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Development of Lead Source-specific Exposure Standards Based on Aggregate Exposure Assessment: Bayesian Inversion from Biomonitoring Information to Multipathway Exposure

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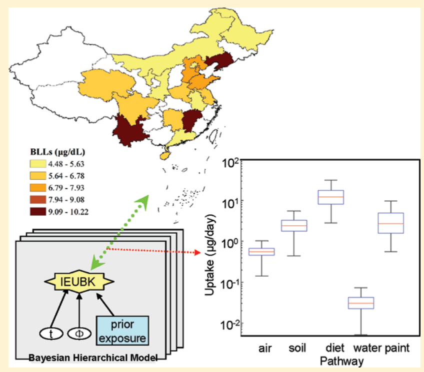
Ⓢ *Supporting Information*

ABSTRACT: Exposure of children to lead is of great concern, and the exposure standards for different media are important for protecting public safety. However, these media-specific standards often fail to ensure the safety of children even when environmental lead levels are lower than the quality standards since humans are often exposed to lead via multiple pathways. To establish exposure standards to protect children from hazards associated with exposure to lead, an analytical tool for assessing aggregate exposure to lead based on Bayesian hierarchical model was developed, and then was used to update the external lead exposure of diet, paint, soil, air and drinking water using the blood lead levels in Chinese children aged 1−6 years. On the basis of updated external exposure, the source allocations for diet, paint, soil, air, and drinking water in China were 65.80 ± 7.92%, 16.98 ± 7.88%, 13.65 ± 5.05%, 3.36 ± 1.75%, and 0.20 ± 0.14%, respectively. Based on the estimated source allocations, the exposure standards were evaluated to be 0.2 $\mu g/m^3$, 24.25 mg/kg, 0.027 $\mu g/L$, 0.051 $\mu g/mg$, 0.042 $\mu g/mg$, 38.02 $\mu g/mg$ for air, soil, water, grains, vegetables, and paint, respectively. Since the standards setting procedure was based on the multipathway aggregate exposure assessment of lead, the newly proposed exposure standards should ensure the safety of children.



■ INTRODUCTION

Exposure of children to lead is a major concern due to its widespread occurrence and adverse health effects.[1,2] There is growing evidence that intellectual development in children is mildly affected by lead pollution at levels of exposure below currently accepted safe exposure thresholds.[3,4] In 2000, the United States (U.S.) adopted the goal of reducing all exposures to lead in order to eliminate elevated blood lead levels (EBLs: blood lead levels ≥ 10 $\mu g/dL$).[4] The exposure standards play an important role for protecting public safety and the U.S. Environmental Protection Agency (EPA) endeavored to set the quality standards low enough so that hazardous situations will not occur when environmental lead levels are just below the quality standards.[5] While a child's total lead exposure is the sum of contributions from numerous sources including air, soil, diet, drinking water, paints, and others, a media-specific standards setting approach has been applied to lead standards in soil, water, and air mainly due to the lack of an analytical tool for assessing aggregate exposure.[5−7] Unfortunately, such media-specific approach resulted in current exposure standards for lead exposure that failed to ensure children's safety.[8] For example in France, even when the environmental lead levels are below the quality standards, the blood lead levels (BLLs) were estimated to be 20 $\mu g/dL$[9] with approximately 1−20% EBLs.[10] Therefore, it is necessary to improve the lead exposure standards by well assessing the aggregate exposure to lead in children.

Aggregate exposure assessment has been applied to the pesticide standards setting in food commodities.[11] In this case, the U.S. EPA developed a procedure to conduct risk assessments that aggregated exposures from dietary, residential, and drinking water sources, and to ensure that exposure to pesticides in food is safe in light of the aggregate exposure.[12] Several papers have also highlighted the aggregate exposure assessment of lead using a forward probability approach.[10,13,14] Glorennec et al.[10] applied the probability method to estimate overall lead exposure through various media (food, water, soil, and dust) and their corresponding source allocations in children in France. Griffin et al.[14] also utilized a similar probability method to assess lead exposure via soil, water, dust, and air to recommend a cleanup goal at the Murray Smelter Superfund site. Such a forward probability approach, however, is lacking in its ability to interpret the internal lead exposure while an exposure assessment should be responsible for the intrinsic heterogeneity at population level.[15] To understand the effects of lead exposure on public health, it is necessary to reconstruct the external exposure from multipathway by establishing the relationship between external exposure and biomonitoring data at population level. Toxicokinetic models

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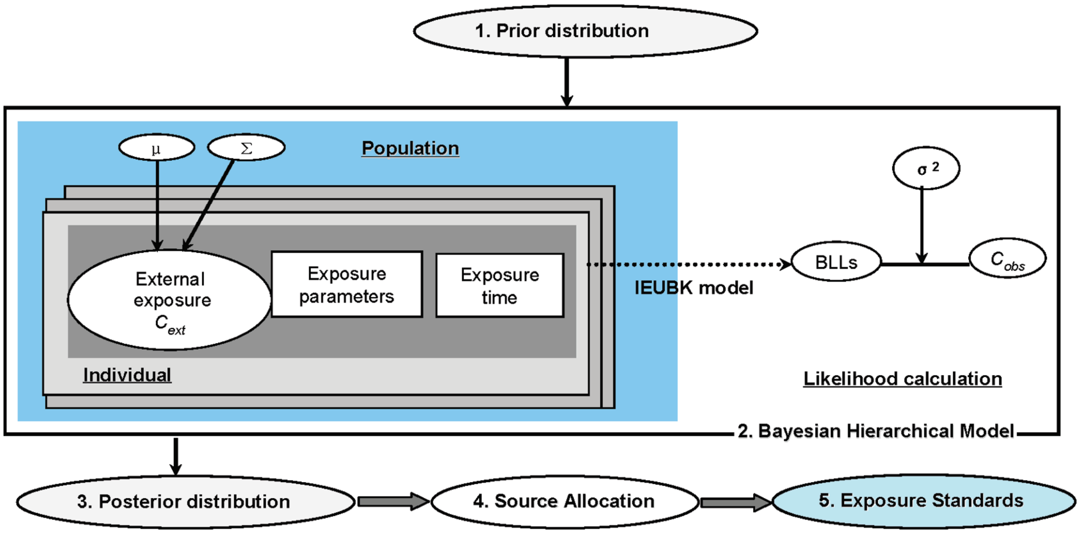

Figure 1. Framework for source allocation estimation and exposure standards setting based on biomonitoring information. Population mean (μ), population variance (Σ), observed values (C_{obs}), blood lead levels (BLLs), measurement variance (σ^2).

provide a useful tool to link external exposure to biomonitoring data, which offers a way to reconstruct the external exposure by combining with the Bayesian inversion technique.[15,16] To our knowledge, however, such a computational technique has not been applied to implement exposure standards at the population level.

There are growing concerns on the high BLLs (3.20−16.53 μg/dL) and EBLs (0.48−80.7%) in children in China,[17,18] whereas the environmental lead levels in the exposure pathways were always reported to be below the corresponding national quality standards.[19−21] The objective of this study was to establish an aggregate exposure assessment method based on Bayesian hierarchical model in order to propose the scientific lead standards of air, soil, grains, vegetables, drinking water, and paint. In this study, the external exposure to lead was updated by Bayesian hierarchical model in order to account for the population intrinsic heterogeneity; and then the source allocations were reevaluated from the reconstructed external exposure to estimate the exposure standards. The newly proposed standards for lead that linked the external exposure and biomonitoring data can protect children from lead exposure, and the results presented here provide a scientific basis for understanding and making policy decisions on lead elimination.

■ MATERIALS AND METHODS

Process for Evaluating Exposure Standards. As shown in Figure 1, the procedure for establishing the quality standards consisted of five steps. At step 1, a prior distribution family was defined to describe the prior information of the external exposure. Then, a three-level Bayesian hierarchical model was built at step 2. At step 3, the posterior external exposure was obtained under the Bayesian hierarchical model, and then the source allocation was calculated using the probabilistic approach[9] based on the posterior external exposure (step 4). In the final step, the exposure standards for multipathway were estimated using the posterior source allocation and Monte Carlo simulation.

Bayesian Hierarchical Model. A Bayesian hierarchical model which consisted of population level, individual level and likelihood calculation was established for inversing the external exposure as illustrated in Figure 1. At the population level, a population distribution for the external exposure (C_{ext}) with a population mean μ and a population variance Σ was utilized to describe the population variability, and the population mean μ and the population variance Σ were distributed to characterize uncertainty of that parameter at individual level.[22] Individual BLLs were simulated through the toxicokinetic model by inputting C_{ext}, exposure parameters and exposure time, and then the simulated BLLs and biomonitoring data (C_{obs}) were related through a residual error model with the mean (zero) and variance (σ^2) in the likelihood calculation, where σ^2 was defined as the error in the BLLs measurement.

Corresponding to the Bayesian theory, the posterior probability density function (PPDF) for the C_{ext} was obtained from the product of the joint prior probability density function (pPDF) for the C_{ext} and the likelihood function, whose function form is on the basis of the measurement model that describes the difference between the model simulation and the observation.[15,23,24] A joint prior probability distribution $p(\sigma^2,\mu,\Sigma,C_{ext})$, was encoded as $p(\sigma^2,\mu,\Sigma,C_{ext}) = p(\sigma^2)p(\mu)p(\Sigma)p(C_{ext}|\mu,\Sigma)$.[15] Hence, the PPDF for C_{ext} can be expressed by eq 1.

$$P(\sigma^2, \mu, \Sigma, C_{ext}|C_{obs}) \propto p(C_{obs}|C_{ext}, \sigma^2)p(\sigma^2)p(\mu)p(\Sigma)p(C_{ext}|\mu, \Sigma) \quad (1)$$

In this study, a noninformative prior was used for $p(\sigma^2)$, and $p(C_{ext}|\mu,\Sigma)$ for all inversion parameters was described by a truncated normal distribution with mean (μ) and the variance (Σ) that lies within the internal $\mu \pm 1.96\sqrt{\Sigma}$ to avoid the implausible value. Prior population mean was assumed to be a normal distribution, which can be expressed as $\mu \sim \mu(M,S^2)$. Using an expert choice, the population variance Σ, was set as an inverse gamma distribution: $\Sigma \sim \text{inv} - \gamma(\alpha,\beta)$, where $\alpha = 3$ and $\beta = 2 \times S^2$.[15,16,24]

The log-normal measurement model that was used in the likelihood function was expressed as eq 2.

$$\ln(C_{obs-i}) = f(C_{ext-i,t}, \Phi_i) + \varepsilon_i \quad (2)$$

where ε_i is the error which was termed as $\varepsilon \sim N(0,\sigma^2)$, f expresses the toxicokinetic model. In this study, the integrated

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exposure uptake biokinetic (IEUBK) model was used as the toxicokinetic model (Supporting Information (SI)) and Φ_i is the model parameter family including exposure parameters and physical parameters for each individual. In this log-normal measurement model, 91 individuals (I) were chosen due to the computational time required, and each individual was described by the residual error model. Hence, eq 2 was applied in the likelihood function (eq 3).

$$p(C_{\text{obs}}|C_{\text{ext}}, \sigma^2) \propto \prod_{i=1}^{I} p(C_{\text{obs}-i}|C_{\text{ext}-i}, \sigma^2) \tag{3}$$

Six age stages (1−6 years of age) were considered in this study, and then eq 3 can be expanded in eq 4 as follows:

$$p(C_{\text{obs}}|C_{\text{ext}}, \sigma^2) \propto \exp\left\{-\frac{1}{2\sigma^2}\sum_{i=1}^{91}\sum_{t=1}^{6}(C_{\text{obs}-i} - f(C_{\text{ext}-1}, t, \Phi_i))^2\right\} \tag{4}$$

Markov chain Monte Carlo (MCMC) computation was applied in this study to inverse the external exposure. The details of the sampling algorithm are provided in the SI. Since three or five chains are usually utilized to test the convergence of the hierarchical model,[15,23,24] five chains were constructed in this study. And all the model simulations were performed using Matlab (version 2008b). The calculation was run on an Intel Pentium 2 × 4 CPU (2.00 GHz) with Red Hat Enterprise Linux 4.

Source Allocation. For each individual, the uptake amount (Ω) and the source allocation (ω) were calculated by eqs 5 and 6

$$\Omega = g(C_{\text{ext}}, t, \Phi) \tag{5}$$

$$\omega_j = \overline{\Omega_{jt}.\ /\ \sum_{j=1}^{5}\Omega_{jt}} \tag{6}$$

where g is the uptake component in the IEUBK model, the subscript j and t represent the exposure pathway and exposure age, respectively. And then the estimation for the source allocation at population level was performed using Monte Carlo simulation.

Exposure Standards. The source allocation has been used to calculate the standards of a chemical in drinking water and soil as eq 7.[6,25] In this study, the standards for lead in other pathways including air, and food, were also calculated by this equation.

$$S_{\text{p}} = \frac{\text{TDI} \times \omega_{\text{p}} \times wt}{U_{\text{p}}} \tag{7}$$

where,ω_{p}, U_{p} and TDI are the allocation of the corresponding pathway, the daily consumption for the specific media and the tolerable daily intake, respectively. The distributions for the daily consumption, bw were all listed in the SI Tables S1 and S2.

Parameters in the IEUBK Model. The IEUBK was developed by the U.S. Environmental Protection Agency for the risk assessment of children due to lead exposure,[26] and it has been widely applied to evaluate the lead risk of children in different countries such as Slovenian,[27] Mexico,[28] and Japan[25] due to similar exposure pathways among different regions. The IEUBK model consists of three components (i.e., exposure, uptake, and biokinetic processes) as shown in the SI. Since the uncertainty of the IEUBK model is strongly related to the pharmacokinetic parameters, the uncertainty analysis was carried out for the pharmacokinetic parameters to assess the multiple exposure of lead in China.

Since the parameters of absorption for the different media directly determine the media-specific uptake in the exposure component and the uptake component, the values for these parameters were randomly drawn from a distribution rather than a fixed point. However, since no more statistical information for the absorption parameters can be achieved, all the absorption parameters were considered as a truncated normal distribution with a mean of default value and a coefficient of variation of 20% as adopted previously.[29] Among the 43 parameters in the biokinetic component, a sensitivity analysis was performed to determine sensitive biochemical parameters according to the method described previously.[22] The sensitivity coefficients of blood volume, body weight, ratio of elimination rate via soft tissues to endogenous fecal lead elimination rate, ratio of endogenous fecal lead elimination rate to urinary lead elimination rate, and lead transfer time from blood to urine were greater than 0.1 (SI, Table S3), meaning that the sensitivities were high. Therefore, for these five parameters, the body weight with a normal distribution was used in this study,[30] and the other four parameters were also set as a truncated normal distribution as for the method for the absorption parameters (SI Table S4).

Biomonitoring Data. Through the China National Knowledge Infrastructure (CNKI) and the Science Citation Index (SCI) databases, we selected BLLs in children aged 1−6 from the literature following the eligibility criteria: (1) BLLs were measured by graphite furnace atomic absorption spectroscopy or hydride generation atomic fluorescence under quality assurance/quality control; (2) the study was designed as stratified sampling, and the sample size was greater than 500; (3) results were presented with enough statistical information such as arithmetic mean (AM), standard deviation (SD), and percentile data, which allow for calculation of the geometric mean (GM) and geometric standard deviation (GSD) for the BLLs in children. Considering the fact that the concentrations of lead in capillary blood are well consistent with those in venous blood with 0.45∼10% bias,[17,31] the BLLs data in both capillary blood and venous blood were all used in this study. Of the 34 provincial-level administrative areas in China, 19 administrative areas have biomonitoring data which met the above criteria, and the references were listed in SI Table S5. Especially, in Huhhot, Yinchuan and Xi'ning, ethnic minority groups comprised 24.95%, 27.71%, and 12.8% of the population, respectively.

We fitted BLLs to the log-normal distribution $\text{Ln}(C_{\text{obs}}) \sim N(\hat{\mu},\hat{\sigma}^2)$[32] using the relationships among the log-normal distributional descriptors (SI). The data for each city as a separate study was combined to one sample size weighted GM BLLs (details see SI). The distribution families were truncated to include 95% of the values, and the individual BLL was randomly selected from such truncated distributions. We sampled the BLL for each age stage at the same percentile point to generate data corresponding to the 91 individuals.

Prior External Exposure. To collect the prior external exposure, we reviewed the literature in CNKI and SCI

Table 1. Childhood BLLs in Different Provinces in China

				BLLs (μg/dL) (GM ± GSD)							
				age (years)							
city	years(blood samples[a])	method[b]	sample Size	0–6	0	1	2	3	4	5	6
Chengdu	2004(2)	AAS	1509	5.91 ± 1.57	4.52 ± 1.69	5.04 ± 1.58	5.70 ± 1.51	5.76 ± 1.79	6.51 ± 1.49	6.37 ± 1.56	6.29 ± 1.50
Huhhot	2004(1)	AAS	1192	5.63 ± 1.49	4.97 ± 1.52	5.34 ± 1.52	4.95 ± 1.64	5.48 ± 1.46	5.62 ± 1.59	6.14 ± 1.43	6.17 ± 1.44
Nanchang	2005(1)	AAS	1653	9.38 ± 1.50	8.89 ± 1.53	8.70 ± 1.50	9.30 ± 1.49	9.66 ± 1.56	9.54 ± 1.48	9.79 ± 1.51	10.05 ± 1.47
Guangzhou	2003–2005(2)	AAS	18 163	4.54 ± 1.72	3.09 ± 2.06	3.99 ± 1.83	4.58 ± 1.66	4.94 ± 1.65	5.04 ± 1.64	5.19 ± 1.60	5.44 ± 1.56
Tianjin	2000–2003(1)	HGAF	5456	7.15 ± 1.43	5.65 ± 1.42	6.24 ± 1.38	6.71 ± 1.42	7.57 ± 1.45	7.75 ± 1.46	8.26 ± 1.45	8.49 ± 1.45
Beijing	2005–2006(1)	AAS	2122	5.21 ± 1.57	4.61 ± 1.82	4.54 ± 1.81	5.23 ± 1.38	4.72 ± 2.05	4.74 ± 2.13	5.78 ± 1.40	6.48 ± 1.37
Wenzhou	2004–2005(2)	AAS	1263	5.82 ± 1.58	5.05 ± 1.66	5.31 ± 1.62	5.77 ± 1.55	5.90 ± 1.58	6.41 ± 1.60	6.02 ± 1.51	6.17 ± 1.57
Shenyang	2000(1)	AAS	1084	9.30 ± 1.46				9.08 ± 1.47	8.89 ± 1.45	9.60 ± 1.48	9.52 ± 1.45
Shijiazhuang	2005(1)	AAS	1581	6.99 ± 1.36			7.24 ± 1.37	6.95 ± 1.36	6.97 ± 1.32	6.81 ± 1.43	
Qingdao	2004(1)	AAS	1814	7.21 ± 1.52				6.77 ± 1.64	6.96 ± 1.50	7.38 ± 1.48	7.65 ± 1.54
Kunming	2002–2004(2)	AAS	814	10.2 ± 1.71			12.6 ± 1.64	8.89 ± 1.81	8.86 ± 1.72	9.89 ± 1.75	12.2 ± 1.64
Xi'ning	2005–2006(2)	AAS	2000	5.80 ± 1.61				5.65 ± 1.57	5.49 ± 1.65	6.30 ± 1.60	6.10 ± 1.72
Hefei	2006(1)	AAS	988	4.91 ± 1.66			4.77 ± 1.29	4.22 ± 1.68	4.68 ± 1.70	4.84 ± 1.65	5.78 ± 1.66
Zhengzhou	2003–2004(1)	AAS	2312	5.84 ± 1.69	5.14 ± 1.75	6.17 ± 1.67	7.00 ± 1.57	6.49 ± 1.72			
Changsha	2004–2005(1)	AAS	1431	6.55 ± 1.72	4.88 ± 1.89	6.23 ± 1.69	5.72 ± 1.77	7.29 ± 1.65	8.21 ± 1.59	6.24 ± 1.89	
Yinchuan	2006(1)	AAS	1158	4.48 ± 2.07	3.84 ± 1.72	4.79 ± 1.62	4.81 ± 1.87	4.90 ± 2.20	4.97 ± 3.18	4.68 ± 2.28	6.34 ± 2.05
Harbin	2004–2006(1)	AAS	1276	5.05 ± 1.70	3.81 ± 1.93	4.19 ± 2.00	4.79 ± 1.86	5.29 ± 1.61	5.45 ± 1.59	5.38 ± 1.63	4.90 ± 1.78
Haikou	2007(1)	AAS	2271	5.99 ± 1.54	3.33 ± 1.76	4.44 ± 1.57	5.32 ± 1.49	5.89 ± 1.54	6.32 ± 1.56	6.26 ± 1.52	6.25 ± 1.51
Xi'an	2004–2006(1)	AAS	2673	5.27 ± 1.56	4.37 ± 1.56	5.08 ± 1.52	5.21 ± 1.56	5.32 ± 1.66	5.59 ± 1.53	5.50 ± 1.57	5.37 ± 1.52
nation			50 760	5.94 ± 1.58	4.48 ± 1.77	5.10 ± 1.65	5.69 ± 1.53	6.14 ± 1.58	6.36 ± 1.55	6.52 ± 1.54	6.89 ± 1.52

[a]1 = capillary blood. 2 = venous blood. [b]AAS = atomic absorption spectrophotometry. HGAF = hydride generation atomic fluorescence.

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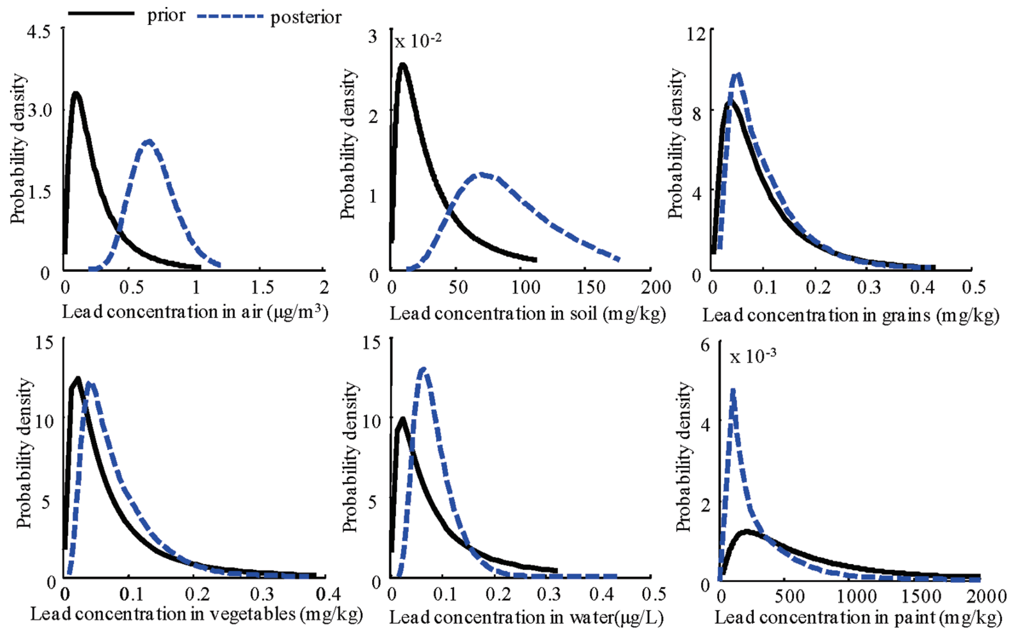

Figure 2. Comparison between probability density functions for prior and posterior lead concentrations in air, soil, grains, vegetables, water, and paint.

databases. Through this research, we defined five pathways, air (μ_a), soil (μ_s), diet including grains (μ_v) and vegetables (μ_d), drinking water (μ_w), and paint (μ_p) to reflect the multipathway exposure of children to lead. The screening criteria, including scientific experimental design, strict quality control, and adequate sample size, were similar to the criteria used in the selection of the biomonitoring data. Since no data on the concentrations of lead in drinking water in China could be collected from literature, lead concentrations for 105 fully flushed drinking water samples that were collected from 34 cities in China from 2009 to 2011 were determined by inductively coupled plasma mass spectroscopy. The details of the analytical method are provided in the SI. Of 105 drinking water samples, the concentrations of lead in 93 samples were below the detection limit (0.1 μg/L), and the concentrations in the remaining 12 samples ranged from 0.14 to 0.39 μg/L. The prior distribution for the lead concentration in the drinking water was evaluated by a maximum likelihood estimation[33] Thus, the GM and GSD of lead in drinking water in China were estimated to be 0.054 μg/L and 2.05 μg/L, respectively. For the dietary exposure to lead, grains (μ_g) and vegetables (μ_v) were selected as the dietary items, since they accounted for ca. 76% of the total dietary lead uptake.[20,34] Considered some unknown factors, the remaining 24% of the total dietary lead uptake was defined as the other uptake. The lead concentrations in diet including grains and vegetables and soil at national level in China have been well reviewed in previous papers.[19,35] The dietary samples were collected from 14 provincial-level administrative area, and the sample size for the selected grain and vegetables in this total diet study are 831 and 554, respectively.[35] To our knowledge, the information from this total diet study is the best, recent, available data to assess the dietary exposure at the national population level. However, since there is no report on the air lead concentration at the national level, we collected the data in 12 cities (SI Table S6), and AM was estimated to be 0.34 $\mu g/m^3$ which is slightly higher than that (0.29 $\mu g/m^3$) in Japan.[25] Since we could not found the GSD in China from the available literature, the GM of lead in air in China was estimated to be 0.25 $\mu g/m^3$ using the GSD (2.28) in Japan.[25] The concentrations of lead in 58 samples of new paint from 12 different producers have been reported,[36] and were used in this study. The concentrations (0.8−153 000 kg/mg) were fitted to a log-normal distribution with a GM of 553 kg/mg and a GSD of 2.59 (kg/mg). All the prior external exposure is summarized in SI TABLE S7. Since the prior external exposure played an important role in the Bayesian hierarchical model to inverse the source allocation, the sensitivity analysis for the prior external exposure was performed (SI).

RESULTS AND DISCUSSION

Biomonitoring Information. In the 1990s, BLLs of children are relatively high (21.8−67.9 μg/dL) in China, mostly due to the rapid industrialization that was occurring at that time.[37] Beginning at the end of the 20th century, changes in environmental policy such as the removal of the lead from gasoline sharply reduced children's BLLs (AM: 9.29 μg/dL, 3.72−25.42 μg/dL) at the beginning of the 21st century.[17] However, from 2001 to 2007 the mean BLL of Chinese children was 8.07 μg/dL (4.55−16.53 μg/dL), and 23.9% of Chinese children had BLLs $\geq$ 10 μg/dL.[38] In some regions, such as in Guiyu, BLLs could not be well controlled as exemplified by the high BBLs (4.40−32.67 μg/dL with a mean concentration of 15.3 μg/dL).[18]

As shown in Table 1, the GM and GSD of the BLLs in 50 760 Chinese children were 5.94 μg/dL and 1.58 μg/dL, respectively, and the corresponding EBLs was as great as 12.74%, which is much higher than the EBLs of 1.6% in the U.S.[4] The results of the current study indicated that increasing age was a significant risk factor for BLLs, while children aged 2−3 had the highest BLLs in the U.S.[39] It should be noted that in some regions such as Guangzhou, Yinchuan and Harbin, while GM values are relatively low (4.54−5.05 μg/dL), the EBLs are high due to their relatively high GSD values (1.70−2.07 μg/dL). According to the corresponding exposure study, the education and occupation of parents, the residential environment such as house floor, community, the eating habit (frequency of biting the pencil and eating puffed food) are concluded as the significant risk factors. Average BLLs of children in Nanchang, Shenyang, and Kunming are higher than 9 μg/dL, and the relatively low BLLs were observed in Guangzhou, Yinchuan and Heifei (4.48−4.91 μg/dL). The high average BLLs of children in Nanchang, Kunming and Shenyang was mainly due to heavy lead pollution.

Thus, different pollution and social-economic statuses lead to the individual variability of BLLs for children. Considering such intrinsic heterogeneity in the population, a comprehensive sample was formed by combining these distinct subsamples to well represent a national level of lead exposure. The largest data size, which can we obtained, was collected although these subsamples could not cover all the provincial-level administrative areas in China.

Reverse Sampling Simulation. The five simulation runs started at dispersed initial points in the parameter space and each run simulated 10 000 times. The first 5000 iterations of each chain were taken as "burn-in" and were discarded to ensure the Marko Chain was stable. The Gelman-Rubin (G-R) diagnostic method was utilized to test the convergence of the sampling, and the chain was considered to be converged when the corrected scale reduction factors (R) was <1.2.[24] As a result, the reverse sampling simulations converged to $R < 1.1$ for all population exposure parameters (SI Table S7). The sensitivity analysis for the prior C_{ext} shows that inversion results are stable as described in the SI.

A random chain was chosen for shaping the population posterior distribution to obtain the GM, GSD and variance (Σ) for the external exposure (SI Table S7). The probability density functions are plotted in Figure 2. The distributions of PPDFs for soil, air and paint largely differ from their corresponding pPDFs, and their GM values of PPDF were increased by 218.67%, 176.18%, and −51.81%, respectively. The variation between PPDF and pPDF for grains was the smallest with only a 6.01% increase in GM, followed by drinking water with an increase of 15.68%, and vegetables with an increase of 33.70% compared with their corresponding pPDFs. On the other hand, the posterior GSD values all decrease from 2.28, 2.67, 2.76, 2.92, 2.76, 2.59 to 1.28, 1.50, 1.90, 1.87, 1.55, 2.11 for air, soil, grains, vegetables, water, and paint, respectively (SI Table S7), indicating that the uncertainties were all reduced compared with their corresponding prior distributions. Such reductions in uncertainties are well documented in Bayesian inversion,[15,22,23] since the Bayesian techniques provide a scientific way to revaluate the uncertainties of the model parameters by incorporating prior knowledge together with observed data in the modeling process.

For a proper assessment of the updated external exposure, the simulated BLLs using prior and posterior C_{ext} were compared with the observed values, respectively. Generally, the residual error was magnified with the cumulative probability increased due to the positive skewness of the log-normal distribution. As shown in Figure 3(a), the prior residual error between the simulated BLLs and the observed BLLs was 0.98 μg/dL, and the residual sum of squares (RSS) was 2.25 (μg/dL)^2. Specifically, the residual error can extend from 3 to 4 μg/dL when the cumulative probability was more than 80%. Alternatively, the simulated values based on the posterior C_{ext} were found to be close to the observed values (Figure 3(b)) with less posterior RSS (0.30 (μg/dL)^2). Therefore, the posterior C_{ext} under the constraint which were imposed by the model structure, model parameters, and the prior exposure represent a more responsible external exposure that can be used to better understand the exposure risk assessment.

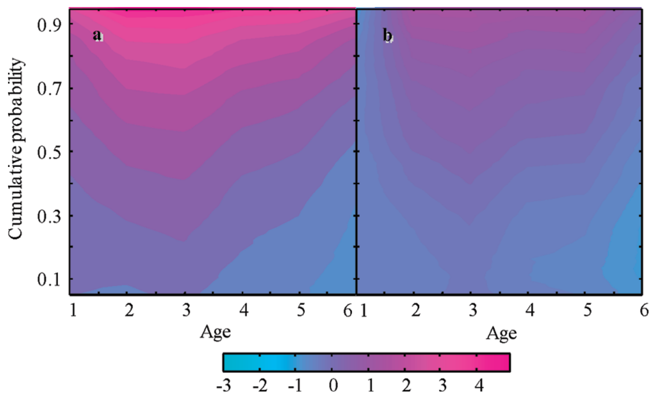

Figure 3. Contour of the residual error between the simulated BLLs and the observed BLLs. (a) Residual errors between the simulated BLLs using the prior probability and the observed BLLs; (b) Residual errors between the simulated BLLs using the posterior probability and the observed BLLs. Color contour shading with a rainbow scale from cyanine to rose red was used to adequately visualize error.

As a result, the conditions for the exposure of Chinese children to lead were reconstructed using the Bayesian inversion combined with IEUBK model. In this inversion procedure, all pathways were set as independent, even though some studies have demonstrated that lead concentrations among distinct pathways were related.[40,41] Using Bayesian inference, better quality information about lead exposure has been achieved from the view of stable inversion results and less posterior RSS.

Source Allocation for Lead Exposure. To determine the source allocation for interpreting the contribution of each exposure pathway to the biomonitoring data, we obtained the cumulative probability density functions of lead uptake via air, soil, food, water, and paint at the national scale according to the posterior external exposure (Figure 4a). The total lead uptake was 18.84 μg/day for children, which was much higher than in Japan.[25] The mean lead uptake via diet, paint, soil, air, and drinking water were 13.80 ± 7.23 μg/day, 3.80 ± 3.28 μg/day, 2.57 ± 1.08 μg/day, 0.57 ± 0.17 μg/day, and 0.034 ± 0.017 μg/day, respectively. Of the 13.80 μg/day via from the dietary exposure, the uptake from the grain and vegetables were 5.39 μg/day and 5.10 μg/day, respectively, and the unknown uptake was 3.31 μg/day. The dietary intake (25.42 ± 13.45 μg/day) of lead is the highest among all pathways, but much lower than those (23.7−110.8 μg/day) during the end of the 20th century in China,[34] which can be attributed to environmental policies regarding lead pollution that were developed at the end of the 20th century.

Figure 4b shows the source allocations for different exposure pathways. The source allocations for diet, paint, soil, air, and drinking water are estimated to be 65.80 ± 7.92%, 17.0 ± 7.88%, 13.7 ± 5.05%, 3.36 ± 1.75%, and 0.20 ± 0.14%, respectively. It is clear that the allocation of dietary exposure is the highest in China, and the contributions by the air and water exposure pathways are relatively low. This contrasts the situation in the U.S. where deteriorating lead paint and contaminated dust and soil are the primary causes of EBLs among U.S children, and the contribution from soil accounted for up to 24% of pediatric EBLs in Arizona in 2004.[4] It should

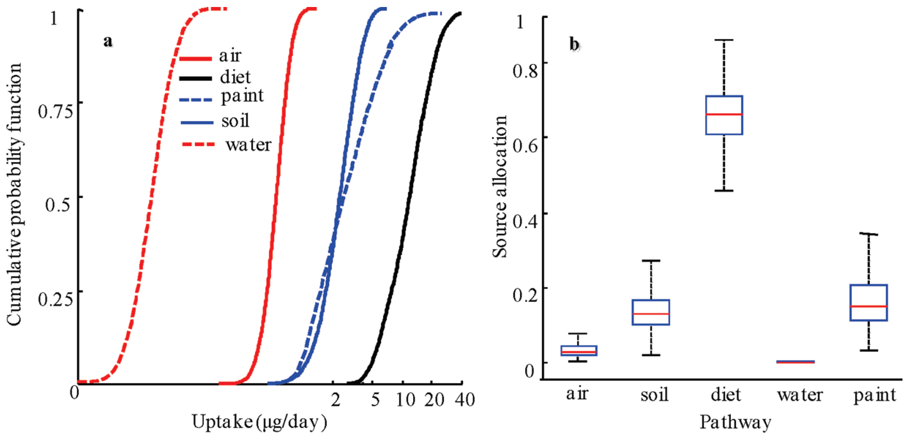

Figure 4. Cumulative probability functions and source allocations of lead uptake for different sources in China. (a) Cumulative probability density functions of the lead uptake for the exposure pathways; (b) Source allocations for different pathways. The central mark on each box in Figure (b) is the median with the edges of the 25th and 75th percentiles. The whiskers extend to the most extreme data points not considered outliers. Outliers were not plotted in our study.

be noted that when using the prior distribution, the source allocations for the diet, paint, soil, air and drinking water exposure pathways were 58.88%, 33.68%, 5.93%, 1.26%, and 0.25%, respectively. With the exception of paint, the source allocations for all pathways increased when using posterior external. Such variation should be considered in environmental policies regarding lead, such as standards setting procedure since the source allocation plays a key role in this procedure. For example, the results of this study suggest that the contribution to total lead exposure from drinking water is even lower than 1%, which is much lower than that (50%) in the guidelines for drinking water proposed by WHO,[6] that was also adopted by China. Thus, such low contribution from drinking water in China estimated here should be reflected in the criterion for lead concentration in drinking water.

Compared to other countries, the relatively high source allocation for diet in China is due to the high concentrations of lead in the food. The high lead concentrations in grains and vegetables were mainly due to enrichment from the soil.[40,41] As a result, great efforts are required to control concentrations of lead in soil to reduce dietary lead exposure, and ultimately to eliminate lead exposure in China.

Standards Setting in Different Media. The present national standards for lead concentrations in different exposure media in China are 1−1.5 $\mu g/m^3$ for air, 50−500 $\mu g/mg$ for soil, 0.01 mg/L for drinking water, 0.2 $\mu g/mg$ for grains, and 0.1−0.3 $\mu g/mg$ for vegetables. The air criterion in China refer to concentrations set by the U.S. EPA,[42] and the drinking water and diet standards refer to the values set by the WHO and CAC (Codex Alimentarius Commission), respectively.[6,43] The U.S. EPA set the quality standard in air as 1.5 $\mu g/m^3$ where an air-blood ratio of 1.9 and maximum BLLs of 3 $\mu g/dL$ were used, and a 20% contribution from air exposure was defaulted as the contribution to BLLs from air.[42] The allocation of 50% was used in the current lead exposure standards setting for drinking water.[6] Thus, the EBLs were evaluated to be 21% and the GM of BLLs was estimated to be 8.16 $\mu g/dL$ even when the concentration of lead in various media was assumed to be half of the corresponding standard in China by using IEUBK, indicating that the current standard for lead in China could pose a high risk to children due to an aggregate exposure to lead.

In this study, the new exposure standards in the various media were evaluated using eq 7 where the TDI was 3.5 $\mu g/kg{\cdot}bw$ per day which was used in the WHO.[6] Since all parameters except for TDI in eq 7 show log-normal or normal distributions, the Monte Carlo simulation was applied to calculate the standards probability distribution as shown in SI, Figure S3. The median standards for air, soil, water, grains, vegetables, and paint are estimated to be 0.57 $\mu g/m^3$ with the range from 0.20 to 1.58 $\mu g/m^3$ (95% confidence interval: CI), 65.15 mg/kg (24.25−138.95 mg/kg, 95% CI), 0.099 $\mu g/L$ (0.027−0.37 $\mu g/L$, 95% CI), 0.14 $\mu g/mg$ (0.051−0.31 $\mu g/mg$, 95% CI), 0.12 $\mu g/mg$ (0.042−0.25 $\mu g/mg$, 95% CI), and 113.59 $\mu g/mg$ (38.02−351.29 $\mu g/mg$, 95% CI) for children aged 1−6, respectively. Similarly, 0.2 $\mu g/m^3$, 24.25 mg/kg, 0.027 $\mu g/L$, 0.051 $\mu g/mg$, 0.042 $\mu g/mg$, and 38.02 $\mu g/mg$, which correspond to 5% percentile of the standards distribution, were recommended as the standards for air, soil, water, grains, vegetables and paint, respectively, in order to protect 95% of Chinese children from the neurotoxic effects of lead. There are no EBLs even when the concentration of lead in various media was assumed to be at concentrations corresponding to the criterion in China by using IEUBK, indicating the proposed quality standards would be a more effective choice. It should be noted that BLLs < 5 $\mu g/dL$ was recently reported to be detrimental to child behavior and cognition.[44,45] Thus, TDI should be reduced a factor of 2 or more, and the exposure standards that evaluated in this study should be reduced as the same scale.

In this study, the exposure standards were evaluated based on a well-established aggregate exposure assessment method by linking the external exposure and biomonitoring data, the newly developed standards of lead should be effective in protecting children from exposure to potentially harmful concentrations of lead. By linking biomonitoring information and computational toxicology can be an effective method to help social and scientific leaders to make informed decisions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Information on the IEUBK model and concerning parameters, MCMC algorithm, statistical method used, analytical method for water lead, sensitivity method and result, and probability distribution figure here is provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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