Mapping blood lead levels in French children due to environmental contamination using a modeling approach

Cleo Tebby, Julien Caudeville, Yasmil Fernandez, Céline Brochot

Science of the Total Environment 808 (2022) 152149

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Mapping blood lead levels in French children due to environmental contamination using a modeling approach

Cleo Tebby [a], Julien Caudeville [b], Yasmil Fernandez [a], Céline Brochot [a,*]

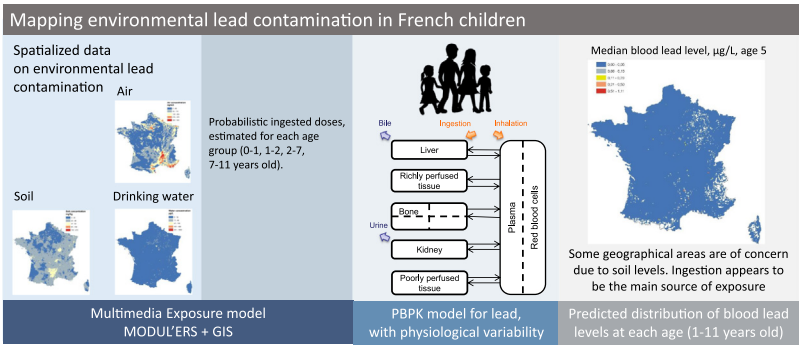
[a] Institut National de l'Environnement Industriel et des Risques (INERIS), Unité Modèles pour l'Ecotoxicologie et la Toxicologie (METO), Parc ALATA BP2, 60550 Verneuil en Halatte, France

[b] Institut National de l'Environnement Industriel et des Risques (INERIS), Unité ISAE, Parc ALATA BP2, 60550 Verneuil en Halatte, France

HIGHLIGHTS

- Spatialized data on environmental lead contamination was used in an exposure model.
- Ingestion and inhalation of lead by children in France was mapped.
- A PBTK model was used to map predicted blood lead levels in children.
- Predicted blood lead levels were compared to biomonitoring data.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 2 July 2021
Received in revised form 16 November 2021
Accepted 29 November 2021
Available online 4 December 2021

Editor: Lotfi Aleya

Keywords:
PBTK model
Multimedia exposure model
Lead (Pb)
Children
Maps
Blood lead levels

ABSTRACT

The decrease in levels of lead in air and drinking water over the last 40 years has resulted in an overall decrease in blood lead levels (BLLs). However, there is no known safe level of lead regarding developmental effects in children. This paper maps predicted BLLs of children in France, resulting from a simulated chronic exposure in two steps, with the aim of identifying areas with environmentally overexposed populations. Probabilistic estimates of BLLs based on environmental contamination were obtained and compared to biomonitoring data. First, the contribution of various environmental exposure pathways was estimated using a multimedia exposure model: spatialized data on soil, drinking water and air contamination, together with data on food contamination and ingestion, was joined using geostatistical approaches. In a second step, a Physiologically Based Toxicokinetic (PBTK) model provided estimates of BLLs. Probabilistic estimates of BLLs were obtained by simulating uncertainty and variability of exposure levels, physiological characteristics and lead-specific parameters in the PBTK model.

The median and 95th percentile of predicted BLLs in children aged 1 to 11 were compared to recent biomonitoring data obtained in France in young children (SATURNINF study): median predictions were overestimated in infants and in agreement with median observed BLLs in children aged 3 to 6. Upper bounds of predicted BLLs were protective due to uncertainties in exposure estimates. The main source of exposure appeared to be drinking water in children over 2 years old, and vegetal food and milk in children under 2 years old. Although elevated drinking water lead levels were not related to large geographical areas, the relatively fine resolution map also pinpointed geographical areas of concern due to elevated soil lead levels.

* Corresponding author.
E-mail address: celine.brochot@ineris.fr (C. Brochot).

http://dx.doi.org/10.1016/j.scitotenv.2021.152149

1. Introduction

Despite a decrease in lead levels in air and gradual replacement of lead plumbing, which together resulted in a 10-fold decrease in blood lead levels (BLLs) over 20 years (Manton et al., 2001), elevated BLLs are still reported. Lead contamination is of special concern in pediatric populations due to the adverse developmental effects of lead and because there is no known safe level regarding developmental effects (WHO, 2011a). Lead exposure in children is often measured in biomonitoring programs which illustrate local variations; for example around 1992 in the US, BLLs greater than 10 μg/dL were observed in 6.1% (Snyder et al., 1995) to 30% (Casey et al., 1994) or even 68% (Melman et al., 1998) of samples in children. In France, in 1995 and 1996, BLLs were greater than 10 μg/dL in 2.1% children aged 1 to 6 years old (Huel, 1997; Chanel, 1999). In 2008, this proportion had dropped to an estimated 0.09% in children aged 6 months to 6 years (Etchevers, 2013). Although the proportion of children at high risk of lead poisoning has decreased, lead remains a major public health concern (WHO, 2011b). For example, elevated BLLs must be reported to health care authorities in France: in 2015, the threshold for reporting cases of elevated BLLs was lowered from 10 μg/dL to 5 μg/dL, to allow for continued identification of most exposed children in a context of an overall decrease in exposure (Arrêté du 8 juin, 2015; Haut Conseil de la Santé Publique, 2014).

Environmental exposure to lead, a natural component of soils and an anthropogenically derived pollutant, can occur through several pathways. Lead can enter the human body through dust inhalation and ingestion, direct ingestion of soil and drinking water, and consumption of plants and animal products grown in contaminated soil (Dudka and Miller, 1999; Hawley, 1985; Rabinowitz et al., 1985). Lead found in tap water usually comes from the corrosion of older fixtures or from the solder that connects pipes.

Multimedia exposure models can be used to quantify the contribution of each source of exposure towards total exposure (McKone and MacLeod, 2003) by modeling lead transfers between environmental compartments. Contamination can be mapped by joining several databases of spatialized environmental data, thus providing a description of the global source-effect chain of exposure as illustrated in a previous study (Caudeville et al., 2012). Regulators rely increasingly on maps as decision-making tools, as illustrated in the recent Environmental Public Health Tracking approach (CDC, 2021). For proper interpretation prior to decision-making, the maps must also provide understanding of the sources of contamination and of the variance of the model outcome. In a context of exposure reduction, the maps of uncertainty help identify areas where additional data would improve spatial representativeness of the variables investigated action prioritization.

Combining databases of georeferenced measures is challenging in practice. Examples of approaches that estimate the exposure dose by integrating georeferenced measures or model predictions include mainly studies on single environmental media, such as soil (McGrath et al., 2004), water (Kavcar et al., 2009), and air (Uzu et al., 2011). Combining databases at a national scale and fine resolution is challenging due to lack of common spatial support of environmental quality measurements and to differences in time scale between punctual measurements or yearly averages for example. Various techniques are thus used to take benefit from all available information (Gay and Korre, 2006; Goovaerts, 2006), such as including information from auxiliary variables when sampling density is low (van de Kassteele et al., 2009; Bernard-Michel, 2006).

In a previous study, environmental lead contamination was mapped using a multimedia exposure model in the Hauts de France region, which represents 7% of population in the North of France, in part of the population aged 2–70 years old (Caudeville et al., 2012): children were identified as being at greater risk to high exposure levels compared to the maximum tolerable daily intake. A multimedia exposure model has also been used to estimate exposure of children in France in a different study (Glorennec et al., 2007), but could not include the more recent, spatialized data on soil contamination (Duigou and Baize, 2010). Previous research has also provided accurate probabilistic estimates of BLLs in the US by coupling IEUBK with an exposure module, Stochastic Human Exposure and Dose Simulation (SHEDS) (Zartarian, 2017), without however including legacy soil lead levels.

Estimates of total environmental exposure of humans to lead can be processed using toxicokinetic models to simulate internal concentration levels in tissues. The kinetic models available in the literature differ in how detailed and realistically the physiological processes related to growth and lead kinetics are described (Pounds and Leggett, 1998; Hogan et al., 1998; Sharma and Reddy, 2012; Leggett, 1993; O'Flaherty et al., 1998; White et al., 1998). Kinetics in bone are of paramount importance under chronic exposure scenarios since bone contains the majority of the body's lead burden (Hu et al., 1998) which can leach into blood and represent a considerable internal source of exposure to lead (Gulson et al., 1995). The ICRP (or Leggett) biokinetic model (Pounds and Leggett, 1998; Leggett, 1993), the Leggett + model (Vork et al., 2013), and the US EPA's Integrated Exposure Uptake Biokinetic (IEUBK) lead model (Hogan et al., 1998; White et al., 1998) have been used in risk assessment (Cornelis et al., 2006; Hassanien and Horvath, 1999; Lindern, 2003; Lindern, 2016). In this paper, BLLs were predicted using the more realistic Physiologically Based Toxicokinetic (PBTK) model developed by O'Flaherty et al. (O'Flaherty et al., 1998; O'Flaherty, 1991a; O'Flaherty, 1991b; O'Flaherty, 1991c; O'Flaherty, 1993; O'Flaherty, 1994; O'Flaherty, 1995; O'Flaherty, 2000) that accounts for bone to blood lead mobilization, describes lead transfers from compartments as blood flow (perfusion) limited and includes growth equations (O'Flaherty, 1993; O'Flaherty, 1995).

The present paper aims to assess geographic differences in exposure to lead and in predicted BLLs in France for young children resulting from ingestion of food, water, and soil (including in contaminated areas), and from inhalation. Thus, the approach used in (Caudeville et al., 2012) was extended to the whole of France and applied by focusing on children, including infants. First, spatialized data on environmental contamination was combined to estimate environmental exposure to lead. A PBTK model was used to identify critical ages by studying the modelled relationship between age, exposure dose, BLLs, and body burden. The multimedia exposure model predictions were used as an input to the PBTK model to generate maps of the distribution of BLLs in France. Finally, the predicted BLLs in France were compared to biomonitoring data.

2. Material and methods

2.1. Multimedia model of exposure to lead

Spatialized probabilistic estimates of lead exposure were obtained using a stochastic multimedia exposure model, MODUL'ERS, previously developed by Ineris (Bonnard, 2003; Bonnard and McKone, 2009; Bonnard, 2017): daily ingested doses were estimated based on lead transfer from the environment (air, soil, water) through local food chains. The model was implemented in the PLAINE GIS-based platform for environmental inequalities analysis (Caudeville et al., 2012; Caudeville, 2012) in order to combine various databases of georeferenced measures using several geostatistical methods, such as kriging, and to estimate air lead levels at the same spatial resolution as the ingested doses. Kriging topsoil concentration levels propagate spatial interpolation uncertainties which are higher in areas of the grid where few data are available, and thus helps to map uncertainty.

Both spatialized data and non-spatialized data were input to the multimedia exposure model subgroups in order to estimate daily ingested doses of lead via locally produced vegetables, store-bought products, soil and drinking water. Spatialized data included environmental lead concentrations for air, water, and soil (Table 1) and population density. Soil contamination was estimated based on atmospheric deposition, leaching, background topsoil lead levels reflecting natural lead levels, and diffuse anthropic sources (Caudeville, 2012). Auxiliary variables were used to complete data when sampling density was low. For example, in many water samples, lead was under the limit of detection: multiple imputation

Table 1
Data used in the multimedia exposure model.

Model parameter	Support and resolution	Spatialization method	Details	Source
Atmospheric deposition and lead level	Centroid of 0.5° × 0.5° grid	Kriging	Predictions for year 2005 by a Eulerian atmospheric dispersion model, including industrial and transport sources over Europe	Levels from the Chimere model (Menut et al., 2013) (INERIS). Annual mean levels and deposits aggregated for year 2005.
Lead in soil	Point: sample; surface: commune[a]	Kriging	Around 100,000 samples, after 1990	Trace metal topsoil database (Duigou and Baize, 2010) and the French Soil Quality Monitoring Network
Background lead in topsoil	1 × 1 km grid	Linear mixed model	Based on 2091 samples	French National Soil Quality Monitoring Network (Arrouays, 2002; Lacarce et al., 2012) and parent material data (INRAE) (ETM, INRA & ADEME Program).
Lead in water	Multiple imputation method: district	Multiple imputation: expectation-maximization algorithm and Bayesian classification model	Levels in water supply systems at a commune scale[a], measured between 2000 and 2012, around 100,000 samples	Sise'eaux database (Davezac, 2008), administrative boundary map of France, map of distribution system easements (Ioannidou et al., 2018)
Soil/dust ingestion	Not spatialized			MODUL'ERS (Bonnard, 2017) adapted from (Davis and Mirick, 2006) and (US EPA (US Environmental Protection Agency), 2011; van Holderbeke, 2007)
Food and water ingestion rates	Averages for each of 9 French areas.		Years 2006–2007, 1455 children, in each region	Children aged 0–2 years old: Surveys around nuclear power plants (Bonnard, 2017), Children over 2: Individual and National Food Consumption, INCA, study (Volatier, 2000), see also (Glorennec et al., 2007) in Ciblex database (Beaugelin-Seiller, 2002; ADEME and IRSN, 2003)
Food contamination	Not spatialized		Years 2007–2009, 19,830 products covering 212 food types	Second French Total Diet Survey, EAT2 (ANSES) (ANSES, 2011)

[a] A "commune" usually covers around 10 km^2.

methods were used to estimate values with better accuracy than by replacing the value by the limit of detection.

Non spatialized data (Table 1) included national data for store-bought foodstuffs contamination and regional, age-specific, dietary habits. Ingestion rates (SI Table 1) were estimated using body weight, water consumption and quantity of soil ingested for each age group. The percentage of food that was homegrown was also included in the model for each grid unit depending on the degree of urbanization and was obtained from a 1991 INSEE (Institut National de la Statistique et des Etudes Economiques) survey in France (Bertrand, 1993). The model does not take bottled water consumption into account: drinking water was assumed to be only produced and consumed locally. Non-environmental contamination, as deteriorated lead paint and breast milk, was not included since no spatialized or individual data was available. The contribution of the dermal exposure pathway is usually low (Stauber et al., 1994) and was not taken into account.

Dietary intakes were estimated assuming 100% bioavailability in food and water and 60% bioavailability in soil and dust (US EPA, 2013). Here the term bioavailability refers to lead that is available for absorption not the absorbed fraction. Drinking water was assumed to be free of suspended particles which may bear lead.

2.2. Lead PBTK model in children

2.2.1. Description

The PBTK model developed by O'Flaherty et al. (O'Flaherty et al., 1998; O'Flaherty, 1991a; O'Flaherty, 1991b; O'Flaherty, 1991c; O'Flaherty, 1993; O'Flaherty, 1994; O'Flaherty, 1995; O'Flaherty, 2000) includes five main compartments with flow limited kinetics except in bone. Bone is subdivided into cortical and trabecular bone. Cortical mature bone is divided into concentric shells, which model bone canaliculi, through which lead diffuses to and from the blood in the innermost shell. Lead is also transferred between all types of bone and plasma through bone formation and remodeling processes. In this paper, the model version described in O'Flaherty (2000) was used, and the number of bone shells was set to seven.

Physiological changes were modelled as functions of age (e.g. bodyweight, bone formation rate, lead transfer rate from immature to mature bone, absorbed fraction of lead) and of bodyweight (e.g. fractional organ volumes, cardiac output, respiratory rate, and glomerular filtration rate) (O'Flaherty, 1991c; O'Flaherty, 1994; O'Flaherty, 2000).

2.2.2. Model evaluation

2.2.2.1. Comparison with kinetics data in children. Consistency between the predictions obtained with the recoded PBTK model and those published during the original model development (O'Flaherty, 1995) were checked, using the parameter values used at the time for four studies (see SI section 2.2.1). Values of several model parameters (BIND, KBIND, P0, D0, R0, partition coefficients) have been changed over time (see SI section 2.1), as an increasing amount of data was available, and the model was further developed and extended. The comparison of our predictions with the data is reported in SI section 2.2.2. As the data on actual lead intakes in children and the resulting kinetics are sparse, the results obtained with the model published by O'Flaherty (1995, 2000) were also compared to those obtained with IEUBK (White et al., 1998) at identical uptakes (see SI section 3.1 for details).

2.2.2.2. Comparison of predicted and observed relationship between blood and plasma lead. The relationship between lead in plasma and lead in whole blood was studied because recent data challenges the way this relationship was modelled, and several parameter values have been used in various studies. Lead binds to red blood cells and only the fraction in plasma is readily diffusible to target organs (Hu et al., 1998; Cake et al., 1996). It is therefore currently unclear whether biomonitoring should use whole blood lead levels, which present fewer interindividual variations (Sommar et al., 2014), or plasma levels, which are lower (Bergdahl et al., 2006) but may be more relevant in a toxicological context and are proportional to exposure (Sommar et al., 2014). These considerations have encouraged recent publication of additional data obtained with more precise equipment (Manton et al., 2001; Bergdahl et al., 1997; Bergdahl et al., 1998; Bergdahl et al., 1999; Hernández-Avila et al., 1998; Hirata et al., 1996; Schütz et al., 1996; Smith et al., 2002) and, in some cases, with care about sample contamination at low lead levels (Manton et al., 2001).

In the model by O'Flaherty, the relationship between lead in plasma and lead in whole blood is based on experimental studies (deSilva, 1981; Manton and Cook, 1984; Manton and Malloy, 1983; Marcus, 1985) (described in SI section 2.1). In this paper, predicted plasma and BLLs were compared to more recent data (Manton et al., 2001; Bergdahl et al., 1997; Bergdahl et al., 1998; Bergdahl et al., 1999; Hernández-Avila et al., 1998;

Hirata et al., 1996; Schütz et al., 1996; Smith et al., 2002; MacMillan et al., 2015) (SI section 3.2) and to the predictions obtained with the Leggett+ model (Vork et al., 2013) and with various updated models (Sommar et al., 2014; Bergdahl et al., 1997; Bergdahl et al., 1998; MacMillan et al., 2015).

2.2.2.3. Predicted kinetics in bone and blood compartments. Predicted lead sequestration in bone and bone to blood mobilization were studied using simulations, with the aim of i) detecting whether elimination or sequestration pathways became saturated at high doses and ii) identifying critical ages for lead accumulation. First, BLLs were predicted from age 1 to 11, assuming constant exposure to ingested doses ranging from 10^{-5} to 10 mg/kg BW/day. In a second step, constant exposures of one-year duration at increasing age and constant exposures of increasing duration were simulated. In both cases, the amount of lead in bone and the BLL in 5- and 11-year-olds was quantified in order to estimate how much of the lead in blood was attributable to ancient exposures and bone to blood mobilization according to the model.

2.2.2.4. Sensitivity analyses of the PBTK model. Sensitivity analyses of the PBTK model were performed, first using the Morris method (Morris, 1991) as a screening approach with 33 parameters, then using the variance-based Sobol method (Saltelli et al., 2008; Sobol et al., 2007) with a subset of influent parameters (SI section 3.3). Sensitivity of two outputs, BLL and body burden, were assessed using first order and total Sobol sensitivity indices, at ages 1, 3, and 11 years old, according to the median exposure scenario estimated for 11-year old children in France.

2.3. Mapping blood lead levels in children in France

Probabilistic, spatialized, estimates of exposure to lead were input into the PBTK model in order to map median, 95th percentile and variance of BLLs, and to estimate the overall probabilistic distribution in France. The distributions represent both exposure and physiological variability and uncertainty.

2.3.1. Exposure scenario

France was mapped as a grid with 59,266 units. Air lead levels were estimated using the multimedia exposure model, assuming constant levels in each grid unit throughout the 11-year simulation period.

In each grid unit, in each age group, and for each year, probabilistic distributions of ingested daily doses were obtained using statistical distributions of environmental contamination data to propagate uncertainty and variability throughout the multimedia exposure model (Caudeville et al., 2012). Exposure was assumed to be constant within four age groups, [0–1] [1–2], [2–7], and [7–11] years old. Each child was assumed to remain in the same grid unit at the same percentile of ingestion exposure throughout the simulation, therefore the variability is a population-based variability and does not represent repeated measurement variability that could be observed for each child.

2.3.2. Estimation of population blood lead levels

The PBTK model was used to predict distributions of population BLLs in each grid unit based on air lead levels and probabilistic ingested doses for each age group. In the PBTK model, variability of physiological parameters and uncertainty on lead-specific kinetic parameters were modelled with normal distributions (see SI section 4.1). Several physiological functions in the PBTK model depend on bodyweight, such as fractional organ volumes, cardiac output, respiratory rate, and glomerular filtration rate. Variability around bodyweight was assumed to follow a normal distribution centered on the bodyweight predicted by the model by O'Flaherty et al. (O'Flaherty, 1993) and with a coefficient of variation of 11% which was based on growth charts (Centers for Disease Control and Prevention (CDC) - National Center for Health Statistics, 2000a; Centers for Disease Control and Prevention (CDC) - National Center for Health Statistics, 2000b; Centers for Disease Control and Prevention (CDC) - National Center for Health Statistics, 2000c; Centers for Disease Control and Prevention (CDC) - National Center for Health Statistics, 2000d) (see SI section 4.2). Maps of median and 95th percentile were generated using 1000 Monte Carlo simulations in each grid unit, sampling from both ingested doses and PBTK parameter distributions. The spatialized population density was thereon used to estimate the probabilistic distribution of the BLL in the population.

Predicted BLLs were compared to French biomonitoring data collected in children, in the Saturn-Inf study, in 2008, which was conducted by the Institut de Veille Sanitaire (InVS) (Etchevers, 2013): BLLs had been measured in 3831 children aged between six months and six years old. The estimated BLL in the population studied was reported to follow a log-normal distribution, with geometric mean 1.5 μg/dL, median 1.5 μg/dL and 95th percentile 34.2 μg/dL. Quantitative comparisons with our predictions were limited because our predicted BLLs were estimated at set ages, whereas biomonitoring data was available as aggregate statistics in age groups. For example, predictions at age two were compared with data obtained in children aged between one and two years old.

2.4. Software

Environmental exposure was assessed using the multimedia model included in MODUL'ERS (Bonnard, 2010) and the PLAINE GIS-based platform (Caudeville et al., 2012). Environmental data was processed using R version 3.6.1 (R Core Team, 2019). The PBTK model published by O'Flaherty was rewritten and implemented in R version 3.6.1 (R Core Team, 2019), using packages deSolve (Soetaert et al., 2010), data.table (Dowle and Srinivasan, 2019), fitdistrplus (Delignette-Muller and Dutang, 2015) and sensitivity (Pujol, 2019), and also implemented in GNU MCSim v6.2.0 (Bois, 2009).

3. Results

3.1. PBTK model evaluation

3.1.1. Comparison with IEUBK predictions in children

Predicted BLLs obtained with IEUBK and the O'Flaherty model, using the IEUBK default exposure scenario, were in agreement in children up to 4 years old. Exposure levels peaked at around 30 μg/day at age 2, resulting in BLLs around 8 μg/dL (Fig. 1). After age 4, the predicted BLLs were higher using the PBTK model.

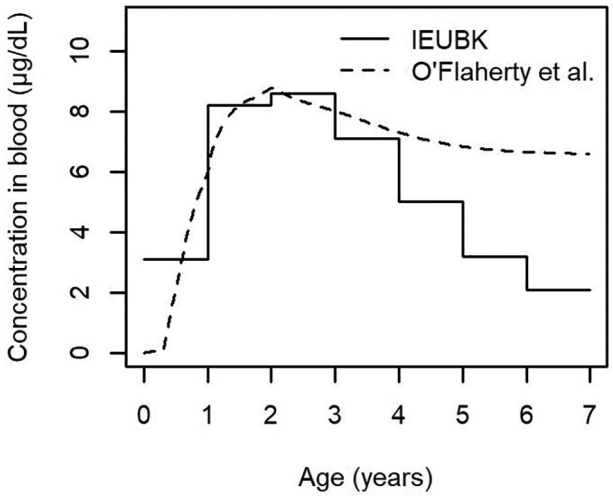


Fig. 1. Predicted blood lead concentration using IEUBK and the PBTK model by O'Flaherty et al.

3.1.2. Evaluation of model characteristics

3.1.2.1. Relationship between plasma and blood lead levels. At environmentally relevant levels (in the range of 0.5–20 μg/dL in blood) the linear relationship between blood and plasma lead levels appeared to be satisfactory, as in (Manton et al., 2001), but the plasma levels were overpredicted in the lower range of BLLs according to recent studies (Manton et al., 2001; Hernández-Avila et al., 1998; Smith et al., 2002; MacMillan et al., 2015) (Fig. 2). At higher BLLs, up to 100 μg/dL, the curvilinear relationship predicted by the model by O'Flaherty et al. appeared to be appropriate, as noted in studies with higher exposures (deSilva, 1981; Manton and Cook, 1984), though these studies may have suffered from overestimation in their lower range. Overall, the relationship was similar, though less steep, to the relationship used in the Leggett + model within a smaller range of BLLs (Fig. 2). New estimates of the capacity (*BIND*) and the dissociation constant (*KBIND*) parameter values (1.92 mg/L and 0.00225 mg/L respectively) provided better predictions of recent blood and plasma data, but these modifications were discarded since they resulted in higher BLLs than predicted by the original model. The upper limit of the domain of applicability appeared to be 100 μg/dL, since the small number of measurements greater than 100 μg/dL were not well predicted (Fig. 2 and SI section 3.2).

Simulations showed that BLLs increased linearly with the ingested daily dose up to 0.01 mg/kg BW/day (SI section 3.4, SI Fig. 11) and reach around 33 μg/dL. At this exposure level, 99.7% of lead in blood is bound to red blood cells. At higher exposure doses, the BLL is no longer representative of the amount of lead being absorbed, sequestered and eliminated, due the relationship between plasma and blood lead levels.

3.1.2.2. Relationship between bone and blood lead levels. The skeletal growth model resulted in age-dependent sequestration in bone and bone to blood mobilization in older children. Simulations showed that under a constant dietary exposure, the sequestration of lead in bone was maximal at age 2 weeks, due to a high absorbed fraction; sequestration then sharply decreased to around 10% at ages 18 months to 5 years old, then gradually increased as the proportion of bone in the body, the proportion of adult bone, and the rate of transfer of lead from cortical to adult bone increased (SI sections 3.5 and 3.6). Bone to blood mobilization only affects BLLs in young children on a short term. When environmental exposure ceases, the amount of lead in bone rapidly decreases because of the small proportion of mature, slowly perfused, cortical bone in children. As a result, in young children, BLLs are mostly representative of very recent exposure. Bone to blood mobilization increases with age. For example, at age 11, although mature cortical bone still only represents 50% of total bone volume, only 31% of bone lead dates from the past year (SI section 3.6).

The sensitivity analyses in 1, 3 and 11-year-olds (see SI section 3.3) showed that BLL was highly sensitive to the parameters related to lead binding to red cells (BIND and KBIND), to the absorbed fraction (frabs_var) of ingested lead and to elimination from plasma by glomerular filtration (plasma_Cl_var). The body burden (which is mostly concentrated in bones) was mostly sensitive to variations in absorbed fraction and elimination by glomerular filtration. The proportion of bone in the body was also highly influential (ske_coef) in particular in 3-year-old children, as well as the transfer from plasma to forming bone (LEAD). In 1-year old children, the cortical vs. trabecular bone ratio and the proportion of bone formation rate occurring in the cortical bone were also important. These results confirm that, in children, lead is mostly sequestered in bone by clearance from plasma during bone formation.

3.2. Maps

3.2.1. Environmental contamination

Environmental exposure was estimated by first mapping the environmental contamination in air, soil and water on a fine resolution: the maps show areas where high exposures are more likely to occur (Fig. 3).

Lead levels in air are highest in industrial areas, around Paris, the Rhone valley and along the Mediterranean coast (Fig. 3A). The map of lead levels in air shows a continuous spatial structure due to high spatial autocorrelation associated with air dispersion. Soil lead concentrations are related to the geology and are highest in areas with volcanic rock, in particular round the Massif Central (Fig. 3B). A small number of hotspots can be identified on the map which match certain sites which are declared as potentially polluted according to the Basol database (SI Fig. 24B). Lead levels in tap water display smaller scale local variations that depend on administrative unit boundaries (Fig. 3C).

3.2.2. Contributions of the various exposure routes

Using the estimated exposure as an input to the PBTK model showed that ingestion was the main source of exposure in children. The estimated contribution of air inhalation for a median exposure level in France was 0.5% in 1-year-olds and 2% in 11-year-olds. Within ingested lead, the contributions of the various sources of exposure depend on the age: children aged 0–2 years old are mostly exposed to lead via vegetal foodstuff and milk; in children over 2 years old the main source of lead exposure is drinking water, followed by vegetal foodstuff (mainly store-bought) (Table 2, averages over all grid units).

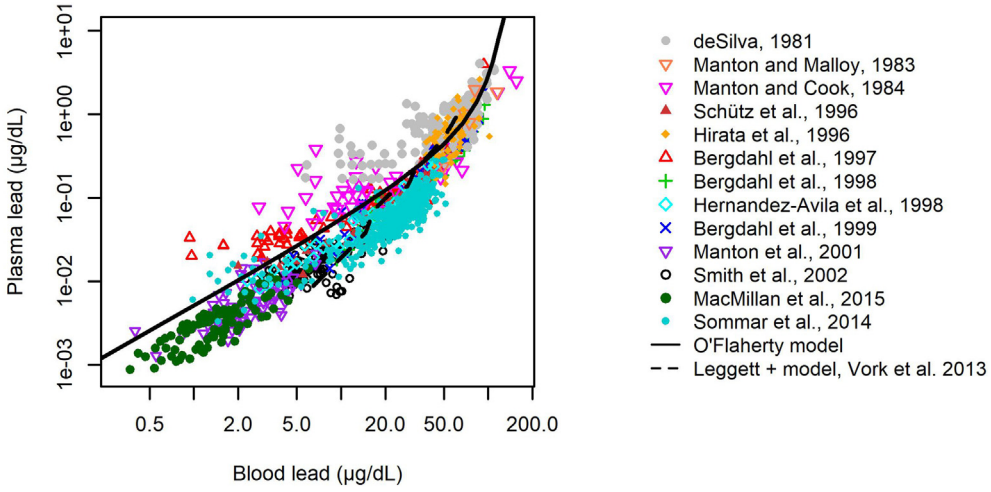


Fig. 2. Relationship between plasma lead level and total blood lead level using data from (deSilva, 1981) as shown in (Marcus, 1985) and data from (Manton et al., 2001; Sommar et al., 2014; Bergdahl et al., 1997; Bergdahl et al., 1998; Bergdahl et al., 1999; Hernández-Avila et al., 1998; Hirata et al., 1996; Schütz et al., 1996; Smith et al., 2002; Manton and Cook, 1984; Manton and Malloy, 1983; MacMillan et al., 2015).

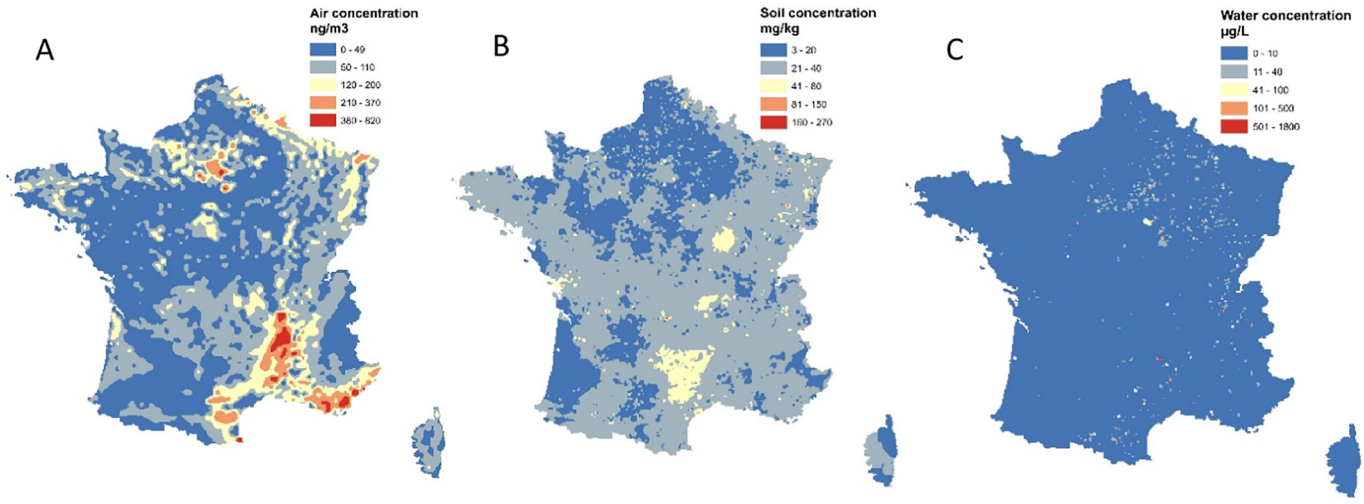


Fig. 3. Map of lead concentrations in air (A), soil (B) and drinking water (C).

3.2.3. Blood lead levels

Median and 95th percentiles of predicted BLLs in France in each age group are reported in Table 3. The median predicted BLL was higher than observed in biomonitoring data for children under 2: BLLs were over predicted 4-fold in children under 1 year old and 2-fold in ages 1 to 2. As much as 39% of children under 1 were predicted to have a BLL greater than 5 µg/dL whereas this was observed in less than 5% of each age group. For ages 3 to 6, the predicted BLLs are in good agreement with those reported in children in 2008 in France (Etchevers, 2013), where median BLL ranged from 1.48 to 1.57 µg/dL in ages 2 to 6 years old (Table 3).

The spatial distribution of the median and 95th percentile of predicted BLLs in five-year-old children in France are represented in Fig. 4 (age 1 and 11 are provided in SI Figs. 20 and 21). At age 5, drinking water is the main source of exposure, which explains that areas of high exposure are located in hotspots. Indeed, in 5 year-olds, the correlation between p50 of BLLs and median drinking water lead level in each grid unit (correlation coefficient between log-transformed values, $r = 0.62$) is higher than the correlation between p50 of BLLs and median soil lead level in each grid unit (correlation coefficient between log-transformed values: $r = 0.26$). The map of variance of the predicted BLLs (SI Fig. 22) indicates higher variability and uncertainty in predictions in areas with elevated blood lead levels and in areas with larger kriging variance in the estimation of soil lead levels (SI Fig. 24B).

4. Discussion

The maps of predicted BLLs in France indicate areas with environmentally overexposed populations. Environmental contamination was mapped to assess environmental inequalities of lead exposure in France. The maps of predicted BLLs reflect a complex set of spatial and environmental factors which operate at different spatial scales.

Certain hotspots can be recognized as legacy sites (identified using the Basol database (French Ministry in Charge of the Environment, n.d.), maintained by the French Ministry in charge of environment, SI Fig. S24B) such as Metaleurop and Mortagne du Nord (Caudeville et al., 2012). However, in many cases, measurements of lead in topsoil were not available around known legacy sites. The kriging approach (Caudeville, 2012) allowed us to propagate spatial interpolation uncertainties which are higher when few data are available to estimate topsoil concentration in the modeling grid (mostly in mountainous areas, see kriging variance in soil levels, SI Fig. 24B).

The discrepancies between predicted and observed BLLs in young children may arise from overestimated media intake in young children. Although other biomonitoring studies have reported 30% higher BLLs in children aged 1 and 2 compared to other age groups in the US (Aelion and Davis, 2019), children under age 1 did not have elevated BLLs in this US study (Aelion and Davis, 2019), and the 30% difference was smaller than our overestimation. The data on quantities of foodstuff ingested by children aged 0–2 years old was obtained from different databases using different methodologies (Bonnard, 2017; Volatier, 2000) and originate from scenarios used in risk assessment. The resulting exposure estimates represent much higher ingested doses in children under two, with a 5.2 median decrease between age 0–1 and age 7–11 groups (SI section 5, Fig. 23), which is consistent with the three-fold decrease observed in BLLs. The discrepancies could also arise from the PBTK model, which overestimated BLLs (though by less than a two-fold factor) in infants in the only study in children where the actual lead intake had been measured and compared to resulting BLLs. The PBTK model had been validated in adults, for which experimental data on the relationship between actual intakes and BLLs is available. Such data is not available in children.

In this paper, uncertainty on exposure and internal kinetics, as well as physiological variability, were propagated through to the final estimates of BLLs, using Monte Carlo simulations. Our predictions included a higher proportion of high BLLs than observed in biomonitoring data. Indeed, the 95th percentile was overpredicted by at least 2-fold at all ages, up to 13-fold in children under 1 year old. The fact that the range of predictions was wider than the observations may indicate that the simulated variability, in particular in the exposure model, may have been too large, or that the uncertainty in predictions was large. Coefficients of variation on physiological and lead-specific internal kinetic parameters was indeed only 10% and would not have caused such discrepancies. On the other hand, the geometric coefficients of variation in soil ingestion and dietary lead intakes were around 200% and the arithmetic coefficient of variation in soil lead levels was around 30%. Furthermore, in the multimedia exposure model, there was a high level of uncertainty and variability on transfer rates between soil and plants which were determined with experimental data and uncertainty on media lead levels was higher in areas far from sampled sites. The wide distribution of predicted BLLs in children over 2 years old may therefore partly be due to uncertainties in exposure levels.

Table 2
Contributions (%) of each source of exposure to total lead ingestion at ages 0–12 years old.

Age group (years)	Soil	Water	Vegetal	Meat	Milk
[0–1]	2.5	14.4	51.6	0.1	31.5
[1–2]	5.2	21.4	48.1	2.5	22.9
[2–7]	5.9	39.5	29.4	5.5	19.7
[7–12]	5.2	40.4	32.3	6.7	15.5

Table 3
Distribution of predicted blood lead levels (BLLs) in France in each age group: median, 95th percentile (P95) and % children with blood lead levels greater than 5 μg/dL. 1000 simulations were performed in each grid unit. Results are weighted by population density in each grid unit. Predictions are compared to observed BLLs collected in the Saturn-Inf biomonitoring study in 2008–2009 (Etchevers, 2013).

Age (years)	Median BLL (μg/dL)		P95 BLL (μg/dL)		Predicted % children with BLL > 5 μg/dL
	Predicted	Observed	Predicted	Observed	
	4.33	1.4	11.6	3.42	38.9
1	2.44	1.53	7.72	3.09	16.4
2	1.43	1.49	6.51	3.33	10.1
3	1.37	1.5	6.33	3.21	9.49
4	1.39	1.57	6.41	4.69	9.81
5	1.49	1.48	6.76	3.34	11.1
6	1.61		7.18		12.7
7	1.40		6.21		8.96
8	1.34		5.94		7.99
9	1.30		5.66		7.34
10	1.27		5.66		7.01
11					

Several sources of uncertainty and variability in exposure and physiology were not modelled. Regarding exposure assessment, many cases of highly exposed children are related to cultural or behavioral factors involving use of contaminated kitchen tools, crockery, or cosmetics, or lead-based paint in households, which are not considered in our environmental exposure model. Adding these individual behavioral factors would have further increased the prevalence of elevated predicted BLLs. Certain physiological variabilities were also not modelled realistically. In particular, the growth model and variability assumed around body weight at a given age does not cover the highest percentiles of observed weight distributions (SI section 4.2): obesity is not taken into account. Since overweight children have a lower proportion of bone in total bodyweight, their BLLs would be lower at a given exposure level. Furthermore, our methodology did not account for individuals moving from one location to another: children were assumed to remain at the same percentile of exposure in their grid unit and in the same grid unit. This is not expected to affect BLLs to a large extent, since blood lead is mostly representative of recent exposure in children according to the PBTK model.

The main sources of exposure to lead were age-dependent and mainly dietary. In the previous analysis by Caudeville et al. (2012) in a Northern French region, the largest contributions to lead exposure were drinking water (38%), followed by soil (15%), vegetal foods (17%), and milk ingestion (13%) in the population aged 2–70 years old. In the present study, the direct contribution of soil was smaller, and the analysis suggested vegetal food stuff and milk may be important exposure sources in children under 2 years old, although there is high uncertainty in this age group. Tap water was an important source of exposure in children over 2 according to our results, contrary to findings in another French exposure modeling

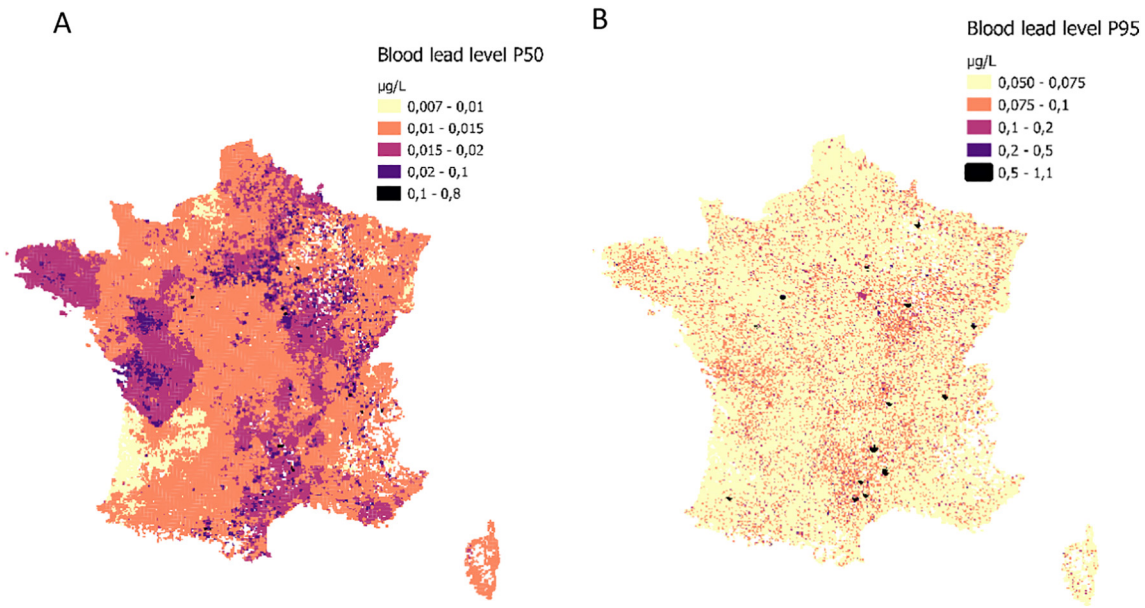


Fig. 4. Median (A) and 95th percentile (B) of predicted blood lead levels in children aged 5 in France. Uninhabited areas are represented in white.

analysis (Glorennec et al., 2007), where over half the children were assumed not to drink tap water. Furthermore, in a modeling approach combining the Stochastic Human Exposure and Dose Simulation (SHEDS) multimedia model with IEUBK (Zartarian, 2017) and using exposure data from the US, soil and dust were the main source of exposure in infants, and water was the other main source of exposure in infants (0–6 months), or food in children aged 1–2 years old.

Lead in air was not directly responsible for elevated BLLs predicted in children. The estimated contribution of air for a median exposure in France is lower than the contribution estimated with IEUBK in an urban environment in UK before 1990 (3% of exposure via inhalation) (Davies et al., 1990), and higher than the geometric mean contribution (0.09%) from inhaled air, estimated with IEUBK, in an urban environment in Australia between 2001 and 2006 (Gulson et al., 2018).

Several improvements of the PBTK model developed by O'Flaherty et al. were envisioned, in particular based on additional data collected since the model was developed. The relationship between plasma and whole BLLs was updated by several authors (see SI sections 2.1 and 3.2, SI Fig. 9); in the present work it was not updated based on the additional experimental data collected from the literature because the updated blood:plasma lead relationship provided less accurate predictions of BLL at environmentally-relevant exposure levels. Other components of the model, such as the fraction of lead excreted by glomerular filtration in children, could also be adjusted to more realistic values. These changes were not retained in the model since the model was developed and validated with a set of equations and parameter values which produced adequate results in a trade-off between physiological accuracy and model parsimony, while maintaining prediction accuracy. Modifications of the parameter values may imply that additional physiological processes must be modelled in order to maintain prediction accuracy.

The discrepancy between BLLs predicted using IEUBK and the higher BLLs predicted using the model by O'Flaherty in children aged 4 and over could be attributable to many of the differences in model structure, which pertain to all ADME processes. It is unlikely to result from higher leaching from bones with the O'Flaherty et al. model, because young children have very little mature cortical bone from which lead can leach into blood. IEUBK is used as a reference in risk assessment and is assumed to provide accurate estimates at least in younger children. However, in children over 4, other studies have also shown a slight discrepancy between IEUBK predictions and biomonitoring data. IEUBK model predictions were within 1 μg/dL of observations reported by Hogan et al. (1998), a biomonitoring study in children aged 0–7 years old, of which 28% of children were over 4 years old. Children aged 6–7 years old were underrepresented. In children over 4, a slight underprediction using IEUBK was reported, which could partly explain that IEUBK predictions were lower than those obtained with the model by O'Flaherty et al. On the other hand, it can also be noted that in a simulation study coupling SHEDS and IEUBK, the median BLL in children aged 2 to 6 years old was slightly overestimated (up to 23%) (Zartarian, 2017). However, the difference in predictions in children older than 4 between IEUBK model and the model by O'Flaherty is larger (up to almost 3-fold) than the differences reported between IEUBK predictions and the biomonitoring data.

5. Conclusions

The combination of a multimedia exposure model and an existing PBPK model for lead provided realistic predictions of median blood lead levels in France in children aged 2 and over, but the variability, and thus the 95th percentile, were slightly overestimated. In children under 2 years old, high uncertainties in exposure lead to overestimation of their BLLs. Mapping environmental contamination by lead and the resulting BLLs in children in France highlights the impact that some particularly highly contaminated geographical sites can have on blood lead levels via consumption of local products, which is important in prevention of saturnism. Regarding environmental exposure, tap water appears to be still a major concern in certain locations in children over 2 years old, as well as vegetal food stuff and milk in particular in children under 2 years old.

This work highlights several uncertainties regarding exposure, which call for additional data and knowledge in transfer between environmental media. In particular, the data on soil contamination is sparse in some areas, soil contamination around many legacy sites is unknown, and environmental exposure estimates in infants are uncertain. Furthermore, the present results are limited to environmental contamination: behaviors such as use of traditional contaminated kitchenware, consumption of bottled water, and other factors such as lead-based paint in households and breast feeding could explain differences in findings with other studies on children's exposure.

CRediT authorship contribution statement

Cleo Tebby: Conceptualization, Methodology, Software, Validation, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Julien Caudeville:** Methodology, Investigation, Data curation, Writing – review & editing, Visualization. **Yasmil Fernandez:** Methodology, Software. **Céline Brochot:** Methodology, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was funded by the French Ministry in charge of Ecology within the Programme 181. The authors also gratefully acknowledge the financial support of the European Unions' Horizon 2020 Research and Innovation Program under Grant agreement no. 733032 HBM4EU (www.HBM4EU.eu).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2021.152149.

References

ADEME, IRSN, 2003. Base de données de paramètres descriptifs de la population française au voisinage d'un site pollué - Database of descriptive parameters of French population near a polluted site.

Aelion, C.M., Davis, H.T., 2019. Blood lead levels in children in urban and rural areas: using multilevel modeling to investigate impacts of gender, race, poverty, and the environment. Sci. Total Environ. 694, 133783.

ANSES, F.a.f.f., 2011. Environmental and occupational health and safety. Second French Total Diet Study (TDS 2), Report 1 - Inorganic Contaminants, Minerals, Persistent Organic Pollutants, Mycotoxins And Phytoestrogens.

Arrêté du 8 juin 2015 modifiant le modèle de la fiche de notification figurant à l'annexe 27 de l'arrêté du 22 août 2011 relatif à la notification obligatoire des maladies infectieuses et autres maladies mentionnées à l'article D. 3113-7 du code de la santé publique. Ministère des Affaires Sociales JORF n°0137 du 16 juin 2015, d.l.S.e.d.D.d.F.

Arrouays, D., 2002. A new projection in France: a multi-institutional soil quality monitoring network. C. R. Acad. Agric. Fr. 88 (5), 93–103.

Beaugelin-Seiller, K., 2002. La banque de données CIBLEX, une compilation de paramètres d'exposition de la population française au voisinage d'un site pollué. in 1ère rencontre nationale de la recherche sur les sites et sols pollués.

Bergdahl, I.A., et al., 1997. Lead concentrations in human plasma, urine and whole blood. Scand. J. Work Environ. Health 23 (5), 359–363.

Bergdahl, I.A., et al., 1998. Plasma and blood lead in humans: capacity-limited binding to delta-aminolevulinic acid dehydratase and other lead-binding components. Toxicol. Sci. 46 (2), 247–253.

Bergdahl, I.A., et al., 1999. Lead in plasma and whole blood from lead-exposed children. Environ. Res. 80 (1), 25–33.

Bergdahl, I.A., et al., 2006. Plasma-lead concentration: investigations into its usefulness for biological monitoring of occupational lead exposure. Am. J. Ind. Med. 49 (2), 93–101.

Bernard-Michel, C., 2006. Indicateurs geostatistiques de la pollution dans les cours d'eau, in Sciences of the Universe [physics]. École Nationale Supérieure des Mines de Paris.
Bertrand, M., 1993. Consommation et lieux d'achat des produits alimentaires en 1991. INSEE (Institut National de la Statistique et des Etudes Economiques).
Bois, F.Y., 2009. GNU MCSim: Bayesian statistical inference for SBML-coded systems biology models. Bioinformatics 25, 1453–1454.
Bonnard, R., 2003. Evaluation de l'impact sur la santé des rejets atmosphériques des tranches charbon d'une grande installation de combustion - Partie 2: Exposition par voies indirectes. INERIS: Verneuil-en-Halatte, France.
Bonnard, R., 2010. Jeux d'équations pour la modélisation des expositions liées à la contamination d'un sol ou aux émissions d'une installation industrielle. Ineris, Verneuil-en-Halatte, France, p. 248.
Bonnard, R., 2017. Paramètres d'exposition de l'Homme du logiciel MODUL'ERS. Ineris, Verneuil-en-Halatte, France.
Bonnard, R., McKone, T.E., 2009. Integration of the predictions of two models with dose measurements in a case study of children exposed to the emissions from a Lead smelter. Hum. Ecol. Risk Assess. 15 (6), 1203–1226.
Cake, K.M., et al., 1996. Partition of circulating lead between serum and red cells is different for internal and external sources of lead. Am. J. Ind. Med. 29 (5), 440–445.
Casey, R., et al., 1994. Prevalence of lead poisoning in an urban cohort of infants with high socioeconomic status. Clin. Pediatr. (Phila) 33 (8), 480–484.
Caudeville, J., 2012. Spatial modeling of human exposure to soil contamination—an example of digital soil assessment. In: Minasny, B., McBratney, A., Malone, B. (Eds.), Digital Soil Assessments And Beyond: Proceedings of the 5th Global Workshop on Digital Soil Mapping 2012. CRC Press, Sydney.
Caudeville, J., et al., 2012. Development of a spatial stochastic multimedia exposure model to assess population exposure at a regional scale. Sci. Total Environ. 432, 297–308.
CDC, 2021. National Environmental Public Health Tracking Network. [cited 2021 9th November 2021]; Available from. https://ephtracking.cdc.gov/DataExplorer/.
Centers for Disease Control and Prevention (CDC) - National Center for Health Statistics, 2000. Data Table of Weight-for-age Charts, Males - Ages 2-20 Years.
Centers for Disease Control and Prevention (CDC) - National Center for Health Statistics, 2000. Data Table of Weight-for-age Charts, Females - Ages 2-20 Years.
Centers for Disease Control and Prevention (CDC) - National Center for Health Statistics, 2000. Data Table of Weight-for-age Charts, Males - Birth - 36 Months.
Centers for Disease Control and Prevention (CDC) - National Center for Health Statistics, 2000. Data Table of Weight-for-age Charts, Females - Birth - 36 Months.
Chanel, O., 1999. Plomb dans l'environnement: quels risques pour la santé? Institut nationalde la santé et de la recherche médicale (INSERM)
Cornelis, C., et al., 2006. Use of the IEUBK model for determination of exposure routes in view of site remediation. Hum. Ecol. Risk Assess. 12 (5), 963–982.
Davezac, H., 2008. L'eau potable en France 2005–2006. Ministère de la Santé, de la Jeunesse, des Sports et de la Vie associative, Paris, France.
Davies, D.J.A., et al., 1990. Lead intake and blood lead in two-year-old U.K. urban children. Sci. Total Environ. 90, 13–29.
Davis, S., Mirick, D.K., 2006. Soil ingestion in children and adults in the same family. J. Expo. Sci. Environ. Epidemiol. 16 (1), 63–75.
Delignette-Muller, M.L., Dutang, C., 2015. fitdistrplus: an R package for fitting distributions. J. Stat. Softw. 64 (4), 1–34.
deSilva, P.E., 1981. Determination of lead in plasma and studies on its relationship to lead in erythrocytes. Br. J. Ind. Med. 38 (3), 209–217.
Dowle, M., Srinivasan, A., 2019. data.table: Extension of `data.frame`.
Dudka, S., Miller, W.P., 1999. Permissible concentrations of arsenic and Lead in soils based on risk assessment. Water Air Soil Pollut. 113 (1), 127–132.
Duigou, N., Baize, D., 2010. Nouvelle collecte nationale d'analyses d'éléments en traces dans les sols (horizons de surface) - (Cd, Cr, Cu, Hg, Ni, Pb, Se, Zn). ADEME, INRA, p. 284.
Etchevers, A., 2013. Imprégnation des enfants français par le plomb en 2008-2009 - Enquête Saturn-Inf 2008-2009 - Enquête nationale de prévalence du saturnisme chez les enfants de 6 mois à 6 ans. INVS: Saint-Maurice: Institut de veille sanitaire (p. 51 pp.).
French ministry in charge of the environment, Basol French database of contaminated or potentially contaminated sites and soils calling for administrative action for prevention or remediation.
Gay, J.R., Korre, A., 2006. A spatially-evaluated methodology for assessing risk to a population from contaminated land. Environ. Pollut. 142 (2), 227–234.
Glorennec, P., et al., 2007. Probabilistic modeling of young children's overall lead exposure in France: integrated approach for various exposure media. Environ. Int. 33 (7), 937–945.
Goovaerts, P., 2006. Geostatistical analysis of disease data: accounting for spatial support and population density in the isopleth mapping of cancer mortality risk using area-to-point Poisson kriging. Int. J. Health Geogr. 5 (1), 52.
Gulson, B.L., et al., 1995. Contribution of tissue lead to blood lead in adult female subjects based on stable lead isotope methods. J. Lab. Clin. Med. 125 (6), 703–712.
Gulson, B., Taylor, A., Stifelman, M., 2018. Lead exposure in young children over a 5-year period from urban environments using alternative exposure measures with the US EPA IEUBK model – a trial. Environ. Res. 161, 87–96.
Hassanien, M.A., Horvath, A., 1999. Lead risk assessment for children in Hungary by predicting their blood lead levels using US EPA integrated exposure uptake biokinetic model. Cent. Eur. J. Public Health 7 (3), 155–159.
Haut Conseil de la Santé Publique, 2014. Determination of New Lead Exposure Risk Management Objectives.
Hawley, J.K., 1985. Assessment of health risk from exposure to contaminated soil. Risk Anal. 5 (4), 289–302.
Hernández-Avila, M., et al., 1998. The influence of bone and blood lead on plasma lead levels in environmentally exposed adults. Environ. Health Perspect. 106 (8), 473–477.
Hirata, M., et al., 1996. Correlation between lead in plasma and other indicators of lead exposure among lead-exposed workers. Int. Arch. Occup. Environ. Health 68 (1), 58–63.
Hogan, K., et al., 1998. Integrated exposure uptake biokinetic model for lead in children: empirical comparisons with epidemiologic data. Environ. Health Perspect. 106 (Suppl 6 (Suppl 6)), 1557–1567.
Hu, H., Rabinowitz, M., Smith, D., 1998. Bone lead as a biological marker in epidemiologic studies of chronic toxicity: conceptual paradigms. Environ. Health Perspect. 106 (1), 1–8.
Huel, G., 1997. Surveillance de la population française vis-à-vis du risque saturnin. Rapport Inserm/RNSP.
Ioannidou, D., et al., 2018. Characterization of environmental health inequalities due to polyaromatic hydrocarbons exposure in France. Int. J. Environ. Res. Public Health 15, 2680.
Kavcar, P., Sofuoglu, A., Sofuoglu, S.C., 2009. A health risk assessment for exposure to trace metals via drinking water ingestion pathway. Int. J. Hyg. Environ. Health 212 (2), 216–227.
Lacarce, E., et al., 2012. Mapping soil Pb stocks and availability in mainland France combining regression trees with robust geostatistics. Geoderma 170, 359–368.
Leggett, R.W., 1993. An age-specific kinetic model of lead metabolism in humans. Environ. Health Perspect. 101 (7), 598–616.
Lindern, I.v., 2003. Assessing remedial effectiveness through the blood lead:soil/dust lead relationship at the Bunker Hill Superfund Site in the Silver Valley of Idaho. Sci. Total Environ. 303 (1), 139–170.
Lindern, I.v., 2016. Estimating children's soil/dust ingestion rates through retrospective analyses of blood lead biomonitoring from the Bunker Hill Superfund Site in Idaho. Environ. Health Perspect. 124 (9), 1462–1470.
MacMillan, J.W., et al., 2015. Physiologically based modeling of lead kinetics: a pilot study using data from a Canadian population. Environ. Sci. Process. Impacts 17 (12), 2122–2133.
Manton, W.I., Cook, J.D., 1984. High accuracy (stable isotope dilution) measurements of lead in serum and cerebrospinal fluid. Br. J. Ind. Med. 41 (3), 313–319.
Manton, W.I., Malloy, C.R., 1983. Distribution of lead in body fluids after ingestion of soft solder. Br. J. Ind. Med. 40 (1), 51–57.
Manton, W.I., Rothenberg, S.J., Manalo, M., 2001. The lead content of blood serum. Environ. Res. 86 (3), 263–273.
Marcus, A.H., 1985. Multicompartment kinetic model for lead: III. Lead in blood plasma and erythrocytes. Environ. Res. 36 (2), 473–489.
McGrath, D., Zhang, C., Carton, O.T., 2004. Geostatistical analyses and hazard assessment on soil lead in Silvermines area,Ireland. Environ. Pollut. 127 (2), 239–248.
McKone, T.E., MacLeod, M., 2003. Tracking multiple pathways of human exposure to persistant multimedia pollutants: regional, continental, and global-scale models. Annu. Rev. Environ. Resour. 28 (1), 463–492.
Melman, S.T., Nimeh, J.W., Anbar, R.D., 1998. Prevalence of elevated blood lead levels in an inner-city pediatric clinic population. Environ. Health Perspect. 106 (10), 655–657.
Menut, L., et al., 2013. CHIMERE 2013: a model for regional atmospheric composition modelling. Geosci. Model Dev. 6 (4), 981–1028.
Morris, M.D., 1991. Factorial sampling plans for preliminary computational experiments. Technometrics 33 (2), 161–174.
O'Flaherty, E.J., 1991. Physiologically-based models for bone-seeking elements. 1. Rat skeletal and bone growth. Toxicol. Appl. Pharmacol. 111 (2), 299–312.
O'Flaherty, E.J., 1991. Physiologically-based models for bone-seeking elements 2. Kinetics of lead disposition in rats. Toxicol. Appl. Pharmacol. 111 (2), 313–331.
O'Flaherty, E.J., 1991. Physiologically-based models for bone-seeking elements. 3. Human skeletal and bone-growth. Toxicol. Appl. Pharmacol. 111 (2), 332–341.
O'Flaherty, E.J., 1993. Physiologically-based models for bone-seeking elements.4. Kinetics of lead disposition in humans. Toxicol. Appl. Pharmacol. 118 (1), 16–29.
O'Flaherty, E.J., 1994. Physiological changes during growth and development. Environ. Health Perspect. 102, 103–106.
O'Flaherty, E.J., 1995. Physiologically-based models for bone-seeking elements.5. Lead absorption and disposition in childhood. Toxicol. Appl. Pharmacol. 131 (2), 297–308.
O'Flaherty, E.J., 2000. Modeling normal aging bone loss, with consideration of bone loss in osteoporosis. Toxicol. Sci. 55 (1), 171–188.
O'Flaherty, E.J., et al., 1998. Evaluation and modification of a physiologically based model of lead kinetics using data from a sequential isotope study in cynomolgus monkeys. Toxicol. Appl. Pharmacol. 149 (1), 1–16.
Pounds, J.G., Leggett, R.W., 1998. The ICRP age-specific biokinetic model for lead: validations, empirical comparisons, and explorations. Environ. Health Perspect. 106 (Suppl. 6), 1505–1511.
Pujol, G., 2019. sensitivity: Global Sensitivity Analysis of Model Outputs.
R Core Team, 2019. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria.
Rabinowitz, M., et al., 1985. Environmental correlates of infant blood lead levels in Boston. Environ. Res. 38 (1), 96–107.
Saltelli, A., Chan, K., Scott, E.M., 2008. In: Saltelli, A., Chan, K., Scott, E.M. (Eds.), Sensitivity Analysis. John Wiley & Sons, Ltd New York.
Schütz, A., et al., 1996. Measurement by ICP-MS of lead in plasma and whole blood of lead workers and controls. Occup. Environ. Med. 53 (11), 736–740.
Sharma, M., Reddy, S.U., 2012. Estimation of Lead elimination rates for liver and kidney using a physiologically-based pharmacokinetic model for improved human risk analysis. Hum. Ecol. Risk. Assess. 18 (3), 627–648.
Smith, D., et al., 2002. The relationship between lead in plasma and whole blood in women. Environ. Health Perspect. 110 (3), 263–268.
Snyder, D.C., et al., 1995. Development of a population-specific risk assessment to predict elevated blood lead levels in Santa Clara County,California. Pediatrics 96 (4 Pt 1), 643–648.
Sobol, I.M., et al., 2007. Estimating the approximation errors when fixing unessential factors in global sensitivity analysis. Reliab. Eng. Syst. Saf. 92, 957–960.

Soetaert, K., Petzoldt, T., Setzer, R.W., 2010. Solving differential equations in R: package deSolve. J. Stat. Softw. 33 (9), 1–25.
Sommar, J.N., et al., 2014. Investigation of lead concentrations in whole blood, plasma and urine as biomarkers for biological monitoring of lead exposure. J. Expo. Sci. Environ. Epidemiol. 24 (1), 51–57.
Stauber, J.L., et al., 1994. Percutaneous absorption of inorganic lead compounds. Sci. Total Environ. 145 (1), 55–70.
US EPA, 2013. Integrated Science Assessment (ISA) for Lead(Pb). US EPA, p. 1886.
US EPA (US Environmental Protection Agency), 2011. Chapter 5: soil and dust ingestion. Exposure Factors Handbook.
Uzu, G., et al., 2011. Characterization of lead-recycling facility emissions at various workplaces: major insights for sanitary risks assessment. J. Hazard. Mater. 186 (2), 1018–1027.
van de Kassteele, J., et al., 2009. External drift kriging of NOx concentrations with dispersion model output in a reduced air quality monitoring network. Environ. Ecol. Stat. 16 (3), 321–339.
van Holderbeke, M., 2007. Review of the soil ingestion pathway in human exposure assessment. Final report. Study in Support of the BeNeKempen Project-subproject on Harmonization of the Human Health Risk Assessment Methodology. VITO.
Volatier, J.-L., 2000. Enquête INCA (enquête individuelle et nationale sur les consommations alimentaires, Collection AFSSA). Editions Technique & Documentation.
Vork, K., Carlisle, J., Brown, J.P., 2013. Estimating Workplace Air And Worker Blood Lead Concentration using an Updated Physiologically-based Pharmacokinetic (PBPK) Model. Office of Environmental Health Hazard Assessment (OEHHA) California Environmental Protection Agency.
White, P.D., et al., 1998. The conceptual structure of the integrated exposure uptake biokinetic model for lead in children. Environ. Health Perspect. 106 (Suppl 6(Suppl 6)), 1513–1530.
WHO, 2011. Evaluation of certain food additives and contaminants. Seventy-third report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series. World Health Organization, Geneva.
WHO, 2011. Lead in Drinking Water - Background Document for Development of WHO Guidelines for Drinking-water Quality.
Zartarian, V., 2017. Children's lead exposure: a multimedia modeling analysis to guide public health decision-making. Environ. Health Perspect. 125 (9), 097009.