Combining data from heterogeneous surveys for aggregate exposure: application to children exposure to lead in France

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Abstract

To assess human health risks related to the environment, it is necessary to aggregate exposure from multiple sources. The objective of this paper was to propose a relevant approach to combine data from heterogeneous populations and methodologies. Five different methods based on Monte-Carlo simulations were tested and compared. Differences were: taking into account or not stratification variable, timeline to assign exposure factors and concentration and way to account for concentration correlations. The methods were applied to estimate lead exposure from food, dust, soil, air, and tap water or French children aged between six months and three years old.

Comparing results' uncertainty, it is recommended to 1) select a reference population representative of the target population, 2) select stratification variables to combine surveys, and 3) simulate a new population by randomly sampling individuals in the reference population and simultaneously assigning human exposure factors and environmental concentrations from other surveys in integrating correlations (MC1S). No difference was observed when taking into account correlations using vectors of determinist data from one survey or rank of correlations with the Iman-Conover method. Regardless the methods used to combine data, dust was the main exposure source, followed by soil and in a less extent by food. Exposures from air and tap water were found to be insignificant for most children.

Highlights

- Five calculation processes were tested to combine dietary and environmental surveys
- Resampling individuals and variables decrease the uncertainty
- Use stratification variables to combine surveys limits risk of error
- The tested methods to account for correlations between exposure factors gave similar results
- Dust and soil were main exposure sources of children in France

Keywords

Environmental health; lead; public health; Monte Carlo simulations; risk assessment.

Abbreviations

BDQA: French database for air quality

BEBE-SFAE: French database of children dietary

BW: Body weight

DL: Dust load

MC: Monte Carlo

MC1: Monte Carlo in first step

MC1S: Monte Carlo in first step with the use of stratification variables

MC2: Monte Carlo in second step

MC2S: Monte Carlo in second step with the use of stratification variables

MCIC: Monte Carlo with the method of Iman and Conover

PH: French database for lead concentration in dwellings

UI: Uncertainty intervals

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1 Introduction

Aggregate exposure can be defined as the sum of several sources of exposure (air, dust, food, water, etc.) via different exposure routes (ingestion, inhalation and dermal absorption). To perform human health risk assessments based on total exposure, it is important to consider aggregate exposure. By nature, biomonitoring data considers aggregate exposure, but this data does not enable the contribution of exposure sources to be assessed. In order to determine management options to mitigate exposure and the associated risks, the identification of exposure sources and factors contributing to total exposure is currently essential. However, the modelling of aggregate exposure is complex from several standpoints. Except in specific cases (Cao et al., 2016), complete surveys seldom collect all exposure sources for the same individual. Therefore, performing aggregate exposure assessments often requires considering data from different databases with different populations and methodologies. In addition, exposure can be expressed at the individual level, which is generally the case for food, or at the population level, which is more common for environmental exposure.

Even though the definition of "aggregate exposure" is soon to be standardised, some authors have recently proposed "aggregate exposure" when considering only one source and one route of exposure. This was the case of Cowan-Ellsberry and Robison (2009), Delmaar et al. (2015) and Gosens et al. (2014) who studied dermal exposure to parabens and phthalates from cosmetics. Other authors have tried to be as exhaustive as possible in the calculation of aggregate exposure. For example, Beko et al. (2013) considered two sources of exposure (dust and air) for phthalates and extrapolated dietary exposure from internal measurements. Pelletier et al. (2017) took into account three routes of indoor residential exposure to semi-volatile organic compounds. Furthermore, Glorennec et al. (2016) assessed aggregate exposure to metals and metalloids in children between three and six years of age in France, considering several sources of exposure in a Monte Carlo (MC) simulation via various surveys. However, in these studies, the strategy used to combine data from different surveys with different levels (individual vs population) to assess aggregate exposure was not discussed. Some tools have been developed in the last few years to assess exposure via different routes and sources. The European projects EuroMix, HBM4EU or SOLUTIONS developed methodologies and guidance for assessing risks in mixture from combined exposure to multiple chemicals for different regulatory sectors. In these projects, mixture risk assessment is limited by the difficulties in considering aggregate exposures from different sources with dietary source combined with non-dietary sources (Bopp et al., 2018). Exposure tools addressing multiple exposure routes were embedded in the EuroMix toolbox, Monte Carlo Risk Assessment software (van der Voet et al., 2015) by adding to diet exposure results from MCRA to non-dietary exposure sources from other software as PACEM for personal care products (Karrer et al., Submitted). Kennedy et al. (2012) developed the Bystander and Residential Exposure Assessment Model (BREAM) to evaluate non-dietary exposure. They then proposed options to develop an aggregate exposure model combining BREAM with the MCRA platform (Kennedy et al., 2015a; Kennedy et al., 2015b). However, this work was restricted to pesticide exposure via agricultural activities and thus only involved workers, bystanders and residents living near agricultural areas. Two software applications for Stochastic Human Exposure and Dose Simulation (SHEDS-Multimedia and SHEDS-Residential) developed by the US. EPA only take into account specific scenarios of non-dietary exposure with no link to dietary exposure. A new tool, SHEDS-High-Throughput (SHEDS-HT), based on SHEDS-Multimedia, combines direct dermal exposure, inhalation and accidental ingestion with the ingestion of food and drinking water by MC simulation (Isaacs et al., 2014). However, SHEDS-HT mainly focused on aggregate exposure from diet and consumer product sources, and the scenario of exposure sources by dust and soil is not clearly developed. Moreover, individual intakes are specified for the American population only. Thus, a harmonised consistent approach for aggregate exposure in case of different sources of exposure is still lacking.

The aim of this work was to set out general principles for assessing aggregate exposure of a target population from various sources (diet, dust, air, soil and tap water) when data come from heterogeneous surveys. Five different calculation processes were tested and compared. The different methods were based on the general principle which consists in creating a simulated population from the individuals of the different surveys via MC simulations. MC simulations are often used to combine risk assessment data (Kennedy et al., 2012; Kennedy et al., 2015a; Kennedy et al., 2015b; Paustenbach, 2000; Safford et al., 2015; Zartarian et al., 2017). They make it possible to draw random samples from distributions of datasets in order to reconstruct the sources of exposure for each individual. These methods, which take into account inter-individual variability as well as uncertainty, provide a more realistic estimate of aggregate exposure for individuals across a population (Paustenbach, 2000).

Lead exposure for the target population of French children between the ages of six months and three years was chosen as a case study to test these methods.

2 Materials and Methods

2.1 Exposure factors

2.1.1 Food consumption (Q_{Food}) and quantities of ingested tap water (Q_{Water})

Food consumption (Q_{Food}) and quantities of ingested tap water (Q_{Water}) for children were evaluated in the national cross sectional survey named BEBE-SFAE (Fantino and Gourmet, 2008) which was conducted in France from January to March 2005 in the population of children aged 15 days to three years. Individual consecutive three-day weighed food was recorded in non-breastfed infants. More than 1260 food products specifically made for toddlers and young children were notified in the database with 850 “specific baby foods” (Fantino and Gourmet, 2008). To be representative of the child population, sampling weights were assigned to each infant. A total of 706 children were recorded in BEBE-SFAE using proportionate quota sampling based on the child’s age, the mother’s occupation and the family’s socioeconomic strategy.

2.1.2 Inhalation rates (IRs)

Inhalation rates were evaluated based on the U.S. EPA recommendations in the Exposure Factors Handbook (2011). For each age group (zero- to one-year old, one- to two-years old, two- to three-years old), mean, 95^{th} percentile and maximum inhalation rate values were available. From these statistics, the mean and standard deviation of a normal truncated distribution were adjusted for each age group.

2.1.3 Dust loads (DLs)

Dust loads were estimated from the publication by Giovannangelo et al. (2007) who studied the distribution of dust loads collected from the floor in 46 German homes, 42 Dutch homes and 34 Swedish homes. Since the data from Sweden were only collected from rugs, they were excluded. The parameters of a truncated lognormal distribution were determined from the logarithms of the geometric means and geometric standard deviations calculated from the German and Dutch results weighted by the number of samples per country.

2.1.4 Quantities of ingested soil (Q_{Soil}) and dust (Q_{Dust})

Quantities of ingested soil (Q_{Soil}) and dust (Q_{Dust}) were derived from the Exposure Factors Handbook (U.S. EPA, 2011) for children under the age of one year and between the ages of one and three years. A truncated lognormal distribution of Q_{Soil} and Q_{Dust}, as proposed by Özkaynak et al. (2011), was fitted.

2.2 Lead contamination surveys

Table 1 summarises the available data from the different surveys, the distributions used, and descriptive statistics for lead concentrations for the various investigated exposure sources and factors. A middle-bound scenario that consists in replacing values below the limit of detection (LOD) or the limit of quantification (LOQ) with LOD/2 or LOQ/2 (EFSA, 2012) was used in the case of censored data for concentrations in food, soil, dust and tap water.

Table 1. Summary of input variables used for the calculation of aggregate exposure to lead for children aged six months to three years.

Input variables		Age	References	Distribution	Mean	SD	Median	P95	Min	Max
Concentration in food ($\mu g_{Pb}.kg^{-1}$)	C_{Food}	0 months – 3 years	Guerin et al. (2017)	Empirical*						
Consumption of food ($g.d^{-1}$)	Q_{Food}	6 months – 3 years	Fantino and Gourmet (2008)	Empirical*						
Dietary exposure ($\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$)	$E_{Dietary}$	6 months – 3 years	BEBE-SFAE survey in this study	Empirical**	0.208	0.095	0.194	0.381	0.020	0.632
Body weight (kg)	BW	6 months – 3 years	BEBE-SFAE survey in this study	Empirical	10.4	2.6	10.0	15.0	3.4	20.0
Consumed quantity of tap water ($mL.d^{-1}$)	Q_{Water}	6 months – 3 years	BEBE-SFAE survey in this study	Empirical	65.3	159.8	0	250-	0	47.0
Inhalation rate ($m^3.d^{-1}$)	IR	6 - 12 months	U.S. EPA (2011)	Normal	5.4	1.6	-	8.0	0	26.25
		1 - 2 years		Normal	8.0	2.9	-	12.8	0	24.77
		2 - 3 years		Normal	8.9	2.9	-	13.7	0	28.17
Ingested soil ($mg.d^{-1}$)	Q_{Soil}	6 - 12 months	U.S. EPA (2011)	Lognormal	-	-	30	200	0	1000
		1 - 3 years		Lognormal	-	-	50	200	0	1000
Ingested dust ($mg.d^{-1}$)	Q_{Dust}	6 - 12 months	U.S. EPA (2011)	Lognormal	-	-	30	100	0	1000
		1 - 3 years		Lognormal	-	-	60	100	0	1000
Dust load ($mg.m^{-2}$)	$DL_{Germany}$	-	Giovannangelo et al. (2007)	Lognormal***	194	4.1	-	-	0	2000
	$DL_{Netherlands}$			Lognormal***	151	5.5	-	-	0	2000
Concentration in dust ($\mu g_{Pb}.m^{-2}$)	C_{Dust}	-	PH survey in this study	Empirical	25.4	61.8	9.0	109.6	1.00	694.8
Concentration in tap water ($\mu g_{Pb}.L^{-1}$)	C_{Water}	-	PH survey in this study	Empirical	2.5	5.4	0.826	12.5	0	47.0
Concentration in soil ($\mu g_{Pb}.g^{-1}$)	C_{Soil}	-	PH survey in this study	Empirical	70.7	106.8	34.8	273.4	2.4	830.9
Concentration in air ($\mu g_{Pb}.m^{-3}$)	C_{Air}	-	BDQA survey in this study	Empirical	7.8	5.6	6.6	17.1	1.4	41.4

*Not given since C_{Food} and Q_{Food} mainly depend on the food.

**Individual dietary exposure, $E_{i\ Dietary}$, had previously been estimated in the report by ANSES (2014) and was included in the BEBE-SFAE survey in this study by combining concentration data from the French infant Total Diet Study (Guerin et al., 2017) with the consumed quantities and body weights available in the BEBE-SFAE survey (Fantino and Gourmet, 2008).

***The geometric mean and geometric

2.2.1 Food contamination by lead (C_{Food})

Food contamination by lead (C_{Food}) was recorded in 2011, from the first infant Total Diet Study (iTDS), conducted in non-breastfed children under three years of age (Hulin et al., 2014). In iTDS, more than 500 chemical substances were analysed in foods. These included substances naturally found in the environment and those originating in human activities (e.g. industrial, agricultural, domestic, etc.). Food items were selected using the results of the BEBE-SFAE survey, enabling home cooking practices to be considered. Overall, the iTDS contained more than 5500 items as consumed foods, including foods such as vegetables, fruits and cakes as well as specific children's food products. To limit censored data, a more sensitive inductively coupled plasma mass spectrometry method was developed and validated for lead in 291 samples (Guerin et al., 2017). With this method, the LOQ was 0.6 or 0.9 $\mu g_{Pb}.kg^{-1}$ for solid and liquid samples respectively. Lead was detected in most samples, where the highest concentrations were mainly found in foods containing chocolate, and a maximum value of 16 $\mu g_{Pb}.kg^{-1}$ was observed (Guerin et al., 2017).

2.2.2 Child home and environmental contamination (C_{Dust}, C_{Soil} and C_{Water})

The "Plomb-Habitat" (PH) survey recorded lead concentration data for tap water, soil and dust in 472 homes of children aged from six months to six years in France between October 2008 and August 2009 (Glorennec et al., 2015; Lucas et al., 2012). Population sample weights were available, to be representative of French dwellings. Lead concentrations in tap water (C_{Water}) were measured in kitchens. The LOQ for lead in tap water was 1 $\mu g.L^{-1}$. The average lead load in dust (C_{Dust}) for each dwelling was evaluated in $\mu g.m^{-2}$. The LOQ for lead in dust was 2 $\mu g.m^{-2}$ for total lead. For concentrations in soil (C_{Soil}), in cases of children playing outside on soft ground (for 315 dwellings), samples were collected from the outdoor playground. The LOQ for lead in soil was 1.3 $\mu g.g^{-1}$ for total lead.

2.2.3 Air contamination (C_{Air})

Lead concentrations in outdoor air were collected from the regulatory monitoring network (BDQA, the French database for air quality). Air quality monitoring has been implemented in each France region in more than 650 rural, urban, suburban areas or linked to the traffic road including more than 3 000 instruments. In this study, annual mean concentrations of lead in outdoor air were considered from 2007 to 2011 no representative French survey exists on air concentrations in inside dwellings, outdoor air lead concentration were used to estimate concentrations in indoor air of children's homes (C_{Air}). Data were not included when the measurements were too low to calculate the annual mean, specifically when annual coverage did not exceed 14% or when it exceeded 100%. Thus, a total of 176 measurements were considered in rural, urban and suburban areas.

2.3 Aggregate exposure model

Daily aggregate exposure to lead was calculated for each individual by combining exposure from the various sources (food, water, soil, dust and air) and via the various routes (ingestion and inhalation). Dermal lead exposure was considered as insignificant compared to the two other routes (EFSA, 2010). In the case of censored data, we applied a middle-bound scenario that consisted in replacing all values below the LOD and LOQ with either LOD/2 or LOQ/2.

$$E_{i,Aggregate} = (E_{i,Dietary} + E_{i,Soil} + E_{i,Dust} + E_{i,Water}) \times \tau_{ingestion} + EiAir \times \tau_{inhalation} \quad (1)$$

To aggregate the various sources, absorption factors are commonly used for the two routes of exposure: ingestion ($\tau_{ingestion}$) and inhalation ($\tau_{inhalation}$). In this case study, the two absorption factors were equal to one.

$$E_{i,Dietary} = \sum(Q_{i,Food} \times C_{Food}) / BW_i \quad (2)$$

$E_{i,Dietary}$ was the dietary exposure to lead of an individual i, expressed in $\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$ and was assessed by the sum of all products between $Q_{i,Food}$, the quantity of food consumed by individual i ($g.day^{-1}$), and C_{Food}, the associated level of lead contamination for the food ($\mu g_{Pb}.g^{-1}$ food). BW_i denoted the body weight of the individual i.

$$E_{i,Water} = Q_{i,Water} \times C_{Water} / BW_i \quad (3)$$

$E_{i,Water}$ was the lead exposure via tap water of an individual i and was expressed in $\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$ with the quantity consumed ($Q_{i,Water}$, in $L.d^{-1}$) and the level of tap-water contamination (C_{Water} ,in $\mu g_{Pb}.L^{-1}$).

$$E_{i,Soil} = Q_{i,Soil} \times C_{Soil} \times 10^3 / BW_i \quad (4)$$

$E_{i,Soil}$ was the lead exposure via soil of an individual i ($\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$) where $Q_{i,Soil}$ was the ingested quantity for the individual i ($mg_{Soil}.d^{-1}$) and C_{Soil} was the level of lead contamination in the soil ($\mu g_{Pb}.g^{-1}$ soil).

$$E_{i,Dust} = (Q_{i,Dust} / DL) \times C_{Dust} / BW_i \quad (5)$$

$E_{i,Dust}$ was the lead exposure via dust of an individual i ($\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$) where $Q_{i,Dust}$ was the quantity of dust ingested by the individual i ($mg_{Dust}.d^{-1}$) and C_{Dust} was the level of lead contamination in the dust ($\mu g_{Pb}.m^{-2}$ dust). DL was a dust load factor expressed in $mg.m^{-2}$.

$$E_{i,Air} = IR_i \times C_{Air} / BW_i \qquad (6)$$

$E_{i,Air}$ was the lead exposure via air of an individual i ($\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$) where IR_i was the inhalation rate for the individual i ($m^3.d^{-1}$) and C_{Air} was the air concentration of lead ($ng_{Pb}.m^{-3}$).

2.4 Methods for combining surveys

A three-step process was proposed to answer the following underlying questions (Fig. 1): (1) How to choose a reference population? (2) Did the different surveys have common variables? If common variables were observed, did they influence concentrations for the different sources? Could these variables be considered as stratification variables and divided into several classes to link the surveys to the reference population? (3) Did the surveys contain sampling weights to correct for under- or over-represented individuals?

Regarding the answers to the above questions, five methods, namely MC1, MC2, MC1S, MC2S and MCIC were tested and compared. These five different methods were based on the general principle which consisted in creating a simulated population from the individuals of the different surveys using second-order MC simulations (Fig. 1). Missing values, which are a common issue in statistical analyses but are not specific to aggregate exposure, were treated by replacement using the mean value.

2.4.1 Step 1: reference population

A reference population was defined as the most representative population of the target population considering major characteristics (age, region, gender, etc.). Then, the characteristics of the reference population had been reproduced in the simulated population. The five tested methods had the same population of reference.

2.4.2 Step 2: selection of stratification variables

Stratification variables were defined as population characteristics (like age, sex, region, etc.) that would be used to link the surveys. Stratification variables were selected in a two-step process:

1. The first step was to identify sociodemographic variables shared between surveys that could influence the input variables.
2. The second step was to test, via a statistical analysis, the significance of the correlations between shared sociodemographic variables and the concentrations for each survey. In case of significant correlations, it proves the importance to integrate the stratification variables when sampling the concentration values in the different surveys.

The impact of using or not stratification variables was tested in comparing the MC1S, MC2S methods which included stratification variables with the MC1, MC2 methods which did not. The MCIC did not include stratification variables.

2.4.3 Steps 3&4: Monte Carlo simulation strategies

The five methods used second-order MC simulations and integrated sampling weights. Values of exposure factors (e.g. quantity of ingested soil/dust or inhalation rate) were randomly selected based on the age of each individual from respective distributions presented in Table 1. Concentration values were assigned to each individual in the newly simulated population using an observed value from the other surveys.

One major difference between the methods was the timeline of assigning exposure factors and concentrations in the simulation process. The two MC1 and MC1S (MC in first step) methods created a simulated population of 100,000 individuals taken randomly from the reference population and assigned exposure factors and concentration values from the other surveys. The MC2 and MC2S (MC in second step) methods first assigned exposure factors and concentration values from the other surveys to each individual in the reference population. Next, 100,000 individuals were randomly sampled from the combined data to create a simulated population. The difference between MC1S/MC2S and MC1/MC2 was that MC1S and MC2S used stratification variables to combine surveys, while this was not the case of MC1 and MC2.

Furthermore, it is possible that surveys include several variables of interest, as for example concentrations of lead in tap water, in dust and in soil for one dwelling in the PH survey, which are highly correlated. In this case, the three concentrations need to be selected together to be assign to individuals in the simulated population. To keep correlations, one proposal applied in MC1S/MC1 and MC2S/MC2 methods was to select vectors of these three concentration variables.

Another method consisted in reproducing correlations between the concentration variables during simulation process This is proposed by the method named MCIC, based on the method of Iman and Conover (Iman and Conover, 1982) which used observed rank correlations and marginal distributions of concentrations.

To quantify the uncertainty associated with each method, the process was repeated 100 times. Thus, for each method, 100 simulated populations of 100,000 individuals were created, and an uncertainty interval was estimated.

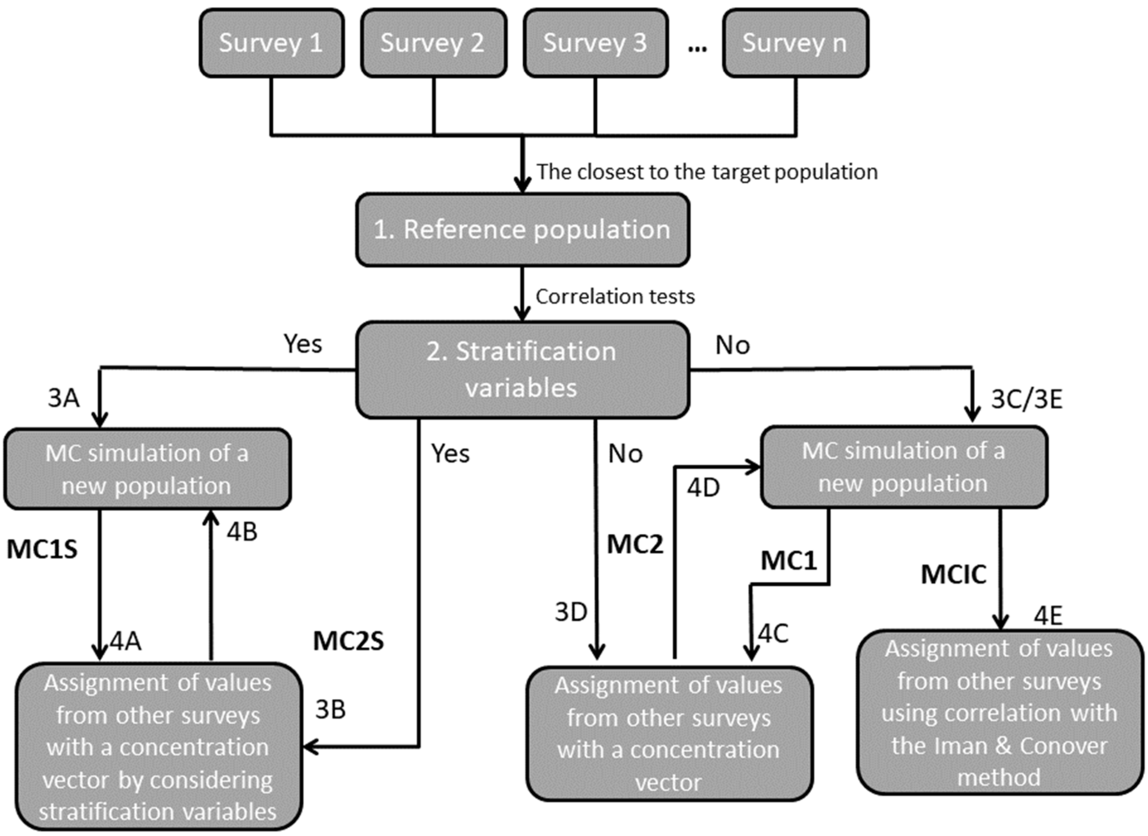

Figure 1. Diagram of different methodologies for combining surveys in order to evaluate aggregate exposure. Step 1: Choice of reference population; Step 2: Choice of stratification variables; Step 3: Simulation of a new population (3A: MC1S, 3C: MC1, 3E: MCIC) or

assignment of values from other surveys with a concentration vector (3B: MC2, 3D: MC2S); Step 4: Assignment of values from other surveys using a concentration vector (4A: MC1S, 4C: MC1) or reproducing correlation with the Iman and Conover method (4E: MCIC) or simulation of a new population (4B: MC2S, 4D: MC2).

2.5 Computation with the R program

MC simulations, distribution fitting and statistical testing were performed in the R program (R Core Team, 2017). The *msm* R package (Jackson, 2011) and the *EnvStat* R package (Millard, 2013) were used to adjust normal and lognormal truncated distributions, respectively. For the selection of stratification variables, Wald tests were performed with univariate general linear models by considering sampling weights using the *survey* R package (Lumley, 2004). The MCIC method was implemented with the *mc2d* R package (Pouillot et al., 2016).

For each exposure source and each of the 100 new populations, descriptive statistics (mean, median, standard deviation and percentiles) were estimated from population results. Mean contributions to aggregate exposure for each exposure source were calculated using the mean of the individual ratios for each exposure source and aggregate exposure multiplied by 100. Contribution values were recorded for the 50%, 10% and 5% of individuals with the highest aggregate exposure. From the 100 values calculated for each statistic, the median and the 2.5th and 97.5th percentiles were displayed in result tables to give estimates with credible intervals reflecting uncertainty. Significant differences were observed when confidence intervals did not overlap.

Furthermore, to evaluate the sensitivity of the various parameters to the evaluation of aggregate exposure, Spearman correlations were computed.

3 Results

3.1 Reference population

Five hundred eleven children aged six months to three years were selected from the BEBE-SFAE survey, as well as 214 dwellings from the PH survey. Two hundred eleven samples for lead contamination were recorded for tap water and dust, as well as 101 samples for soil. In this case study, the BEBE-SFAE population was chosen as the reference population. Firstly, it had the highest number of studied children. Secondly, children were the core issue in BEBE-SFAE survey, with physiological and sociodemographic data for each child. Thus, BEBE-SFAE was considered more representative than PH of the target population of children aged between 6 months and 3 years old in France. BDQA was not specific to a population group and thus could not be used as the reference population.

3.2 Selection of stratification variables

The variables common to the BEBE-SFAE and PH surveys were age, gender and region. The only variable they had in common with BDQA was region. Two region classifications were studied: the first corresponded to the 22 administrative regions of France (before they were modified in 2016) and the second had five classes: Paris region, North-West, North-East, South-East, and South-West.

Table 2 shows p-value results for the weighted univariate general linear models with the *survey* package. Regarding the univariate analysis, a relationship clearly appeared between the 22-class region variable and all input variables (p-value < 0.001***). A significant relationship with the five-class region variable was only observed with air concentrations. Age was significantly correlated with all factors except dust concentrations. The gender of the children did not appear to be related to any input variables.

Thus, it was decided to stratify the reference population according to the two common variables of the BEBE-SFAE and PH surveys, which were age and region (22-class regions). Stratification between BEBE-SFAE and BDQA was performed considering the 22-class regions. If a class of the stratification variable (age-region here) was present in the reference population but absent from PH or BDQA, it was decided to assign data from younger age within the same region or, if that was not possible, to take the mean of the whole population.

Table 2. Results for the selection of the age, region (22-class and five-class) and gender stratification variables, for the input variables used in the various surveys. P-value results under 0.05 were considered significant and are notified in bold.

Input variables	Survey	Sociodemographic parameters			
		Age	22 Regions	5 Regions	Sex
Dietary exposure	BEBE-SFAE	**<0.001**	**<0.001**	0.218	0.204
Tap water concentration	PH	**0.002**	**<0.001**	0203	0.115
Dust concentration	PH	0.559	**<0.001**	0.448	0.223
Soil concentration	PH	**0.040**	**<0.001**	**<0.001**	0.372

Air concentration	BDQA	-	**<0.001**	**<0.001**	-

3.3 Comparison of methods for combining surveys

To simplify, details for the method comparisons were displayed only for aggregate exposure. Similar results were obtained for the various exposure sources with the exception of dietary exposure.

3.3.1 Monte Carlo in first step or in second step?

Regarding the median estimates at the P50 and P95 levels for aggregate exposure, the different methods produced values between 0.85 and 0.95 $\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$ and between 8.7 and 10 $\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$, respectively (Fig. 2, Table 3). The lowest standard deviation values were 9.8 and 11 $\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$, meaning that variability was lower with method 2 (MC2S and MC2).

The results showed no significant difference between the two methods, as the uncertainty intervals (UIs) of the methods with MC in first step and MC in second step overlapped (MC1S vs MC2S, and MC1 vs MC2). However, it was observed that the MC2 methods had larger UIs, especially for highly exposed children (Fig. 2 and Fig. 3). At the 99th percentile, the upper bound of the UI was twice as high with MC in second step (greater than or equal to 88 $\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$ for MC2S and MC2) than with MC in first step (around 40 $\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$ for MC1S and MC1). This higher uncertainty could also be observed for the contribution of the various sources to aggregate exposure, especially for higher percentiles (Table 4). For example, for the 5% of children with the highest exposure levels from soil, the upper bound of contribution for MC2S reached 16% while it was 6% for the MC1S method.

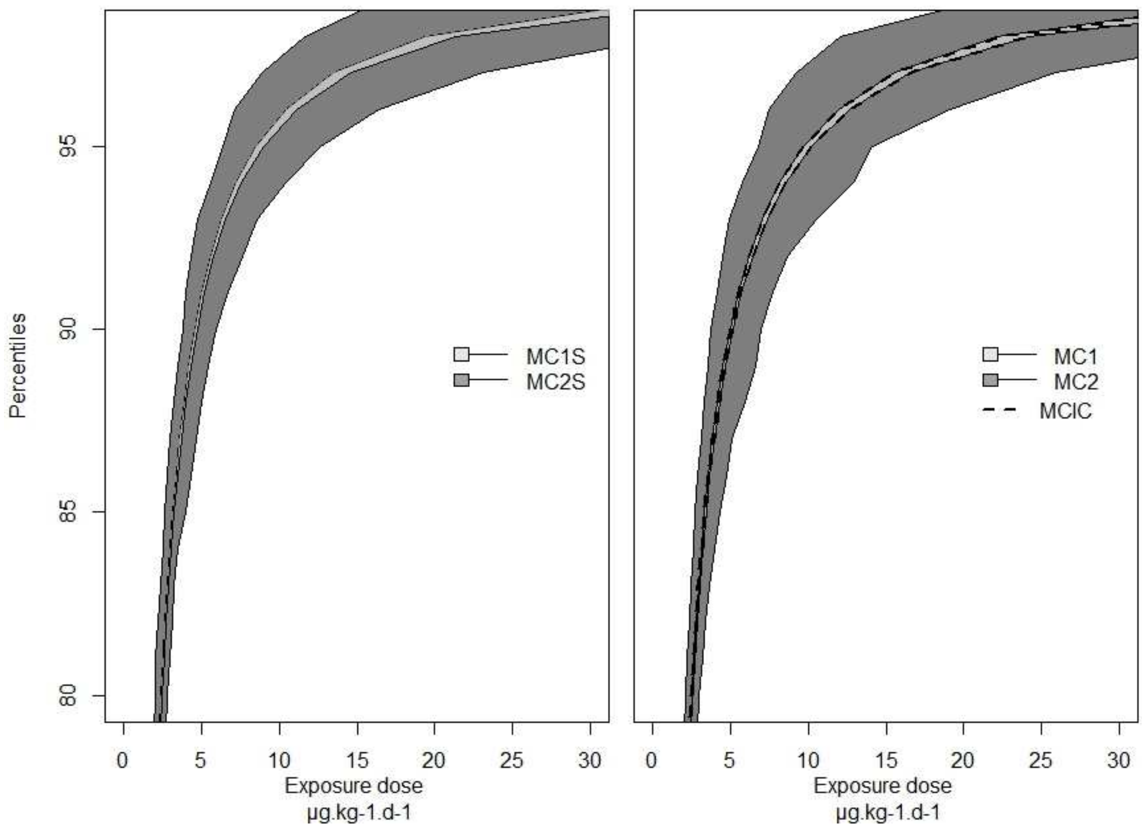

Figure 2. Distributions of aggregate exposure ($\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$) to lead in children between the ages of six months and three years in France with methods using stratification variables (on the left) and methods without stratification (on the right). Ninety-five percent uncertainty intervals appear in grey.

3.3.2 Stratification or no stratification?

Significant differences were observed between results for aggregate exposure and the percentiles of other exposure taking into account stratification with MC in first step (MC1S vs MC1, Table 3). Methods without stratification produced around 10% higher significant values of aggregate exposure (e.g. P50 observed at 0.86 $\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$ and 0.95 $\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$ for the MC1S and MC1 methods respectively). For tap water, the values were around 50% lower with MC1 than with MC1S (0.07 $\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$ vs 0.14 $\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$ for the 95th percentile). The same significant differences were observed for contributions (Table 4).

Table 3. Descriptive statistics for aggregate lead exposure as well as lead exposure via food, soil, dust, tap water and air ($\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$) in children aged six months to three years in France. Estimates are expressed as median values and 95% uncertainty intervals presented in square brackets.

Exposure sources	Methods	Mean	SD	P25	P50	P75	P90	P95	P99
Aggregate exposure	MC1S	3.1 [3.0 - 3.3]	22 [17 - 58]	0.49 [0.48 - 0.49]	0.86 [0.85 - 0.86]	1.9 [1.9 - 1.9]	4.6 [4.6 - 4.7]	8.8 [8.6 - 9.0]	37 [36 - 39]
	MC2S	2.8 [2.0 – 5.6]	9.8 [4.8 - 55]	0.48 [0.45 - 0.52]	0.85 [0.78 - 0.95]	1.9 [1.6 - 2.2]	4.6 [3.8 - 5.7]	8.7 [5.9 - 12]	36 [18 - 88]
	MC1	3.5 [3.3 - 3.8]	27 [19 - 77]	0.55 [0.54 - 0.55]	0.95 [0.94 - 0.96]	2.0 [2.0 - 2.0]	5.1 [5.0 - 5.1]	10 [9.7 - 10]	42 [40 - 44]
	MC2	3.2 [2.4 - 8.2]	11 [4.9 - 89]	0.55 [0.50 - 0.59]	0.95 [0.86 - 1.1]	2.0 [1.8 - 2.4]	5.2 [4.0 - 6.4]	9.4 [6.5 - 15]	42 [20 - 105]
	MCIC	3.5 [3.3 - 3.7]	26 [19 - 55]	0.55 [0.54 - 0.56]	0.95 [0.94 - 0.96]	2.0 [2.0 - 2.0]	5.1 [5.0 - 5.1]	10 [9.7 - 10]	42 [40 - 44]
Food	MC1S	0.22 [0.22 - 0.22]	0.09 [0.09 - 0.09]	0.16 [0.16 - 0.16]	0.21 [0.21 - 0.21]	0.27 [0.27 - 0.27]	0.34 [0.33 - 0.34]	0.38 [0.38 - 0.39]	0.52 [0.52 - 0.53]
	MC2S	0.22 [0.22 - 0.22]	0.09 [0.09 - 0.09]	0.16 [0.16 - 0.16]	0.21 [0.21 - 0.21]	0.27 [0.27 - 0.27]	0.34 [0.34 - 0.34]	0.38 [0.38 - 0.39]	0.52 [0.52 - 0.53]
	MC1	0.22 [0.22 - 0.22]	0.09 [0.09 - 0.09]	0.16 [0.16 - 0.16]	0.21 [0.21 - 0.21]	0.27 [0.27 - 0.27]	0.34 [0.33 - 0.34]	0.38 [0.38 - 0.39]	0.52 [0.52 - 0.54]
	MC2	0.22 [0.22 - 0.22]	0.09 [0.09 - 0.09]	0.16 [0.16 - 0.16]	0.21 [0.21 - 0.21]	0.27 [0.27 - 0.27]	0.34 [0.33 - 0.34]	0.38 [0.38 - 0.39]	0.52 [0.52 - 0.52]
	MCIC	0.22 [0.22 - 0.22]	0.09 [0.09 - 0.09]	0.16 [0.16 - 0.16]	0.21 [0.21 - 0.21]	0.27 [0.27 - 0.27]	0.34 [0.33 - 0.34]	0.38 [0.38 - 0.39]	0.52 [0.52 - 0.54]
Soil	MC1S	0.39 [0.39 - 0.40]	0.77 [0.75 - 0.80]	0.06 [0.06 - 0.06]	0.15 [0.15 - 0.15]	0.39 [0.38 - 0.39]	0.95 [0.93 - 0.96]	1.6 [1.5 - 1.6]	3.6 [3.5 - 3.7]
	MC2S	0.39 [0.33 - 0.45]	0.72 [0.53 - 1.0]	0.06 [0.06 - 0.07]	0.15 [0.13 - 0.17]	0.39 [0.34 - 0.46]	0.95 [0.80 - 1.2]	1.5 [1.2 – 1.9]	3.3 [2.3 - 5.3]
	MC1	0.43 [0.42 - 0.43]	0.86 [0.80 - 0.96]	0.09 [0.09 - 0.09]	0.22 [0.21 - 0.22]	0.46 [0.46 - 0.47]	0.92 [0.91 - 0.94]	1.4 [1.4 - 1.5]	3.5 [3.4 - 3.6]
	MC2	0.43 [0.36 - 0.53]	0.73 [0.49 - 1.7]	0.09 [0.08 - 0.12]	0.22 [0.19 - 0.25]	0.46 [0.40 - 0.54]	0.92 [0.77 - 1.2]	1.4 [1.1 - 1.8]	3.5 [2.2 - 5.4]
	MCIC	0.43 [0.42 - 0.43]	0.86 [0.81 - 0.93]	0.09 [0.09 - 0.09]	0.22 [0.21 - 0.22]	0.46 [0.46 - 0.47]	0.93 [0.91 - 0.93]	1.4 [1.4 - 1.4]	3.5 [3.4 - 3.6]
Dust	MC1S	2.5 [2.3 - 2.7]	22 [17 - 57]	0.07 [0.07 - 0.07]	0.26 [0.25 - 0.26]	0.97 [0.95 - 0.99]	3.5 [3.4 - 3.6]	7.7 [7.6 – 7.9]	36 [35 - 39]
	MC2S	2.2 [1.4 - 4.9]	9.8 [4.7 - 55]	0.08 [0.06 - 0.09]	0.26 [0.21 - 0.33]	0.94 [0.77 - 1.2]	3.4 [2.5 - 4.6]	7.7 [4.9 - 11.4]	35 [18 - 87]
	MC1	2.8 [2.6 - 3.1]	27 [19 - 77]	0.08 [0.08 - 0.08]	0.28 [0.28 - 0.29]	1.1 [1.1 - 1.1]	4.0 [3.9 - 4.1]	8.9 [8.6 - 9.1]	41 [39 - 43]
	MC2	2.6 [1.7 - 7.6]	11 [4.8 - 89]	0.08 [0.06 - 0.10]	0.29 [0.23 - 0.38]	1.2 [0.78 - 1.5]	4.1 [2.9 - 5.7]	9.0 [6.0 - 15]	41 [19 - 105]
	MCIC	2.8 [2.6 - 3.1]	26 [19 - 55]	0.08 [0.08 - 0.08]	0.28 [0.28 - 0.29]	1.1 [1.1 - 1.1]	4.0 [3.9 - 4.1]	8.9 [8.6 - 9.1]	41 [39 - 43]
Tap water	MC1S	0.03 [0.03 - 0.03]	0.16 [0.16 - 0.17]	0 [0 - 0]	0 [0 - 0]	0.007 [0.006 - 0.007]	0.04 [0.04 - 0.04]	0.14 [0.13 - 0.15]	0.64 [0.64 - 0.69]
	MC2S	0.03 [0.03 - 0.04]	0.16 [0.10 - 0.20]	0 [0 - 0]	0 [0 - 0]	0.007 [0.006 - 0.009]	0.04 [0.03 - 0.05]	0.14 [0.07 - 0.22]	0.64 [0.48 - 1.2]
	MC1	0.02 [0.02 - 0.02]	0.09 [0.09 - 0.10]	0 [0 - 0]	0 [0 - 0]	0.007 [0.007 - 0.007]	0.03 [0.03 - 0.03]	0.07 [0.07 - 0.07]	0.34 [0.32 - 0.35]
	MC2	0.02 [0.01 - 0.03]	0.08 [0.04 - 0.17]	0 [0 - 0]	0 [0 - 0]	0.007 [0.006 - 0.008]	0.03 [0.02 - 0.04]	0.07 [0.05 - 0.11]	0.34 [0.17 - 0.62]

	MCIC	0.02 [0.02 - 0.02]	0.09 [0.08 - 0.10]	0 [0 - 0]	0 [0 - 0]	0.007 [0.007 - 0.007]	0.03 [0.03 - 0.03]	0.07 [0.07 - 0.07]	0.34 [0.32 - 0.35]
Air	**MC1S**	0.005 [0.005 - 0.005]	0.005 [0.005 - 0.005]	0.002 [0.002 - 0.002]	0.003 [0.003 - 0.003]	0.006 [0.006 - 0.006]	0.009 [0.009 - 0.009]	0.012 [0.012 - 0.012]	0.025 [0.025 - 0.026]
	MC2S	0.005 [0.004 - 0.005]	0.005 [0.004 - 0.006]	0.002 [0.002 - 0.002]	0.003 [0.003 - 0.004]	0.006 [0.005 - 0.006]	0.009 [0.008 - 0.010]	0.012 [0.010 - 0.015]	0.025 [0.018 - 0.034]
	MC1	0.005 [0.005 - 0.005]	0.005 [0.005 - 0.005]	0.003 [0.003 - 0.003]	0.004 [0.004 - 0.004]	0.007 [0.007 - 0.007]	0.010 [0.010 - 0.010]	0.013 [0.013 - 0.013]	0.024 [0.024 - 0.025]
	MC2	0.005 [0.005 - 0.006]	0.005 [0.004 - 0.006]	0.003 [0.002 - 0.003]	0.004 [0.004 - 0.004]	0.007 [0.006 - 0.007]	0.010 [0.009 - 0.011]	0.013 [0.011 - 0.016]	0.024 [0.018 - 0.032]
	MCIC	0.005 [0.005 - 0.005]	0.005 [0.004 - 0.005]	0.003 [0.003 - 0.003]	0.004 [0.004 - 0.004]	0.007 [0.007 - 0.007]	0.010 [0.010 - 0.010]	0.013 [0.013 - 0.013]	0.024 [0.024 - 0.025]

3.3.3 Taking into account correlations by using a vector of observations or reproducing correlations

The different methods for taking into account concentration correlations (MCIC vs MC1) produced similar results, as the UIs overlapped.

Table 4. Mean contributions (%) of the various sources of exposure for the 50%, 10% and 5% of children (aged six months to three years) with the highest aggregate lead exposure. Estimates are expressed as median values and 95% uncertainty intervals presented in square brackets.

		50% most exposed	10% most exposed	5% most exposed
Food	**MC1S**	13 [13 - 13]	2.5 [2.5 - 2.6]	1.3 [1.3 - 1.4]
	MC2S	13 [11 - 14]	2.5 [1.5 - 3.5]	1.3 [0.8 - 2.0]
	MC1	12 [12 - 12]	2.3 [2.3 - 2.3]	1.2 [1.2 - 1.2]
	MC2	12 [10 - 13]	2.3 [1.5 - 3.2]	1.2 [0.61 - 1.9]
	MCIC	12 [12 - 12]	2.3 [2.2 - 2.3]	1.2 [1.1 - 1.2]
Soil	**MC1S**	27 [27 - 27]	12 [12 - 13]	5.7 [5.2 - 6.1]
	MC2S	27 [24 - 30]	12 [3.8 - 20]	5.3 [1.3 - 16]
	MC1	28 [28 - 28]	10 [9.8 - 11]	5.5 [5.1 - 6.0]
	MC2	28 [24 - 32]	9.5 [5.1 - 15]	5.0 [1.1 - 14]
	MCIC	28 [27 - 28]	10 [9.7 - 11]	5.6 [5.1 - 6.0]
Dust	**MC1S**	57 [57 - 58]	84 [84 - 85]	93 [92 - 93]
	MC2S	57 [53 - 62]	84 [75 - 94]	93 [82 - 98]
	MC1	59 [58 - 59]	87 [87 - 88]	93 [93 - 94]
	MC2	59 [54 - 64]	87 [82 - 93]	94 [85 - 98]
	MCIC	59 [58 - 59]	87 [87 - 88]	93 [93 - 94]
Tap water	**MC1S**	2.3 [2.3 - 2.4]	0.93 [0.85 - 1.0]	0.29 [0.26 - 0.34]
	MC2S	2.4 [1.6 - 3.2]	0.61 [0.03 - 2.4]	0.21 [0.01 - 1.3]
	MC1	1.2 [1.1 - 1.2]	0.33 [0.28 - 0.37]	0.14 [0.12 - 0.17]
	MC2	1.2 [0.66 - 1.9]	0.24 [0.04 - 1.1]	0.10 [0.005 - 0.64]
	MCIC	1.3 [1.2 - 1.4]	0.25 [0.17 - 0.34]	0.11 [0.07 - 0.19]
Air	**MC1S**	0.25 [0.25 - 0.26]	0.06 [0.05 - 0.06]	0.03 [0.03 - 0.03]
	MC2S	0.25 [0.20 - 0.29]	0.05 [0.03 - 0.09]	0.03 [0.02 - 0.05]
	MC1	0.28 [0.27 - 0.28]	0.05 [0.05 - 0.06]	0.03 [0.03 - 0.03]
	MC2	0.28 [0.22 - 0.33]	0.05 [0.03 - 0.08]	0.03 [0.01 - 0.05]
	MCIC	0.28 [0.27 - 0.28]	0.06 [0.05 - 0.06]	0.03 [0.03 - 0.03]

3.4 Contribution of exposure sources to aggregate lead exposure

Results obtained with the MC1S method are presented in this section.

3.4.1 Aggregate exposure

The 50th percentile of aggregate exposure was 0.86 $\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$, the 95th percentile was 8.8 $\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$, and the 99th percentile was 37 $\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$ (Table 3). Lead exposure levels in children varied considerably between the different exposure sources with a low contribution of air and water and a high contribution of soil and dust. More specifically, exposure via dust contributed the most to aggregate exposure, in particular for the most exposed children, as it reached up to 93% of aggregate exposure at the P95 level. It was followed by exposure via soil, food, tap water and air (Table 4).

C_{Dust} and DL were the exposure factors most influencing aggregate exposure, followed by C_{soil}, Q_{soil} and Q_{Dust} (Table 5). Aggregate exposure was weakly sensitive to body weight (BW).

3.4.2 Exposure via dust

Dust exposure values varied from 0.26 $\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$ for the 50th percentile to 7.7 for the 95th percentile (Table 3). The contribution of dust ingestion to total exposure was 57% for median aggregate exposure (Table 4). Regarding the top 10% most exposed children, the contribution to aggregate exposure was 84%. C_{Dust} was positively correlated, at 0.572, with total exposure (Table 5). Conversely, DL was negatively correlated, at -0.531.

3.4.3 Exposure via soil

Exposure via soil was the second largest factor contributing to aggregate exposure (Table 4). The observed soil exposure values ranged from 0.15 $\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$ for the 50th percentile to 1.6 $\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$ for the 95th percentile, reaching 3.6 $\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$ for the 99th percentile (Table 3). The contribution of exposure via soil decreased from 27% for the top 50% of the population to 5.7% for the top 5% most exposed children (Table 4). Aggregate exposure was moderately sensitive to C_{Soil} (0.387) and Q_{Soil} (0.287) (Table 5).

Table 5. Correlations between exposure factors and lead concentrations with aggregate lead exposure in children aged six months to three years.

		MC1S	MC2S	MC1	MC2	MCIC
Body weight	**BW**	0.048 [0.041 - 0.055]	0.047 [-0.017 - 0.121]	-0.046 [-0.051 - -0.039]	-0.046 [-0.126 - 0.043]	-0.046 [-0.052 - -0.039]
Soil	Q_{Soil}	0.287 [0.282 - 0.292]	0.291 [0.180 - 0.361]	0.324 [0.317 - 0.329]	0.323 [0.226 - 0.399]	0.325 [0.319 - 0.335]
	C_{Soil}	0.387 [0.382 - 0.391]	0.385 [0.305 - 0.457]	0.331 [0.326 - 0.336]	0.316 [0.230 - 0.407]	0.341 [0.270 - 0.393]
Dust	Q_{Dust}	0.190 [0.185 - 0.190]	0.188 [0.098 - 0.188]	0.169 [0.164 - 0.169]	0.168 [0.089 - 0.168]	0.170 [0.165 - 0.170]
	C_{Dust}	0.572 [0.567 - 0.576]	0.576 [0.502 - 0.633]	0.559 [0.554 - 0.563]	0.560 [0.494 - 0.622]	0.546 [0.518 - 0.570]
	DL	-0.531 [-0.535 - -0.527]	-0.532 [-0.611 - -0.468]	-0.536 [-0.541 - -0.532]	-0.533 [-0.608 - -0.457]	-0.541 [-0.550 - -0.533]
Tap water	Q_{Water}	0.037 [0.032 - 0.037]	0.035 [-0.036 - 0.035]	0.042 [0.037 - 0.042]	0.048 [-0.048 - 0.048]	0.046 [0.040 - 0.046]
	C_{Water}	0.032 [0.037 - 0.043]	-0.036 [0.035 - 0.105]	0.037 [0.042 - 0.049]	-0.048 [0.048 - 0.136]	0.040 [0.046 - 0.054]
Air	**IR**	0.136 [0.131 - 0.143]	0.146 [0.057 - 0.223]	0.087 [0.081 - 0.094]	0.084 [-0.005 - 0.159]	0.096 [0.013 - 0.157]
	C_{Air}	-0.039 [-0.045 - -0.032]	-0.037 [-0.111 - 0.058]	0.004 [-0.001 - 0.011]	-0.004 [-0.088 - 0.100]	0.004 [-0.002 - 0.011]

3.4.4 Exposure via food

The 50th and 95th percentiles of exposure from food were observed respectively at 0.21 and 0.34 $\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$, reaching up to 0.52 $\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$ for children in the top 1% for lead exposure (Table 3). Dietary exposure moderately contributed to aggregate exposure, with its contribution decreasing from 13% for the top half of the child population to 1.3% when children were more heavily exposed to lead (Table 4).

3.4.5 Exposure via air and tap water

Exposure levels via air and tap water in children were very low compared to the other exposure sources (Table 3). Exposure via air was observed at 0.012 $\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$ at the 95th percentile and accounted for 0.03% of aggregate exposure (Table 4). As with exposure via air, exposure from tap water did not significantly contribute to the evaluation of aggregate exposure, with values reaching 0.14 $\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$ and with a contribution below 0.29% for the top 5% of children most exposed to lead.

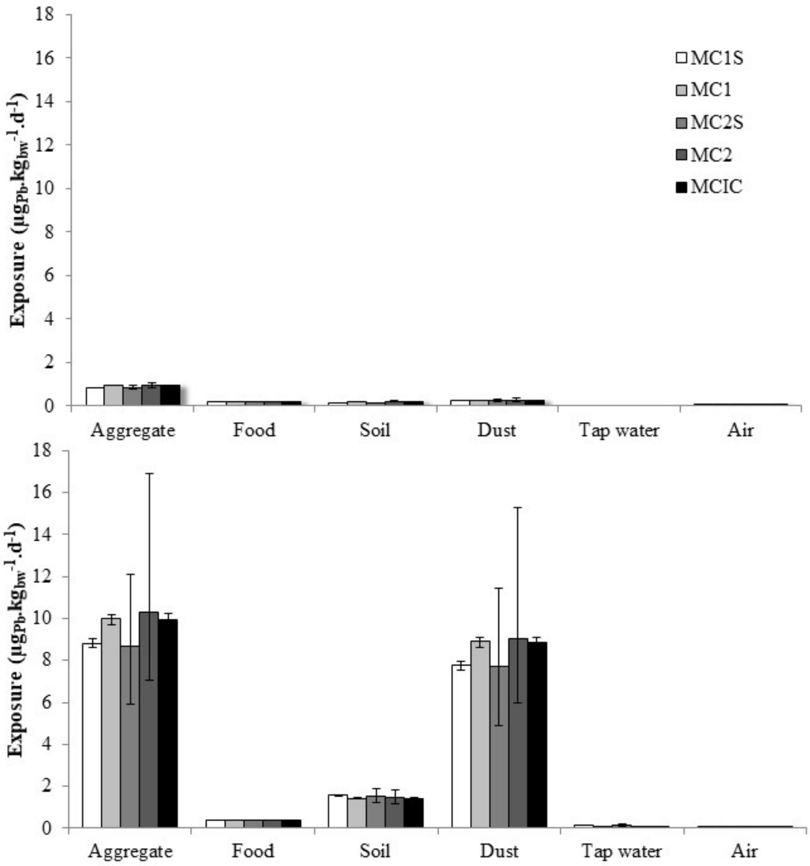

Figure 3. Histogram of the medians estimated for the 50^{th} percentile (above) and the 95^{th} percentile (below) of exposure ($\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$) to lead for children aged six months to three years, for aggregate exposure and for the various sources with the five implemented methods. Error bars show the P5 and P95 of the uncertainty intervals.

4 Discussion

4.1 Recommendations for aggregate exposure

To estimate aggregate exposure from different sources, it is ideal to have all exposure information for the same group of individuals with the same consistency regarding the units and methods, but this is rare in practice (Kennedy et al., 2015a). Thus, the main difficulty in the assessment of aggregate exposure involves combining data from several independent surveys and populations. Scientific articles related to aggregate exposure generally used different methodologies based on pre-existing models (Safford et al., 2015) or different softwares (MCRA, SHEDS, PACEM, BROWSE, etc.) with probabilistic simulations.

SHEDS-HT for example, combines dietary exposure from individual data with theoretical values concentrations from distributions fitted on data for the other exposure sources. In the case of MCRA, the software combines dietary exposure individual data with non-dietary exposure data (empirical or theoretical) evaluated first by another software. Thus, providing a harmonized method for combining different surveys with empirical data in case of aggregate exposure was the main aim of this paper. It can also be applied to reconstruct the information for the whole dataset for an existing study where different level of information was studied for different sub-populations. This is the case for some biomonitoring surveys, where measurements of chemicals are performed for sub-populations. It may also be applied for researchers and practitioners to combine data as a unique database to have a unique survey for different purposes.

To establish general steps to aggregate exposure from several surveys, five methods for combining data were compared using children (6 month to 3 years old) lead exposure case study in integrating uncertainties. They combined surveys focused on dietary exposure (BEBE-SFAE combined with TDSi), contamination in homes (PH surveys) and in air (BDQA survey). All methods provided consistent results and showed that dust was the main exposure source although there were some significant differences between exposure levels due to the difference in the methodology to combines these surveys. Moreover, uncertainties considerably varied between methods. Bonnel et al. (2015) also concluded that combining surveys with different populations and methodologies increased the probability to include biases due to sampling or measurements. Thus, it is primordial to consider and follow the recommended steps to decrease biases and uncertainties.

The first step consists in selecting a reference population between the three surveys to simulate a new population of 100 000 individuals. It is an important step as its sociodemographic characteristics and parameters will be duplicated in the simulated population. Thus, the reference of the population needs to be the most representative of the target population to considerably decrease these biases.

In the second step, it is recommended to consider stratification variables when sociodemographic variables shared between the reference population and the other survey variables are significantly correlated with concentration/exposure levels. Indeed, specific parameters such as sociodemographic variables, especially when they influence the quality of the other variables, may decrease the inclusion of biases when they are used to combine data (Bayart and Bonnel, 2015). When stratification variables was not considered, as with MC1 and MC2 methods, aggregate exposure values tended to be overestimated (around 11% for P50), compared to the methods considering stratification. The selection of stratification variables is thus an important step in the calculation of aggregate exposure allowing to merge appropriate exposure values for a specific sub-population. Stratification variables should be carefully selected, with the presence of classes in sufficient but not too high numbers. Indeed, the variables should not contain too many classes, otherwise it will be difficult to find connections between surveys and the probability of drawing the same value will increase. Conversely, when the number of classes is too low, there is a risk of not reproducing the observed correlations. To define the number of classes, it is recommended to test their impact when making statistical tests of the correlation significance between possible stratification variables and the concentration levels. In this study, the age and the region variables were used as stratification variables. Although gender is often used to combine data (Biesterbos et al., 2013; Comiskey et al., 2017; Kennedy et al., 2015a; Kennedy et al., 2015b), this parameter was not used as a stratification variable because it was not correlated with the concentrations in soil, dust and tap water. Furthermore, combining different consumption surveys with stratification variables are very current on the case of personal care products and cosmetics (Biesterbos et al., 2013; Comiskey et al., 2017) due to the lack of data for product usage for the subjects. Biesterbos et al. (2013) recommended for the combination of data to use gender, age and the level of education as they are important factors in the case of exposure assessment of personal care product. Comiskey et al. (2017) also merged data by pairing subjects with similar demographics (age range, gender, and geography) assuming that they will have similar habits and practices.

The last step is to combine data using MC simulations. Our results showed that the UIs of the methods with MC in second step (MC2 and MC2S) were very large. These two methods showed high uncertainty in exposure values through the 100 new populations, especially for the most heavily exposed children. A difference of around 20% in the aggregate exposure values was observed at the 50th percentile between one simulation and the next. This difference could reach more than 50% for the 95th percentile. This meant that the exposure values were not stable from one simulation to the next. Moreover, the variability within a population simulated with MC in second step was lower than with MC in first step. Thus, high exposure values were given less consideration with MC in second step. Consequently, it is recommended to use the MC1S method which randomly samples individuals in the reference population and simultaneously assigns exposure factors and concentration values from other surveys. In this study, this resulted in consistent and stable exposure values between the 100 simulations.

In the case of multiple and independent data sets, correlations are often observed for analysis process. In this study, PH survey included several variables of interest, i.e. concentrations of lead in tap water, in dust and in soil for one dwelling, which were highly correlated between them. To keep these correlations, we selected vectors of these three concentration variables in MC1S/MC1 and MC2S/MC2 methods, and reproduced correlations between the concentration variables during simulation process by the Iman-Conover method (Iman and Conover, 1982) with the MCIC method. In astrophysics field, methods treats correlations between multiple data sets and give appropriate relevant weights of multiple data sets with mutual correlations by the creation of a hyperparameter matrix. The marginalization can be carried out with a brute-force grid evaluation of the hyperparameters, or it can be explored by using MC methods which directly sample the posterior distribution (Ma and Berndsen, 2014). Other methods such as copula methods (Haas, 1999), or principal component analysis (Cowan-Ellsberry and Robison, 2009) can be used to take into account correlations during simulations. Regarding ways of taking into account correlations during simulation processes, there was no significant difference between MCIC method and the selection of a vector of concentrations (MC1). MC1 has the advantage to avoid additional uncertainty related to the choice of simulation correlations, while MCIC has the advantage of being easier to implement with popular commercial add-ins to Excel® such as @risk, Cristal Ball.

4.2 Aggregate children lead exposure in France

In this paper, dust and soil were found to be the most significant sources of exposure to lead in France for children under the age of three years. Similar results were observed in France (Glorennec et al., 2016) and the USA (Zartarian et al., 2017) for the most heavily exposed children between the ages of three and six years. Indeed, between soil and dust, dust is more likely to accumulate trace metals (Acosta et al., 2015; Gabarron et al., 2017). The ingestion of lead from soil and dust is very significant in children due to their more intense hand-mouth behaviour (Gabarron et al., 2017; Glorennec et al., 2012). Contaminated soil and especially dust have been identified as contributors to blood lead levels in children in France (Etchevers et al., 2014; Etchevers et al., 2015; Glorennec et al., 2010; Oulhote et al., 2013). Exposure via dust in this paper is six times higher than observed by Glorennec et al. (2016) in children aged three to six years. This is due to some differences in exposure factors and in concentration data used to evaluate exposure. Indeed, Glorennec et al. (2016) used for dust and soil ingestion a lognormal distribution with a standard deviation of 3.2 and truncated to the highest observed value whereas in this study, the lognormal distribution was simulated with a standard deviation of around 26, allowing a larger range of possible values as shown in original data. This difference emphasises the importance of carefully choosing exposure parameters in order to increase the confidence level of the analysis. As exposure factors came from studies with different periods and regions, error could appeared in exposure estimates. For example, Q_{Soil} and Q_{Dust} which moderately impacted aggregate exposure have often been discussed (Dor et al., 2012; Moya and Philips, 2014; Özkaynak et al., 2011; U.S. EPA, 2011; von Lindern et al., 2016; Wilson et al., 2013). In the present study, Q_{Soil} and Q_{Dust} were taken from the Exposure Factors Handbook (U.S. EPA, 2011) which derived distributions from 12 key studies mainly conducted in North America between the 1980s and 1990s. However, since the 90's, activity patterns, micro-environments and hygiene practices have been improved (Moya and Philips, 2014). Furthermore, these data came from studies conducted in North America, while this case study focused on the French population. Soil ingestion quantities can vary depending on the geographic location, climate, season, or soil characteristics. To our knowledge, no data on quantities of ingested soil and dust and on inhalation rate, are available for children in Europe. Thus, there is a need of further research on exposure factors to improve data quality and exposure assessment in Europe.

After the ingestion of soil and dust, food ingestion was the source that most contributed to total exposure to lead from the half of the most exposed children. For low exposure (25th percentile), dietary exposure is higher than other sources of exposure. As dietary exposure values were directly recorded in the reference population (i.e. BEBE-SFAE survey), it had already been aggregated by construction with sample pooling, leading to low variations in exposure in the simulated population. Consequently, no significant differences between methods were observed for dietary exposure. Dietary exposure were relatively similar with the median and 95th percentile values observed at 0.21 and 0.38 $\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$ in this study, while values for older children were found at 0.37 and 0.42 $\mu g_{Pb}.kg_{bw}^{-1}.d^{-1}$. Similarly, dietary exposure was the main contributor to aggregate lead exposure for older children for the half of the population exposed to lead, with notable contributions by milk, fresh soft drinks, vegetables and bread (Glorennec et al., 2016), and then was overtaken by the exposure of dust and soil for the most exposed children. Lower exposure values from food and higher from dust and soil were observed in the present work compared to results at European level from

(EFSA, 2010). The differences may come that dust and soil concentrations from the PH study were higher (35mg/kg in mean to 831 in max for soil for ex.) than the single mean value used by EFSA 2010 (23mg par kg, for soil). Moreover, EFSA used single mean value for ingestion rate (100 mg per day) and body weight (12.5 kg) whereas we used probabilistic distributions. In that way, the ingestion rate can reach 1000 mg per day in the present work.
The contribution of tap water and air to aggregate exposure was very low for children under the age of three years. This is consistent with findings for older French children (Glorennec et al., 2016) as well as for the exposure in air children in the USA (Zartarian et al., 2017). Lead concentrations inside dwellings were extrapolated from outdoor measurements despite they can be influenced by environmental tobacco smoke (Etchevers et al., 2014; Lucas et al., 2014). Consequently, the extrapolated inhalation exposure was a weaker part due to lack of relevant data.

EFSA (2010) estimated that the external dose corresponding to the $BMDL_{01}$ of 12 µg/L (blood lead level) for developmental neurotoxicity was 0.50 $\mu g.kg^{-1}$ $bw.d^{-1}$. All values of the margin of exposure from aggregate sources were low and below to 10, which meant that a risk could not be excluded for all children. Furthermore, biomonitoring studies (Etchevers et al., 2014) showed that most children under 6 years old exceed the BMD01. Consequently, current levels of lead exposure, are a public health concern in France.

5 Conclusion

This work proposed a step-by-step approach for performing aggregate exposure assessments by comparing different methods for combining heterogeneous surveys. The first step consisted in selecting a representative reference population of the target population. In the second step, it was recommended to consider stratification variables when combining surveys to prevent exposure values from being overestimated. In the last step, it was recommended to create a simulated population from the reference population and to simultaneously assign exposure factors and concentration values from the other surveys using the stratification variables. This timeline approach lowers the uncertainty of aggregate exposure. The methodology was implemented to evaluate aggregate exposure to lead in the population of children between the ages of six months and three years in France. Dust was the main exposure source, followed by soil and food in a lesser extent.

This work is a first application of the proposed methodology which needs to be applied in other case studies.

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Conflicts of Interest

The authors declare no conflicts of interest.

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