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1	Combining data from heterogeneous surveys for aggregate exposure: application to
2	children exposure to lead in France
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16 Abstract

17 To assess human health risks related to the environment, it is necessary to aggregate exposure 18 from multiple sources. The objective of this paper was to propose a relevant approach to 19 combine data from heterogeneous populations and methodologies. Five different methods 20 based on Monte-Carlo simulations were tested and compared. Differences were: taking into 21 account or not stratification variable, timeline to assign exposure factors and concentration 22 and way to account for concentration correlations. The methods were applied to estimate lead 23 exposure from food, dust, soil, air, and tap water or French children aged between six months 24 and three years old.

25 Comparing results' uncertainty, it is recommended to 1) select a reference population 26 representative of the target population, 2) select stratification variables to combine surveys, 27 and 3) simulate a new population by randomly sampling individuals in the reference 28 population and simultaneously assigning human exposure factors and environmental 29 concentrations from other surveys in integrating correlations (MC1S). No difference was 30 observed when taking into account correlations using vectors of determinist data from one 31 survey or rank of correlations with the Iman-Conover method. Regardless the methods used to 32 combine data, dust was the main exposure source, followed by soil and in a less extent by 33 food. Exposures from air and tap water were found to be insignificant for most children.

34

35 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
- 42

43 Keywords

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

45

46 Abbreviations

47 BDQA: French database for air quality

- 48 BEBE-SFAE: French database of children dietary
- 49 BW: Body weight
- 50 DL: Dust load
- 51 MC: Monte Carlo
- 52 MC1: Monte Carlo in first step
- 53 MC1S: Monte Carlo in first step with the use of stratification variables
- 54 MC2: Monte Carlo in second step
- 55 MC2S: Monte Carlo in second step with the use of stratification variables
- 56 MCIC: Monte Carlo with the method of Iman and Conover
- 57 PH: French database for lead concentration in dwellings
- 58 UI: Uncertainty intervals
- 59

60 Fundings

- 61 This work took in account studies on human subjects, especially children. These studies were
- 62 approval by an appropriately constituted committee for human subjects.
- 63 This research did not receive any specific grant from funding agencies in the public,
- 64 commercial, or not-for-profit-sectors.

65 **1 Introduction**

66 Aggregate exposure can be defined as the sum of several sources of exposure (air, dust, food, 67 water, etc.) via different exposure routes (ingestion, inhalation and dermal absorption). To 68 perform human health risk assessments based on total exposure, it is important to consider 69 aggregate exposure. By nature, biomonitoring data considers aggregate exposure, but this data 70 does not enable the contribution of exposure sources to be assessed. In order to determine 71 management options to mitigate exposure and the associated risks, the identification of 72 exposure sources and factors contributing to total exposure is currently essential. However, 73 the modelling of aggregate exposure is complex from several standpoints. Except in specific 74 cases (Cao et al., 2016), complete surveys seldom collect all exposure sources for the same 75 individual. Therefore, performing aggregate exposure assessments often requires considering 76 data from different databases with different populations and methodologies. In addition, 77 exposure can be expressed at the individual level, which is generally the case for food, or at 78 the population level, which is more common for environmental exposure.

79 Even though the definition of "aggregate exposure" is soon to be standardised, some authors 80 have recently proposed "aggregate exposure" when considering only one source and one route 81 of exposure. This was the case of Cowan-Ellsberry and Robison (2009), Delmaar et al. (2015) 82 and Gosens et al. (2014) who studied dermal exposure to parabens and phthalates from 83 cosmetics. Other authors have tried to be as exhaustive as possible in the calculation of 84 aggregate exposure. For example, Beko et al. (2013) considered two sources of exposure (dust 85 and air) for phthalates and extrapolated dietary exposure from internal measurements. 86 Pelletier et al. (2017) took into account three routes of indoor residential exposure to semi-87 volatile organic compounds. Furthermore, Glorennec et al. (2016) assessed aggregate 88 exposure to metals and metalloids in children between three and six years of age in France, 89 considering several sources of exposure in a Monte Carlo (MC) simulation via various 90 surveys. However, in these studies, the strategy used to combine data from different surveys 91 with different levels (individual vs population) to assess aggregate exposure was not 92 discussed. Some tools have been developed in the last few years to assess exposure via 93 different routes and sources. The European projects EuroMix, HBM4EU or SOLUTIONS 94 developed methodologies and guidance for assessing risks in mixture from combined 95 exposure to multiple chemicals for different regulatory sectors. In these projects, mixture risk 96 assessment is limited by the difficulties in considering aggregate exposures from different 97 sources with dietary source combined with non-dietary sources (Bopp et al., 2018). Exposure

98 tools addressing multiple exposure routes were embedded in the EuroMix toolbox, Monte 99 Carlo Risk Assessment software (van der Voet et al., 2015) by adding to diet exposure results 100 from MCRA to non-dietary exposure sources from other software as PACEM for personal 101 care products (Karrer et al., Submitted). Kennedy et al. (2012) developed the Bystander and 102 Residential Exposure Assessment Model (BREAM) to evaluate non-dietary exposure. They 103 then proposed options to develop an aggregate exposure model combining BREAM with the 104 MCRA platform (Kennedy et al., 2015a; Kennedy et al., 2015b). However, this work was 105 restricted to pesticide exposure via agricultural activities and thus only involved workers, 106 bystanders and residents living near agricultural areas. Two software applications for 107 Stochastic Human Exposure and Dose Simulation (SHEDS-Multimedia and SHEDS-108 Residential) developed by the US. EPA only take into account specific scenarios of non-109 dietary exposure with no link to dietary exposure. A new tool, SHEDS-High-Throughput 110 (SHEDS-HT), based on SHEDS-Multimedia, combines direct dermal exposure, inhalation 111 and accidental ingestion with the ingestion of food and drinking water by MC simulation 112 (Isaacs et al., 2014). However, SHEDS-HT mainly focused on aggregate exposure from diet 113 and consumer product sources, and the scenario of exposure sources by dust and soil is not 114 clearly developed. Moreover, individual intakes are specified for the American population 115 only. Thus, a harmonised consistent approach for aggregate exposure in case of different 116 sources of exposure is still lacking.

117 The aim of this work was to set out general principles for assessing aggregate exposure of a 118 target population from various sources (diet, dust, air, soil and tap water) when data come 119 from heterogeneous surveys. Five different calculation processes were tested and compared. 120 The different methods were based on the general principle which consists in creating a 121 simulated population from the individuals of the different surveys via MC simulations. MC 122 simulations are often used to combine risk assessment data (Kennedy et al., 2012; Kennedy et 123 al., 2015a; Kennedy et al., 2015b; Paustenbach, 2000; Safford et al., 2015; Zartarian et al., 124 2017). They make it possible to draw random samples from distributions of datasets in order 125 to reconstruct the sources of exposure for each individual. These methods, which take into 126 account inter-individual variability as well as uncertainty, provide a more realistic estimate of 127 aggregate exposure for individuals across a population (Paustenbach, 2000).

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

131 **2 Materials and Methods**

132 2.1 **Exposure factors**

133 **2.1.1** Food consumption (Q_{Food}) and quantities of ingested tap water (Q_{Water})

134 Food consumption (Q_{Food}) and quantities of ingested tap water (Q_{Water}) for children were 135 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 136 137 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 138 139 toddlers and young children were notified in the database with 850 "specific baby foods" 140 (Fantino and Gourmet, 2008). To be representative of the child population, sampling weights 141 were assigned to each infant. A total of 706 children were recorded in BEBE-SFAE using 142 proportionate quota sampling based on the child's age, the mother's occupation and the 143 family's socioeconomic strategy.

144

145 **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, 95th 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.

151

152 **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.

160 2.1.4 Quantities of ingested soil (Q_{Soil}) and dust (Q_{Dust})

161 Quantities of ingested soil (Q_{Soil}) and dust (Q_{Dust}) were derived from the Exposure Factors 162 Handbook (U.S. EPA, 2011) for children under the age of one year and between the ages of 163 one and three years. A truncated lognormal distribution of Q_{Soil} and Q_{Dust} , as proposed by 164 Özkaynak et al. (2011), was fitted.

165

166 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.

Input variables		Age	References	Distribution	Mean	SD	Median	P95	Min	Max
Concentration in food (µg _{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
		6 - 12 months		Normal	5.4	1.6	-	8.0	0	26.25
Inhalation rate (m ³ .d ⁻¹)	IR	1 - 2 years	U.S. EPA (2011)	Normal	8.0	2.9	-	12.8	0	24.77
		2 - 3 years		Normal	8.9	2.9	-	13.7	0	28.17
Independence of $(ma d^{-1})$	0	6 - 12 months	US EPA (2011)	Lognormal	-	-	30	200	0	1000
ingested son (ing.u)	QSoil	1 - 3 years	0.5. EFA (2011)	Lognormal	-	-	50	200	0	1000
Ingested dust (mg.d ⁻¹)	0	6 - 12 months	US EPA (2011)	Lognormal	-	-	30	100	0	1000
	QDust	1 - 3 years	0.5. EFA (2011)	Lognormal	-	-	60	100	0	1000
Duct 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 (µg _{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 (μg_{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 (µg _{Pb} .m ⁻³)	C _{Air}	-	BDQA survey in this study	Empirical	7.8	5.6	6.6	17.1	1.4	41.4

172	Table 1. Summary of input	variables used for the ca	lculation of aggregate expo	sure to lead for children	aged six months to three years.
		5	<i>y</i> 00 0 <i>i</i>	5	0

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

174 **Individual dietary exposure, E_{i Dietary}, had previously been estimated in the report by ANSES (2014) and was included in the BEBE-SFAE

175 survey in this study by combining concentration data from the French infant Total Diet Study (Guerin et al., 2017) with the consumed quantities

176 and body weights available in the BEBE-SFAE survey (Fantino and Gourmet, 2008).

177 ***The geometric mean and geometric

178 Food contamination by lead (C_{Food}) 2.2.1

179 Food contamination by lead (C_{Food}) was recorded in 2011, from the first infant Total Diet 180 Study (iTDS), conducted in non-breastfed children under three years of age (Hulin et al., 181 2014). In iTDS, more than 500 chemical substances were analysed in foods. These included 182 substances naturally found in the environment and those originating in human activities (e.g. 183 industrial, agricultural, domestic, etc.). Food items were selected using the results of the 184 BEBE-SFAE survey, enabling home cooking practices to be considered. Overall, the iTDS 185 contained more than 5500 items as consumed foods, including foods such as vegetables, fruits 186 and cakes as well as specific children's food products. To limit censored data, a more 187 sensitive inductively coupled plasma mass spectrometry method was developed and validated 188 for lead in 291 samples (Guerin et al., 2017). With this method, the LOQ was 0.6 or 0.9 189 µg_{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 190 191 value of 16 µg_{Pb}.kg⁻¹ was observed (Guerin et al., 2017).

192

193 2.2.2 Child home and environmental contamination (CDust, CSoil and CWater)

194 The "Plomb-Habitat" (PH) survey recorded lead concentration data for tap water, soil and 195 dust in 472 homes of children aged from six months to six years in France between October 196 2008 and August 2009 (Glorennec et al., 2015; Lucas et al., 2012). Population sample weights 197 were available, to be representative of French dwellings. Lead concentrations in tap water 198 (C_{Water}) were measured in kitchens. The LOQ for lead in tap water was 1 μ g.L⁻¹. The average 199 lead load in dust (C_{Dust}) for each dwelling was evaluated in µg.m⁻². The LOQ for lead in dust 200 was 2 μ g.m⁻² for total lead. For concentrations in soil (C_{Soil}), in cases of children playing 201 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. 202

203

204 2.2.3 Air contamination (CAir)

205 Lead concentrations in outdoor air were collected from the regulatory monitoring network 206 (BDQA, the French database for air quality). Air quality monitoring has been implemented in 207 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 208 209 outdoor air were considered from 2007 to 2011 no representative French survey exists on air 210 concentrations in inside dwellings, outdoor air lead concentration were used to estimate 211 concentrations in indoor air of children's homes (C_{Air}). Data were not included when the 212 measurements were too low to calculate the annual mean, specifically when annual coverage 213 did not exceed 14% or when it exceeded 100%. Thus, a total of 176 measurements were 214 considered in rural, urban and suburban areas.

215 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.

221
$$E_{i,Aggregate} = (E_{i,Dietary} + E_{i,Soil} + E_{i,Dust} + E_{i,Water}) \times \tau_{ingestion} + EiAir \times \tau_{inhalation} (1)$$

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.

225
$$E_{i,\text{Dietary}} = \sum (Q_{i,\text{Food}} \times C_{\text{Food}}) / BW_i \quad (2)$$

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.

230 231

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

E_{i,Water} was the lead exposure via tap water of an individual i and was expressed in $\mu g_{Pb}.kg_{bw}^{-1}$ 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 $(\mu g_{Pb}.g^{-1} \text{ soil})$.

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

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 (m³.d⁻¹) and C_{Air} was the air concentration of lead (ng_{Pb}.m⁻ 246 ³).

247 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.

260

261 **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.

267 **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:

- The first step was to identify sociodemographic variables shared between surveys that
 could influence the input variables.
- 273
 2. The second step was to test, via a statistical analysis, the significance of the
 274 correlations between shared sociodemographic variables and the concentrations for
 275 each survey. In case of significant correlations, it proves the importance to integrate
 276 the stratification variables when sampling the concentration values in the different
 277 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.

281

282 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.

288 One major difference between the methods was the timeline of assigning exposure factors and 289 concentrations in the simulation process. The two MC1 and MC1S (MC in first step) methods 290 created a simulated population of 100,000 individuals taken randomly from the reference 291 population and assigned exposure factors and concentration values from the other surveys. 292 The MC2 and MC2S (MC in second step) methods first assigned exposure factors and 293 concentration values from the other surveys to each individual in the reference population. 294 Next, 100,000 individuals were randomly sampled from the combined data to create a 295 simulated population. The difference between MC1S/MC2S and MC1/MC2 was that MC1S 296 and MC2S used stratification variables to combine surveys, while this was not the case of 297 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.

308 To quantify the uncertainty associated with each method, the process was repeated 100 times.

309 Thus, for each method, 100 simulated populations of 100,000 individuals were created, and an

- 310 uncertainty interval was estimated.
- 311 312



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).

321

322 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).

329 For each exposure source and each of the 100 new populations, descriptive statistics (mean, 330 median, standard deviation and percentiles) were estimated from population results. Mean 331 contributions to aggregate exposure for each exposure source were calculated using the mean 332 of the individual ratios for each exposure source and aggregate exposure multiplied by 100. 333 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 334 335 and 97.5th percentiles were displayed in result tables to give estimates with credible intervals 336 reflecting uncertainty. Significant differences were observed when confidence intervals did 337 not overlap.

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

340

341 **3 Results**

342 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 BEBESFAE survey, with physiological and sociodemographic data for each child. Thus, BEBESFAE 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.

352

353 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.

- 371
- 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.

Innut voriables	Cumulan	Sociodemographic parameters					
Input variables	Survey	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		
		15					

Air concentration	BDQA	-	<0.001	<0.001	-
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375

376

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.

380

381 **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 μ g_{Pb}.kg_{bw}⁻¹.d⁻¹ and between 8.7 and 10 μ g_{Pb}.kg_{bw}⁻¹.d⁻¹, respectively (Fig. 2, Table 3). The lowest standard deviation values were 9.8 and 11 μ g_{Pb}.kg_{bw}⁻¹.d⁻¹, meaning that variability was lower with method 2 (MC2S and MC2).

387 The results showed no significant difference between the two methods, as the uncertainty 388 intervals (UIs) of the methods with MC in first step and MC in second step overlapped 389 (MC1S vs MC2S, and MC1 vs MC2). However, it was observed that the MC2 methods had 390 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 391 392 88 μ g_{Pb}.kg_{bw}⁻¹.d⁻¹ for MC2S and MC2) than with MC in first step (around 40 μ g_{Pb}.kg_{bw}⁻¹.d⁻¹ for MC1S and MC1). This higher uncertainty could also be observed for the contribution of 393 394 the various sources to aggregate exposure, especially for higher percentiles (Table 4). For 395 example, for the 5% of children with the highest exposure levels from soil, the upper bound of 396 contribution for MC2S reached 16% while it was 6% for the MC1S method.



398

Figure 2. Distributions of aggregate exposure ($\mu g_{Pb} k g_{bw}^{-1} d^{-1}$) to lead in children between the 399 400 ages of six months and three years in France with methods using stratification variables (on 401 the left) and methods without stratification (on the right). Ninety-five percent uncertainty 402 intervals appear in grey.

403

404 3.3.2 Stratification or no stratification?

405 Significant differences were observed between results for aggregate exposure and the 406 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 407 of aggregate exposure (e.g. P50 observed at 0.86 $\mu g_{Pb} k g_{bw}^{-1} d^{-1}$ and 0.95 $\mu g_{Pb} k g_{bw}^{-1} d^{-1}$ for 408 409 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). 410 411 The same significant differences were observed for contributions (Table 4).

412 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 413 children aged six months to three years in France. Estimates are expressed as median values and 95% uncertainty intervals presented in square

414 brackets.

Exposure sources	Methods	Mean	SD	P25	P50	P75	P90	P95	P99
	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]
Aggregate	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]
Aggregate exposure	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]
	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]
Food	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]
	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]
Soil	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]
	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]
Dust	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]
	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]
Ton water	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]
Iap water	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]
	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]
Air	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]

415 3.3.3 Taking into account correlations by using a vector of observations or 416 reproducing correlations

417 The different methods for taking into account concentration correlations (MCIC vs MC1)

418 produced similar results, as the UIs overlapped.

419

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
	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]
Food	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]
	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]
Soil	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]
	MC1S	57 [57 - 58]	84 [84 - 85]	93 [92 - 93]
	MC2S	57 [53 - 62]	84 [75 - 94]	93 [82 - 98]
Dust	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]
	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]
Tap water	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]
	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]
Air	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]

425 3.4 **Contribution of exposure sources to aggregate lead exposure**

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

427 **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 µg_{Pb}.kg_{bw}^{-1}.d^{-1}, and the 99th percentile was 37 µg_{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).

438

439 **3.4.2** Exposure via dust

440 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 441 percentile (Table 3). The contribution of dust ingestion to total exposure was 57% for median 442 aggregate exposure (Table 4). Regarding the top 10% most exposed children, the contribution 443 to aggregate exposure was 84%. C_{Dust} was positively correlated, at 0.572, with total exposure 444 (Table 5). Conversely, DL was negatively correlated, at -0.531.

445

446 **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 μ g_{Pb}.kg_{bw}⁻¹.d⁻¹ for the 50th percentile to 1.6 μ g_{Pb}.kg_{bw}⁻¹.d⁻¹ for the 95th percentile, reaching 3.6 μ 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).

		MC1S	MC2S	MC1	MC2	MCIC
Body weight	BW	0.048 [0.041 - 0.055]	0.047 [-0.017 - 0.121]	-0.046 [-0.0510.039]	-0.046 [-0.126 - 0.043]	-0.046 [-0.0520.039]
	QSoil	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]
5011	Csoil	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]
	QDust	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]
Dust	CDust	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 [-0.5350.527]	-0.532 [-0.6110.468]	-0.536 [-0.5410.532]	-0.533 [-0.6080.457]	-0.541 [-0.5500.533]
	QWater	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]
Tap water	CWater	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]
	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]
Air	CAir	-0.039 [-0.0450.032]	-0.037 [-0.111 - 0.058]	0.004 [-0.001 - 0.011]	-0.004 [-0.088 - 0.100]	0.004 [-0.002 - 0.011]

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

455 **3.4.4 Exposure via food**

The 50th and 95th percentiles of exposure from food were observed respectively at 0.21 and 0.34 μ g_{Pb}.kg_{bw}⁻¹.d⁻¹, reaching up to 0.52 μ 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).

461

462 **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 μ 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 μ g_{Pb}.kg_{bw}⁻¹.d⁻¹ and with a contribution below 0.29% for the top 5% of children most exposed to lead.



470

Figure 3. Histogram of the medians estimated for the 50th percentile (above) and the 95th 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.

475

476 **4 Discussion**

477 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. 485 SHEDS-HT for example, combines dietary exposure from individual data with theoretical 486 values concentrations from distributions fitted on data for the other exposure sources. In the 487 case of MCRA, the software combines dietary exposure individual data with non-dietary 488 exposure data (empirical or theoretical) evaluated first by another software. Thus, providing a 489 harmonized method for combining different surveys with empirical data in case of aggregate 490 exposure was the main aim of this paper. It can also be applied to reconstruct the information 491 for the whole dataset for an existing study where different level of information was studied for 492 different sub-populations. This is the case for some biomonitoring surveys, where 493 measurements of chemicals are performed for sub-populations. It may also be applied for 494 researchers and practitioners to combine data as a unique database to have a unique survey for 495 different purposes.

496 To establish general steps to aggregate exposure from several surveys, five methods for 497 combining data were compared using children (6 month to 3 years old) lead exposure case 498 study in integrating uncertainties. They combined surveys focused on dietary exposure 499 (BEBE-SFAE combined with TDSi), contamination in homes (PH surveys) and in air (BDQA 500 survey). All methods provided consistent results and showed that dust was the main exposure 501 source although there were some significant differences between exposure levels due to the 502 difference in the methodology to combines these surveys. Moreover, uncertainties 503 considerably varied between methods. Bonnel et al. (2015) also concluded that combining 504 surveys with different populations and methodologies increased the probability to include 505 biases due to sampling or measurements. Thus, it is primordial to consider and follow the 506 recommended steps to decrease biases and uncertainties.

507 The first step consists in selecting a reference population between the three surveys to 508 simulate a new population of 100 000 individuals. It is an important step as its 509 sociodemographic characteristics and parameters will be duplicated in the simulated 510 population. Thus, the reference of the population needs to be the most representative of the 511 target population to considerably decrease these biases.

512 In the second step, it is recommended to consider stratification variables when 513 sociodemographic variables shared between the reference population and the other survey 514 variables are significantly correlated with concentration/exposure levels. Indeed, specific 515 parameters such as sociodemographic variables, especially when they influence the quality of 516 the other variables, may decrease the inclusion of biases when they are used to combine data 517 (Bayart and Bonnel, 2015). When stratification variables was not considered, as with MC1 518 and MC2 methods, aggregate exposure values tended to be overestimated (around 11% for 519 P50), compared to the methods considering stratification. The selection of stratification 520 variables is thus an important step in the calculation of aggregate exposure allowing to merge 521 appropriate exposure values for a specific sub-population. Stratification variables should be 522 carefully selected, with the presence of classes in sufficient but not too high numbers. Indeed, 523 the variables should not contain too many classes, otherwise it will be difficult to find 524 connections between surveys and the probability of drawing the same value will increase. 525 Conversely, when the number of classes is too low, there is a risk of not reproducing the 526 observed correlations. To define the number of classes, it is recommended to test their impact 527 when making statistical tests of the correlation significance between possible stratification 528 variables and the concentration levels. In this study, the age and the region variables were 529 used as stratification variables. Although gender is often used to combine data (Biesterbos et 530 al., 2013; Comiskey et al., 2017; Kennedy et al., 2015a; Kennedy et al., 2015b), this 531 parameter was not used as a stratification variable because it was not correlated with the 532 concentrations in soil, dust and tap water. Furthermore, combining different consumption 533 surveys with stratification variables are very current on the case of personal care products and 534 cosmetics (Biesterbos et al., 2013; Comiskey et al., 2017) due to the lack of data for product 535 usage for the subjects. Biesterbos et al. (2013) recommended for the combination of data to 536 use gender, age and the level of education as they are important factors in the case of 537 exposure assessment of personal care product. Comiskey et al. (2017) also merged data by 538 pairing subjects with similar demographics (age range, gender, and geography) assuming that 539 they will have similar habits and practices.

540 The last step is to combine data using MC simulations. Our results showed that the UIs of the 541 methods with MC in second step (MC2 and MC2S) were very large. These two methods 542 showed high uncertainty in exposure values through the 100 new populations, especially for 543 the most heavily exposed children. A difference of around 20% in the aggregate exposure 544 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 545 546 values were not stable from one simulation to the next. Moreover, the variability within a 547 population simulated with MC in second step was lower than with MC in first step. Thus, 548 high exposure values were given less consideration with MC in second step. Consequently, it 549 is recommended to use the MC1S method which randomly samples individuals in the 550 reference population and simultaneously assigns exposure factors and concentration values

from other surveys. In this study, this resulted in consistent and stable exposure valuesbetween the 100 simulations.

553 In the case of multiple and independent data sets, correlations are often observed for analysis 554 process. In this study, PH survey included several variables of interest, i.e. concentrations of 555 lead in tap water, in dust and in soil for one dwelling, which were highly correlated between 556 them. To keep these correlations, we selected vectors of these three concentration variables in 557 MC1S/MC1 and MC2S/MC2 methods, and reproduced correlations between the 558 concentration variables during simulation process by the Iman-Conover method (Iman and 559 Conover, 1982) with the MCIC method. In astrophysics field, methods treats correlations 560 between multiple data sets and give appropriate relevant weights of multiple data sets with 561 mutual correlations by the creation of a hyperparameter matrix. The marginalization can be 562 carried out with a brute-force grid evaluation of the hyperparameters, or it can be explored by 563 using MC methods which directly sample the posterior distribution (Ma and Berndsen, 2014). 564 Other methods such as copula methods (Haas, 1999), or principal component analysis 565 (Cowan-Ellsberry and Robison, 2009) can be used to take into account correlations during 566 simulations. Regarding ways of taking into account correlations during simulation processes, 567 there was no significant difference between MCIC method and the selection of a vector of 568 concentrations (MC1). MC1 has the advantage to avoid additional uncertainty related to the 569 choice of simulation correlations, while MCIC has the advantage of being easier to implement 570 with popular commercial add-ins to Excel® such as @risk, Cristal Ball.

571

4.2 Aggregate children lead exposure in France

572 In this paper, dust and soil were found to be the most significant sources of exposure to lead 573 in France for children under the age of three years. Similar results were observed in France 574 (Glorennec et al., 2016) and the USA (Zartarian et al., 2017) for the most heavily exposed 575 children between the ages of three and six years. Indeed, between soil and dust, dust is more 576 likely to accumulate trace metals (Acosta et al., 2015; Gabarron et al., 2017). The ingestion of 577 lead from soil and dust is very significant in children due to their more intense hand-mouth 578 behaviour (Gabarron et al., 2017; Glorennec et al., 2012). Contaminated soil and especially 579 dust have been identified as contributors to blood lead levels in children in France (Etchevers 580 et al., 2014; Etchevers et al., 2015; Glorennec et al., 2010; Oulhote et al., 2013). Exposure via 581 dust in this paper is six times higher than observed by Glorennec et al. (2016) in children aged 582 three to six years. This is due to some differences in exposure factors and in concentration 583 data used to evaluate exposure. Indeed, Glorennec et al. (2016) used for dust and soil 584 ingestion a lognormal distribution with a standard deviation of 3.2 and truncated to the highest 585 observed value whereas in this study, the lognormal distribution was simulated with a 586 standard deviation of around 26, allowing a larger range of possible values as shown in 587 original data. This difference emphasises the importance of carefully choosing exposure 588 parameters in order to increase the confidence level of the analysis. As exposure factors came 589 from studies with different periods and regions, error could appeared in exposure estimates. 590 For example, Q_{Soil} and Q_{Dust} which moderately impacted aggregate exposure have often been 591 discussed (Dor et al., 2012; Moya and Philips, 2014; Özkaynak et al., 2011; U.S. EPA, 2011; 592 von Lindern et al., 2016; Wilson et al., 2013). In the present study, Q_{Soil} and Q_{Dust} were taken 593 from the Exposure Factors Handbook (U.S. EPA, 2011) which derived distributions from 12 594 key studies mainly conducted in North America between the 1980s and 1990s. However, 595 since the 90's, activity patterns, micro-environments and hygiene practices have been 596 improved (Moya and Philips, 2014). Furthermore, these data came from studies conducted in 597 North America, while this case study focused on the French population. Soil ingestion 598 quantities can vary depending on the geographic location, climate, season, or soil 599 characteristics. To our knowledge, no data on quantities of ingested soil and dust and on 600 inhalation rate, are available for children in Europe. Thus, there is a need of further research 601 on exposure factors to improve data quality and exposure assessment in Europe.

602 After the ingestion of soil and dust, food ingestion was the source that most contributed to 603 total exposure to lead from the half of the most exposed children. For low exposure (25th 604 percentile), dietary exposure is higher than other sources of exposure. As dietary exposure 605 values were directly recorded in the reference population (i.e. BEBE-SFAE survey), it had 606 already been aggregated by construction with sample pooling, leading to low variations in 607 exposure in the simulated population. Consequently, no significant differences between 608 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 $\mu g_{Pb} k g_{bw}^{-1} d^{-1}$ in this study, 609 while values for older children were found at 0.37 and 0.42 $\mu g_{Pb} k g_{bw}^{-1} d^{-1}$. Similarly, dietary 610 611 exposure was the main contributor to aggregate lead exposure for older children for the half of 612 the population exposed to lead, with notable contributions by milk, fresh soft drinks, 613 vegetables and bread (Glorennec et al., 2016), and then was overtaken by the exposure of dust 614 and soil for the most exposed children. Lower exposure values from food and higher from 615 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.

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EFSA (2010) estimated that the external dose corresponding to the BMDL₀₁ of 12 μ g/L (blood lead level) for developmental neurotoxicity was 0.50 μ 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.

635

636 **5** Conclusion

637 This work proposed a step-by-step approach for performing aggregate exposure assessments 638 by comparing different methods for combining heterogeneous surveys. The first step 639 consisted in selecting a representative reference population of the target population. In the 640 second step, it was recommended to consider stratification variables when combining surveys 641 to prevent exposure values from being overestimated. In the last step, it was recommended to 642 create a simulated population from the reference population and to simultaneously assign 643 exposure factors and concentration values from the other surveys using the stratification 644 variables. This timeline approach lowers the uncertainty of aggregate exposure. The 645 methodology was implemented to evaluate aggregate exposure to lead in the population of 646 children between the ages of six months and three years in France. Dust was the main 647 exposure source, followed by soil and food in a lesser extent.

648 This work is a first application of the proposed methodology which needs to be applied in 649 other case studies.

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658 **Conflicts of Interest**

659 The authors declare no conflicts of interest.

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