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Assessing multimedia/multipathway exposures to inorganic arsenic at population and individual level using MERLIN-Expo

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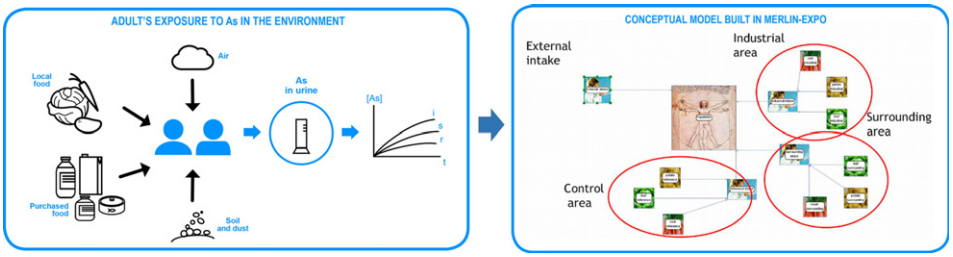
HIGHLIGHTS

- Inorganic arsenic exposure to adults has been simulated using MERLIN-Expo.
- Flexible scenarios were built using sub-models included in the model library.
- Individual time-activity and consumption data were included in the assessment.
- Simulated urine As levels in subjects under-predict biomonitoring data (up to 40%).
- Exposure estimates at individual and population level overlap.

GRAPHICAL ABSTRACT



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ABSTRACT

In this study, we report on model simulations performed using the newly developed exposure tool, MERLIN-Expo, in order to assess inorganic arsenic (iAs) exposure to adults resulting from past emissions by non-ferrous smelters in Belgium (Northern Campine area). Exposure scenarios were constructed to estimate external iAs exposure as well as the toxicologically relevant As (tAs, i.e., iAs, MMA and DMA) body burden in adults living in the vicinity of the former industrial sites as compared to adults living in adjacent areas and a reference area. Two scenarios are discussed: a first scenario studying exposure to iAs at the aggregated population level and a second scenario studying exposure at the individual level for a random sub-sample of subjects in each of the three different study areas. These two scenarios only differ in the type of human related input data (i.e., time-activity data, ingestion rates and consumption patterns) that were used, namely averages (incl. probability density functions, PDFs) in the simulation at population level and subject-specific values in the simulation at individual level.
The model predictions are shown to be lower than the corresponding biomonitoring data from the monitoring campaign. Urinary tAs levels in adults, irrespective of the area they lived in, were under-predicted by MERLIN-Expo by 40% on average. The model predictions for individual adults, by contrast, under-predict the

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); BCF, bioconcentration factor; BDW, body weight; DMA, dimethylarsinic acid; MMA, monomethylarsinic acid; PDF, probability density function; iAs, inorganic arsenic; tAs, toxicologically relevant arsenic; PBPK model, physiologically based pharmaco-kinetic model.

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biomonitoring data by 7% on average, but with more important under-predictions for subjects at the upper end of exposure. Still, average predicted urinary tAs levels from the simulations at population level and at individual level overlap, and, at least for the current case, lead to similar conclusions. These results constitute a first and partial verification of the model performance of MERLIN-Expo when dealing with iAs in a complex site-specific exposure scenario, and demonstrate the robustness of the modelling tool for these situations.

1. Introduction

The Merlin-Expo tool (Ciffroy et al., 2016–in this issue) was used to simulate a previously conducted exposure assessment on historical inorganic As (iAs) exposure to adults living in the vicinity of a former industrial site with zinc smelting activities in the North-Eastern part of Belgium, in order to verify the model with respect to real world biomonitoring data. The Merlin-Expo tool is an exposure assessment software tool that has been developed over the course of two successive EU funded projects, 2FUN (FP6) and 4FUN (FP7). The software tool allows carrying out lifetime exposure assessments at the individual or population level, integrating exposure through multiple pathways.

Even though most of the smelters that were responsible for the historical iAs contamination had already closed down and the few remaining factories had modernised their production, the original biomonitoring campaign was primarily set up because exposure of the inhabitants of the surrounding areas still continues up to date, since the soil and dust are still contaminated with iAs. Moreover, the residues (ashes, slags and muffles) from the smelting operations were used in the hardening of roads and industrial terrains, and the discharge of waste water into the surface water has led to the contamination of groundwater (Van Holderbeke et al., 2009). Next to data in environmental matrices (soil, dust, air, etc.) and home-grown and purchased food products, data on individual food consumption, time-activity patterns for subjects living in different sub-zones of the study area are also available in order to reconstruct individual exposure.

Exposure to As is a global public health concern because iAs is widely distributed and associated with numerous adverse health effects. The International Agency for Research on Cancer (IARC) classified arsenic and iAs compounds as 'carcinogenic to humans' (Group 1) based on sufficient evidence of carcinogenicity in humans (IARC, 1973, 1980, 1987). Apart from it being a well-established cause of skin, lung and bladder cancers in humans, it is also associated with skin lesions, diabetes, cardiovascular disease and other disorders (Dangleben et al., 2013).

The biological availability, physiology and toxicological effects of arsenic depend on its chemical form. Inorganic As exists in the environment as arsenite As(III) or arsenate As(V), but As(III) is much more toxic, more soluble and more mobile than As(V) (Mandal and Suzuki, 2002). Arsenate is the predominant compound; arsenite is mainly found under anaerobic conditions (Chu, 2006). Inorganic As is metabolized in humans via conversion of As(V) to As(III) with subsequent methylation to mono- and di-methylated arsenicals (MMA and DMA, respectively) (Dangleben et al., 2013). Toxicity is thus complex and multi-faceted and is still not yet fully understood.

Although As is ubiquitous in the environment, diet is the largest source of both inorganic and organic arsenic for typical individuals (Hughes et al., 2007). Whereas in many foods (i.e. milk and dairy products, beef and pork, poultry, and cereals) iAs are the main chemical species (typically 65–75%), in fish, fruits and vegetables organic As species predominate (often more than 90%) (Mandal and Suzuki, 2002). Arsenobetaine is the major form of As in fish and seafruit, a compound that contributes very little to toxic effects of As after consumption (Hughes et al., 2007).

In the current paper we report on the results of MERLIN-Expo model simulations on two distinct exposure scenarios estimating both external exposure to iAs and the body burden of toxicologically relevant As (i.e., iAs, MMA and DMA, referred to as tAs) in adults living in the vicinity of the former industrial sites at population and individual level, respectively, and compare these with the biomonitoring data from Belgian monitoring campaign (Flemish Government (2008); Van Holderbeke et al., 2008) in order to verify the model performance of MERLIN-Expo when simulating complex scenarios that account for subject mobility, i.e., length of stay at different locations with varying exposure levels in the vicinity of the hot spots, and individual food consumption patterns. Adopting an assessment approach at individual-level improves on more commonly performed generic exposure assessments at population level, by including intake of iAs from local and purchased food products, and taking into account the mobility of participants, mobility between areas, which results in a more comprehensive assessment of individual recent intake of inorganic arsenic.

2. Materials and methods

2.1. Case study area

The area considered in 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 As. Based on the distance and wind direction from the former locations of the zinc smelters, the investigated region was divided into the three following areas: industrial, surrounding and reference area (for details see Van Holderbeke et al., 2008). 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

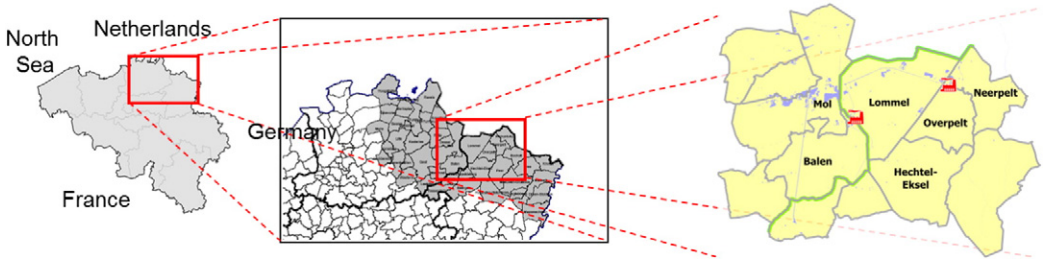

Fig. 1. The Northern Campine region in Belgium and the municipalities included in this case study and the large-scale monitoring campaign of 2006–2008.

smelters and includes districts of the municipalities of Hechtel and Eksel (Fig. 1).

2.2. Exposure modelling and conceptual model

2.2.1. Exposure modelling

MERLIN-Expo contains a library of environmental multimedia and human exposure models and input data for a large set of inorganic and organic substances (Ciffroy et al., 2016–in this issue). Its modular design allows conducting exposure assessments of complex dynamic systems evolving over time (Avila et al., 2003). The tool integrates multimedia models (atmosphere, water, soil), bioaccumulation models for a variety of biota (e.g., vascular plants, fish, cow), and human PBPK models in the same platform, 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.

Human external exposure in MERLIN-Expo can be modelled either at population or at individual level using different models in the library. Whereas the "Human Intake" model calculates the external exposure for one person, the "Population intake" model assembles the total external exposure to multiple persons from different sources, respectively. Details on the different multimedia and exposure models included in the MERLIN-Expo model library are provided by Ciffroy et al. 2016 (in this issue) and are also available on the MERLIN-Expo website (http://merlin-expo.eu/).

To accurately predict internal exposure to iAs, a complex physiologically-based pharmacokinetic (PBPK) model is required to estimate the levels of different species of arsenic and its metabolites in human tissues and urine after oral or inhalation exposure. Such a model has to consist of interconnected individual PBPK sub-models for inorganic arsenic (As(V) and As(III)), monomethylarsenic acid (MMA(V)), and, dimethylarsenic acid (DMA(V)) (El-Masri and Kenyon, 2008). As no PBPK model dealing with As speciation is implemented yet in the MERLIN-Expo model library, the external exposure predictions from the human or population intake models in MERLIN-Expo mentioned above, were exported to Microsoft® Excel version 2010 (Microsoft Corporation, Redmond, Washington, United States) in order to calculate the tAs concentration in urine, and the contribution of the different exposure pathways to the internal As exposure levels. The latter was done using an empirical relationship developed by US EPA (Walker and Griffin, 1998) to estimate daily iAs intake from soil, dust, water, food and air. The model does not consider the intake of organic As. The model assumes that 65% of the absorbed dose of iAs is excreted via urine (Buchet et al., 1983). Model equations are shown below (absorption factors are listed in the Supplementary information to this paper; Table 8):

$$DABS_{AIR} = F_{AIR} \times D_{AIR}$$
$$DABS_{FOOD} = F_{FOOD} \times D_{FOOD}$$
$$DABS_{WATER} = F_{WATER} \times D_{WATER}$$
$$DABS_{SOIL/DUST} = F_{SOIL/DUST} \times D_{SOIL/DUST}$$
$$ABS = \sum DABS_i$$
$$As_{tox,urine} = \frac{ABS \times 1000 \times 0.65}{Cr_{ur}}$$

where:

$DABS$	absorbed dose from air, food, water or soil/dust in μg/day
F	absorption factor of air, food, water or soil/dust
D	external exposure dose via air, food, water or soil/dust in μg/day
ABS	total absorbed dose in μg/day
$As_{tox,urine}$	urinary excretion of toxicologically relevant arsenic in μg/g creatinine
Cr_{ur}	creatinine concentration in urine (mg/day)

Measured concentrations of tAs in urine were based on a single voiding rather than on a 24 h urine sample and may therefore be affected by urine concentration or dilution depending on the fluid balance. To compensate for this, the creatinine concentration in the urine samples was measured and tAs concentrations are expressed as a ratio of the creatinine concentration.

The creatinine excretion rate Cr_{ur} (in mg/day) can be calculated as follows (Van Holderbeke et al., 2008):

$$IF\ gender = female\ THEN\ Cr_{ur} = \left(22 - \frac{age}{9}\right) \times BW$$

$$IF\ gender = male\ THEN\ Cr_{ur} = \left(28 - \frac{age}{6}\right) \times BW$$

where:

age	age of the participant in y
BW	body weight of the participant in kg

2.2.2. Conceptual model

One of the challenges at the start of the 4FUN project was to translate the considered complex real-world biomonitoring study into a transparent 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 iAs needed to be considered. The sources of iAs 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). 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/or national food surveys, i.e., i.e., they have similar iAs concentrations for all inhabitants irrespective of where they live within the study area (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, 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 to iAs at the aggregated population level and one studying exposure at the individual level for a random sub-sample of 30 subjects (i.e., 10 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 consumption data) that were used, namely averages (including probability density functions (PDFs) for some parameters) in the simulation at population level and subject-specific values in the simulation at individual level (for more details, see Section 2.4.1 and the Supplementary Information to this paper). Both scenarios mentioned above do not consider fish consumption. Because fish and sea food are major sources of As, be it mainly organic and less toxic As, an additional scenario was run including fish consumption for comparison (see also Section 3.2).

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

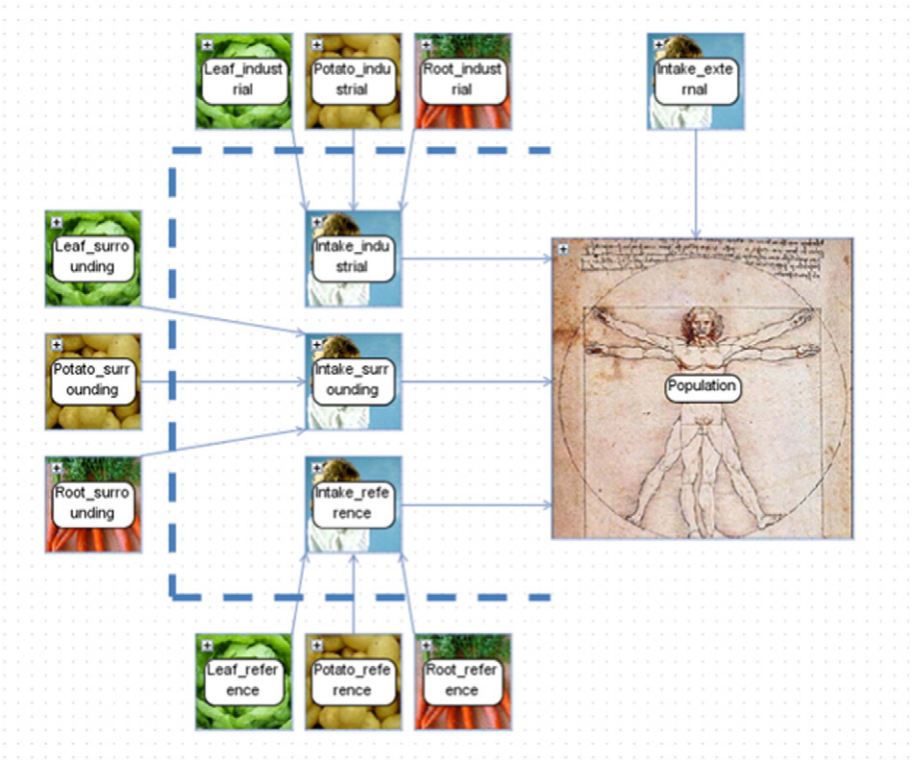

Fig. 2. Conceptual model built in MERLIN-Expo linking of the different fate and exposure modules used to simulate internal As exposure in adults. The human intake and population models calculate external and internal exposure, respectively. For the current simulations the internal exposure is modelled using the empirical model of Walker and Griffin (1998). The leaf, potato and root models are only included when local vegetable consumption is considered (indicated with dotted lines).

this study). Probabilistic simulations were performed on both scenarios by running Monte Carlo simulations with 1000 iterations. The simulated time periods amounted to 1 year (i.e., starting from day 0 till day 365). Interaction between soil and dust ingestion was accounted for by applying a correlation coefficient R^2 of 1 (Van Holderbeke et al., 2008).

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, have been derived from a large-scale environmental and biomonitoring campaign (hereafter referred to as "monitoring campaign") that was conducted previously in the considered case study area (Van Deun et al., 2008a,b; Van Holderbeke et al. 2008). The remaining data, mainly on concentrations in external food stuff, were found elsewhere (EFSA - European Food and Safety Agency, 2014; Leblanc et al., 2005).

2.4.1. Environmental data sets

During the monitoring campaign, measurements of iAs 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 areas (Van Deun et al., 2008a,b). 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). The average concentrations together with the PDFs used for the probabilistic calculations, are listed in Table 1. Measurement data for iAs in soil and air particles for the external area were taken from literature (Cornelis et al., 2013).

Concentrations in locally produced vegetables were predicted by MERLIN-Expo using soil-plant specific bioconcentration factors. Here, MERLIN-Expo makes a distinction between root crops, leafy vegetables and potatoes (Ciffroy et al., 2016–in this issue). A limited number of iAs measurements in locally produced vegetables were available from the monitoring campaign (Van Deun et al., 2008a,b) for comparison. Additionally, iAs exposure via the consumption of 38 purchased food products was also considered in this study (EFSA - European Food and Safety Agency, 2014; Leblanc et al., 2005; see also Section 2.4.2). The iAs concentrations in external/purchased food products in μg/kg fw ranged from 0.044–0.5 in meat products, 12.4 to 11.7 in bread and cereals, over 15.87 in rice to 3.31–26.79 in vegetables. The concentration in tap water was 2.56 μg/l. Details on separate food items are listed in Table 3 of the SI.

Area, plant and/or chemical specific parameters required by the plant modules to calculate iAs concentrations in locally produced vegetables (e.g., air temperature, relative humidity, actual evapotranspiration and transfer factors from soil to leaf, potato, and root) were taken from previous surveys or literature (Allen et al., 1998; ClimaTemps Brussels climate and temperature, 2015; Cornelis et al., 2013; Fierens et al., 2014; WeatherOnline Ltd, 2015). All these values can be found in the Supplementary Information (Tables 4 and 5).

2.4.2. Human related data sets

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. All participants from the monitoring campaign were asked to fill out a questionnaire inquiring about current and past home locations, food consumption patterns, time-activity patterns, birth date, and so on (Van Holderbeke et al., 2008 and confidential, unpublished results). The actual average time fractions spend by subjects in- and outdoors used for the model simulations as reported by adults at aggregated population level and at individual level as reported in the questionnaires are shown in Table 1 and Table 2 of the SI to this paper. 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., adults living in the reference area spending working hours in the industrial area).

Table 1
Concentrations of iAs in soil, dust, indoor and outdoor air particles (average and PDF).

Medium	Unit	Average As conc.	PDF
Industrial area			
Soil[a]	mg/kg dw	7.3	logn(mean = 7.3, sd = 3.6, trmin = 2.0, trmax = 16.0)
Dust[a]	mg/g	0.0109	logn(mean = 0.0109, sd = 0.0065, trmin = 0.0023, trmax = 0.0263)
Indoor air particles[a]	mg/m^3	1.90E-06	logn(mean = 1.90E-06, sd = 1.70E-07, trmin = 1.70E-06, trmax = 2.40E-06)
Outdoor air particles[a]	mg/m^3	4.00E-07	logn(p1 = 5.0, x1 = 2.00E-07, p2 = 95.0, x2 = 1.40E-06)
Surrounding area			
Soil[a]	mg/kg dw	5.9	logn(mean = 5.9, sd = 2.0, trmin = 2.4, trmax = 12.0)
Dust[a]	mg/g	0.0075	logn(mean = 0.0075, sd = 0.0038, trmin = 0.0026, trmax = 0.0206)
Indoor air particles[a]	mg/m^3	2.20E-06	logn(mean = 2.20E-06, sd = 7E-07, trmin = 1.70E-06, trmax = 4E-06)
Outdoor air particles[a]	mg/m^3	7.00E-07	logn(p1 = 5.0, x1 = 2.00E-07, p2 = 95.0, x2 = 2.80E-06)
Reference area			
Soil[a]	mg/kg dw	4.4	logn(mean = 4.4, sd = 0.7, trmin = 3.1, trmax = 5.3)
Dust[a]	mg/g	0.0058	logn(mean = 0.0058, sd = 0.0028, trmin = 0.0028, trmax = 0.0124)
Indoor air particles[a]	mg/m^3	1.90E-06	logn(mean = 1.90E-06, sd = 5.70E-08, trmin = 1.80E-06, trmax = 2.00E-06)
Outdoor air particles[a]	mg/m^3	4.0E-07	logn(p1 = 5.0, x1 = 2.00E-07, p2 = 95.0, x2 = 1.2E-06)
External area			
Soil[b]	mg/kg dw	4.2	logn(mean = 4.2, sd = 1.5, trmin = 1.8, trmax = 7)
Dust[a]	mg/g	0.0058	logn(mean = 0.0058, sd = 0.0028, trmin = 0.0028, trmax = 0.0124)
Indoor air particles[c]	mg/m^3	4.8E-06	–
Outdoor air particles[c]	mg/m^3	4.8E-06	–

[a] Van Deun et al. (2008a,b).
[b] Bierkens et al. (2006).
[c] Cornelis et al. (2013).

With respect to the food consumption survey, information was available on intake rates (e.g., the number of glasses, table spoons, slices, and so) on 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) (Tables 6 and 7 of SI to this paper). Because fish consumption was not surveyed in the biomonitoring campaign, an average consumption for men and women of 25.9 and 22.6 g/day respectively (BVCP, 2004), is taken into account in some of the simulations (Van Holderbeke et al., 2008). 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.

Next to data used as input to MERLIN-Expo (e.g., concentration in soil, external food, …) other data were used for verifying the performance of the proposed modelling approach, i.e. iAs concentrations in locally grown vegetables and tAs concentrations determined in the urine of the 1220 adults consisting of an equal amount of men and women (19–79 years old) from the monitoring campaign (Van Holderbeke et al., 2008 and confidential, unpublished results). As levels in urine are considered to reflect recent exposure over the last period of 10 to 40 days. Urinary As levels are expressed as a ratio of the creatinine concentration to compensate for difference in the fluid balance of the urine samples.

3. Results and discussion

Our focus is on describing and discussing the modelling results of the two simulations performed with MERLIN-Expo as described 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 all project 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, iAs exposure of adults was studied at the population level, i.e., simulations were compared to average urinary tAs concentrations in adults living in the different areas. Also, local food consumption (predicted by using site-specific parameter values for the plant models) as well as purchased food consumption and complex time-activity patterns obtained from questionnaires were considered in this scenario.

The average predicted levels of tAs in urine for the different areas are compared with the concentrations of tAs biomonitoring data determined during the monitoring campaign (Bruckers, 2008). This comparison is shown in Fig. 3 for women and Fig. 4 for men. No differences in exposures between male and female participants were observed. Also, no correlation between age and exposure was found (data not shown). For all three areas, MERLIN-Expo under-predicts biomonitoring data by 39% (max 43% in reference area) for women and 37% for man (maximum 40% for both the industrial and surrounding areas) on average, but the predictions fall within the range (average ± standard deviation) of the measured tAs urine concentrations from the monitoring campaign.

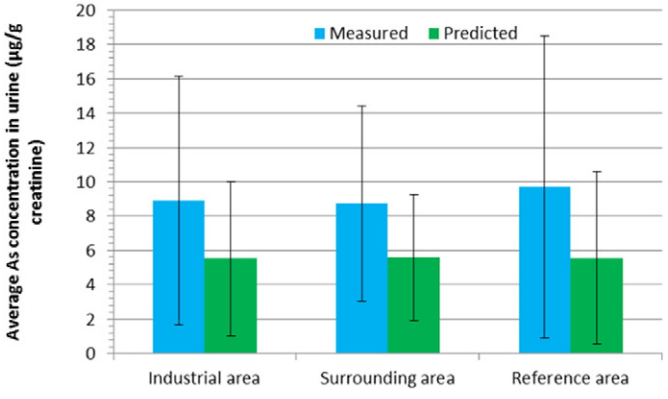

Fig. 3. Measured versus predicted concentrations of tAs in urine (average ± standard deviation; in µg/g creatinine) of female adults living in the three considered areas.

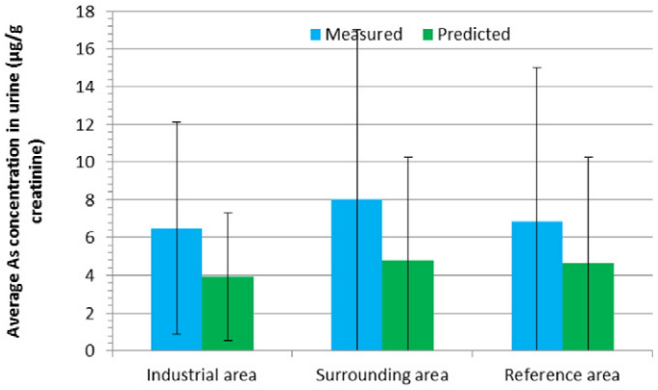

Fig. 4. Measured versus predicted concentrations of tAs in urine (average ± standard deviation; in µg/g creatinine) of male adults living in the three considered areas.

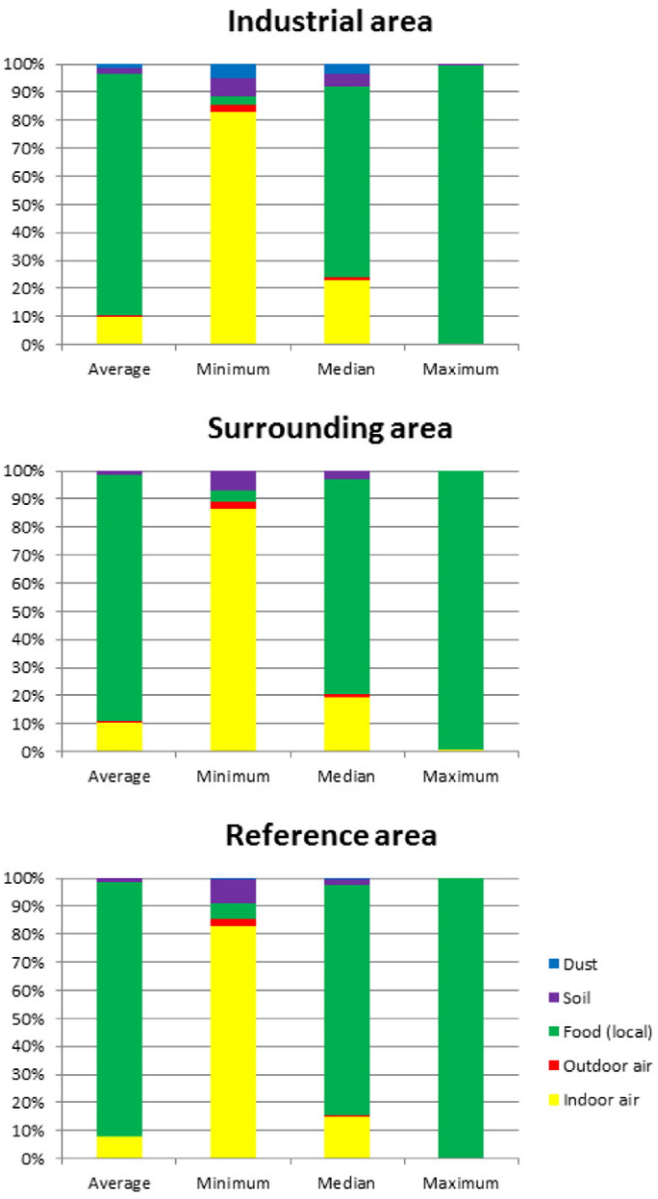

Fig. 5. Relative contribution (average, minimum, median and maximum) of the different site-specific exposure pathways (excluding of exposure via external non-local food) to internal As exposure in adults living in the industrial, surrounding and reference area.

The predicted tAs levels in urine obtained from the model runs are only a partial verification of the MERLIN-Expo model performance because the actual calculations to estimate the internal body burden are performed outside MERLIN-Expo using the empirical US-EPA exposure model from Walker and Griffin (1998) described in Section 2.2.1. Still, as the model estimates for external exposure that are generated in MERLIN-Expo are used as an input for converting them to internal levels using the empirical model, and Walker and Griffin (1998) have previously demonstrated that the US-EPA empirical model reasonably predict both central tendency and high-end exposures, our results increase confidence in the model performance of MERLIN-Expo with regard to its ability to integrate and predict external exposure to iAs.

The main exposure pathway, contributing almost 99% to the internal human tAs exposure for all three areas, is ingestion of purchased food (data not shown), followed by inhalation via indoor air (1.1%) and the consumption of locally produced food (0.9%). Soil and dust ingestion contribute for 0.02% each. The relative contribution of these site-specific sources, i.e., excluding purchased food, is shown in Fig. 5. The relative contribution of the local exposure routes differs according to the statistic considered, i.e., average, minimum, maximum or median exposure values. It is observed that whereas the relative contributions of inhalation of indoor air and ingestion of soil and dust are of fair importance for the lower end of exposure, the relative contribution of locally consumed foodstuffs is dominant when the upper end of the internal tAs exposure is considered. Of the purchased/non-local food products, bottled water, bread, coffee, soup and tap water are the top 5 food items contributing to exposure in all areas (data not shown). Between areas, no differences exist as these foodstuffs are purchased from (non-local) distribution networks. Comparing the two individual exposure scenarios with and without fish consumption, shows that the contribution of fish consumption to the internal tAs exposure is negligible (data not shown). These results on the relative contribution of different foodstuffs are in agreement with results from the biomonitoring campaign (Van Holderbeke et al., 2008), i.e. the same top 5 food items and their relative share to the overall exposure are similar when measurement data and MERLIN-Expo predictions are compared. Moreover, the current results are grosso modo in correspondence with the conclusions from a survey on dietary exposure to iAs in the European populations conducted by EFSA - European Food and Safety Agency (2014), i.e., that for adults the main contributor to dietary exposure to iAs was the food group 'Grain-based processed products', in particular, wheat bread and rolls. Other food groups that were important contributors to iAs exposure were rice, milk and dairy products (main contributor in infants and toddlers), and drinking water.

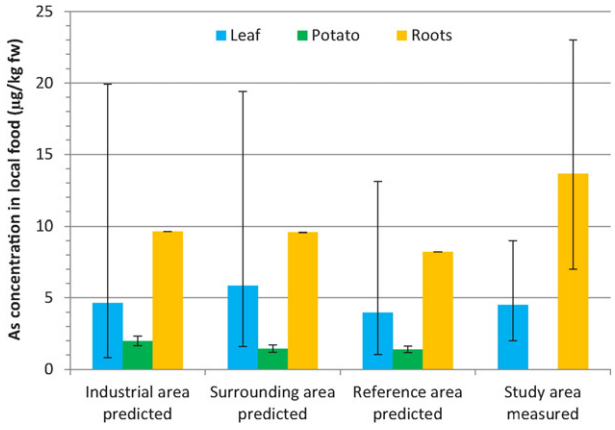

Fig. 6. Modelled (industrial, surrounding and reference area) and measured (study area) median As concentrations in locally produced leafy vegetables, potatoes and root crops. The measured concentrations in lettuce and carrots are shown in this graph as "beaf" and "root" because uptake in lettuce and carrots In MERLIN-Expo is simulated using the BCF-uptake model for leafy and root vegetable, respectively.

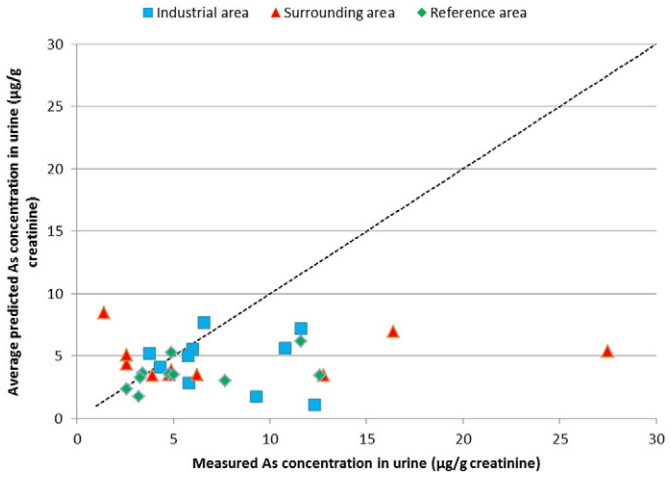

Fig. 7. Measured vs. predicted (average) concentrations of As in urine (in µg/g creatinine) of 30 adults living in the industrial (blue), surrounding (red) or reference (green) area.

During the measurement campaign (Van Deun et al., 2008b), some samples were taken of locally produced lettuce and (peeled) carrots and analysed for iAs levels. As generic BCF models for both leafy and root vegetables are included in MERLIN-Expo, a comparison can be made between the predicted and measured data. Because only limited measurements are available for the industrial and surrounding area separately, measured data are pooled and referred to as "study area" in Fig. 6. The model results show an average under-prediction of 1.5 for the carrots, and a nearly 1:1 prediction for lettuce (Fig. 6).

3.2. Simulation based on individual exposure levels

Next to simulations based on population averages, modelling was also performed using individual exposure data, i.e., individual urinary tAs levels matched to the corresponding age and sex as well as the corresponding time-activity and consumption patterns derived from the questionnaires.

Fig. 7 shows the measured versus the predicted average concentration of tAs in urine of the 30 individual adults living in the three study areas. The results show an average model under-prediction of about 7%. However, tAs over- or under-predictions are much larger for individuals at the upper end of exposure, mainly for subjects living in the surrounding area. tAs predictions in urine for adults living in this area range from an under-prediction with a factor 5 for 1 individual to an over–prediction with a factor 6 for another individual. When these 2 outliers are left out, the tAs levels for individuals in this area are slightly under-predicted by 9%. Why these outliers occur mainly in the surrounding area is not yet clear. Potential sources of uncertainty are, among others, the lack of knowledge on detailed gradients of iAs in environmental matrices, exact food consumption and time-activity patterns (results of questionnaires are only an approximation) and

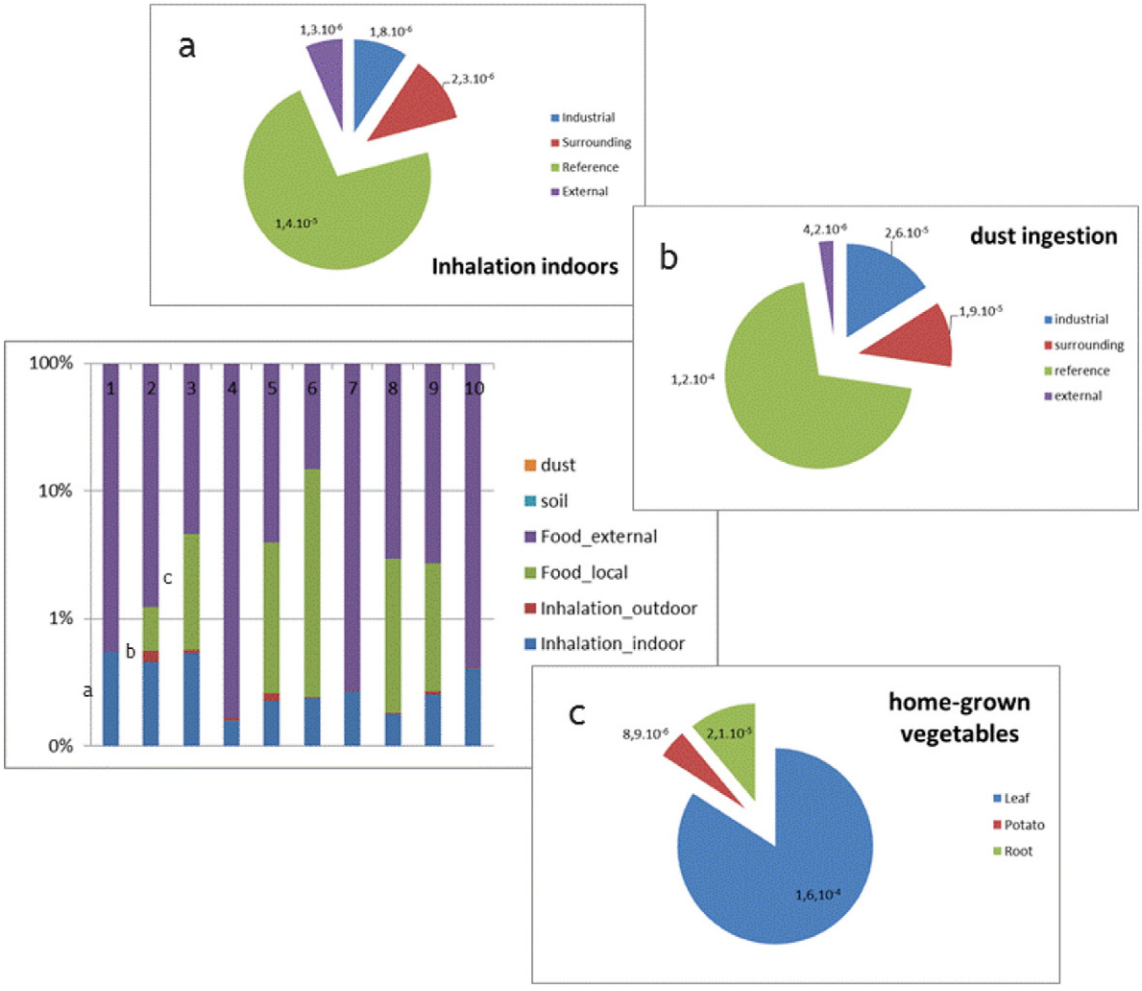

Fig. 8. Contribution of different exposure pathways (%) to the exposure to 10 subjects living in the reference area (bar chart) and details on the contribution on separate exposure routes (mg/d) (pie charts) for single participants for indoor inhalation (subject #a), ingestion of dust indoors (subject #b) and ingestion of home grown vegetables (subject #c).

analytical difficulties with analysing iAs in biological matrices (locally produced vegetables).

In this scenario, no fish consumption was considered. Therefore, an additional scenario considering fish consumption was included. The results showed that, although fish can be an important source of arsenic in the human diet, it is mainly of organic origin, and as such inclusion of fish consumption does not alter the model predictions significantly (data not shown).

When compared to the model simulations at population level, which showed an average under-prediction of about 40% of the concentrations of tAs in urine as compared to the measured average levels of the biomonitoring data, the individual exposure predictions only slightly under-predicted tAs urinary concentrations with on average 7%, but with more significant under-predictions for subjects at the upper end of exposure. Still, urinary tAs levels from the simulations at population level and at individual level overlap, and, at least for the current case, lead to similar conclusions. Because very often individual exposure data are missing, this implies that probabilistic simulations using population data do provide sufficiently reliable safety margins to allow risk assessors to undertake appropriate actions given the site-specific exposure settings considered.

Because we have details on time-activity and food consumption for each subject individually, the contribution of different exposure pathways to each of them can be further dissected. This is illustrated in Fig. 8 for subjects living in the reference area, but could equally well be shown for all other areas. Subjects from the reference area are chosen because they showed (in our random sample) on average a higher mobility and their exposure was less dominated by one or a few exposure routes, as opposed to individuals living in, e.g., the industrial area. Fig. 8 shows the relative contribution of the different exposure routes (%) for each of the 10 subjects in the reference area (bar chart). Additionally, for three of the subjects in the bar graph (subjects #a, #b and #c), the linked pie charts show the relative contribution of (i) the individual dose (mg/d) received via inhalation in- and outdoors, (ii) the ingestion via dust in the different sub-areas, and (iii) the ingestion via consumption of locally produced vegetables and the type of vegetables involved. In this example, the dose received via inhalation for the different participants ranges from 1.8×10^{-5} to 4.0×10^{-5} mg/d indoors and from 7.5×10^{-8} to 9.0×10^{-6} mg/d outdoors. The dose received via diet ranges from 0 to 1.1×10^{-3} mg/d for local food consumption and from 4.5×10^{-3} to 1.3×10^{-2} mg/d for purchased food consumption, respectively. For soil and dust we calculated dose ranges of (2.5×10^{-7} to 4.7×10^{-6} mg/d) and (4.0×10^{-5} to 5.4×10^{-5} mg/d), respectively. Detailed knowledge on individual exposure as illustrated above could eventually be used to undertake remedial actions at subject level.

Whereas the variability that is observed between measured and predicted urinary arsenic concentrations for each individual subject may relate to variability in behaviour, in the contaminated media contacted, and in physiological parameters that influence the toxicokinetics of arsenic, plausible explanations for differences between measured and predicted urinary arsenic concentrations for an individual include uncertainty on soil/dust and dietary ingestion rates, urinary volumes, arsenic concentration in food, and the soil and dust data collection methods. Moreover, additional sources of arsenic or exposure routes have been ignored, such as passive smoking and dermal exposure. In short, variability comes from differences in outcome due to inter-subject variation in factors contributing to risk; uncertainty comes from lack of knowledge in the underlying science. The methods to perform sensitivity analyses in MERLIN-Expo could be used to elucidate these matters but this is outside the scope of this paper.

4. Conclusions

Human exposure to arsenic has been studied in a site-specific residential setting, based on measured levels of iAs in the surrounding environment. The individual-level assessment approach improves on more commonly performed generic exposure assessments at population level, by including intake of iAs from local and purchased food products, and taking into account the mobility of participants, mobility between areas, resulting in a comprehensive assessment of individual recent intake of inorganic arsenic. No different exposures between male and female participants and no correlation between age and exposure were found. The exposure of the adults living in the case study area to iAs is largely determined by external factors (external or purchased food). Region specific contamination (local food consumption, soil and dust ingestion, and inhalation via indoor and outdoor air) becomes more important at higher levels of exposure.

For simulations addressing average exposure at the population level, an under-prediction of maximum 40% was observed for females when compared to the measurement data from the monitoring campaign. For the individual simulations, the average under-prediction was reduced to 7%. The results of both modelling approaches overlap for each of the areas studied. Such an agreement between model predictions and measurement, as seen both at population and individual level, is generally judged acceptable in a purely predictive framework, i.e., the model seems sufficiently generic to be applied for arsenic contamination under specified exposure conditions, even when the measurement data were not used to calibrate the models beforehand.

In summary, in this paper we demonstrate Merlin-Expo's flexible and intuitive ways to build exposure scenarios, including both direct and indirect exposure routes for a large number of individuals. As a standalone modelling tool, or in conjunction with other models, as demonstrated in these simulations, we have demonstrated MERLIN-Expo's capability to reconstruct human exposure 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 able, in this and in the other case studies presented in this issue, 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.2016.04.038.

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