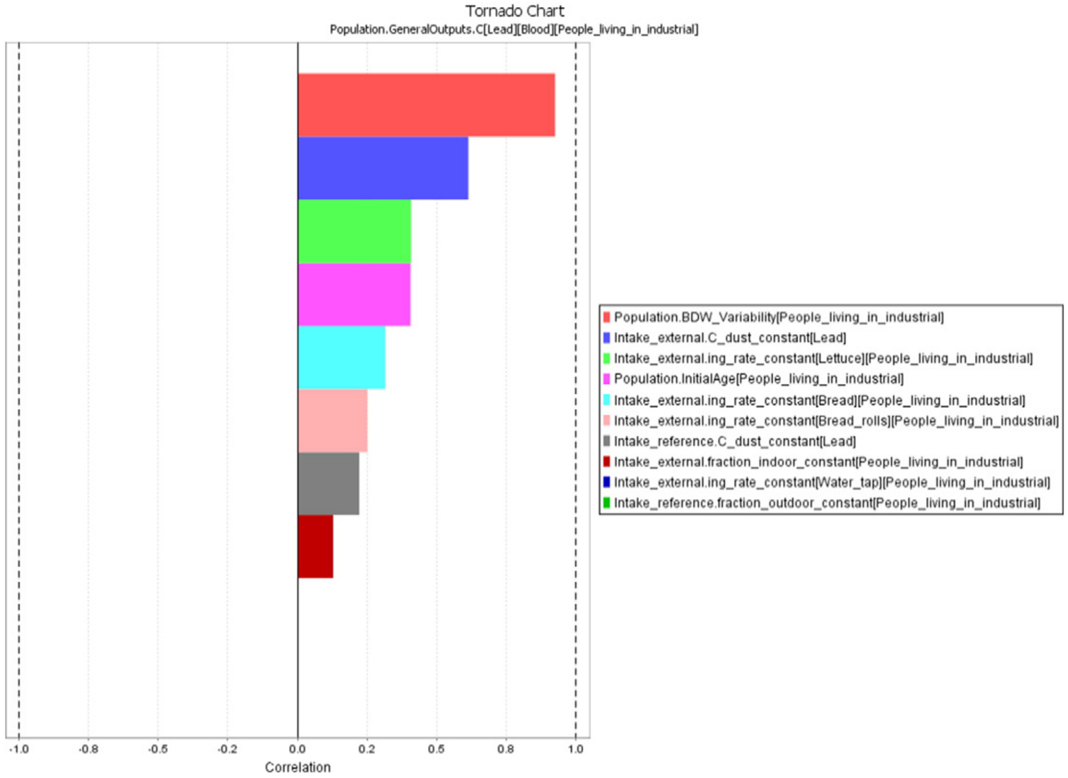

Fig. 7. Tornado chart of total order sensitivity indices for most influential parameters of the Pb exposure model, determining the blood Pb levels in children living in the industrial area as calculated using the EFAST method.

The model complexity was determined by the description of the environment and exposure pathways (number of modules selected and their interconnections, default values or site-specific values for parameterisation), but also on the statistical analyses performed (deterministic or probabilistic). All these different levels of complexity could be efficiently handled with MERLIN-Expo. Sensitivity analyses were run to identify and rank key input parameters of the predicted exposure, i.e., the input parameters related to the body weight and initial age of the children, the time spent outdoors and ingestion rates for soil/dust and some foodstuffs.

While these results constitute a first verification of the model performance of MERLIN-Expo further validation and benchmarking efforts are required for a larger number of inorganic pollutants and different exposure settings (Ciffroy et al., under revision). Specifically in the context of PBPK modelling, as these models involve numerous biological processes, resulting in numerous state variables, that can cover a wide range of chemical doses (low–high dose) or exposure scenarios (short or long term exposure, continuous vs. discrete exposure) it is almost impossible to have all the experimental data needed to validate each model prediction. Still, the PBPK model implemented in MERLIN-Expo was evaluated using independent datasets for different compounds (lead, perfluorinated compounds, dioxins…) and for different populations (adults, children) by comparing the model predictions to experimental data (Quindroit and Brochot, MERLIN-Expo book, In press). For each evaluation, the parameterization of the model was either done by collecting data on the toxicokinetic processes from the literature or by adapting our model to models already published and evaluated independently. For lead, we compared our predictions to the ones obtained by the IEUBK model specific to children (data not shown).

Next to aspects of variability addressed in this paper also the uncertainty attached to each of the modelling parameters need further attention. In the current paper only the effect of variability of the input parameters due to the heterogeneity of target population has been addressed. Without uncertainty, our predictions of the blood lead levels are in reasonable agreement with the measured levels in children (a slight over-estimation is observed), and the predicted variability is similar to the measured variability. It might be expected however that high parametric uncertainty can increase the range of the model outputs and therefore more experimental values (validation data) may fall within the range of the simulation output and inferred as valid. Therefore, further attention should go to the impact of uncertainty attached to the various model parameters on the final modelling results in order to further validate the model.

In summary, in this paper we demonstrate Merlin-Expo's flexible and intuitive ways to build complex scenarios, including both direct and indirect exposure routes for a large number of individuals and demonstrating its capability to reconstruct human biomonitoring data. The current case study can be seen as reference case that provides guidance to future users on how to apply the tool in residential exposure setting related to historical heavy metal contamination and how to interpret the results from the assessments. Although MERLIN-Expo was shown, in this and in the other case studies presented in this issue, able to be used for various exposure scenarios, there is still room for further improvement and/or updating. For instance, new models and/or features could be included that would further facilitate scenario building and/or the interpretation of the results.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.scitotenv.2016.03.194.

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