Association of Endocrine Disrupting Chemicals Levels in Serum, Environmental Risk Factors, and Hepatic Function Among 5- to 14-Year-Old Children

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Research

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Abstract

Background: Endocrine-disrupting chemicals (EDCs) might increase the risk of childhood diseases by disrupting hormone-mediated processes that are critical for growth and development during childhood, however, the association among the exposure level of EDCs such as Nonylphenol (NP), Bisphenol A (BPA), Dimethyl phthalate (DMP) in children and environmental risk factors, as well as hepatic function has not been elaborated.

Objectives: This study aimed to discuss this interesting relationship among NP, BPA, DMP concentrations in serum, environmental risk factors, hepatic function of 5- to 14-year-old children in industrial zone, residential zone and suburb in northern district of Guizhou Province, China.

Methods: In Zunyi city, 1,006 children participated in cross-sectional health assessments from July to August 2018, and their parents completed identical questionnaires on the environmental risk factors of EDCs exposure to mothers and children. Serum NP, BPA and DMP concentrations were measured by high performance liquid chromatography (HPLC). Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), AST/ALT, total bilirubin (TBIL), direct bilirubin (DBIL) and indirect bilirubin (IBIL) were detected with automatic biochemical analyzer.

Results: The median concentrations of serum NP, BPA, and DMP in the participants were 45.85 ng/mL, 26.31 ng/mL and 31.62 ng/mL, respectively, which were higher than the environmental concentration limits of the U.S. National Environmental Protection Agency (EPA). Hair gels used during pregnancy, types of domestic drinking water, nail polish and cosmetics used by children were significantly positive correlated with serum NP concentration ($P < 0.05$). Gender, feeding pattern, plastic water cup used during pregnancy, hair spray and perfume use for children, duration of children birth, materials for baby bottle or cup and ways to plastic products were significantly positively correlated with serum BPA concentration ($P < 0.05$). Gender, perms used during pregnancy, hair spray and perfume use for children, using plastic lunch box during pregnancy, duration of children birth, exposure to pesticides, parents' occupations were significantly positively correlated with serum DMP concentrations ($P < 0.05$). Serum NP ($\beta = 0.296$, $P = 0.036$) and DMP ($\beta = 0.316$, $P = 0.026$) concentrations and TBIL level were significantly positively correlated. Serum NP concentration and the levels of IBIL ($\beta = 0.382$, $P = 0.006$) are significantly positively correlated. Cosmetics used during pregnancy significantly increased AST level ($\beta = 2.641$, $P = 0.021$). There was a positive correlation between the frequency of hair spray and perfume use for children and the AST ($\beta = 4.241$, $P = 0.022$).

Conclusion: NP, BPA and DMP, which were commonly detected in the serum of children aged 5-14 years old in Zunyi City, Northern Guizhou Province, China, were closely related to the environmental risk factors of exposure environment during pregnancy, infancy and school age. Exposure to NP, BPA and DMP would have negative effects on hepatic function, and these effects showed differences in gender and geographical location. Notably, The relationships were more evident in girls than in boys.

Highlights

1. Association between serum EDCs level and risk factors among 5-14 year old children.
2. Association in serum NP–BPA–DMP levels and hepatic function.
3. Serum EDCs level in school-age children was highest in industrial zone.
4. Differences in EDCs level and hepatic function in terms of sex and geographic area.

Introduction

The pollution of endocrine disrupting chemicals (EDCs), including Nonylphenol (NP), bisphenol A (BPA), phthalate (PAE), etc., has attracted more and more attention from the worldwide in recent years. EDCs, as exogenous compounds, can potentially interfere with the endocrine system, including hormone synthesis, release, transport and metabolism, during the development of the body (Bergman et al. 2015). EDCs can enter the human through skin contact, ingestion, respiration, placenta transfer and other ways (Gore et al. 2011), and be detected in human urine, blood, breast milk and adipose (Koch et al. 2012; Gore et al. 2015). The exposure levels of NP, BPA and PAE in human blood in different regions of the world were different, which were shown in Figure 1. Recent studies have shown that EDCs were closely related to human growth and development (Mao et al. 2012), diabetes (DM) (Predieri et al. 2020), metabolic disorders (Senthil et al. 2011), immune deficiency and cancer (Bansal et al. 2018; Kass et al. 2012). NP, BPA and PAE are typical representatives of EDCs due to their frequent usage in daily life (NIEHS. 2010). NP is an important fine chemical raw material and intermediate, mainly used in the production of surfactants, textile printing and dyeing auxiliaries, lubricating oil additives, pesticide emulsifiers and rubber stabilizers, etc. At present, the world's total production capacity was 500,000 tons/year, and China's current production capacity was 60,000 tons/year (Mao et al. 2012; Careghini et al. 2015). BPA, as an important monomer of polycarbonate and epoxy resin, is applied to the manufacture of various consumer goods, such as water cups, baby bottles, medical devices, etc. (Rezg et al. 2014). The output of BPA in China already reached 1.575 million tons/year in 2019, with increase of 9.38% from the previous year (Xiao et al. 2019). PAEs is a chemical mainly used as plasticizer to soften PVC (Larsson et al. 2014). China was currently the largest producer and consumer of phthalates in the world. Singh et al. 1972 reported that DMP exposure had maternal toxicity and effects on embryo/fetal viability, growth and morphogenesis (Singh et al. 1972). However, few studies detected DMP concentrations in biomarker, hence, DMP, as a representative of the PAEs' metabolites, was chosen for detection in blood in this study. Therefore, the relationship between NP, BPA and PAEs exposure and health damage has become a research hotspot of environmental hygiene (Li et al. 2011).

In recent years, the economy of northern region of Guizhou in Western China was developing rapidly. The residents were suffering from the impact of environmental pollution, While enjoying the fruitful results of economic development, environmental problems were increasingly prominent with the further development of economy and the deepening of industrialization and urbanization. However, the general concern about the pollution of EDCs in northern Guizhou of china was not enough. 5-14-year-old school-age children were in a rapid period of growth and development, and the organ functions that have not been fully developed were more vulnerable to damage (Xie et al. 2015). Our previous studies showed that NP had adverse effects on reproduction, immunity and nervous system of rats (Jie et al. 2010a; Fan et al. 2010; Jie et al. 2013). Additionally, the serum NP level of Type 2 diabetes patients was higher than the levels in healthy controls (Luo et al. 2016). It was also reported that EDCs can affect the growth and development of fetus through placenta (Mose et al. 2007; Balakrishnan et al. 2010), and further lead to precocious puberty (Qiao et al. 2010), sexual development abnormality (Cai. 2013), obesity (Dai. 2014), psychological (Maserejian et al. 2014) and behavioral abnormality (Minatoya et al. 2018; Braun et al. 2014) in children through hypothalamus-pituitary-gonad axis (Fan and Yan. 2010). Intrauterine perinatal period and child growth and development period are two key periods of human growth and development. Research on reducing and preventing children diseases caused by EDCs exposure has gradually become one of the research focuses currently. Nowadays, research on the effects of EDCs on children's hepatic function is very scarce (Seth et al.1982). Therefore, this study aimed to take children aged 5-14-year as the subjects, for the first time to explore the association between the exposure level of serum NP, BPA and DMP in children and the main environmental risk factors, as well as the correlation between the exposure level of serum NP, BPA and DMP and the indicators of hepatic function. Furthermore, this study was to try to provide epidemiological evidence for diseases caused by EDCs exposure and explore their pathogenic mechanism.

Materials And Methods

1.1 Study location

The survey location was Zunyi City, which is the largest city in the north of Guizhou Province in Southwest China (Figure 2). This area was rich in coal resources and belongs to a typical acid rain area. The urban air pollution was characterized by "coal smoke, dust, industrial waste gas and motor vehicle exhaust composite" pollution. The pH value of atmospheric precipitation in this area was low, once as low as 3.2, which was a typical industrial city with serious environmental pollution (Yu et al. 2016). The city's jurisdiction included three districts: Huichuan District, Honghuagang District, and Bozhou District, which represented industrial zone, residential zone and suburb, respectively. The survey covered a total geographic area (105 square kilometers) with a total population of more than 6.24 million.

1.2 Study design and subjects

The study was a population-based, cross-sectional study, which conducted from July to August 2018 in Zunyi city, Guizhou Province. One thousand and six school-age children aged 5-14 who had summer physical examination in the People's Hospital of Honghuagang District, Zunyi City were randomly sampled, and questionnaire survey was carried out. Their parents or guardians completed identical questionnaires on the environmental risk factors of EDCs exposure to mothers and children. The blood samples were collected by the laboratory professionals of Honghuagang District People's Hospital and one part of them were used for serum tests by automatic biochemical analyzer, and the concentration of NP, BPA and DMP were measured by high performance liquid chromatography (HPLC) in serum separated from the other part of blood samples. The research scheme has been proved by the ethics committee of Zunyi Medical University (Certificate No.: 2015-1-017). A flowchart of exposure protocols and selection process of the participants was shown in Figure 3.

1.3 Questionnaires and bloodserum collection

The revised questionnaire on the environmental risk factors of EDCs exposure to mothers and children (Li. 2013) was used to list the environmental risk factors of EDCs exposed to kids aged 5-14 in Zunyi City. The questionnaire included: (1) basic information; (2) risk factors of exposure during pregnancy; (3) risk factors of exposure during infancy; (4) risk factors of exposure in children's current life. All detailed data was shown in Table 1. The data were collected in the form of an interview with parents or guardians, which was filled in by the uniformly trained investigators. Under the guidance of regulations, the related operations of this study and the research content of this study were explained in details to all research subjects and their personal privacy was kept strictly confidential.

5 ml of children's fasting peripheral venous blood was taken in the laboratory of the hospital, and then the serum was separated, numbered and stored in a -80°C refrigerator for HPLC.

1.4 Serum analysis

1.4.1 Detection of serum concentrations of NP, BPA and DMP

The serum concentrations of NP, BPA and DMP in the children were measured by HPLC. The lower limit of detection (LOD) for BPA concentration was 0.36 ng/mL. The LOD level for both DMP and NP concentrations was 0.5 ng/mL. Concentrations of EDCs below the LOD were assigned a value of 1/2 LOD. The peak time of NP, BPA and DMP standard samples was 3.7 min, 1.6 min and 3.6 min, respectively.

1.4.2Biochemical test of hepatic function

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), AST/ALT, total bilirubin (TBIL), direct bilirubin (DBIL) and indirect bilirubin (IBIL) in the children’ serum were analyzed with automatic biochemical analyzer (model 7600; Hitachi, Ltd., Tokyo, Japan). 462 hepatic function test reports were collected.

1.5Statistical analysis

JMP software (version 14, SAS Institute Inc, Cary, USA) was used to analyze and verify whether NP, DMP and BPA are related before all the data analysis. SPSS20.0 (Inc., Chicago, IL, USA) was used to process the data of this study. The enumeration data was described by the number of cases (composition ratio). Variance analysis was used for multiple groups comparison, and the level data of nonparametric statistics were analyzed by rank combination test. Differences in exposure levels by sex, age, and address were assessed. Multiple linear regression analysis was used to analyze the association among the levels of serum NP, BPA, DMP exposure, hepatic function and environmental risk factors. Binary logistic regression test was used to analyze the relationship between the level of serum NP, BPA, DMP exposure and hepatic function. The association between NP, BPA, DMP exposure concentration and the status of hepatic function outcomes in the children was estimated firstly, then an additional stratified analysis was conducted to explore the sex , age, and address differences. P-values < 0.05 were considered to be significant. Coded and labeled categorical variables showed in Supplementary Table 1.

Results

3.1Profile of the participants

A total of 1,006 questionnaires with serum information were collected. Among them, 544 participants were boys (54.1%), and 462 were girls (45.9%). The numbers of children from grade 1 to grade 3 (45%) and from grade 4 to grade 6 (33.9%) in primary school were top two, and the number of children aged 5-6 were the least (4%), details was shown in Table 1.

Table 1. Sociodemographic characteristics of the participants.

Characteristics	Subjects Number	NP			DMP			BPA		
	(Percentage)	25 th	50 th	75 th	25 th	50 th	75 th	25 th	50 th	75 th
Gender										
Male	544(54.1)	42.88	45.42	48.92	26.02	28.13	33.98	23.44	27.57	33.60
Female	462(45.9)	42.69	45.13	48.79	25.86	28.76	36.73	24.05	27.44	33.81
Grade										
Preschool	25(2.5)	41.00	43.15	48.38	27.29	28.91	47.44	23.64	25.79	34.61
Grade 1-3	453(45.0)	42.71	45.20	48.55	25.81	28.63	36.04	23.47	27.41	32.91
Grade 4-6	341(33.9)	42.91	45.20	48.99	25.72	28.14	33.46	23.31	26.35	32.87
Grade one of junior high school	187(18.6)	42.50	45.28	48.87	26.23	28.47	35.46	24.64	29.30	36.82
Age										
5-6 years old	40(4.0)	42.37	45.90	55.58	26.42	29.63	40.44	21.90	25.79	35.13
7-8 years old	334(33.2)	42.67	45.07	47.90	25.44	27.90	35.98	23.56	26.68	31.99
9-10 years old	261(25.9)	43.76	45.67	50.16	25.97	28.63	34.17	23.47	27.12	32.91
11-12 years old	218(21.7)	42.75	45.20	48.79	25.83	28.25	33.46	24.07	27.17	33.99
13-14 years old	153(15.2)	42.48	45.21	48.48	26.23	28.24	35.34	24.67	28.72	37.08
Address for children										
Huichuan District (industrial zone)	282(28.0)	45.09	50.29	53.15	26.36	30.60	48.28	24.65	29.91	44.65
Honghuagang District (residential zone)	414(41.2)	42.52	44.71	46.98	25.75	28.19	33.98	24.45	28.54	33.53
Bozhou District (suburb)	310(30.8)	42.04	43.87	45.93	25.72	27.90	30.29	22.19	25.96	28.74
Decoration times										
Undecorated	611(60.7)	42.50	45.20	48.89	25.97	28.23	35.19	23.44	27.12	32.91
Decoration 1-3 times	395(39.3)	43.00	45.28	48.55	25.84	28.47	35.22	24.07	28.64	35.04

Feeding pattern											
Pure breast milk	494(49.1)	42.53	45.18	49.14	26.01	28.44	36.09	24.40	27.47	33.58	
Mainly breast milk, supplemented by milk powder	260(25.8)	42.43	44.75	48.38	26.06	28.21	34.17	23.82	28.05	33.99	
Milk powder feeding is the main method, supplemented by breast-feeding	113(11.2)	43.87	45.89	48.79	25.83	28.50	33.55	21.91	25.97	30.26	
Milk feeding only	139(13.8)	43.75	45.67	49.13	25.72	27.30	32.06	23.64	27.92	35.90	
Frequency of perms used during pregnancy											
0	973(96.7)	42.71	45.20	48.79	25.92	28.22	34.83	23.67	27.57	33.99	
1-2 times	33(3.3)	45.11	47.12	50.39	26.92	34.17	55.73	22.47	24.44	29.50	
Frequency of hair gels used during pregnancy											
0	930(92.4)	42.67	45.20	48.75	25.92	28.27	35.15	23.67	27.47	33.60	
Several times	76(7.6)	43.35	45.88	49.73	26.11	28.72	35.50	22.81	27.89	34.08	
Frequency of cosmetics used during pregnancy											
0	894(88.9)	42.69	45.18	48.79	25.86	28.44	35.22	23.67	27.47	33.68	
1-2 times	111(11.1)	42.99	46.04	49.04	26.02	27.09	35.00	23.12	27.89	33.94	
Frequency of using plastic lunch box during pregnancy											
1 to 3 times each day	11(1.1)	42.14	43.62	44.58	27.62	28.63	34.78	21.77	28.23	39.28	
3 to 10 times a month	16(1.6)	43.79	45.92	52.86	26.57	26.92	33.68	23.41	26.77	34.08	
3 to 10 times a year	451(44.8)	42.88	45.31	48.72	25.74	28.33	36.05	23.62	27.57	33.55	
Never	528(52.5)	42.69	45.21	49.14	26.23	28.27	34.15	23.70	27.47	33.73	

Frequency of plastic water cup used during pregnancy										
Daily	7(0.7)	41.20	43.83	47.72	26.36	27.65	70.51	28.85	29.57	42.57
Often	525(52.2)	42.95	45.69	49.14	25.92	28.16	35.44	23.67	27.47	33.60
Occasionally	182(18.1)	42.43	45.21	47.27	26.03	29.08	34.38	22.36	28.30	33.99
Never	292(29.0)	42.50	44.85	48.38	25.81	28.59	34.73	23.60	27.10	33.27
Types of domestic drinking water										
Commercial bucketed water	865(86.0)	42.69	45.18	48.72	25.83	28.23	35.32	23.67	27.47	33.99
Well water	20(2.0)	43.62	45.51	47.10	26.64	28.03	34.78	24.44	29.39	30.78
Boiled tap water	49(4.9)	42.52	46.58	50.81	26.19	28.54	33.17	23.48	27.27	31.85
Commercial bottled water	9(0.9)	41.23	44.83	46.57	25.71	26.58	90.37	25.29	33.55	51.00
Mountain spring water	30(3.0)	44.84	46.20	49.45	26.74	31.08	36.39	25.96	29.81	36.82
Other	33(3.3)	43.46	45.50	51.65	27.31	28.13	33.87	21.42	26.23	30.75
Frequency of pacifiers used										
Occasional used	218(21.7)	42.95	45.55	48.38	25.77	27.78	33.73	23.56	30.01	36.42
Often used	67(6.7)	42.61	45.88	49.73	26.05	31.76	37.40	26.35	32.13	45.75
Never used	721(71.7)	42.70	45.18	48.90	25.97	28.47	35.15	23.47	26.99	32.69
Numbers of plastic toys										
None	41(1.1)	42.33	43.96	46.90	25.74	27.69	36.41	23.17	28.92	38.27
≤ 10 pieces	135(13.4)	43.01	45.71	49.63	25.67	29.61	35.34	22.49	26.70	29.57
≤ 50 pieces	300(29.8)	42.88	45.36	48.89	25.97	28.63	36.12	23.82	26.93	31.34
≤ 100 pieces	321(31.9)	42.67	45.21	48.79	25.86	27.80	34.17	23.61	27.81	33.53
≥100 pieces	209(20.8)	42.74	45.81	49.15	26.02	28.52	34.60	24.07	30.26	40.45
Materials for food storage										
No microwave	638(63.4)	42.48	44.75	47.67	25.68	27.96	33.02	23.79	27.93	35.89

Chinaware	317(31.5)	42.32	44.65	48.31	25.79	27.96	32.38	24.51	28.12	34.84
Heat-resistant plastics	19(1.9)	43.35	46.66	49.93	25.57	26.82	29.08	26.70	31.33	47.07
Heat-resistant plastic wrap	13(1.3)	43.85	46.34	50.77	25.55	26.91	32.26	23.42	29.50	39.17
Aluminum foil	19(1.9)	42.70	44.13	46.70	25.24	26.74	33.07	25.55	30.09	34.55
Frequency of hair dyes used by children										
Never	980(97.4)	42.75	45.26	48.91	25.92	28.33	35.34	23.61	27.47	33.73
1-2 times	26(2.6)	41.83	44.36	47.05	25.97	27.96	33.22	24.56	28.30	35.20
Frequency of hair spray and perfume use for children										
Never	737(73.3)	42.70	45.18	48.53	25.93	28.30	35.34	23.71	27.89	33.99
1-2 times	267(26.7)	42.87	45.31	49.32	25.92	28.22	35.00	23.31	26.66	33.21
Frequency of nail polish and cosmetics used by children										
Never	703(69.9)	42.51	45.06	48.75	25.93	28.22	35.76	24.11	28.22	35.18
1-2 times	301(30.1)	42.99	45.52	48.82	25.92	28.50	33.67	22.81	26.28	31.51
Frequency of plastic tableware used by children										
Never	356(35.4)	42.43	44.73	49.45	26.20	28.35	35.34	22.95	27.35	33.53
1-3 times in a period of 1-3 months	592(58.8)	42.99	45.51	48.89	25.84	28.13	34.71	24.16	27.47	33.73
≥ 10 times in one month	58(5.8)	42.70	45.46	48.25	26.92	30.34	37.56	26.06	30.54	43.04
Frequency of fish and shellfish intake in children										
Daily	10(1.0)	43.18	47.05	48.07	25.57	25.81	34.75	22.60	24.95	40.73
Once to three times a week	294(29.2)	42.98	45.42	48.39	25.69	27.29	32.98	24.64	28.45	39.06
Occasionally	626(62.2)	42.48	45.18	49.08	26.14	28.60	35.34	23.50	27.41	31.32

several times a year										
Never	76(7.6)	43.37	45.90	48.83	25.97	28.54	42.25	23.44	26.50	34.48
Update frequency of plastic toys										
Weekly	119(11.8)	44.09	47.25	50.31	26.87	29.08	34.50	25.50	31.34	40.50
Monthly	90(8.9)	42.30	44.74	49.04	25.94	30.93	40.79	23.14	29.36	40.31
Half a year	343(34.1)	42.82	45.18	47.27	25.77	28.21	37.09	23.62	28.35	34.03
Each year	430(42.7)	42.73	45.21	49.14	25.83	28.05	33.45	23.67	26.53	30.13
Never	24(2.4)	42.33	45.15	47.10	26.49	28.13	35.34	22.01	27.85	38.27
Duration of children birth										
Premature infant	80(8.0)	43.00	46.00	49.01	26.26	27.96	35.48	21.55	25.08	29.66
Late delivery infant	32(3.2)	42.30	44.36	48.58	25.83	27.44	30.62	25.29	29.91	32.61
Full-term	894(88.9)	42.70	45.20	48.75	25.92	28.44	35.34	23.82	27.63	35.14
Materials for baby bottle or cup										
Glass	529(52.6)	42.48	45.21	48.89	25.92	28.44	35.10	23.62	27.28	33.60
Silica gel	70(7.0)	43.74	45.91	50.39	25.96	27.35	30.78	24.35	28.54	32.72
Plastic	252(25.0)	43.09	45.36	47.77	25.72	28.02	34.78	24.17	27.57	32.13
Stainless steel	147(14.6)	42.73	45.65	49.63	26.25	28.91	37.12	22.07	27.63	36.59
Other	8(0.8)	42.18	42.51	45.42	29.46	40.00	48.56	32.91	42.94	76.69
Whether exposed to pesticides										
Yes	38(3.8)	43.38	46.01	47.73	25.41	27.80	31.40	21.99	25.96	35.20
No	968(96.2)	42.70	45.24	48.89	25.93	28.33	35.34	23.69	27.57	33.60
Parent occupation classification										
Government companies	139(13.8)	42.65	45.18	48.52	25.80	28.14	31.95	24.75	27.29	37.48
Medical related occupation	43(4.3)	43.96	45.88	48.07	26.19	28.13	34.17	21.64	26.66	31.55

Free small business (catering, service, etc.)	307(30.5)	42.73	45.52	49.63	25.84	28.04	35.34	24.16	28.19	33.66
Migrant Workers	45(4.5)	43.74	45.71	49.45	25.59	27.78	33.99	22.51	25.12	29.22
Farming	72(7.2)	42.01	43.76	46.80	26.11	30.62	42.30	22.40	26.06	29.27
Education related	43(4.3)	43.62	45.89	48.41	27.66	32.30	36.13	25.96	29.39	33.53
Others	357(35.5)	42.75	45.04	48.75	25.97	28.76	35.34	23.68	27.47	34.62
Ways to plastic products										
Drinking utensils, cups	161(16.0)	42.71	45.42	48.25	25.81	28.10	32.18	23.01	27.27	32.13
Containers for meals, snacks, fruits, etc.	83(8.3)	43.76	45.91	49.37	26.25	28.54	43.24	24.11	26.65	31.80
Plastic toys (LEGO etc.)	254(25.2)	42.32	44.74	47.72	25.39	27.36	34.78	24.16	28.30	33.35
Small household items (toothbrushes, plastic bags, plastic wrap, etc.)	355(35.3)	42.88	45.24	49.14	26.42	28.72	36.53	23.62	27.80	36.59
School supplies	129(12.8)	43.42	46.05	49.30	25.72	28.23	33.98	22.68	25.96	31.28
Others	24(2.4)	43.02	45.20	48.07	26.49	28.13	34.17	25.10	30.28	42.41

3.2 Standard curve and concentration of NP, BPA and DMP

The NP, BPA and DMP standard solutions were calibrated by HPLC, and the results of linear regression equation were calculated (Supplementary Table 2). The correlation coefficient of these linear regression equations were ≥ 0.999 . NP concentration was around 40.72 - 77.03 ng/ml, with an average of 45.85 ng/ml; BPA concentration was about 14.15 - 216.12 ng/ml, with an average of 26.31 ng/ml; and DMP concentration was around 22.51-132.07 ng/ml, with an average of 31.62 ng/ml.

3.3 Comparison of the concentrations of NP, BPA and DMP in serum by address, gender and age

There was significant difference in the serum concentrations of NP, BPA, DMP in school-age children in Huichuan District (industrial zone), Honghuagang District (residential zone) and Bozhou district (suburb) ($F_{NP} = 548.961$, $P_{NP} < 0.001$; $F_{BPA} = 189.198$, $P_{BPA} < 0.001$, $F_{DMP} = 112.476$, $P_{DMP} < 0.001$). The serum concentrations of NP ($P < 0.001$), BPA ($P < 0.001$), DMP ($P < 0.001$) in school-age children in industrial zone were higher than those in residential zone and

suburb. The average concentration of NP in boys was $45.97 \pm 4.50 \mu\text{g/ml}$, and in girls was $45.71 \pm 4.42 \mu\text{g/ml}$; the average concentration of BPA in boys was $31.29 \pm 11.08 \mu\text{g/ml}$, and in girls was $28.00 \pm 11.87 \mu\text{g/ml}$; the average concentration of DMP in boys was $31.91 \pm 12.53 \mu\text{g/ml}$, and in girls was $33.28 \pm 15.61 \mu\text{g/ml}$. There was no significant gender difference in the concentration between boys and girls (Figure 4 and Supplementary Table 2). The results analysis showed in Supplementary Figure 2.

3.4 Correlation between serum EDCs (NP, BPA and DMP) concentrations and environmental risk factors

NP, BPA, and DMP concentrations in serum were used as dependent variables, and the environmental risk factors on the questionnaire were used as independent variables. The environmental risk factors that affected NP, BPA, and DMP concentrations in serum were analyzed by multiple linear regression.

The regression coefficients of hair gels used during pregnancy ($P = 0.012$), types of domestic drinking water ($P < 0.001$), nail polish and cosmetics used by children ($P < 0.001$) were positive, indicating that these three factors were significantly positively correlated with NP concentration (Figure 5A). The other seven factors, including gender ($P = 0.004$), feeding pattern ($P = 0.047$), plastic water cup used during pregnancy ($P = 0.042$), hair spray and perfume use for children ($P = 0.019$), duration of children birth ($P = 0.002$), materials for baby bottle or cup ($P = 0.002$) and ways to plastic products ($P = 0.034$) were significantly positively correlated with BPA concentration, indicating that these environmental factors could increase BPA concentration in serum in in school-age children (Figure 5B). Gender ($P = 0.038$), perms used during pregnancy ($P < 0.001$), hair spray and perfume use for children ($P = 0.012$), using plastic lunch box during pregnancy ($P = 0.007$), duration of children birth ($P = 0.006$), exposure to pesticides ($P = 0.008$), parents' occupations ($P = 0.041$) were positively correlated with DMP concentrations, indicating that these environmental factors could increase DMP concentrations in children's serum (Figure 5C).

3.5 Correlations between serum EDCs (NP, BPA and DMP) concentrations and hepatic function

3.5.1 Effects of EDCs on serum TBIL level

Binary logistic regression analysis of data showed the associations of serum DMP ($OR: 1.371$, 95% $CI: 1.038-1.811$, $P = 0.026$) and NP ($OR: 1.344$, 95% $CI: 1.019-1.772$, $P = 0.036$) concentrations with serum TBIL level (Supplementary Table 4).

3.5.2 Effects of EDCs on serum DBIL level

Univariate logistic regression analysis of data showed an association of serum NP concentration ($OR: 1.465$, 95% $CI: 1.114-1.928$, $P = 0.006$) with serum DBIL level (Supplementary Table 5).

3.6 Data of hepatic function tests

In 462 hepatic function assay reports, the AST level of school-age children was between 2-107 U/L, with an average of 17.926 U/L; the ALT level was about 4.1-69 U/L, with an average of 27.184 U/L; the ALT/AST ratio was in 0.29-7, with an average of 1.834; the TBIL level was around 1.2-112 $\mu\text{mol/L}$, with an average of 10.545 $\mu\text{mol/L}$; the DBIL level was between 0.2-10.8 $\mu\text{mol/L}$, with an average of 0.2 $\mu\text{mol/L}$; The IBIL value was between 0.4-36.3 $\mu\text{mol/L}$, with an average of 8.161 $\mu\text{mol/L}$ (Supplementary Table 6).

3.7 Comparison of TBIL, DBIL and IBIL levels by gender, age and address

The values of TBIL, DBIL and IBIL in the serum of school-age children in Zunyi were different on the gender, and the concentrations of TBIL and IBIL were different on the address. There was no statistical difference in the results of hepatic function at the age (Figure 6).

3.8 Correlation between environmental risk factors and hepatic function

The results of hepatic function as the dependent variable and the risk factors on the questionnaire as the independent variables, the results of the multiple linear regression analysis were shown in Table 6. Cosmetics used during pregnancy were positively correlated with ALT ($P = 0.050$) and AST ($P = 0.021$). There was a positive correlation between the frequency of hair spray and perfume use for children and the AST ($P = 0.022$) (Supplementary Table 7).

3.9 Correlations of EDCs (NP, BPA and DMP) concentrations with hepatic function by gender, age, and address

When the concentration of serum NP, BPA and DMP in school-age children was quartered, there was a significant difference in the association trend between NP and AST by sex ($P_{\blacksquare_2} = 0.031$, $P_{\blacksquare_4} < 0.001$) (Figure 7A), and there was also a significant association between NP and ALT/AST in women ($P_{\blacksquare_1} < 0.001$, $P_{\blacksquare_2} = 0.042$, $P_{\blacksquare_3} = 0.009$) (Figure 7B). By address, the correlation between NP and AST was significantly different in Bozhou district ($P_{\blacktriangle_1} = 0.02$, $P_{\blacktriangle_3} = 0.006$) (Figure 7C). The correlation between DMP and AST was also different in Bozhou district ($P_{\blacktriangle_2} = 0.003$) (Figure 7D). The correlation between DMP and ALT/AST was also different in Bozhou district ($P_{\bullet_2} = 0.049$, $P_{\blacktriangle_1} = 0.003$) (Figure 7E). The correlation between BPA and DBIL was different in Huichuan district ($P_{\bullet_1} = 0.006$, $P_{\bullet_2} = 0.008$, $P_{\bullet_3} = 0.007$) (Figure 7F). There was no difference by age.

Discussion

In the previous research on NP pollution in rivers and tap water in Zunyi city, the NP concentration in tap water in Huichuan District (industrial zone) was 6 times that of Honghuagang District (residential zone), which exceeded the standard of NP in the fresh water of U.S. EPA (6.6 $\mu\text{g/L}$) (Careghini et al. 2015). NP as a heat stabilizer of polyvinyl chloride (PVC), in household equipment could be released into drinking water, which contributed to the increase of concentration of NP in tap water (Jie et al. 2017). The northern part of Guizhou was a karst landform with relatively hard water. Residents usually use barrel water and bottled water for daily use. The NP easily migrated and accumulated in the human (Cheng et al. 2015; Xuesong et al. 2017). Based on the above facts, the type of drinking water in family was a significant positive cause of the accumulation concentration of NP in children's serum. Fu et al. (2008) reported the NP solubility was higher in summer than in winter (Fu et al. 2008), which coincided with this study. However, the specific reasons need to be further explored.

Trasande et al. (2013) found that there was a significant correlation between PAEs metabolites and gender. It was found that a certain dose and duration of BPA exposure could change the number of follicles and hormone production in female rats (Trasande et al. 2013). Other studies have shown that the concentration of bisphenol in urine of pregnant women was related to the increase of gestational age, suggesting that EDCs exposure would affect the duration of pregnancy (Patel et al. 2017). Veiga et al. (2018) found that prenatal exposure to BPA had an impact on the length of pregnancy and childbirth, and this effect was gender-differentiated (Veiga et al. 2018). These studies suggested that exposure of BPA and PAEs with estrogen-like effect were different in gender, and childbirth duration was related to exposure concentration. This was consistent with the conclusion that gender and childbirth duration were the main factors affecting EDCs exposure in the results of this study. It has been reported that BPA and NP could promote the production of human chorionic gonadotropin (hCG) (USCDC. 2010), and exposure to

EDCs during pregnancy had adverse effects on offspring (Paulesu et al. 2018). NP had weak estrogen activity, and estrogen receptor (ER) could induce male infertility by negatively affecting sperm quality (Jin et al. 2013). The above studies indicated that the critical period of female womb development and the reproductive health of male partners may be affected by NP, BPA or PAEs (Liu et al. 202; Pant et al. 2014). Therefore, the frequent use of hair dye, hair spray and plastic cups during pregnancy had great influence on the concentrations of NP and DMP in fetal serum.

At present, most of the studies on the effects of NP, BPA and DMP on liver were based on animal models. It was found that NP exposure increased ALP level in rats (Rattan et al. 2017; Liu et al. 2019). In BPA-fed rats, ALP and AST levels decreased significantly, but ALT levels did not change significantly (Kazemi et al. 2016). The previous animal experiments of the research group also strongly suggested that the elevation of ALT and AST in serum was a sign of hepatic damage caused by NP (Kazemi et al. 2017). Khalil et al. (2014) reported that NP exposed to rats showed estrogen toxicity in liver and testis (Khalil et al. 2014). Huang et al. (2019) showed that perinatal exposure to 4-NP could affect the synthesis of fatty acids in the liver of F₁ and F₂ of rats offspring (Huang et al. 2019). The mechanism of biological research implied that the toxic effect of EDCs was partly caused by oxidation and inducing hepatocyte death (Mansouri et al. 2019). This was basically consistent with the results of this study, although this study only indicated a weak correlation between NP, BPA, DMP and hepatic function results.

There were few epidemiological studies regarding the effect of NP, BPA and DMP on liver. Some experts found that the increase of ALT and AST was related to PAEs exposure in the research of the potential effect of PAEs on normal hepatic function and cardiac metabolism in men (Yu et al. 2018). Previous studies have also demonstrated that in subjects over 60 years old, BPA level in urine was significantly correlated with ALT, AST, and γ -GTP levels (Milošević et al. 2017; Lang et al. 2008). Meanwhile, the group with higher BPA concentration showed significant abnormality in hepatic function (OR ratio: 2.66) (Melzer et al. 2010). On the contrary, another study did not reveal a significant relationship between BPA exposure level and AST level in obese children ($\beta = 1.48$, $P = 0.12$) (Lee et al. 2014). Lee et al. (2014) analyzed the BPA concentration in serum and serum liver level of children in all age groups, and found that the dose-correlation between them was more obvious in boys, and specially in children aged 7-9 years. In contrast, there was a sex differences in women in the level of NP and hepatic function, not in age in this study. The inconsistency may be caused by the number of samples. The number of subjects of Lee's study was only 113. The differences in this study were not only in gender, but also in geographical distribution. The correlation between serum concentrations of NP, BPA, DMP and hepatic function were significant by address, especially in industrial zone and suburb. This may come from that the old urban area of industrial zone was an economic and political center where the catering industries was numerous, and the frequency of drinking tap water and plastic bottled water was relatively high, indicating that EDC_s exposure was related to urban pollution, commercialization and urbanization, etc.

Due to the special estrogen action of EDCs, research on gender differences has been a hot topic that has been recently concerned and discussed, but no consistent conclusion has been made so far (Lee et al. 2017). At present, there were several opinions as followed: (1) there was gender difference (Di Lorenzo et al. 2002) in E₂ receptor (ERs) in hypothalamus and hippocampus (Figueiredo et al. 2002; Fitch et al. 1998). EDC could affect gender expression by changing steroid levels (androgen or 17- β estradiol, E₂) and/or intracellular E₂ receptor, or acting as an agonist or antagonist of intracellular or membrane ERs (Di Lorenzo et al. 2002). (2) More and more evidences supported the theory of endogenous hormones (Kanit et al. 2000; Liu and Sun 2018). Endogenous testosterone, sex hormone binding globulin (SHBG) and thyroid binding globulin (TBG) (Liu and Sun. 2018) are hormone related biomarkers, which represent potential targets of EDCs function in human. The level of free circulating hormone was influenced by binding sex hormone receptor (Fitch and Denenberg. 1998). For example, estrogen can increase T4 binding

globulin (TBG) concentration in the serum, thus increasing the total serum T4 concentration (Beatty. 1979; Ding et al. 2006; Ding et al. 2009). (3) Other studies have shown that EDCs with estrogen-like effect combined to estrogen receptor (Di Lorenzo et al. 2002) or through E₂ plasma transporter, which has overall estrogen effect on ER and enhances the response of endogenous estrogen (Ain et al. 1987; Deyssig and Weissel. 1993). In addition, EDC may act through other homologous intracellular steroid receptors (Arafah. 1994; Kuiper et al. 1997; Hutchison. 1997; Hotchkiss et al. 2002). EDCs' gender differences is more complicated, and further studies are need to be done.

Perinatal exposure to NP could interfere with estrogen and progesterone levels in pregnant rats, cause changes in hepatic structure and function in neonatal rats, and lead to threatened abortion and dystocia (Meng et al. 2019). Other studies have shown that the exposure of perinatal mice to BPA would damage the antioxidant defense system of female mice, cause oxidative damage to the liver, and contribute to metabolic disorders (Meng et al. 2019). Sub-micro BPA could induce human liver cell proliferation and DNA damage in vitro experiments, and was an important risk factor for liver cancer (Kim et al. 2018). The maternal perinatal exposure to NP, BPA, DMP had adverse effects on the hepatic function of the offspring, which was consistent with previous experiment. This study directly firstly calculated the direct risk factors for mother' exposure during pregnancy and school-age children: frequency of using cosmetics during pregnancy and the frequency of children using hairspray and perfume. No related research has been reported before, and so further researches are needed be done.

There are some shortcomings in this study. First, the design of this study was only a cross-sectional design, and a forward-looking longitudinal study is needed to be continued. Second, questionnaire is susceptible to a bias.

Conclusion

School-age children aged 5–14 years in northern Guizhou have been generally exposed to the pollution of NP, BPA, and DMP, which were closely related to the environmental risk factors of maternal exposure during pregnancy, infancy and school age. The association between their exposure and adverse effects on hepatic function was apparent in children. Among environmental risk factors, the number of times the mothers used cosmetics during pregnancy, and the number of times that school-age children used hair gels and perfumes had a greater impact on hepatic function damage. These high levels of exposure should further be reduced through lifestyle changes. There are currently few studies about population research, and further epidemiological investigations should be conducted to to reduce children's exposure to NP, BPA, and DMP as soon as possible.

Declarations

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Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Contributions

Jie Xu and Jie Yu designed the study. Xiangjun Fu, Deliang Zheng, Xuefeng Yang, Pan Wang, Jie Yu and Jie Xu analyzed and interpreted the data. Xiangjun Fu, Jie Yu and Jie Xu are responsible for designing and revising the questionnaire. Xiangjun Fu, FangXu Tuo, Lin Wang, Shixu Li and Jie Yu participated in the investigation. Jie Yu and Xiangjun Fu wrote the manuscript, Jie Xu revised the manuscript.

Consent for publication

All the authors read and approved this paper.

Ethics statement

The Ethics Committee of the Zunyi Medical University approved the study (2015-1-017). All methods were performed in accordance with guidelines and regulations of the Zunyi Medical University.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Comparison of concentrations of three EDCs (NP, BPA and PAE) measured in different countries (areas). A) NP concentration; B) DMP concentration; C) BPA concentration. The exposure values in the vertical coordinate in these figures are obtained from the original concentration in the literature was log-transformed.

Figure 2

Study location. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

Figure 3

Flowchart depicting exposure protocols and selection process of the participants.

Figure 4

Comparison of the serum concentrations of NP, BPA and DMP of school-age children by address, gender and age. Mann-Whitney U test was used between two groups' comparison, Kruskal-Wallis H test was used in comparison of multiple groups. #: vs Huichuan district group, $P < 0.05$; *: vs Honghuagang District group, $P < 0.05$. A. Comparison of the concentrations of NP, BPA and DMP in serum by address, B. Comparison of NP, BPA, DMP in the serum of school-age children by sex, C. Comparison of NP, BPA, DMP in the serum of school-age children by age.

Figure 5

Forest map of correlations between NP, BPA, and DMP and risk factors in multiple linear regression. A: Multiple linear regression relationships between NP and risk factors, B: Multiple linear regression relationships between BPA and risk factors, C: Multiple linear regression relationships between DMP and risk factors. Red color represented basic information. Yellow color represented risk factors of exposure during infancy and exposure in children's current life, Blue color represented risk factors of exposure during mothers pregnancy. CI: Confidence interval.

Figure 6

Comparison of values of TBIL, DBIL and IBIL by address, gender and age. Mann-Whitney U test was used in comparison between two groups, and comparison among multiple groups was analyzed by Kruskal-Wallis H test. The abscissa was address, gender, and age separately, and the ordinate was the mean with 95% CI of each hepatic function value. If $P < 0.05$, it indicated statistical significance, and data without statistical significance was not shown in figures. A: Comparison of the results of TBIL in serum of school-age children by gender; B: Comparison of the results of TBIL in serum of school-age children by address; C: Comparison of the results of DBIL in serum of school-age children by gender; D: Comparison of the results of IBIL in serum of school-age children by gender; E: Comparison of the results of IBIL in serum of school-age children by address. Abbreviations: OR: odds ratio. CI: confidence interval. ALT: Alanine aminotransferase. AST: Aspartate aminotransferase. TBIL: Total bilirubin. DBIL: Direct bilirubin. IBIL: Indirect bilirubin. NP: Nonylphenol. BPA: Bisphenol A. DMP: Dimethyl phthalate.

Figure 7

Correlation of 3 EDCs (NP, BPA and DMP) concentrations with hepatic function by gender, age and address. Note: The abscissa was the interquartile range of NP, BPA and DMP concentrations. The ordinate was the 95% CI value of β obtained by multiple linear regression with hepatic function indicator as the dependent variable and the concentrations of NP, BPA and DMP as the independent variable. The legend *, which implied statistically significant, was marked if there is no vertical line crossing through the abscissa. A: The relationship between NP and AST by sex. B: The relationship between NP and ALT/AST by sex. C: The relationship between NP and AST by address. D: The relationship between DMP and AST by gender. E: The relationship between DMP and ALT/AST by address. F: The relationship between BPA and DBIL by address. Data with no statistically significant not shown in figures.

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