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Associations of multiple exposures to persistent toxic substances with the risk of hyperuricemia and subclinical uric acid levels in BIOAMBIENT.ES study

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ABSTRACT

Hyperuricemia is becoming a serious public health issue, which is highly influenced by environmental factors, although there is still controversial information on the potential influence of the exposure to Persistent Toxic Substances (PTSs) in the general population. In this study we aimed to assess the association. PTS exposure with uric acid homeostasis in a sample of the Spanish population.

Participants were recruited during 2009–2010 in all the main geographical areas of Spain. Exposure to 34 PTSs was estimated by chemical analyses of serum levels of 6 Polychlorinated Biphenyls (PCBs, n = 950), 13 Organochlorine Pesticides (OCPs, n = 453), 6 Perfluoroalkyl Substances (PFAs, n = 755), 7 Polybrominated Diphenyl Ethers (PBDEs, n = 365), urinary Cadmium (n = 926), and Lead in whole blood (n = 882). The two study outcomes were defined as the prevalence of hyperuricemia in the study population and uric acid levels, the latter only in individuals with no previous diagnosis of hyperuricemia. Statistical analyses were performed by means of binomial logistic regression and linear regression, and mixture effects were screened using Weighted Quantile Sum Regression (WQS).

Serum concentrations of γ-HCH, *o,p´*-DDE, PCB-138, PCB-153, PFOA, and urinary Cadmium were associated with an increased risk of hyperuricemia, while PBDE-153 showed an inverse association with the effect. Furthermore, exposure to Cadmium, PCB-138, and to PCB-153 was positively associated with uric acid levels. Results were consistent after lipid adjustment or standardization. WQS analyses revealed a major contribution of PCB-153 within the PCB mixture on both the risk of hyperuricemia and uric acid levels. Sensitivity analyses were performed by adjusting for dietary habits, fasting glucose and estimated glomerular filtration rate.

Overall, we found novel associations between human exposure to mixtures of PTSs and disturbances in uric acid homeostasis. However, we cannot completely rule out potential residual confounding effect or reversed-causality related to the cross-sectional design.

1. Introduction

Uric acid (UA) is an end-product of hepatic purine metabolism in humans (de Oliveira and Burini, 2012), and blood levels are dependent on the balance between the production (either from dietary purine intake or endogenous production) and excretion (renal [65–75%] or gastrointestinal [25–35%]) (Perez-Ruiz et al., 2002). Failures in renal excretion account for 90% of the morbidity related to increased UA

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levels (Mandal and Mount, 2015).

Elevated serum UA levels can have pathological implications. In fact, an estimated 5% of the individuals with UA > 9 mg/dL develop gout, a systemic condition characterized by the deposition of monosodium urate crystals in body tissues, particularly joints (Ragab et al., 2017). Gout is early manifested in acute joint inflammation, while medium to long-term manifestations include renal stones and tophi (Ragab et al., 2017). Of special concern is the apparently close relationship between hyperuricemia and other chronic systemic diseases, such as hypertension, diabetes mellitus, cardiovascular disease, obesity, or metabolic syndrome, which are usually presented as bidirectional comorbidities (Katsiki et al., 2013; Kuo et al., 2015; Mazzali et al., 2010; Mortada, 2017).

Hyperuricemia figures during recent decades indicate that it is becoming increasingly prevalent, particularly in developed countries (Neogi, 2008). Previous research has identified a number of non-modifiable risk factors, such as age, sex, ethnicity, and specific genetic variants that may induce an increased risk of hyperuricemia (MacFarlane and Kim, 2014). In addition, the important variations in the prevalence of hyperuricemia according to geographical areas and sociodemographic characteristics (Song et al., 2018) suggest a relevant causal role of environmental factors in the pathogenesis.

Virtually all humans are daily exposed to persistent toxic substances (PTSs), which are highly resistant to the degradation and tend to accumulate and very often biomagnify along the food chain (Porta et al., 2003). PTSs include organic molecules, such as Organochlorine Pesticides (OCPs), which have been widely used both in agriculture and public health interventions; Polychlorinated Biphenyl (PCBs), a wide group of 209 congeners which have been used in multitude of industrial applications, e.g., in thermal insulation or as coolants (ATSDR, 2000); Perfluoroalkyl Substances (PFAs), used in a variety of consumer products and industrial processes, e.g. liquid repellant, industrial surfactants, firefighting foams (Schultz et al., 2003); or Polybrominated Diphenyl Ethers (PBDEs), very often present as flame retardants in the composition of electronics, textiles, building materials, or furnishings, among others (Fromme et al., 2016). PTSs also include inorganic elements such as heavy metals, many of them naturally present in the environment, but also widely used for industrial, agricultural, domestic and technological purposes (Tchounwou et al., 2012).

Previous epidemiological and experimental research has evidenced adverse chronic health outcomes linked to long-term human exposure to low-doses of PTSs (or even mixtures of them), such as OCPs or PFAs with metabolic syndrome (Lin et al., 2009; Mustieles et al., 2017) and hypertension (Arrebola et al., 2015); PCBs, PBDEs, or heavy metals with cardiovascular disease risk (Gump et al., 2014; Ruiz-Hernandez et al., 2017; Singh and Chan, 2017) or chronic kidney disease (Lunyera and Smith, 2017). There are some epidemiological evidences supporting a role of PTS exposure in the development of hyperuricemia and/or gout, both in accidentally-exposed populations [e.g furans in Japan (Imamura et al., 2009), PFAs in the United States (Steenland et al., 2010), PFAs in Italy (Costa et al., 2009), and polychlorinated dibenzo-*p*-*d*ioxins and PFAs in Taiwan (Chang et al., 2013; Qin et al., 2016)], as well as in baseline populations [e.g. lead in China (Dai et al., 2015), or PFAs, OCPs, Polychlorinated Dibenzo-*p*-*D*ioxins, and dioxin-like PCBs in the United States (Gleason et al., 2015 pp. 2007–2010; Lee et al., 2013)].

BIOAMBIENT.ES project is encompassed in a Spanish National Human Biomonitoring program (HBM) (Pérez-Gómez et al., 2013), which was promoted by the Spanish Ministry of Agriculture, Food and the Environment. The project aims to enhance the current understanding of the distribution of priority PTSs in the Spanish population and to establish reference values, by analyzing a representative sample of the Spanish working population (Bartolomé et al., 2015; Cañas et al., 2014; Huetos et al., 2014; López-Herranz et al., 2016; Ramos et al., 2017).

The present research aims to expand the current knowledge of the potential metabolic disrupting effect of PTSs, by examining their associations with uric acid homeostasis in the BIOAMBIENT.es population.

2. Methods

2.1. Study population

The present research is based on BIOAMBIENT.ES study, which was designed to recruit a representative sample of the Spanish workforce. The study population was recruited between March 2009 and July 2010 among those occupationally active individuals who underwent their annual medical check-up. An extensive description of the study has been published elsewhere, including the protocols, recruitment process, characteristics of the study population, and PTS concentrations (Pérez-Gómez et al., 2013; Bartolomé et al., 2017; Cañas et al., 2014; Esteban et al., 2013; Huetos et al., 2014; López-Herranz et al., 2016; Ramos et al., 2017). Self-administered questionnaires were used to gather information on socio-demographic, lifestyle and environmental variables, tobacco exposure, and diet.

Clinical information was gathered from the hospital records and during the annual occupational medical check-up of each participant. For the present study, we considered two outcomes:

1. Prevalent hyperuricemia (dichotomous, hyperuricemic/normouricemic). A participant was considered hyperuricemic if he/she met ≥1 of the following criteria: a) serum uric acid levels ≥7.0 mg/dL in males or ≥ 6.0 mg/dL in females, at recruitment or in previous screenings, b) had been prescribed any pharmacological treatment for lowering uric acid levels, and/or c) had been diagnosed with gout by a clinician.
2. Serum uric acid levels (interval, mg/dL) in the analyses at recruitment.

From the 1880 individuals that provided biological samples, 950 (50.5%) had clinical information on diagnosis of hyperuricemia in their records. From these, a total of 134 had been diagnosed with hyperuricemia, which means a prevalence of 14.1%. Serum uric acid analyses at recruitment was available from all the mentioned 950 individuals.

2.2. Ethical approval

The study was performed in accordance with legal/ethical principles and regulations concerning research involving individual information and biological samples, including “Organic Law 15/1999 on Personal Data protection and its Regulations”, “Law 41/2002, on Autonomy of Patients and rights and obligations relating to health information and documentation”, “General Health Law 14/1986”, Declaration of Helsinki, and UNESCO Universal Declaration on the Human Genome and Human Rights. The study protocol was approved by Comité Ético Científico and the Legal Department of IBERMUTUAMUR.

2.3. Sample preparation and chemical analysis of persistent pollutants

Exposure to selected PTSs was estimated from chemical analyses of their concentrations in serum, blood or urine. Protocols of sample preparation, chemical analyses, and quality control have been previously described (Bartolomé et al., 2017; Cañas et al., 2014; Esteban et al., 2013; Huetos et al., 2014; López-Herranz et al., 2016; Ramos et al., 2017).

A total of 34 PTSs were included in this study: serum polybrominated diphenyl ethers (PBDEs, congeners −28, −47, −99, −100, −153, −154, −183), serum perfluorinated alkyl substances (PFAs, perfluorooctane sulfonate [PFOS]; perfluorooctanoic acid [PFOA]; perfluorohexane sulfonate [PFHxS]; perfluorononanoic acid [PFNA]; perfluorodecanoic acid [PFDA]; N-Methylperfluorooctane

Sulfonamide [N-MeFOSAA]), serum organochlorine pesticides *p,p´- and o,p´*-DDE; *p,p´*- and *o,p´*-DDT; aldrin; dieldrin; endrin; hexachlorobenzene [HCB]; heptachlor; heptachlor epoxide; α-, β-, and γ-hexachlorocyclohexane [α-, β-, and γ-HCH]); and Polychlorinated Biphenyls (PCBs, congeners −28, −52, −101, −138, −153, −180), urinary Cadmium (Cd), and Lead in whole blood (Pb). Chemical analyses of the 34 PTSs were performed between 2010 and 2017, although each family was analyzed during a maximum period of 8 months.

Total cholesterol and triglycerides were quantified in serum samples by means of an enzymatic method coupled to spectrophotometry at 500 nm (Bernert et al., 2007), and total serum lipids were estimated as described elsewhere (Phillips et al., 1989). Urinary creatinine was analyzed by Jaffé method using a commercial kit (Spinreact, Spain). Estimated Glomerular filtration rate was calculated using CDK-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula (Levey et al., 2009)

From the 1880 recruited individuals, clinical information was available from 950. PCBs were analyzed in all the 950 individuals, while a subset of 453 was screened for OCPs, 755 for PFAs, 925 for Cd, and 882 for Pb.

2.4. Statistical analysis

First, associations between individual PTS concentrations and hyperuricemia were studied by binomial unconditional logistic regression, calculating odds ratios (ORs) with their corresponding 95% confidence intervals (CIs). PTS concentrations were entered as log-transformed variables when their levels of quantification were > 60%, or as dichotomous variables (> LOQ vs < LOQ) in those PTS with levels of quantification < 60%. When PTS concentrations were used as continuous variables, concentrations below the limit of quantification (LOQ) were replaced by the LOQ divided by the square root of two. Chemicals with no sample > LOD (i.e. α-HCH, Heptachlor, Aldrin, Endrin, and *o,p´*-DDT) were not considered in any of the multivariable analyses.

As a measure of a potential cumulative effect, we explored the risk of hyperuricemia in those individuals with the highest number of chemicals at increased concentrations. For this purpose, we selected those chemicals significantly associated with hyperuricemia in the individual models and considered that a study participant was highly exposed to a specific PTS when he/she showed concentrations in the 4th quartile (for PTSs with quantification levels > 25%) or > LOQ (for PTSs with quantification levels < 25%). Then, the total number of PTSs at high concentrations was calculated in each participant and categorized as a dichotomous variable (≥2/ < 2 PTSs), and its association with the risk of hyperuricemia assessed by unconditional logistic regression. These analyses were restricted to the 92 individuals who had been analyzed for the five PTS families of interest.

The linear regression analyses of the associations between PTS concentrations and uric acid levels were carried out without the 134 individuals previously diagnosed with hyperuricemia, given that the receipt of medical intervention might have artificially modified their uric acid levels. The shape of the associations were assessed by using locally weighted scatterplot smoothing (LOWESS) and Generalized Additive Models (GAM), and further analyses were performed by means of multivariable linear regression.

All the logistic and linear regression models were adjusted for variables whose inclusion in any model produced changes > 10% in beta coefficients and/or those reported as potential confounders in previous studies, i.e., sex (male/female), age (yrs), body mass index (kg/m^2), weight loss during the previous 6 months (< 1 Kg/1–5 Kg/ ≥6 Kg), region of residence (North, Center, East, South), smoking habit (non-smoker/smoker/former smoker), alcohol consumption (non-consumer/consumer), and education (primary or lower/secondary/university).

In order to assess the robustness of our findings, four sensitivity analyses were performed. Given that certain dietary habits are considered a risk factor for hyperuricemia, but can also be a source of PTS exposure in the general population, we re-built the models adjusting for self-reported habitual consumption of the following items: fruit, meat, eggs, fish, pasta/rice/potatoes, bread, vegetables, legumes, cold cuts, dairy products, and sweets (e.g. biscuits, cakes). Food consumption was categorized in 5 levels: ≤1/week, 1/week, 2–4/ week, 5–6/week, ≥1/ day, and entered in each model using a forward stepwise technique based on changes in Akaike information criterion (AIC). Models were also adjusted for fasting glucose and estimated glomerular filtration rate, given the existing evidences supporting that elevated uric acid levels might be a consequence of a decreased renal function and/or insulin resistance (Li et al., 2013; Prasad Sah and Qing, 2015). Furthermore, and considering that serum lipids may be associated with the underlying metabolic perturbation of participants as well as influence the concentrations of the most lipophilic families (e.g. OCPs, PCBs, and PBDEs), we also performed the multivariable models using wet-basis concentrations of these families, with and without adjustment by total serum lipids (Tables 3 and 4). Additionally, the models were repeated after removing individuals with diagnosis of diabetes, hypertension and/or renal disease (data not shown in tables but mentioned in the results section).

The potential mixture effect within the different PTS families was assessed using Weighted Quantile Sum Regression (WQS, Carrico et al., 2015), which combines the individual associations into a weighted index, and estimates the specific weight of each chemical on the mixture. Associations between each WQS index and its corresponding outcome were further studied by using multivariable linear or logistic regression, when appropriate, adjusting for the same covariates included in the individual models. Given the different sample size of each family of pollutants, we performed WQS index calculation on each individual family, and therefore the individual contribution of each chemical reflects its relative effect within its family. In addition, we also performed WQS analyses entering all the chemicals positively associated with the effects in the multivariable models, although these results should be taken with care given the limited number of individuals. Each WQS model was calculated by entering the chemicals of the same family with ≥60% samples > LOQ. The WQS analyses were performed with quartile-scored pollutant concentrations, using a training set defined as a 40% random sample of the dataset, being the remaining 60% used for model validation. The final weights were calculated using a total of 400 bootstrap steps.

The statistical significance level was set at $p = 0.05$, although p-values < 0.10 were considered as marginally-significant. R statistical computing environment v3.4.0 (http://www.r-project.org/) was used for data analyses, with gWQS package v1.0.0 for the calculations of WQS index.

3. Results

Table 1 summarizes the main sociodemographic, anthropometric, clinical and lifestyle characteristics of each population subsample in which each group of PTSs was analyzed. Median age ranged from 35.4 to 38.1 years. There was a similar proportion of males and females, with the exception of the subsample included in the OCP analyses, that showed a higher proportion of males than females (68% vs 32%, respectively). The population had predominantly secondary studies (57%–61%) and the majority of the participants were recruited in the central area of the country (38.4% - 40.4%). Median (25th–75th percentiles) uric acid levels were 3.6 mg/dL (4.8–5.9), and there were 134 (14%) of individuals with hyperuricemia. These characteristics did not substantially differ when restricting the analyses to normouricemic individuals (Supplemental Material, Table S1). Total serum lipids were positively and significantly associated with both the risk of hyperuricemia (OR = 1.25, p = 0.001) and uric acid levels (beta = 0.03, p = 0.001), the latter only in normouricemic individuals.

Table 1
Characteristics of the study population according to the groups of PTSs analyzed.

	PBDEs (n = 365)		PFAs (n = 342)		OCPs (n = 453)		PCBs (n = 950)		Cd (n = 925)		Pb (n = 882)	
	n	%	n	%	n	%	n	%	n	%	n	%
Sex												
Male	195	53.4	164	48.0	308	68.0	497	52.3	482	52.1	458	51.9
Female	170	46.6	178	52.0	145	32.0	453	47.7	443	47.9	424	48.1
Education												
Primary or lower	44	12.1	54	15.8	57	12.6	121	12.7	118	12.8	109	12.4
Secondary	221	60.5	195	57.0	278	61.4	574	60.4	558	60.3	528	59.9
University	100	27.4	93	27.2	118	26.0	255	26.8	249	26.9	245	27.8
Region of recruitment												
North	111	30.4	92	26.9	118	26.1	252	26.5	244	26.4	235	26.6
North-East	7	1.9	9	2.6	5	1.1	16	1.7	16	1.7	16	1.8
Center	142	38.9	138	40.4	175	38.6	365	38.4	362	39.1	343	38.9
East	53	14.5	55	16.1	74	16.3	166	17.5	163	17.6	154	17.5
South	59	16.2	57	16.7	86	19.0	167	17.6	156	16.9	150	17.0
Smoking habit												
Non-smoker	204	55.9	205	59.9	260	57.4	538	56.6	524	56.6	503	57.0
Smoker	149	40.8	129	37.7	178	39.3	384	40.4	373	40.3	352	39.9
Former smoker	12	3.3	8	2.3	15	3.3	28	2.9	28	3.0	27	3.1
Alcohol consumption												
Non-consumer	43	11.8	34	9.9	42	9.3	99	10.4	93	10.1	87	9.9
Consumer	322	88.2	308	90.1	411	90.7	851	89.6	832	89.9	795	90.1
Weight loss during last 6 months												
< 1 Kg	272	74.5	274	80.1	344	75.9	736	77.5	713	77.1	675	76.5
1–5 Kg	67	18.4	55	16.1	77	17.0	158	16.6	156	16.9	152	17.2
≥6 Kg	26	7.1	13	3.8	32	7.1	56	5.9	56	6.1	55	6.2
Place of residence												
City center	267	74.2	244	71.8	322	71.6	672	71.6	658	71.8	627	71.7
Other	93	25.8	96	28.2	128	28.4	266	28.4	259	28.2	247	28.3

	Percentiles			Percentiles			Percentiles			Percentiles			Percentiles			Percentiles		
	25th	50th	75th	25th	50th	75th	25th	50th	75th	25th	50th	75th	25th	50th	75th	25th	50th	75th
Age (yrs)	31.0	37.4	44.9	31.7	38.1	46.1	30.4	35.4	41.7	31.0	37.4	44.3	31.0	37.4	44.3	30.9	37.1	44.0
Abdominal perimeter (cm)	78.0	87.0	94.0	77.0	86.0	95.0	80.0	87.0	95.0	78.0	86.0	95.0	78.0	86.0	95.0	78.0	86.0	95.0
Body Mass Index (Kg/m^2)	23.1	25.3	28.0	22.5	25.2	28.1	23.3	25.4	27.9	22.9	25.2	28.0	22.9	25.2	28.0	22.9	25.2	28.0
Total serum lipids (g/L)	5.1	5.9	6.6	5.1	5.9	6.8	5.1	5.8	6.6	5.1	5.8	6.6	5.1	5.8	6.6	5.1	5.8	6.6
Uric acid (mg/dL)	3.6	4.8	5.9	3.6	4.5	5.9	4.0	5.1	6.1	3.6	4.7	6.0	3.6	4.7	6.0	3.6	4.7	6.0

A description of PTS concentrations in the study population is displayed in Table 2. We did not find substantial differences in the concentrations when only individuals with no hyperuricemia were selected (Supplemental Material, Table S2). PTS levels and predictors have been extensively discussed elsewhere (Bartolomé et al., 2017; Cañas et al., 2014; Huetos et al., 2014; López-Herranz et al., 2016; Ramos et al., 2017).

The results of the multivariable logistic regression analyses between individual PTS levels and the risk of hyperuricemia in the study population are shown in Table 3. Serum concentrations of PCB-138, PCB-153, PCB-180, PFOA, as well as urinary Cadmium were associated with an increased risk of hyperuricemia, while PBDE-153 showed an inverse association with the risk. Furthermore, participants with γ-HCH and *o,p´*-DDE concentrations > LOQ also showed a marginally-significant increased risk (in comparison to those with concentrations < LOQ). The observed associations did not substantially change after adjustment for total serum lipids or when the concentrations of the most lipophilic chemicals were expressed on a lipid basis (Table 3). Adjustments for dietary items only produced relevant changes in the estimates for PFOA, in which the magnitude of the association decreased (Supplementary Material, Table S3), but after adjustment for CDK-EPI and fasting glucose (Supplementary Material, Table S3). However, new significant associations emerged after adjustment for dietary items or fasting glucose and urinary creatinine, with PBDE-100 and PCB-180 being positively associated with the risk of hyperuricemia (Supplemental Material, Table S3). Stratification by sex or deletion of individuals with diagnosis of diabetes, cardiovascular disease and/or hypertension did not substantially affect the results (data not shown).

From the 92 individuals that had available analyses of the three groups of PTSs (PCBs, organochlorine pesticides, and PFAs), a total of 37 (40.3%) had increased levels of ≥2 of the PTSs individually associated with the risk of hyperuricemia (i.e., PFOA, PFNA, γ-HCH, PCB-101, PCB-138, PCB-153 and/or PCB-180). These participants showed a higher risk of developing hyperuricemia, but the association was only marginally significant, probably due to the limited sample size (OR = 1.70, p = 0.066) (data not shown in tables).

Table 4 shows the results from the multivariable linear regression analyses between PTS concentrations and serum uric acid levels in normouricemic individuals. These analyses were restricted to those participants without diagnosed hyperuricemia because the treatment of the disease will likely modify the levels of uric acid. Serum concentrations of PCB-138 and PCB-153, as well as urinary Cadmium, showed positive associations with uric acid levels, while PBDE-153 was inversely associated with uric acid. The observed associations did not substantially change when the concentrations of the most lipophilic chemicals were expressed on a lipid-basis or after adjustment for total serum lipids (Table 4). Adjustment for dietary items did not produce relevant changes in the models, but new associations emerged after adjustment for CDK-EPI and fasting glucose, with PFHxS, PFOA, and HCB being also positively associated with uric acid levels (Supplemental Material, Table S4). No relevant differences were observed after stratification by sex (Data not shown in tables).

As explained above, given the different sample size of each family of PTSs, we calculated a WQS index for each of the three families, and

Table 2
PTS concentrations the study population.

	Units	Percentiles						
		5th	10th	25th	50th	75th	90th	95th
PBDE-28	(ng/g lipid)	< LOQ	< LOQ	< LOQ	< LOQ	0.07	0.13	0.19
PBDE-47	(ng/g lipid)	< LOQ	< LOQ	< LOQ	0.06	0.29	0.80	1.41
PBDE 99	(ng/g lipid)	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	0.19	0.30
PBDE-100	(ng/g lipid)	< LOQ	< LOQ	< LOQ	< LOQ	0.15	0.31	0.52
PBDE-153	(ng/g lipid)	0.15	0.21	0.32	0.47	0.71	1.10	1.55
PBDE-154	(ng/g lipid)	0.06	0.06	0.08	0.15	0.26	0.40	0.50
PBDE-183	(ng/g lipid)	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	0.13	0.25
PFHxS	(ng/mL)	< LOQ	< LOQ	0.45	0.73	1.07	1.50	2.04
PFOA	(ng/mL)	0.82	1.03	1.34	1.83	2.53	3.44	4.32
PFOS	(ng/mL)	2.35	3.21	5.14	7.23	10.11	14.03	17.76
PFNA	(ng/mL)	0.44	0.50	0.64	0.88	1.26	1.69	1.91
PFDA	(ng/mL)	0.14	0.14	0.24	0.35	0.54	0.76	0.99
N-Me-FOSA	(ng/mL)	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ
HCB	(ng/g lipid)	< LOQ	6.50	14.09	28.09	56.49	114.40	207.99
α-HCH	(ng/g lipid)	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ
β-HCH	(ng/g lipid)	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	0.07	0.12
γ-HCH	(ng/g lipid)	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	0.03	0.05
Heptachlor	(ng/g lipid)	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ
Heptachlor epoxide	(ng/g lipid)	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	0.01
Aldrin	(ng/g lipid)	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ
Endrin	(ng/g lipid)	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ
Dieldrin	(ng/g lipid)	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	0.02	0.02
p,p´-DDE	(ng/g lipid)	31.59	45.75	83.10	152.50	280.34	519.44	696.63
o,p´-DDE	(ng/g lipid)	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ
p,p´-DDT	(ng/g lipid)	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	5.80	9.40
o,p´-DDT	(ng/g lipid)	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ
PCB-28	(ng/g lipid)	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ
PCB-52	(ng/g lipid)	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ
PCB-101	(ng/g lipid)	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	< LOQ	51.37
PCB-138	(ng/g lipid)	5.37	9.59	19.01	34.45	56.25	84.54	109.64
PCB-153	(ng/g lipid)	7.03	13.83	24.80	45.14	74.24	112.49	149.25
PCB-180	(ng/g lipid)	10.17	18.63	30.73	58.30	96.51	156.39	194.63
Cadmium	(ng/mL)	< LOQ	< LOQ	0.17	0.27	0.48	0.77	0.99
Lead	(ng/mL)	0.11	0.31	0.63	1.06	1.81	2.84	3.55

LOQ: Limit of quantification.

therefore the contribution of each chemical reflects its relative effect within its family. WQS index for PCBs was positively and borderline-significantly associated with both the risk of hyperuricemia (exp [beta] = 2.02; p < 0.001) and uric acid concentrations (beta = 0.43; p = 0.01). PCB -153 concentrations accounted for the majority of the mixture effect in the two models (44% in the model for hyperuricemia and 59% in the model for uric acid levels) (Fig. 1). With the rest of families, we did not achieved any index significantly associated with the effects, although they did not produce any significant results with the WQS indices, neither in the logistic regression (exp[beta] = 1.75; p = 0.475) nor in the linear regression (beta = 0.62; p = 0.690), probably because of the limited number of individuals with available chemical analyses, that restricted the models to n = 174 and n = 173, respectively (Data not shown in tables/figures).

4. Discussion

In this article we present novel results suggesting a potential role of human exposure to mixtures of PTSs on the pathogenesis of hyperuricemia. We found not only associations of exposure levels with the risk of diagnosed hyperuricemia, but also with subclinical uric acid levels.

To the best of our knowledge, our findings of epidemiological associations of PCBs −138 and − 153 with uric acid homeostasis have not been previously reported, although some effects have been evidenced in animals treated with mixtures of PCBs (Burgin et al., 2001; Kutlu et al., 2007). Regarding metal exposure, cadmium showed particularly consistent positive associations through all the levels of adjustment, both with hyperuricemia and uric acid levels. In this regard, Sun et al. also reported positive associations of Cd blood levels with uric acid levels in a Chinese population, which also appeared to be independent of eGFR (Sun et al., 2017). Furthermore, Dai et al. (2015) reported a positive cross-sectional association between blood Pb levels and the risk of hyperuricemia in China. However, Sponder et al. (2014) did not find significant associations between biomarkers of Cd and Pb exposure with uric acid levels in 164 patients with coronary artery disease from Austria. Steenland et al. (2010) reported significant cross-sectional positive associations of PFOA and PFOS exposure with hyperuricemia in a highly-exposed US population, which were in line with those from Geiger et al. (2013) and Shankar et al. (2011) using NHANES data. Also in the NHANES population, serum OCPs, PCDDDs, and dioxin-like PCBs (but not non-dioxin-like PCBs) were positively associated with the risk of hyperuricemia (Lee et al., 2013).

The negative coefficients for all PDBEs in the multivariable models for hyperuricemia and uric acid levels (which were statistically significant for congener −153) were unexpected and warrant further research. To the best of our knowledge, these associations have not been previously reported at an epidemiological level. In experimental studies, Ernest et al. found a marginally-significant reduction in uric acid levels with increasing exposure doses of brominated flame retardants in adult male rates (Ernest et al., 2012)), although Van den Steen et al. did not observed significant differences between exposed and non-exposed European starlings (Van den Steen et al., 2010)

Humans are typically exposed to complex mixtures of potentially metabolic-disrupting environmental pollutants, which represent an important issue in the risk assessment process. Relevant mixture effects can be observed even when the single concentrations are below their safety levels (Kortenkamp, 2014), and variations in the concentrations of one chemical might even alter the bioavailability of the others

Table 3
PTS concentrations and risk of hyperuricemia. Logistic regression models with individual pollutants.

	Wet-basis models					Lipid-basis models					Wet basis models + adjustment for serum lipids				
	Units	OR	95% CI		p-Value	Units	OR	95% CI		p-Value	Units	OR	95% CI		p-Value
			lower	upper				lower	upper				lower	upper	
PBDE-28	(≥LOQ vs < LOQ)	0.88	0.41	1.81	0.727	(≥LOQ vs < LOQ)	0.88	0.41	1.81	0.727	(≥LOQ vs < LOQ)	0.88	0.41	1.81	0.724
PBDE-47	(≥LOQ vs < LOQ)	0.74	0.36	1.51	0.413	(≥LOQ vs < LOQ)	0.74	0.36	1.51	0.413	(≥LOQ vs < LOQ)	0.74	0.36	1.51	0.409
PBDE-100	(≥LOQ vs < LOQ)	0.56	0.26	1.16	0.124	(≥LOQ vs < LOQ)	0.56	0.26	1.16	0.124	(≥LOQ vs < LOQ)	0.56	0.26	1.16	0.123
PBDE 99	(≥LOQ vs < LOQ)	0.79	0.32	1.84	0.602	(≥LOQ vs < LOQ)	0.79	0.32	1.84	0.602	(≥LOQ vs < LOQ)	0.77	0.31	1.80	0.565
PBDE-154	(ng/mL)	0.73	0.41	1.26	0.280	(ng/g lipid)	0.93	0.55	1.49	0.782	(ng/mL)	0.70	0.38	1.23	0.234
PBDE-153	(ng/mL)	0.52	0.30	0.86	0.012	(ng/g lipid)	0.49	0.28	0.83	0.009	(ng/mL)	0.50	0.29	0.83	0.009
PBDE-183	(≥LOQ vs < LOQ)	1.36	0.77	2.28	0.266	(≥LOQ vs < LOQ)	1.32	0.75	2.22	0.314	(≥LOQ vs < LOQ)	1.35	0.76	2.28	0.278
PFHxS	(ng/mL)	1.36	0.72	2.58	0.337	(ng/mL)	1.36	0.72	2.58	0.337	(ng/mL)	1.33	0.70	2.54	0.377
PFOA	(ng/mL)	1.83	0.93	3.68	0.083	(ng/mL)	1.83	0.93	3.68	0.083	(ng/mL)	1.78	0.90	3.45	0.095
PFOS	(ng/mL)	1.70	0.86	3.49	0.138	(ng/mL)	1.70	0.86	3.49	0.138	(ng/mL)	1.67	0.84	3.41	0.151
PFNA	(ng/mL)	1.68	0.80	3.61	0.176	(ng/mL)	1.68	0.80	3.61	0.176	(ng/mL)	1.68	0.80	3.61	0.176
PFDA	(ng/mL)	1.01	0.52	1.97	0.967	(ng/mL)	1.01	0.52	1.97	0.967	(ng/mL)	1.00	0.51	1.94	0.998
N-Me-FOSA	(≥LOQ vs < LOQ)	0.49	0.03	3.39	0.522	(≥LOQ vs < LOQ)	0.49	0.03	3.39	0.522	(≥LOQ vs < LOQ)	0.50	0.03	3.46	0.531
HCB	(ng/mL)	1.12	0.77	1.66	0.546	(ng/g lipid)	1.12	0.76	1.65	0.564	(ng/mL)	1.12	0.76	1.66	0.554
β-HCH	(≥LOQ vs < LOQ)	1.16	0.53	2.40	0.699	(≥LOQ vs < LOQ)	1.16	0.53	2.40	0.699	(≥LOQ vs < LOQ)	1.16	0.53	2.41	0.694
γ-HCH	(≥LOQ vs < LOQ)	1.85	0.90	3.69	0.086	(≥LOQ vs < LOQ)	1.85	0.90	3.69	0.086	(≥LOQ vs < LOQ)	1.78	0.87	3.58	0.109
Heptachlor epoxide	(≥LOQ vs < LOQ)	1.66	0.63	4.08	0.287	(≥LOQ vs < LOQ)	1.66	0.63	4.08	0.287	(≥LOQ vs < LOQ)	1.59	0.60	3.93	0.326
Dieldrin	(≥LOQ vs < LOQ)	1.05	0.50	2.09	0.898	(≥LOQ vs < LOQ)	1.05	0.50	2.09	0.898	(≥LOQ vs < LOQ)	1.10	0.53	2.20	0.796
p,p´-DDE	(ng/mL)	1.30	0.95	1.79	0.103	(ng/g lipid)	1.27	0.92	1.75	0.144	(ng/mL)	1.27	0.93	1.75	0.143
o,p´-DDE	(≥LOQ vs < LOQ)	2.73	0.77	8.59	0.096	(≥LOQ vs < LOQ)	2.73	0.77	8.59	0.096	(≥LOQ vs < LOQ)	2.66	0.75	8.39	0.106
p,p´-DDT	(≥LOQ vs < LOQ)	1.30	0.45	3.58	0.620	(≥LOQ vs < LOQ)	1.30	0.45	3.58	0.620	(≥LOQ vs < LOQ)	1.26	0.38	3.92	0.700
PCB-28	(≥LOQ vs < LOQ)	2.45	0.12	19.46	0.451	(≥LOQ vs < LOQ)	2.45	0.12	19.46	0.451	(≥LOQ vs < LOQ)	2.36	0.11	18.74	0.473
PCB-52	(≥LOQ vs < LOQ)	1.63	0.24	6.57	0.542	(≥LOQ vs < LOQ)	1.63	0.24	6.57	0.542	(≥LOQ vs < LOQ)	1.49	0.22	6.03	0.621
PCB-101	(≥LOQ vs < LOQ)	1.24	0.60	2.43	0.550	(≥LOQ vs < LOQ)	1.24	0.60	2.43	0.550	(≥LOQ vs < LOQ)	1.22	0.59	2.39	0.580
PCB-138	(ng/mL)	1.40	1.09	1.83	0.012	(ng/g lipid)	1.32	1.03	1.74	0.036	(ng/mL)	1.32	3	1.74	0.033
PCB-153	(ng/mL)	1.43	1.10	1.91	0.009	(ng/g lipid)	1.35	1.04	1.80	0.032	(ng/mL)	1.35	1.04	1.80	0.030
PCB-180	(ng/mL)	1.34	1.02	1.79	0.039	(ng/g lipid)	1.25	0.96	1.68	0.114	(ng/mL)	1.27	0.97	1.69	0.09
Cadmium	(ng/mL)	1.40	1.06	1.87	0.019	(ng/mL)	1.40	1.06	1.87	0.019	(ng/mL)	1.35	1.02	1.80	0.036
Lead	(ng/mL)	1.12	0.90	1.42	0.313	(ng/mL)	1.12	0.90	1.42	0.313	(ng/mL)	1.12	0.90	1.41	0.329

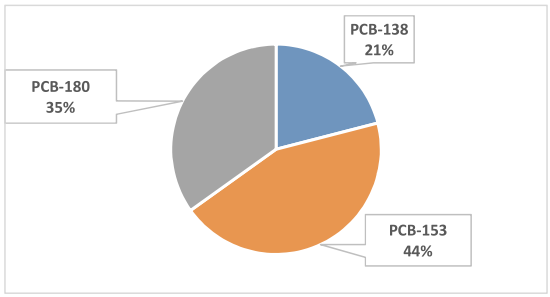
CI: confidence interval; Pollutant concentrations were log-transformed; OR: Odds Ratio.
Models were adjusted for sex (male/female), age (yrs), body mass index (kg/m^2), weight loss during the last 6 months (< 1 Kg/1–5 Kg/≥6 Kg), region of recruitment (North, Center, East, South), smoking habit (non-smoker/smoker/former smoker), alcohol consumption (non-consumer/consumer), education (primary or lower/secondary/university); place of residence (city center/other).

Table 4
PTS concentrations and serum uric acid levels (mg/dL) in individuals with no previous diagnosis of hyperuricemia. Linear regression models.

	Wet-basis models					Lipid-basis models					Wet basis models + adjustment for serum lipids				
	Units	beta	95% CI		p-Value	Units	beta	95% CI		p-Value	Units	beta	95% CI		p-Value
			lower	upper				lower	upper				lower	upper	
PBDE-28	(≥LOQ vs < LOQ)	−0.07	−0.18	0.04	0.202	(≥LOQ vs < LOQ)	−0.07	−0.18	0.04	0.202	(≥LOQ vs < LOQ)	−0.07	−0.18	0.04	0.205
PBDE-47	(≥LOQ vs < LOQ)	0.00	−0.10	0.10	0.977	(≥LOQ vs < LOQ)	0.00	−0.10	0.10	0.977	(≥LOQ vs < LOQ)	0.00	−0.10	0.10	0.981
PBDE-100	(≥LOQ vs < LOQ)	−0.05	−0.16	0.05	0.316	(≥LOQ vs < LOQ)	−0.05	−0.16	0.05	0.316	(≥LOQ vs < LOQ)	−0.05	−0.16	0.05	0.313
PBDE-99	(≥LOQ vs < LOQ)	−0.02	−0.14	0.11	0.799	(≥LOQ vs < LOQ)	−0.02	−0.14	0.11	0.799	(≥LOQ vs < LOQ)	−0.02	−0.14	0.11	0.781
PBDE-154	(ng/mL)	0.41	−0.71	1.53	0.469	(ng/g lipid)	0.45	−0.64	1.54	0.423	(ng/mL)	0.42	−0.74	1.57	0.480
PBDE-153	(ng/mL)	−0.08	−0.15	−0.01	0.023	(ng/g lipid)	−0.09	−0.16	−0.02	0.017	(ng/mL)	−0.09	−0.16	−0.02	0.018
PBDE-183	(≥LOQ vs < LOQ)	0.00	−0.09	0.10	0.918	(≥LOQ vs < LOQ)	0.00	−0.09	0.09	0.975	(≥LOQ vs < LOQ)	0.00	−0.09	0.10	0.948
PFHxS	(ng/mL)	0.05	−0.04	0.15	0.270	(ng/mL)	0.05	−0.04	0.15	0.270	(ng/mL)	0.05	−0.04	0.15	0.271
PFOA	(ng/mL)	0.04	−0.06	0.14	0.425	(ng/mL)	0.04	−0.06	0.14	0.425	(ng/mL)	0.04	−0.06	0.14	0.459
PFOS	(ng/mL)	0.06	−0.03	0.158	0.192	(ng/mL)	0.06	−0.03	0.16	0.192	(ng/mL)	0.06	−0.03	0.157	0.207
PFNA	(ng/mL)	0.04	−0.07	0.145	0.525	(ng/mL)	0.04	−0.07	0.15	0.525	(ng/mL)	0.04	−0.07	0.145	0.525
PFDA	(ng/mL)	0.01	−0.08	0.11	0.777	(ng/mL)	0.01	−0.08	0.11	0.777	(ng/mL)	0.01	−0.08	0.11	0.804
N-Me-FOSA	(≥LOQ vs < LOQ)	−0.05	−0.35	0.24	0.727	(≥LOQ vs < LOQ)	−0.05	−0.35	0.24	0.727	(≥LOQ vs < LOQ)	−0.05	−0.35	0.24	0.737
HCB	(ng/mL)	0.04	−0.02	0.10	0.230	(ng/g lipid)	0.04	−0.02	0.10	0.207	(ng/mL)	0.04	−0.02	0.10	0.215
β-HCH	(≥LOQ vs < LOQ)	−0.05	−0.17	0.07	0.448	(≥LOQ vs < LOQ)	−0.05	−0.17	0.07	0.448	(≥LOQ vs < LOQ)	−0.05	−0.17	0.07	0.449
γ-HCH	(≥LOQ vs < LOQ)	0.06	−0.05	0.18	0.281	(≥LOQ vs < LOQ)	0.06	−0.05	0.18	0.281	(≥LOQ vs < LOQ)	0.06	−0.06	0.18	0.297
Heptachlor epoxide	(≥LOQ vs < LOQ)	0.05	−0.13	0.23	0.598	(≥LOQ vs < LOQ)	0.05	−0.13	0.23	0.598	(≥LOQ vs < LOQ)	0.05	−0.14	0.23	0.621
Dieldrin	(≥LOQ vs < LOQ)	0.08	−0.05	0.20	0.224	(≥LOQ vs < LOQ)	0.08	−0.05	0.20	0.224	(≥LOQ vs < LOQ)	0.08	−0.05	0.21	0.212
p,p´-DDE	(ng/mL)	0.02	−0.03	0.07	0.391	(ng/g lipid)	0.02	−0.03	0.07	0.423	(ng/mL)	0.02	−0.03	0.07	0.424
o,p´-DDE	(≥LOQ vs < LOQ)	0.04	−0.20	0.27	0.772	(≥LOQ vs < LOQ)	0.04	−0.20	0.27	0.772	(≥LOQ vs < LOQ)	0.03	−0.20	0.27	0.786
p,p´-DDT	(≥LOQ vs < LOQ)	0.04	−0.15	0.23	0.685	(≥LOQ vs < LOQ)	0.04	−0.15	0.23	0.685	(≥LOQ vs < LOQ)	0.05	−0.16	0.26	0.619
PCB-28	(≥LOQ vs < LOQ)	−0.23	−0.67	0.21	0.309	(≥LOQ vs < LOQ)	−0.23	−0.67	0.21	0.309	(≥LOQ vs < LOQ)	−0.24	−0.68	0.21	0.297
PCB-52	(≥LOQ vs < LOQ)	−0.06	−0.33	0.21	0.663	(≥LOQ vs < LOQ)	−0.06	−0.33	0.21	0.663	(≥LOQ vs < LOQ)	−0.07	−0.34	0.20	0.615
PCB-101	(≥LOQ vs < LOQ)	−0.10	−0.22	0.02	0.112	(≥LOQ vs < LOQ)	−0.10	−0.22	0.02	0.112	(≥LOQ vs < LOQ)	−0.10	−0.23	0.02	0.103
PCB-138	(ng/mL)	0.03	0.00	0.07	0.032	(ng/g lipid)	0.03	0.00	0.07	0.066	(ng/mL)	0.03	0.00	0.07	0.032
PCB-153	(ng/mL)	0.03	0.00	0.07	0.035	(ng/g lipid)	0.03	−0.01	0.07	0.098	(ng/mL)	0.03	0.00	0.07	0.035
PCB-180	(ng/mL)	0.03	−0.01	0.06	0.117	(ng/g lipid)	0.02	−0.02	0.06	0.248	(ng/mL)	0.03	−0.01	0.06	0.117
Cadmium	(ng/mL)	0.08	0.04	0.13	< 0.001	(ng/mL)	0.08	0.04	0.13	< 0.001	(ng/mL)	0.08	0.04	0.13	0.001
Lead	(ng/mL)	0.01	−0.02	0.04	0.563	(ng/mL)	0.01	−0.02	0.04	0.563	(ng/mL)	0.01	−0.02	0.05	0.536

CI: confidence interval; Pollutant and uric acid concentrations were log-transformed.
Models were adjusted for sex (male/female), age (yrs), body mass index (kg/m^2), weight loss during the last 6 months (< 1 Kg/1–5 Kg/≥6 Kg), region of recruitment (North, Center, East, South), smoking habit (non-smoker/smoker/former smoker), alcohol consumption (non-consumer/consumer), education (primary or lower/secondary/university); Place of residence (city center/other).

Hyperuricemia (n=950)			Uric acid levels (n=816)		
exp(Beta)	Standard Error	p-value	Beta	Standard Error	p-value
2.02	0.20	<0.001	0.43	0.17	0.010



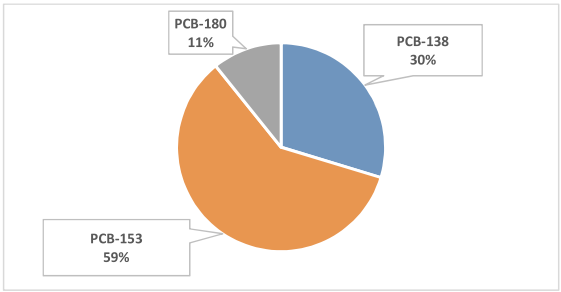


Fig. 1. Estimation of the mixture effect of PCBs on the risk of hyperuricemia and uric acid levels using WQS.

(Pollock et al., 2017). These variations in exposure levels might be behind the discrepancies in different studies concerning their adverse health effects and therefore, we believe that epidemiological studies should address combined effects in populations from different geographical locations in order to elucidate the real effect of PTS mixtures. In addition, several PTSs frequently show positive intra-family correlations due to their similar physico-chemical properties (Artacho-Cordon et al., 2015; Darrow et al., 2017), and this can lead to false-positive findings as well as to an overestimation of the magnitude of the associations when the effects are evaluated for individual chemicals. In our study we used WQS analyses to ascertain potential mixture effects, which pointed to a relevant effect of PCB-153 within the PCB mixtures on the risk of hyperuricemia as well as on uric acid levels. In fact, those BIOAMBIENT.ES participants showing ≥2 PTSs at increased concentrations experienced an higher risk of hyperuricemia. In comparison to other approaches, WQS has been reported to have good sensitivity and specificity when studying the mixture effect of environmental pollutants, although its performance decreases when exposures are highly correlated (Czarnota et al., 2015). We also need to consider that underlying biological mechanisms are not considered in this models and, hence, further confirmation in mechanistic studies would be of interest.

There are large uncertainties regarding the potential mechanisms of action of PTSs. Previous experimental studies have hypothesized that certain pollutants might have an effect on uric acid homeostasis through a disruption of antioxidant enzymes and subsequent generation of reactive oxygen intermediates, that has been suggested for, e.g., Pb (Kilikdar et al., 2011) or PFAs (Panaretakis et al., 2001). In addition, we previously reported associations of chronic exposure to OCPs and PCBs with the induction of alternative pathways to the glutathione detoxification route in humans, which might result in increased oxidative stress (Artacho-Cordón et al., 2016). It is also possible that the observed associations were a consequence of a PTS-induced chronic nephrotoxicity through, for example, their interaction with anion transporters involved in renal excretion (Kataria et al., 2015a). Indeed, adverse renal outcomes have been linked to human exposure to Pb (Sharma et al., 2013), PFAs, PAHs, and some PCBs, among others (Kataria et al., 2015b). Furthermore, it has also been speculated that the associations of PFAs with uric acid can be a consequence of a competition for the same renal transporters involved in the excretion of both substances (Steenland et al., 2010). Though, adjustment for estimated glomerular filtration rate did not change the previously-observed associations in the BIOAMBIENT.ES population (Supplemental Material, Tables S3 and S4), which suggests the existence of additional mechanisms of action different than renal dysfunction, or at least not accounted for by CDK-EPI.

The present study includes a relatively large study population with residents from all Spanish regions, as well as a wide range of PTSs. Additionally, the large amount of epidemiological and clinical data collected in BIOAMBIENT.ES allowed us to adjust for most of the known potential confounders. Despite the cross-sectional design, which limits the assumption of a causal effect, the fact that we found associations of PTS exposure with both prevalent hyperuricemia in the whole population, as well as with uric acid levels in normouricemic participants, reinforces the hypothesized role of PTS exposure in the disruption of uric acid homeostasis, particularly in the case of PCBs −138 and − 153.

Another strength of this study is the adjustment for dietary habits, which are acknowledged as major determinants of both PTS exposure as well as hyperuricemia and, consequently, likely to confound the associations. However, the inclusion of dietary covariates might cause overadjustment, given that diet typically accounts for the majority of PTS exposure (Arrebola et al., 2018) and, in this case, the direction of the associations would be as follows: diet ➔ PTSs ➔ hyperuricemia. Indeed, the magnitude association between PFOA and the risk of hyperuricemia considerably decreased after adjustment for dietary items. In addition, this cross-sectional study might be prone to reversed-causality, i.e., individuals diagnosed of hyperuricemia might have modified their dietary habits and, therefore, their PTSs internal levels. However, this would mainly affect the logistic regression models and not so much the linear regression analyses (which included only individuals with no diagnosis of hyperuricemia). A similar issue also applies to the models adjusting for glomerular filtration rate and fasting glucose, which were performed to test if these comorbidities explained the observed associations. However, these comorbidities might also share common certain mechanisms of pathogenesis with hyperuricemia (e.g. oxidative stress), and this might induce some degree of overadjustment in the analyses. Therefore, and even though the suggestive increased number of significant associations found in these models, we preferred to use a conservative approach and only assume those corresponding to the models with the lower level of adjustment. In relation to serum lipids, several PTSs, e.g., OCPs and PCBs (Arrebola et al., 2014) or Cadmium (Noor et al., 2018), have been suggested to disrupt lipid homeostasis, which is closely related to hyperuricemia (Jayashankar et al., 2016; Bonakdaran and Kharaqani, 2014; Peng et al., 2015). Therefore, serum lipids might act as a confounder in the models. However, serum lipids might also be mediator, a collider, part of the causal pathway between SLs and hyperuricemia, or even a consequence of a PTS-induced disruption of uric acid. For these reasons, and considering the controversies regarding the need for considering serum lipids when assessing potential health effects of PTSs (Porta et al., 2009), we performed two sensitivity analyses, by entering the

concentrations of lipophilic chemicals on a lipid basis, with and without adjustment. The fact that we did not observe a relevant influence of serum lipids in the associations might be related to the fasting conditions in which the individuals were sampled, that would promote a status of equilibrium across body compartments (Porta et al., 2009), or simply because serum lipids are not relevant confounders in the associations between PTSs and hyperuricemia. Our conceptual framework for the adjustment for diet and serum lipids is presented as Supplemental Material, Fig. S1.

Furthermore, we cannot rule out the presence of undetected residual confounding that might bias the results and/or potential confounders not taken into account, e.g. physical exercise. In addition, we cannot exclude potential chance findings related to multiple testing. However, if we consider the most conservative results (non-adjusted for diet, CDK-EPI or fasting glucose), our statistically significant associations in each model exceed the 5% that would be expected as a consequence of chance findings using a p-value of 0.05. The risk of chance findings is even higher in dichotomized variables (Bennette and Vickers, 2012) and, therefore, our discussion is mostly focused on the results with continuous predictors. Furthermore, in our opinion, even if the reported associations were not considered true, their underlying causes would be worth of further investigation since they might be a proxy of other unknown external causes of the disease.

5. Conclusions

We found evidences of associations between human exposure to mixtures of PTSs and disturbances in uric acid homeostasis, that appeared to be independent of common sociodemographic and lifestyle characteristics, dietary habits, glucose homeostasis and kidney function. However, we cannot rule out a potential residual confounding or reversed-causality and further confirmation using longitudinal studies is required.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.12.030.

Conflict of interest

The authors declare no conflicts of interest to disclose.

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