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Cohort profile: China National Human Biomonitoring (CNHBM)—A nationally representative, prospective cohort in Chinese population

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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.

Data Use and Availability

Primary data users are the national agencies that collaborated in the design and development of the CNHBM. Information from the study is made available through an extensive series of publications and articles in scientific and technical journals. Anonymized data are available to other investigators through collaborative agreements. The CNHBM welcomes researchers interested in collaboration. For more information contact the corresponding author of this paper, Xiaoming Shi [shixm@chinacdc.cn].

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.106252.

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Abstract

Objective: Globally, developed countries such as the United States, Canada, Germany, Korea, have carried out long-term and systematic biomonitoring programs for environmental chemicals in their populations. The China National Human Biomonitoring (CNHBM) was to document the extent of human exposure to a wide array of environmental chemicals, to understand exposure profiles, magnitude and ongoing trends in exposure in the general Chinese population, and to establish a national biorepository.

Methods: CNHBM adopted three-stage sampling method to obtain a nationally representative sample of the population. A total of 21,888 participants who were permanent residents in 31 provinces were designed to interviewed in this national biomonitoring (152 monitoring sites × 3 survey units × 2 sexes × 6 age groups × 4 persons = 21,888 persons) in 2017–2018. Unlike the US National Health and Nutrition Examination Survey, the CNHBM will follow the same participants in subsequent cycles allowing for dynamic, longitudinal data sets for epidemiologic follow-up. Each survey cycle of CNHBM will last 2 years and each subsequent cycle will occur 3 years after the prior cycle's completion.

Results: In 2017–2018, the CNHBM created a large cohort of Chinese citizens that included districts/counties questionnaire, community questionnaire collecting information on villages/communities, individual questionnaire, household questionnaire, comprehensive medical examination, and collection of blood and urine samples for measurement of clinical and exposure biomarkers. A total of 21,746 participants were finally included in CNHBM, accounting for 99.4% of the designed sample size; and 152 PSUs questionnaires, 454 community questionnaires, 21,619 family questionnaires, 21,712 cases of medical examinations, 21,700 individual questionnaires, 21,701 blood samples and 21,704 urine samples were collected, respectively. Planned analyses of blood and urine samples were to measure both inorganic and organic chemicals, including 13

heavy metals and metalloids, 18 poly- and per-fluorinated alkyl substances, 12 phthalate metabolites, 9 polycyclic aromatic hydrocarbons metabolites, 4 environmental alkylated phenols, and 2 benzene metabolites.

Conclusions: CNHBM established the first nationally representative, prospective cohort in the Chinese population to understand the baseline and trend of internal exposure of environmental chemicals in general population, and to understand environmental toxicity.

Keywords

CNHBM; Human biomonitoring; Environmental chemicals; Internal exposure; Prospective cohort

1. Introduction

The sustained economic and industrial growth in China over the past four decades has been accompanied by increased levels of environmental contamination in air, water, food and soil (Kan, 2009). To date, most Chinese environmental health studies have focused on ongoing air, soil, or water pollution throughout much of the country (Huang et al., 2017; Chen and Ye, 2014; Rodríguez-Lado et al., 2013). The China Ecological Environment Status Bulletin in 2018 reported that 217 of the 338 cities (64.2%) exceeded the annual ambient air quality standard; 32.1% of major water bodies in China were classified as IV, V and above, which only can be used for agricultural or industrial water and cannot be used as a source of drinking water (Ministry of Ecology and Environment, 2018). Environmental stress in China is comprised of various exogenous chemical substances, including heavy metals and metalloids (HMMs), phthalates, alkylated phenols, poly- and per-fluorinated alkyl substances (PFAS), and other contaminants (Lian et al., 2019; Sun et al., 2018; Shifaw, 2018; Shi et al., 2018; Peng et al., 2018; Lu et al., 2018; Liu et al., 2018; Gao et al., 2018). These environmental chemicals are widespread in environmental media and human exposures to them have been associated with a wide range of adverse health outcomes (Escher et al., 2020).

In recent years, environmental protection has been listed as a basic national policy in China. A series of laws and regulations on environmental protection were formulated and promulgated to intensify the efforts of environment protection and emission reduction (Chen et al., 2019). For well characterized pollutants, treatment and measures have been adopted. However, for HMMs and persistent organic pollutants (POPs), their ability to migrate and enrich multiple environmental media ultimately concealing both their source and location makes remediation efforts more difficult and human exposure more likely.

Although reports of HMMs and POPs contamination in environmental media in China are widespread, their presence in the environment may not translate directly into human exposure. HMMs and POPs enter the body through multiple routes and pathways, depending upon the specific toxicant, and may gradually accumulate in the body causing a series of adverse reproductive, mutagenic, developmental, and neurological outcomes (Boskabady et al., 2018; Dorea, 2018; Abdul et al., 2015; World Health Organization, 2013). Exposure to these chemicals has been widely reported in the United States (CDC, 2019), Canada (Health Canada, 2019), Korea (Seo et al., 2015) and other countries; however, the extent of human

exposure to these chemicals across demographic groups in China has not been evaluated. It is often difficult to ascertain individual exposure through external exposure measurements (e.g., water, food, soil), especially when exposures are multi-pathway in nature. Hence, accurate internal exposure estimates are critical for health effect assessment (Zhang et al., 2010).

Biomonitoring of exposure measures the concentration of environmental chemicals, their metabolites or reaction products in human biological matrices such as blood, urine and hair, integrating contributions from all exposure routes and pathways (Sobus et al., 2015). These measures represent chemical exposures that are taken up into the body systemically and are useful for evaluating the relationship between total exposure and biological effects (Zota et al., 2016). Therefore, human biomonitoring is regarded as the “gold standard” for assessing human exposure to environmental chemicals (Sobus et al., 2015). With systematic human biomonitoring, long-term temporal trends of toxicant exposure and health effects on the population can be determined. Large-scale, representative biomonitoring in various populations has tremendous scientific and social value as it provides background or reference for the formulation and evaluation of effective environmental management policies (Zota et al., 2016). Population-based biomonitoring programs are not exclusively laboratory-based efforts, but rather require collaboration among many public health disciplines and community representatives to be most effective. Working with national, regional and local health officials, academia and community leaders can help identify potential political, cultural and economic barriers and solutions for successful implementation of a biomonitoring program (Awasthi et al., 2018).

Globally, developed countries such as the United States, Canada, Germany, and Korea have carried out long-term and systematic biomonitoring programs for environmental chemicalsin their populations (CDC, 2019; Health Canada, 2019; Schulz et al., 2012; Seo et al., 2015; Gil et al., 2011). Due to funding, personnel, and technological challenges, few developing countries have implemented nationally representative biomonitoring projects. In 2017–2018, the National Institution of Environmental Health (NIEH) of the China CDC designed and initiated the population-representative China National Human Biomonitoring (CNHBM). This effort will enable estimates of Chinese population-based predictors of exposure, similar to those determined in the United States using NHANES, while addressing the limitations of NHANES in its inclusion of children and longitudinal follow-up thereby the study make it possible to assess the role of environmental chemicals in the development and incidence of adverse health outcome.

The CNHBM study is to create a large, nationally representative cohort of Chinese citizens that includes comprehensive epidemiologic surveillance, clinically-relevant measurements including blood pressure, anthropometric measures and clinical biomarkers, and measurement of environmental chemical biomarkers. Specifically, it aims at: (1) obtain a national baseline internal exposure to environmental chemicals in the Chinese population, to track whether the long-term changes of environmental chemicals were decreasing, and to identify the basic demographic characteristics of the general population that influence internal exposure levels to chemicals and risk factors of these exposures; (2) assess the health risks and exposure pathways of environmental chemicals; and to establish a national

biobank for storage of serum, plasma, urine, and DNA to enable future design of human health risk assessments for environmental chemicals exposures; and (3) establish a national biomonitoring network for environmental chemicals and to provide scientific information to serve as the basis of governmental decision-making related to the mitigation and prevention of exposures.

2. Methods

2.1. Cohort description

A three-stage sampling design was used in CNHBM. In each province, primary sampling units (PSUs) of districts/counties were clustered hierarchically based primarily on their urbanization rates and secondarily on their industry employment rates. Each PSU represented on average 9 million residents (range 2.8–13 million). Of the 2869 districts and counties in 31 provinces in China, 152 districts/counties were selected as monitoring sites to obtain a nationally representative sample (Fig. 1). From these sites, three villages/communities (units) were selected using probability-proportional-to-size (PPS) sampling to represent the approximate urban/rural participant ratio of the site. Units with an insufficient number of residents (<2000) for the next sampling stage were combined with the nearest villages/communities as one unit (This situation generally occurs in rural areas). In each unit, 4 residents were randomly selected to fill each sex and age (3–5, 6–11, 12–18, 19–39, 40–59, and 60–79 years) category (n = 48 per unit) from a census of each PSU who met the inclusion criteria. A total of 21,888 permanent residents (i.e., 152 PSUs × 3 survey units × 2 sexes × 6 age groups × 4 persons) were ultimate.

Totally, 5.2% selected PSUs (districts/counties) were replaced because they were geographically isolated or remote, and 6.1% of the survey units (villages/communities) were replaced because permanent residents in the sampled communities could not meet sampling requirements. After selection, investigators contacted these residents to determine sample-person eligibility. Once this sampling frame was available, the list of all individuals in these units (villages/communities) was developed in order to select randomly from among those individuals. All persons in the sampled lists would be contacted by the phone or face to face to confirm whether they were willing to participate in the survey. Selected individuals were replaced if they (1) were not residents or were out-of-contact, (2) refused participation, or (3) were unable to complete the interview and examination. The response rate was 64%. At baseline (2017–2018), a total of 21,746 individuals aged 3–79 years residing in 31 provinces were sampled. To date, two papers on the CNHBM sampling design have been published. In 2018, Cao et al. reported the details of the sampling process, including the sample selection methods and the calculation of sampling error (Cao et al., 2018). Qu et al. evaluated the reliability and accuracy of sampling surveys by assessing non-sampling error (Qu et al., 2019). The CNHBM was approved by the Ethics Review Board of NIEH, China CDC. Each participant was introduced to the aim and content of this program and its risks and benefits of participation. All participants provided written informed consent by themselves or their legal representative prior to participation.

2.2. Cohort Follow-up

Each survey cycle will last 2 years and each subsequent cycle will occur 3 years after the prior cycle's completion. For example, the first cycle occurred from 2017 to 2018 and the next cycle commenced in 2020–2021. Due to the large sample size of this study, CNHBM was designed to complete the baseline survey in batches, conducting the field survey in 13 provinces in 2017 and in the other 18 provinces in 2018. Participants included in 2017 will be followed up in 2020. Participants included in 2018 will be followed up in 2021. Unlike the NHANES, the CNHBM will follow the same participants in subsequent cycles allowing for dynamic, longitudinal data sets for epidemiologic follow-up. Each participant has a unique medical examination number and ID, making the follow-up process straightforward. This dynamic prospective cohort examines a nationally representative sample of about 22,000 people each cycle located in 152 districts/counties, and the decedents or those lost to follow-up are to be replaced with age, sex, residence matched participants in the same PSU.

2.3. Data collection

We initiated the prospective cohort with a cross-sectional baseline survey which included a PSU questionnaire collecting information on districts/counties, community questionnaire collected information on villages/communities, individual questionnaire, household questionnaire, comprehensive medical examination, and collection of blood and urine samples for measurement of clinical and exposure biomarkers. Depending upon the age of the participant, the rest of the examination included tests and procedures to assess the various aspects of health listed above; for example, the cognitive function was only measured in the older adults. Each participant received 200 RMB compensation and a report of their medical findings. All information collected in the survey is kept confidential, and de-identified in the database, and privacy is protected by public laws.

2.3.1. Questionnaire—The CNHBM questionnaire consisted of two parts: 1) PSU (districts/counties) questionnaire and survey unit (villages/communities) questionnaire, and 2) an individual and household questionnaire for collecting participant's demographic, health history and lifestyle information. The questionnaire was conducted by a trained interviewer with a computer-assisted personal interview system in the hospital where the physical examination was performed. When the interview was conducted in remote rural areas or the participants were elderly people who were not fluent in Mandarin, interviewers who spoke the local dialect were used.

PSU and survey unit questionnaires were performed by a local office of the county or district CDC to collect demographic, socioeconomic, medical and health service data, sources of industrial and agricultural pollution of PSUs or survey units and environmental chemical external exposure factors. The household questionnaire was conducted to assess the general household characteristics, household economic status, indoor pollution and environmental chemical exposure sources. Table 1 summarizes the household questionnaire components. Individual questionnaires were used to collect information on both children and adults including demographic, socioeconomic, dietary, and health-related history of participants. Guardians were asked to fill in the questionnaire for participants aged 3–17 years while participants aged 18 and older were invited to complete the adult questionnaire. In addition,

participants aged above 60 were assessed for cognitive function using a Mini-Mental State Examination (MMSE).

2.3.2. Health examination and sample collection—All participants were provided a free comprehensive physical examination as one of the benefits for participating in the study including anthropometric measures (weight, height, waist circumference), a medical examination, ophthalmology, otorhinolaryngology, oral health, dermatology, neurology and imaging examinations (electrocardiograms, B-mode ultrasound imaging, and chest X-ray examination). Blood samples were collected by a trained phlebotomist the morning after an overnight fast (> 8 hrs) and a spot urine sample was also collected. Table 2 summarizes the medical examination components of the CNHBM. Most of the examinations were performed by clinicians in local hospitals. For sampled communities far from hospital, medical testing equipment was transported and certified doctors and technicians conducted the testing.

2.3.3. Blood and urine sample measurements—A fasting, venipuncture blood (4–16 mL) sample and a convenience urine sample (50–80 mL) were collected of each participant with volume varying with age. For children aged 3–5, 4 mL of blood with heparin anticoagulant and 50 mL of urine were collected. For children aged 6–11, 4 mL blood with heparin, 8 mL blood without anticoagulant, and 50 mL of urine were collected. For participants aged 12 and older, 4 mL of blood with heparin, 12 mL blood with non-anticoagulant, and 80 mL of random urine were collected. Blood and urine samples were used for the clinical laboratory examination and biomarkers examination including zymogram, inflammatory markers, hormones, lipids, fasting glucose and biomarkers of chemical toxicant exposures. The remaining serum, hemocytes, blood clots and urine were cryopreserved at −80 °C and archived in the biorepository for future use.

Planned analyses of baseline (2017–2018) blood and urine samples include measurements of both inorganic and organic chemicals. Specifically, 13 HMMs, 18 PFAS, 12 phthalate metabolites, 9 polycyclic aromatic hydrocarbons (PAHs) metabolites, 4 environmental alkylated phenols, and 2 benzene metabolites were measured (Table 3).

2.3.4. Chemical analyses—For HMMs, 0.5 mL blood was diluted with 0.1% nitric acid and 0.01% Triton X-100 solution, and 1 mL urine was diluted with 1% nitric acid. Then the blood and urine were centrifuged and the supernatant was analyzed by inductively coupled plasma-mass spectrometry (ICP-MS). The method limit of detections (LODs) were 0.02–1.4 ng/mL in blood and 0.02–1.2 ng/mL in urine. For PFAS, 200 μL serum was extracted by ion-pair solution, based on the concept that ionizable species are more readily extracted into organic solvents as ion pairs. The extracted solution then was concentrated to dryness under nitrogen. The residue was redissolved in methanol and water and quantified using ultra-high pressure liquid chromatography-tandem mass spectrometry (UPLC-MS/MS). The LODs were 0.01–0.1 ng/mL. For PAHs metabolites, 1 mL urine was hydrolysed using β-glucuronidase enzyme with additional sulfatase activity. Then the hydrolysate was extracted by liquid-liquid extraction and analyzed by isotope dilution gas chromatographyhigh resolution mass spectrometry after derivatization. The method detection limits were between 10 and 20 ng/L. For 12 phthalate metabolites, 2 mL urine was processed by enzymatic deconjugation of the glucuronidated analytes, and then extracted by

solid phase extraction using Oasis MAX cartridges (60 mg, 3 mL). The eluate was diluted with initial mobile phase and then detected by isotope dilution-UPLC-MS/MS. The method detection limits were between 0.1 and 0.8 ng/ mL. For 4 phenol alternatives (phenols Bisphenol A, bisphenol F, Tetrachlorobisphenol A, Tetrabromobisphenol A), 2 mL urine was hydrolyzed by the use of β-glucuronidase/sulfatase. After hydrolysis, sample was extracted by solid phase extraction using Oasis HLB cartridges (60 mg, 3 mL). The eluate was concentrated to dryness followed by redissolving in initial mobile phase. It was then detected by UPLC-MS/ MS. The method detection limits were between 0.03 and 0.35 ng/mL. For benzene metabolites, trans, *trans*-muconic acid (t, t-MA) and S-phenylmercapturic acid (S-PMA) in urine were determined. Analyses in 1.0 mL urine samples were extracted using solid phase extraction (Oasis HLB 96 well plate, 60 mg, 60 μm). The eluate was evaporated to dryness followed by reconstituting with initial mobile phase. It is then analyzed using UPLC-MS/MS. The method lower detection limits were 5 ng/mL and 0.1 ng/mL for t,t-MA and S-PMA, respectively.

2.3.5. Quality control—An advanced computer assisted personal interviewing (CAPI) was used to collect and process all of the data from CNHBM, nearly eliminating the need for paper forms and manual coding operations. Survey information is available to staff of NIEH, China CDC within 24 h of collection, which enhances the capability of collecting quality data and allows for faster release of the results to the public. The data of physical examinations and clinical lab-based tests were entered by trained investigators into the computer twice with EpiData software and cross-validated. Copies of the original results of all physical examinations and clinical lab-based tests were mailed to the NIEH, China CDC for archiving and future reference.

Six qualified laboratories were selected as key laboratories to finish the detection work. Quality assessment/quality control (QA/QC) procedures were performed in the contract laboratories for environmental chemical detection. Standard operating procedures and quality control manuals were employed as internal QA/QC including standardized sample preparation procedures, standardized reagents, and standard or certified reference materials (SRM and CRM, respectively). QC materials were well-characterized and stable for years to allow tracking of long-term QC. QC or blind split samples are typically the same matrix as the study specimens and have concentrations of target compounds in the mid-range of the assay calibration. If available, CRM or SRM were used to prepare QC samples. Staff from NIEH, conducted annual laboratory inspections and reviewed the QC data from each laboratory. In each analytical run, 2–4 quality control materials, blanks, and calibrants were analyzed concurrently with unknown samples. QC measurements were assessed according to Westgard rules. Accuracy was based upon National Institute of Standards and Technology (NIST) standard reference materials that were analyzed periodically among sample runs. When runs were deemed out-of-control, the samples were reanalyzed. No data from runs deemed out-of-control were used in our analyses. Comparison results (such as E_n-value) of unknown samples within six selected laboratories showed that HMMs (such as lead, cadmium, mercury, arsenic and so on) were of high consistence after interlaboratory comparison. Summary QC data will be reported with our publications.

3. Results

Table 4 describes the baseline characteristics of participants from CNHBM. A total of 21,746 participants aged 3–79 years were included in the CNHBM, and the participants were divided into six age groups for statistical analysis with nearly equal numbers of each sex. The ratio of urban and rural residents was 45.2% (9817) to 54.8% (11,884), which was close to the urbanization rate of China in 2017/18 (Xu, 2018).

As defined by the six major geographical divisions in China, 5904 participants were from Eastern China, accounting for 27.2% of the participants; and 4943 (22.8%) from Central Southern China, 3314 (15.2%) from Southwestern, 3122 (14.4%) from Northern China, 2449 (11.3%) from Northeastern China, and 2014 (11.3%) from Northwestern China. Among the participants, 18,794 were Han Chinese, accounting for 86.4%. A total of 1122 (10.3%) participants aged 19 and older were illiterate. Among the participants who had received education, the largest number (30.4%) received education for 7–9 years followed by 18.8% for 10–12 years. In terms of occupation, 7433 (68.2%) participants aged 19 and older were engaged in tertiary industry (providing services to consumers), followed by primary industry (extracting and collecting natural resources) with 2235 (20.5%), and 1136 (10.4%) for secondary industry (converting natural resources into finished products). The highest prevalence of cigarette smoking was in participants aged 40–59 (30.4%) while the highest prevalence of alcohol consumption was observed in participants aged 19–39 (50.7%).

The mean BMI for the total population was 21.1 ± 5.0 kg/m^2. Systolic blood pressure and diastolic blood pressure increased with age with means of 125.1 ± 21.3 mmHg and 77.1 ± 12.8 mmHg, respectively. The highest prevalence of hypertension was observed in the participants aged 60–79 (50.3%). The mean value of red blood cells, hemoglobin, and creatinine were 4.8 ± 0.6*10^9/L, 140.0 ± 18.6 g/L, and 63.9 ± 22.5 mmol/L. The mean value of uric acid, blood urea nitrogen, and glucose were 303.9 ± 91.1 mmol/L, 4.9 ± 1.9 mmol/L, and 5.1 ± 1.3 mmol/L.

HMMs in blood samples and urine samples in all 21,746 participants were designed to be determined. Until now, HMMs in 5884 blood samples and 5859 urine samples have been analyzed respectively. The information about this subsample has been discirbed in Table S1 as supplementary materials (N = 5884), who were from 10 specific provinces such as Beijing, Guangdong, Hainan, Hubei, Jiangsu, Shandong, Shanxi, Shaanxi, Yunnan, Chongqing. Generally, the characteristics of the 5884 subsample were consistent with the total samples of 21,746 participants. Levels of HMMs in a subset of the China participants are shown in Table 5. The geometric mean (GM) of blood and urinary lead was 19.83 μg/L and 0.58 μg/L, respectively. The GM of blood and urine cadmium was 0.48 μg/L and 0.32 ug/L in 2017–2018. The GM of blood total arsenic levels was 1.00 μg/L. The GM of urinary total arsenic was 18.61 μg/L. In 2017–2018, the GMs of blood and urine total mercury and blood and urine chromium were 1.00 μg/L, 0.20 μg/L, 0.37 μg/L, and 0.44 μg/L respectively.

4. Discussion

CNHBM established the first nationally representative, prospective cohort in the Chinese population. Biomonitoring in China began in the early 1950s. Qualitative determination of urinary porphyrins in lead-exposed workers was used to assist in the diagnosis of lead poisoning. Urinary phenol monitoring of occupational benzene exposure in the mid-1960s marks the beginning of biomonitoring to directly detect environmental pollutants (Liu and Liu, 1966). From 1981 to 1989, the Chinese Center for Disease Control and Prevention (China CDC) collected 11,294 biospecimens in 35 cities of 28 provinces to assess dichlorodiphenyltrichloroethane (DDT) and HMM exposures in China (Liu and Liu, 1966). *Ding, et al* reported the internal exposure levels of HMMs in 18,120 people aged 6–60 years in eight provinces and cities in China in 2009 (Ding et al., 2012, Ding et al., 2014a, Ding et al., 2014b). Although these studies in China represent a promising start, they are not nationally representative or focused on specific subpopulations in occupational exposure settings, and lacked information on vulnerable subgroups (e.g., small children and the elderly). Given the long-term, complex, and ubiquitous nature of environmental pollution in China, the need to gather human data on multiple key environmental chemicals in a large-scale, multi-regional biomonitoring effort in all age groups is warranted. This effort will provide information on toxicants to which people are frequently exposed, biological levels of these chemicals, trends in exposure over time and the main risk factors of internal exposure (Zhang et al., 2010).

The most widely cited national biomonitoring effort was conducted by the US Centers for Disease Control and Prevention as a part of the US National Health and Nutrition Examination Survey (NHANES), which were publicly available for download and analysis providing the most comprehensive human biomonitoring database in the United States (Fain, 2017; Centers for Disease Control and Prevention, 2018; Braun et al., 2008; Bao et al., 2019). Other population-based surveys have been developed and implemented specifically for environmental exposure assessment. The Canadian Health Measures Survey released Canadian environmental chemical biomonitoring which report present data collected between 2007 and 2017 for more than 200 environmental chemicals measured in about 27,000 people aged 3–79 from the general Canadian population. The German Environment Agency (Umweltbun-desamt - UBA) has released the 2014–2017 results of the German Environmental Survey (GerES V) in 2020 (Murawski et al., 2020). GerES tests urine and blood for various HMMs, plasticizers, parabens, cotinine, polycyclic aromatic hydrocarbons and PFAS (Schulz et al., 2012). The National Health and Nutrition Examination of Korea began to monitor the blood levels of lead, cadmium and mercury in humans from 2005 to 2006 (Seo et al., 2015).

The CNHBM has several strengths. First, it is the first nationally representative, prospective cohort in the Chinese population. The potential of healthy volunteer bias is limited due to the multi-stage cluster random sampling design. It also includes the unique exposure of the cohort population and the scheduled follow-up of each participant every 3 years with a repeated medical examination to update exposure and outcome information, which will permit extensive evaluation of the relationships between multiple environmental chemical exposures, epigenetic and risk of health outcome on a level unachievable before now.

Second, the CNHBM cohort design includes the collection of biological data including information on environmental chemical exposures in blood and urine and dietary exposures. A biorepository was created enabling future study of this population as new chemicals or diseases emerge. DNA samples stored from the cohort were important resources for studies of the effects of genes and gene-environment interactions on emerging environmental issues. Third, an interdisciplinary research team was composed of experts in environmental health, epidemiology, biostatistics, chemistry, and toxicology, which enabled diverse laboratory analyses and evaluation of health effects.

Several limitations should also be mentioned. First, even with the strong support of the NIEH of China CDC, we cannot rule out the possibility of withdrawal bias in follow-up of these participants dispersed in 152 PSUs in China. Like many cohort studies, there was considerable attrition due to mortality and migration by the time of the adult follow-up. Second, we cannot exclude the possibility of recall bias during the data collection process, although we asked the same questions of participants and their relatives for reliability checking. Third, the absence of infant, children aged 2 and younger and the elderly aged 80 and older rendered it less suitable to study the evolution of disease in these populations. Fourth, six qualified laboratories were selected as key laboratories to finish the detection work, which may lead to bias in the QA/QC, even though standard operating procedures and quality control manuals were employed in the process. Fifth, until now, HMMs in 5884 blood samples and 5859 urine samples only provided preliminary results rather than national baseline exposure in the present study. Finally, internal exposure of environmental chemicals from blood or urine samples may be not the optimal biomarkers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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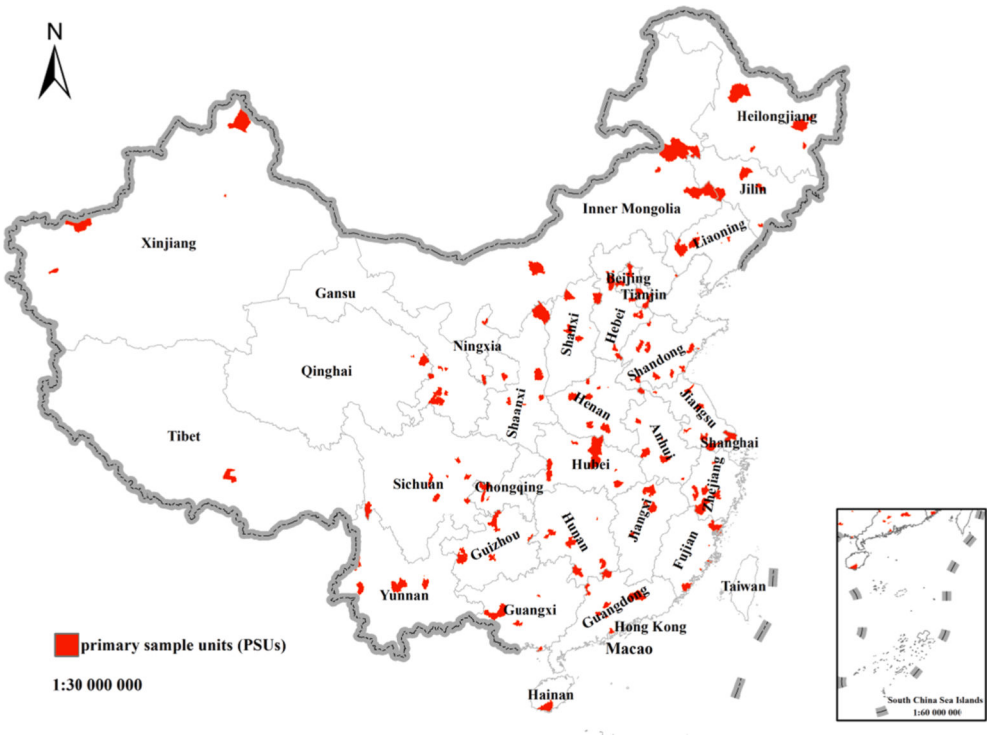

Fig. 1. The distribution of 152 primary sampling units in China National Human Biomonitoring.

The China National Human Biomonitoring adopted three-stage sampling method to obtain a nationally representative sample of the population. Finally, a total of 21,888 participants who were permanent residents in 31 provinces were designed to be interviewed in this national biomonitoring (152 monitoring sites × 3 survey units × 2 sexes × 6 age groups × 4 persons = 21,888 persons).

Table 1

A summary of questionnaire components: China National Human Biomonitoring.

Questionnaire	Description
PSUs questionnaire	
Natural environment	• Geographic position; the total area; landform; and the main soil types in the area
Demographic data (last year, from local statistical bureau)	Total population of the region; crude death rate; infant mortality rate; and urban population ratio
National economic indexes (last year, from local statistical bureau)	The region's gross national product last year; the percentage of gross national product; net income per head in the region last year; and per capita net income
Health care (last year, from local department of health)	The average number of medical staff per 10,000 people; number of hospital beds per 10,000 people; the number of pension institutions; and the number of elderly people living in pension institutions
Environmental quality (last year, from local department of environmental protection)	Per capita water resources; status of water pollution; Air quality of community; and solid waste
Pollution source (last year, from local department of environmental protection)	Centralized pollution treatment facilities within the jurisdiction; industrial pollution sources; agricultural pollution sources; and urban domestic pollution source
Community unit questionnaire	
Industrial pollution sources (last year, from local department of environmental protection)	• Time of establishment of the factory; crew size; location; effluent volume; tailpipe emission; and solid waste discharge
Agricultural pollution sources (last year, from local department of environmental protection)	Large-scale livestock and poultry farms and communities; household specialized in breeding; aquaculture plant; and plant factories
Centralized pollution source (last year, from local department of environmental protection)	Domestic waste treatment plant; sewage treatment plant; and hazardous waste (clinical waste) treatment facilities
Individual questionnaire	
Personal Profile	Gender; nationality; birthplace; time to begin local residence; education level; and marital status
Occupation	Current work situation; and previous work status
Daily behavior	Smoking status; alcohol consumption; and hair dye
Dietary status	The main place for three meals; the main source of drinking water; and the frequency and quantity of each type of food
Physical activity	Time required for daily commute; and main modes of travel on/off duty
Sleep quality	The average length of sleep per night; sleep disorders; and whether to take sleeping pills and other treatment of insomnia drugs
Women's situation	Age of first menstruation; menstrual status; pregnancy status; and the use of cosmetics
Household questionnaire	
Housing characteristics	How many family members has lived there and when did the family begin to live there; housing type; built-up area; and usable floor area
House ventilation	Ventilation system type; frequency of window opening ventilation in different seasons; and heating ways in winter
Household income	Family annual income and expenditure; and source of income
Household fuel use	Kitchen type and ventilation measures; major domestic fuels; and frequency of cook at home every week
Indoor environmental pollution	Residential decoration and time; furniture purchase and time; air purification measures; and use of domestic chemicals

Table 2

A summary of medical examination: China National Human Biomonitoring.

Medical examination	Measurements
Physical Examination Questionnaire	Current medications, disease history; family disease history; Quantity and time of 24 h alcohol intake and tobacco use; Frequency and time of 24 h nutrient use; and time of 24 h drug use
Physical examination	Anthropometric characteristics: weight; height; waist circumference; and blood pressure
	Internal medicine: nutritional status; cardiovascular examination; respiratory health; liver and spleen examination
	Surgery: thyroid; lymphatic system; spine; thorax; limbs; and joint
	Ophthalmology: vision; color vision; and fundus oculi
	Otorhinolaryngology: nose; throat; tonsil; and olfactory sensation
	Oral health: olfactory sensation; and dental periphery
	Dermatology: assessment for skin conditions by observation with naked eyes; and skin-scratch test
	Neurology: assessment for peripheral neuropathy
	Imaging examinations (optional): electrocardiograms; ultrasonic B; and X-ray examinations
Clinical lab-based tests	Blood routine test: white blood cells (WBC); red blood cells (RBC); platelet count (PLT); lymphocyte; hemoglobin etc.
	Blood zymogram level: alanine aminotransferase(ALT); aspartate aminotransferase(AST); gamma glutamyltransferase (GGT); lactic dehydrogenase (LDH); serum apoprotein A1; serum apoprotein B blood urea nitrogen (BUN); creatinine etc.
	Lipids: total cholesterol (TC), triglycerides (TG), high-and low-density cholesterol lipoprotein (HDL-C, LDL-C), fasting plasma glucose (FPG)
	Inflammatory markers: C-reactive protein.
	Hormone: Serum triiodothyronine [T3]; Serum thyroxine [T4]; Estradiol [E2]; Testosterone [T] Urine routine examination: urine specific gravity; urine pH; urine protein; urine nitrite; urinary gallbladder etc.

Table 3

Environmental chemicals at the baseline of China National Human Biomonitoring.

Environmental chemicals	Compounds
Biosample collection	Fasting blood (serum, hemocytes, blood clotting): 4 mL for subjects aged 3–5 years; 12 mL for subjects aged 6–11 years; and 16 mL for subjects aged 12–79 years.
	Random urine samples: 50 mL for subjects aged 3–11 years; 80 mL for subjects aged 12–79 years; 12 and over for 80 mL; and 3–11 years for 50 mL
Inorganic chemicals (13 compounds)	Arsenic (As), Cadmium (Cd), Chromium(Cr), Lead (Pb), Mercury (Hg), Manganese (Mn), Cobalt (Co), Nickle (Ni), Selenium (Se), Molybdenum (Mo), Stannum (Sn), Stibium (Sb), Thallium(Tl)
Poly- and per-fluorinated alkyl substances (PFAS) (17 compounds)	perfluorobutanoic acid (PFBA), perfluoropentanoic acid (PFPeA), perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorododecanoate acid (PFDoDA), perfluorotridecanoate acid (PFTriDA), perfluorotetradecanoic acid (PFTeDA), perfluorobutane sulfonate (PFBS), perfluoroheptanesulfonate (PFHpS), perfluorooctane sulfonate (PFOS), 4:2 Chlorinated Polyfluorinated Ether Sulfonate (4:2Cl-PFESA), 6:2 Chlorinated Polyfluorinated Ether Sulfonate (6:2 CI-PFESA), 8:2 Chlorinated Polyfluorinated Ether Sulfonate (8:2Cl-PFESA)
Phthalate alternative metabolites in urine: (11 compounds)	Mono-methyl phthalate (MMP), Mono-ethyl phthalate (MEP), Mono-*iso*-butyl phthalate (MiBP), Mono-n-butyl phthalate (MnBP), Mono-benzyl phthalate (MBzP), Mono-2-ethylhexyl, phthalate (MEHP), Mono-cyclohexyl phthalate (MCHP), Mono-n-octyl phthalate (MOP), Mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), Mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), Mono-isononyl phthalate (MiNP), Mono-isodecyl phthalate (MiDP)
Metabolites of polycyclic aromatic hydrocarbon (PAHs) in urine: (9 compounds)	1-hydroxynaphthalene, 2-hydroxynaphtha-lene, 2-hydroxyfluorene, 3-hydroxyfluorene, 1-hydroxyphenanthrene, 2-hydroxyphenan-threne, 1-hydroxypyrene, 3-hydroxychrysene, 6-hydroxychrysene
Environmental phenol alternative in urine: (4 compounds)	Bisphenol A, bisphenol F, Tetrachlorobisphenol A, Tetrabromobisphenol A
Benzene metabolites in urine (2 compounds)	Trans, *trans*-muconic acid(t, t-MA), N-Acetyl-S-(phenyl)-L-cysteine

Table 4

Baseline characteristics of participants in China National Human Biomonitoring.

Characteristics	Aged 3–5	Aged 6–11	Aged 12–18	Aged 19–39	Aged 40–59	Aged 60–79	Total
No. of participants	3618	3616	3609	3631	3637	3635	21,746
Age	4.1 ± 0.8	8.5 ± 1.7	14.5 ± 1.9	31.1 ± 5.5	49.4 ± 5.5	66.6 ± 5.1	29.1 ± 23.0
Gender							
Female	1812 (50.1)	1804 (49.9)	1803 (50.0)	1818 (50.1)	1825 (50.2)	1821 (50.1)	10,883 (50.0)
Male	1806 (49.9)	1812 (50.1)	1806 (50.0)	1813 (49.9)	1812 (49.8)	1814 (49.9)	10,863 (50.0)
Districts							
Northern	520 (14.4)	511 (14.1)	510 (14.1)	524 (14.4)	528 (14.5)	529 (14.6)	3122 (14.4)
Northeastern	336 (9.3)	336 (9.3)	334 (9.3)	336 (9.3)	337 (9.3)	335 (9.2)	2014 (9.3)
Eastern	985 (27.2)	983 (27.2)	986 (27.3)	980 (27.0)	986 (27.1)	984 (27.1)	5904 (27.1)
Central south	823 (22.7)	827 (22.9)	819 (22.7)	825 (22.7)	825 (22.7)	824 (22.7)	4943 (22.7)
Southwest	545 (15.1)	552 (15.3)	553 (15.3)	557 (15.3)	552 (15.2)	555 (15.3)	3314 (15.2)
Northwestern	409 (11.3)	407 (11.3)	407 (11.3)	409 (11.3)	409 (11.2)	408 (11.2)	2449 (11.3)
Nationality							
Han	3059 (84.5)	3062 (84.7)	3135 (86.9)	3135 (86.3)	3202 (88.0)	3201 (88.1)	18,794 (86.4)
Tibet	83 (2.3)	94 (2.6)	90 (2.5)	97 (2.7)	91 (2.5)	96 (2.6)	551 (2.5)
Zhuang	65 (1.8)	71 (2.0)	72 (2.0)	64 (1.8)	63 (1.7)	57 (1.6)	392 (1.8)
Mongolia	69 (1.9)	64 (1.8)	63 (1.7)	58 (1.6)	45 (1.2)	41 (1.1)	340 (1.6)
Hui	54 (1.5)	51 (1.4)	38 (1.1)	42 (1.2)	39 (1.1)	55 (1.5)	279 (1.3)
Man	55 (1.5)	44 (1.2)	33 (0.9)	45 (1.2)	41 (1.1)	31 (0.9)	249 (1.1)
Li	35 (1.0)	31 (0.9)	30 (0.8)	31 (0.9)	28 (0.8)	25 (0.7)	180 (0.8)
Uyghur	29 (0.8)	25 (0.7)	25 (0.7)	22 (0.6)	18 (0.5)	19 (0.5)	138 (0.6)
Dong	23 (0.6)	27 (0.7)	25 (0.7)	20 (0.6)	21 (0.6)	22 (0.6)	138 (0.6)
Other	146 (4.0)	147 (4.1)	98 (2.7)	117 (3.2)	89 (2.4)	88 (2.4)	685 (3.2)
Residence							
Rural	1634 (45.2)	1638 (45.3)	1637 (45.4)	1643 (45.2)	1644 (45.2)	1641 (45.1)	9837 (45.2)
Urban	1984 (54.8)	1978 (54.7)	1972 (54.6)	1988 (54.8)	1993 (54.8)	1994 (54.9)	11,909 (54.8)
Education							
Illiterate				74 (2.0)	264 (7.3)	784 (21.6)	1122(10.3)

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Characteristics	Aged 3–5	Aged 6–11	Aged 12–18	Aged 19–39	Aged 40–59	Aged 60–79	Total
<6 years	–	–	–	96 (2.6)	345 (9.5)	630 (17.3)	1071(9.8)
6 years	–	–	–	254 (7.0)	568 (15.6)	693 (19.1)	1515(13.9)
7–9 years	–	–	–	1143 (31.5)	1260 (34.6)	910 (25.0)	3313(30.4)
10–12 years	–	–	–	834 (23.0)	768 (21.1)	448 (12.3)	2050(18.8)
≥13 years	–	–	–	1210 (33.3)	424 (11.7)	156 (4.3)	1790(16.4)
Missing	–	–	–	20 (0.6)	8 (0.2)	14 (0.4)	42(0.4)
Occupation							
Primary industry	–	–	–	462 (12.7)	883 (24.3)	890 (24.5)	2235(20.5)
Secondary industry	–	–	–	580 (16.0)	475 (13.1)	81 (2.2)	1136(10.4)
Tertiary Industry	–	–	–	2555 (70.4)	2255 (62.0)	2623 (72.2)	7433(68.2)
Missing	–	–	–	34 (0.9)	23 (0.6)	41 (1.1)	98(0.9)
Smoking							
Smoker	–	–	137 (3.8)	1057 (29.1)	1104 (30.4)	1002 (27.6)	3300(22.7)
Non-Smoker	–	–	3424 (94.9)	2555 (70.4)	2517 (69.2)	2617 (72.0)	11113(76.6)
Missing	–	–	48 (1.3)	19 (0.5)	16 (0.4)	16 (0.4)	99(0.7)
Drinking							
Alcohol drinker	–	–	638 (17.7)	1841 (50.7)	1629 (44.8)	1220 (33.6)	3545(24.4)
Non-drinker	–	–	2928 (81.1)	1769 (48.7)	1998 (54.9)	2396 (65.9)	10461(72.1)
Missing	–	–	43 (1.2)	21 (0.6)	10 (0.3)	19 (0.5)	506(3.5)
Sea fish							
Never	1769 (48.9)	1735 (48.0)	1879 (52.1)	1698 (46.8)	1678 (46.1)	1870 (51.4)	10,629 (48.9)
<once per week	637 (17.6)	743 (20.5)	685 (19.0)	774 (21.3)	849 (23.3)	771 (21.2)	4459 (20.5)
once per week	396 (10.9)	386 (10.7)	337 (9.3)	354 (9.7)	324 (8.9)	279 (7.7)	2076 (9.5)
Twice per week	218 (6.0)	182 (5.0)	163 (4.5)	192 (5.3)	159 (4.4)	137 (3.8)	1051 (4.8)
3 time per week	77 (2.1)	76 (2.1)	71 (2.0)	83 (2.3)	82 (2.3)	58 (1.6)	447 (2.1)
≥4 time per week	136 (3.8)	119 (3.3)	103 (2.9)	173 (4.8)	170 (4.7)	148 (4.1)	849 (3.9)
Missing	385 (10.6)	375 (10.4)	371 (10.3)	357 (9.8)	375 (10.3)	372 (10.2)	2235 (10.3)
Seashell							
Never	2453 (67.8)	2374 (65.7)	2435 (67.5)	2268 (62.5)	2401 (66.0)	2753 (75.7)	14,684 (67.5)
<once per week	489 (13.5)	612 (16.9)	575 (15.9)	618 (17.0)	551 (15.1)	365 (10.0)	3210 (14.8)
once per week	157 (4.3)	155 (4.3)	129 (3.6)	177 (4.9)	145 (4.0)	69 (1.9)	832 (3.8)

Characteristics	Aged 3–5	Aged 6–11	Aged 12–18	Aged 19–39	Aged 40–59	Aged 60–79	Total
Twice per week	66 (1.8)	65 (1.8)	71 (2.0)	92 (2.5)	71 (2.0)	47 (1.3)	412 (1.9)
≥ 3 time per week	51 (1.4)	46 (1.3)	52 (1.4)	82 (2.3)	63 (1.7)	52 (1.4)	346 (1.6)
Missing	402 (11.1)	364 (10.1)	347 (9.6)	394 (10.9)	406 (11.2)	349 (9.6)	2262 (10.4)
Height (cm)							
Female	107.4 ± 9.5	135.0 ± 13.5	158.1 ± 8.6	158.8 ± 6.2	156.6 ± 7.0	153.0 ± 7.3	144.9 ± 20.6
Male	108.8 ± 9.4	134.4 ± 12.9	165.5 ± 11.7	170.9 ± 7.4	167.9 ± 7.1	164.8 ± 6.9	152.1 ± 24.7
Weight (kg)							
Female	27.5 ± 24.7	32.3 ± 10.6	51.2 ± 11.4	58.5 ± 10.6	60.1 ± 10.2	58.0 ± 10.3	51.0 ± 16.3
Male	26.2 ± 20.4	32.8 ± 11.5	56.8 ± 16.1	71.7 ± 13.7	70.7 ± 11.4	65.5 ± 11.3	57.5 ± 21.1
Body mass index (kg/m^2)	15.8 ± 2.4	17.1 ± 3.4	20.4 ± 4.0	23.9 ± 4.1	24.7 ± 3.5	24.5 ± 3.6	21.1 ± 5.0
Hypertension							
With hypertension	–	–	135 (3.7)	461 (12.7)	1121 (30.8)	1828 (50.3)	3545(24.4)
Without hypertension	–	–	3222 (89.3)	3089 (85.1)	2430 (66.8)	1720 (47.3)	10461(72.1)
Missing	–	–	252 (7.0)	81 (2.2)	86 (2.4)	87 (2.4)	506(3.5)
Systolic blood pressure (mmHg)	–	–	110.3 ± 13.1	118.4 ± 15.2	129.1 ± 19.2	141.7 ± 21.9	125.1 ± 21.3
Diastolic blood pressure (mmHg)	–	–	68.4 ± 9.5	75.9 ± 11.6	81.5 ± 12.2	82.1 ± 12.6	77.1 ± 12.8
Red blood cell (10^9/L)	4.7 ± 0.5	4.8 ± 0.6	4.9 ± 0.6	4.9 ± 0.7	4.8 ± 0.7	4.7 ± 0.6	4.8 ± 0.6
Hemoglobin (g/L)	129.1 ± 13.0	134.4 ± 13.7	142.6 ± 17.6	146.0 ± 20.7	144.6 ± 20.2	143.4 ± 18.7	140.0 ± 18.6
Creatinine (mmol/L)	46.3 ± 19.6	52.6 ± 18.1	65.3 ± 18.6	71.5 ± 20.1	72.1 ± 20.4	74.8 ± 21.5	63.9 ± 22.5
Uric acid (mmol/L)	267.1 ± 68.6	284.8 ± 74.2	337.9 ± 96.4	316.3 ± 98.9	306.1 ± 94.7	310.5 ± 91.6	303.9 ± 91.1
Blood urea nitrogen (mmol/L)	4.3 ± 1.7	4.4 ± 1.5	4.5 ± 2.1	4.8 ± 1.6	5.3 ± 1.9	5.8 ± 2.1	4.9 ± 1.9
Glucose (mmol/L)	4.5 ± 0.7	4.8 ± 0.7	4.8 ± 0.6	5.0 ± 1.1	5.4 ± 1.5	5.8 ± 1.8	5.1 ± 1.3

Table 5

Blood and urine metal levels (μg/L) in China National Human Biomonitoring in 2017–2018 (n = 5884).

Metal	Geometric mean	<LOD (%)[a]	P_{10}	P_{25}	Median	P_{75}	P_{90}
Blood sample (n = 5884)							
Lead	19.83	0.48	10.94	14.37	19.93	27.63	38.80
Cadmium	0.48	3.06	0.09	0.19	0.43	1.10	3.78
Mercury	1.00	1.84	0.28	0.55	1.05	2.11	3.64
Arsenic	0.90	4.66	0.26	0.56	0.95	1.79	3.14
Chromium	0.44	10.27	<LOD	0.22	0.41	1.13	2.16
Urine Sample (n = 5859)							
Lead	0.58	10.99	<LOD	0.45	0.89	1.49	2.23
Cadmium	0.32	4.30	0.06	0.13	0.34	0.82	1.72
Mercury	0.20	17.96	<LOD	0.08	0.22	0.60	1.46
Arsenic	18.61	0.39	6.12	10.79	19.00	33.44	55.35
Chromium	0.37	22.46	<LOD	0.15	0.38	0.72	1.22

[a]The limit of determination for lead, cadmium, mercury, arsenic, and chromium in blood was 0.035 μg/L, 0.025 μg/L, 0.01 μg/L, 0.04 μg/L, and 0.05 μg/L; it was 0.01 μg/L, 0.02 μg/L, 0.015 μg/L, 0.10 μg/L, and 0.10 μg/L for urine.