http://dx.doi.org/10.4082/kjfm.2016.37.5.267 • Korean J Fam Med 2016;37:267-272

KJFM
Korean Journal of Family Medicine

eISSN: 2092-6715

■ Original Article

The Relationship between the Blood Level of Persistent Organic Pollutants and Common Gastrointestinal Symptoms

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Background: Persistent organic pollutants (POPs) are toxic materials that cannot be broken down naturally and that easily accumulate in the body. Although several studies have attempted to reveal the effects of POPs on the endocrine and nervous system and on cancer, few studies focus on the relationship between low-dose POPs and public health. We attempted to find a relationship between the level of POPs and common gastrointestinal symptoms, including abdominal discomfort, diarrhea, and constipation.

Methods: We recruited 121 subjects who visited Kyungpook National University Hospital for a health screening. Plasma concentrations were evaluated for 40 kinds of POPs including 17 types of polychlorinated biphenyls and 23 types of organochlorine pesticides. Furthermore, the Korean version of the Rome III criteria was used to identify gastrointestinal symptoms.

Results: Our results showed that abdominal discomfort had an inverse relationship with several polychlorinated biphenyls. Moreover, an inverted U-shaped relationship was observed between abdominal discomfort and several other organochlorine pesticides including p,p'-dichlorodiphenyldichloroethane and p,p'-dichlorodiphenyltrichloroethane, and the effects of these pesticides on abdominal discomfort were similar to that of organochlorine pesticides on obesity and metabolic syndrome.

Conclusion: Our results suggest that mild and unspecified gastrointestinal symptoms with no clear cause could be related to POPs levels.

Keywords: Persistent Organic Pollutants; Abdominal Discomfort; Diarrhea; Constipation

Received: March 27, 2016, Revised: March 27, 2016, Accepted: May 19, 2016
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INTRODUCTION

Persistent organic pollutants (POPs) are toxic chemicals that accumulate in animals and plants through the food chain and do not decompose in the environment through photochemical, biological, or chemical processes. The most common types of POPs are polychlorinated biphenyls (PCBs) and organochlorine pesticides (OCPs). PCBs have been commonly used in electrical equipment, dielectric coolants, dielectric fluids, paints, and coating materials for over five decades. In particular, the major use of the chemicals was as a sealant in the doors and windows of buildings constructed from the 1950s to the 1970s. PCBs have been detected in the indoor air of those buildings at high concentrations even after several decades have passed.[1-4] OCPs have been commonly used worldwide because of their low cost and outstanding insecticidal activity.[5] However, those POPs are highly toxic substances characterized by their high residual property, bioconcentration potential, and long-distance mobility. Responsive measures have been devised around the globe because of the increased damage to ecosystems and human health. A total of 21 POPs have been listed in the 'Stockholm Convention on Persistent Organic Pollutants' for which regulations are required that the 21 POPs were mentioned in the 2004 and 2009 lists. Restrictions on the use of POPs have slowly reduced the environmental load of POP compounds in many countries throughout the world since the early 1970s.[6] Despite these efforts, a recent study showed that workers in a transformer recycling company and their family members had highly elevated levels of PCB in their blood[7] and the association of POPs with various diseases is still being reported because of the unique properties of POPs, indicating that consistent monitoring is required.

Previous studies mainly investigated the high concentrations of POPs and proposed an association with a wide range of symptoms[8,9] including acneiform eruption, dermal pigmentation, and increased eye discharge. Recent studies have analyzed the effects of low levels of POPs and reported that POPs at low concentrations are associated with estrogenic activity,[10] diabetes mellitus,[11-13] endocrine diseases such as obesity,[14,15] brain and psychomotor development,[16] and cancer.[17] However, almost no studies have investigated the association of the intake of POPs from food in humans[18-20] with symptoms of gastric problems.

Abdominal discomfort is currently one of the most common digestive symptoms. One study suggested that a statistically significant decrease was observed in the quality of life as the severity of abdominal discomfort increased,[18] and another study showed that various types of abdominal complaints are associated with depression and anxiety.[21] Because abdominal discomfort is a subjective symptom and the exact cause has not been clarified, evaluation of the various causes is crucial. A previous study suggested that the high PCB level group in the body is a possible cause of abdominal discomfort.[22] However, this study mainly analyzed the difference in the symptoms of groups classified according to the history of exposure to PCBs and had not clearly stated the relationship of the subjective symptoms with the different concentrations of PCBs. For these reasons, the aim of this study was to analyze the association of POP concentrations with various gastrointestinal symptoms including abdominal discomfort, diarrhea, and constipation from multiple perspectives.

METHODS

1. Subjects

This study recruited 121 healthy subjects who visited Kyungpook National University Hospital for a health screening from March to July 2012. Subjects who had no previous psychiatric disorders or severe chronic conditions such as cancer were included in the study, and all subjects gave their written informed consent. Based on the a study showing a correlation of POP concentrations with the onset of obesity,[15] the body mass index (BMI) of subjects was considered during the recruitment process, and 51 subjects with a recorded BMI of >25 kg/m^2 were included in the study. All subjects were asked to answer the survey questionnaire. The study was approved by the Ethics Committee of Kyungpook National University Hospital (KNUH 2012-02-018).

2. Physical Measurements

Weight, height, the thickness of subcutaneous fat at the triceps muscles, blood pressure, pulse, and waist, hip, and thigh circumferences were measured and BMI calculated.

Subjects were categorized according to smoking status as nonsmoker, former smoker, or current smoker and according to alcohol drinking status as nondrinker, former drinker, or current drinker, and drinkers were asked about the average frequency of their alcohol consumption and the mean dose of alcohol per drinking session in the past year before their visit.

3. Questionnaire

The presence of symptoms including gastrointestinal symptoms such as diarrhea, constipation, and abdominal discomfort were evaluated using the Korean version of the Rome III (Rome III-K) criteria for the diagnosis of irritable bowel syndrome (IBS). The Rome III-K is the translated version[23] of the Rome III criteria[24] published by the Korean Society of Neurogastroenterology and Motility in 2006. The Rome III criteria with a sensitivity of 80.3% and specificity of 50.0% are relatively useful in diagnosing functional bowel disorders in Koreans.

4. Measurement of Plasma Concentrations of Persistent Organic Pollutants

This study examined 17 types of PCBs including PCB74, PCB99, PCB105, PCB118, PCB138, PCB146, PCB153, PCB156, PCB157, PCB164, PCB167, PCB172, PCB172, PCB177, PCB178, PCB180, PCB183, and PCB187 and 23 types of OCPs including hexachlorobenzene, α-hexachlorocyclohexane (α-HCH), β-HCH, γ-HCH (lindane), δ-HCH, *cis-/trans*-nonachlor, heptachlor, *cis-/trans*-heptachlor epoxide, *cis-/trans*-chlordane, oxychlordane, aldrin, dieldrin, endrin, mirex, 4,4'-dichlorodiphenyltrichloroethane (4,4'-DDT), 4,4'-dichlorodi-

phenyldichloroethylene (4,4'-DDE), 4,4'-dichlorodiphenyldichloroethane (4,4'-DDD), 2,4'-DDT, 2,4'-DDE, and 2,4'-DDD. The samples were preprocessed through clean-up with a Silica-Florisil cartridge and HLB cartridge using solid-phase extraction. For instrumental analyses, we used high-resolution gas chromatography and mass spectrometry with high-resolution tandem mass spectrometry (JMS-800 T; JEOL, Tokyo, Japan).

5. Statistical Analysis

The levels of POPs were categorized into five groups using quintiles to identify the association of POP concentrations with the onset of symptoms. Multivariate logistic regression analysis was performed to determine the association of the quintiles of plasma POPs with gastrointestinal symptoms including abdominal discomfort, diarrhea, and constipation. Moreover, we conducted an additional analysis using diagnosis of IBS as a dependent variable. The χ^2 test for trends was used to evaluate linear patterns for the effects of POP levels on abdominal symptoms. We used the statistical software IBM SPSS for Windows ver. 20.0 (IBM Co., Armonk, NY, USA) and considered a P-value <0.05 as statistically significant; however, considering the small sample size, we also commented on results with 0.05≤ P-value <0.1 as marginally significant.

RESULTS

1. General Characteristics of the Subjects

The subjects consisted of 61 men and 60 women, and the mean age of the subjects was 49.5 years old (range, 38 to 66 years old). Sixty-nine subjects were current smokers, and the others were nonsmokers (n=20) or former smokers (n=32). Ninety-two subjects were drinkers: 25 subjects consumed <70 g alcohol/wk and the others consumed ≥70 g alcohol/wk. The mean±standard deviation BMI was 24.74±3.37 kg/m^2. Constipation, diarrhea, and abdominal discomfort were reported by 58, 72, and 57 subjects, respectively. Details on general characteristics of the subjects are described in Table 1.

2. Adjusted Odds Ratios (95% Confidence Intervals) of the Prevalence of Abdominal Discomfort, Diarrhea, and Constipation according to the Quintiles of POP Plasma Concentrations

Depending on the quintiles of plasma concentrations of POPs, subjects were divided into five groups as Q1 (0%–20%), Q2 (20%–40%), Q3 (40%–60%), Q4 (60%–80%) and Q5 (80%–100%). Q1 (0%–20%) was used as the reference quintile. And the odds ratios for every quintile were obtained for each symptom. Logistic regression analysis adjusted for age, sex, smoking, drinking, and BMI[15] was performed to identify the correlation between the POP concentrations and the severity of abdominal symptoms. Table 2 presents the results with statistical significance.

A number of POPs showed statistical significance with gastrointestinal symptoms such as abdominal discomfort, diarrhea, and constipation. In the case of abdominal discomfort, the odds ratios of the fourth quintile decreased to 0.23–0.30, compared with those of the first quintile of PCBs. Statistical significance was found for PCB99 and PCB118 (P<0.05), indicating an inverse association. On the other hand, the odds ratios of the second and third quintiles increased to approximately 5 on average compared with those of the first quintile for OCPs including p,p'-DDD and p,p'-DDT (P<0.05) and then showed a gradually decreasing tendency, indicating an inverted U-shaped association. A P-trend of 0.01 was considered statistically significant. The graph in Figure 1 represents the odds ratios for the quintiles of the plasma concentrations of POPs generating abdominal discomfort.

In the case of diarrhea, the odds ratio of the second quintile was greater than that of the first quintile for PCB183 (P<0.05), and a gradually decreasing tendency was observed in the odds ratios of the fourth and fifth quintiles. PCB183 showed statistical significance with a P-trend of 0.04, indicating an inverted U-shaped association.

In the case of constipation, the plasma concentrations of several PCBs were inversely associated with the gastrointestinal symptoms. The odds ratios of PCBs (PCB74, PCB146, PCB153, and PCB164) leading to constipation decreased to 0.13–0.23 in the third quintile compared with the first quintile (all P<0.05), and were maintained between approximately 0.3–0.5 in the fourth and fifth quintiles. The odds ratios of β-HCH (an OCP) leading to constipation decreased to 0.6 on average in the second through fourth quintiles compared with the first

Table 1. General characteristics of subjects

Characteristic	Value
Sex	
Male	61 (50.4)
Female	60 (49.6)
Age (y)	49.50±7.23
Body mass index (kg/m^2)	24.74±3.37
Male	24.91±0.40
Female	24.56±0.47
Percentage fat	28.87±8.09
Male	23.29±0.96
Female	33.67±0.75
Smoking	
Current smoker	20 (16.5)
Nonsmoker	69 (57.0)
Ex-smoker	32 (26.4)
Alcohol	
None	29 (23.9)
≥70 g/wk	67 (55.4)
<70 g/wk	25 (20.7)
Gastrointestinal symptoms	
Abdominal discomfort	57 (47.1)
Constipation	58 (47.9)
Diarrhea	72 (59.5)
History	
Hypertension	20 (16.5)
Diabetes	12 (9.9)
Dyslipidemia	17 (14)

Values are presented as number (%) or mean±standard deviation.

http://dx.doi.org/10.4082/kjfm.2016.37.5.267

Table 2. Adjusted odds ratios (95% confidence intervals) of the prevalence of abdominal discomfort, diarrhea and constipation according to quintiles of plasma concentrations of persistent organic pollutants

Variable	Q1 (0%–20%) (n=24)	Q2 (20%–40%) (n=24)	P-value	Q3 (40%–60%) (n=24)	P-value	Q4 (60%–80%) (n=24)	P-value	Q5 (80%–100%) (n=24)	P-value	P-trend
Abdominal discomfort										
PCB99	Reference	1.22 (0.33–4.49)	0.761	0.84 (0.25–2.86)	0.780	0.23 (0.06–0.84)	0.026	0.32 (0.09–1.13)	0.076	0.198
PCB118	Reference	0.93 (0.26–3.37)	0.909	1.05 (0.29–3.74)	0.944	0.25 (0.07–0.96)	0.044	0.95 (0.29–3.12)	0.934	0.606
PCB138	Reference	1.02 (0.28–3.76)	0.974	0.49 (0.14–1.68)	0.258	0.30 (0.08–1.06)	0.061	0.41 (0.12–1.38)	0.150	0.606
PCB146	Reference	1.62 (0.44–6.00)	0.467	0.78 (0.23–2.71)	0.699	0.27 (0.07–1.05)	0.060	1.05 (0.31–3.53)	0.933	0.367
p,p'-DDD	Reference	5.97 (1.49–24.00)	0.012	5.08 (1.29–19.95)	0.020	3.86 (0.99–15.13)	0.052	2.94 (0.78–11.02)	0.110	0.010
p,p'-DDT	Reference	5.62 (1.34–23.54)	0.018	4.56 (1.14–18.23)	0.032	2.80 (0.72–10.85)	0.137	1.62 (0.42–6.24)	0.480	0.014
Diarrhea										
PCB183	Reference	4.03 (0.81–20.01)	0.088	0.64 (0.18–2.29)	0.491	0.77 (0.23–2.60)	0.669	0.35 (0.10–1.19)	0.092	0.036
PCB187	Reference	1.88 (0.41–8.71)	0.420	0.97 (0.26–3.66)	0.961	0.24 (0.07–0.85)	0.027	0.67 (0.18–2.45)	0.542	0.295
β-HCH	Reference	2.42 (0.60–9.69)	0.213	0.83 (0.24–2.95)	0.778	3.44 (0.95–12.41)	0.060	1.45 (0.43–4.86)	0.549	0.239
Constipation										
PCB74	Reference	0.70 (0.20–2.48)	0.581	0.13 (0.03–0.52)	0.004	0.29 (0.08–1.03)	0.056	0.53 (0.16–1.83)	0.316	0.198
PCB146	Reference	0.59 (0.16–2.17)	0.425	0.22 (0.06–0.83)	0.025	0.28 (0.08–1.03)	0.055	0.52 (0.15–1.78)	0.297	0.440
PCB153	Reference	0.52 (0.13–1.99)	0.336	0.19 (0.05–0.72)	0.015	0.41 (0.11–1.46)	0.167	0.34 (0.10–1.20)	0.092	0.607
PCB164	Reference	0.63 (0.16–2.47)	0.509	0.23 (0.06–0.84)	0.026	0.35 (0.09–1.28)	0.111	0.35 (0.10–1.19)	0.092	0.797
PCB187	Reference	0.68 (0.17–2.64)	0.573	0.46 (0.13–1.65)	0.231	0.33 (0.10–1.14)	0.079	0.52 (0.15–1.81)	0.301	1.000
β-HCH	Reference	0.66 (0.17–2.59)	0.551	0.58 (0.16–2.07)	0.400	0.67 (0.20–2.24)	0.512	0.26 (0.07–0.91)	0.034	0.797

Odds ratios were adjusted for age, sex, smoking, drinking, and body mass index.
Q, quintile; PCB, polychlorinated biphenyl; DDD, dichlorophenyldichloroethane; DDT, dichlorophenyltrichloroethane; HCH, hexachlorocyclohexane.

quintile. Moreover, the odds ratios decreased to 0.26 in the fifth quintile with statistical significance.

However, in the analysis using the diagnosis of IBS as a dependent variable, there was no significant association between the POP levels and the frequency of IBS diagnosis (all P>0.05).

DISCUSSION

Gastrointestinal symptoms including abdominal discomfort, diarrhea, and constipation were found to be statistically significantly correlated with a number of POPs examined in this study. Abdominal discomfort had an inverted U-shaped association with OCPs including p,p'-DDD and p,p'-DDT. This association is similar to the association between POPs and obesity and metabolic syndrome found in previous investigations.[14,15,25] Even though BMI was adjusted to reduce the effects of obesity and metabolic syndrome, similar association patterns for POPs were seen with other diseases including obesity. Based on these previous results, the plasma concentrations of some POPs were anticipated to be associated with abdominal discomfort.

In a previous study on the relationship between the degree of exposure to POPs and gastric complaints, no significant difference was found in the severity of gastric complaints in subjects working in buildings exposed to POPs compared with the control group.[22] Although the number of POPs included in this study was small,[22] the outcomes are predicted to be drawn from the nonlinear association proposed in the study with subjects under low-dose exposure to POPs.

This investigation provides stronger evidence than that of previous studies by comparing the plasma concentrations of various POPs with the severity of abdominal discomfort. For abdominal discomfort, greater odds ratios for OCPs were found in lower plasma concentrations (quintiles 2 and 4) than in higher plasma concentrations (quintiles 4 and 5). Considering that gastrointestinal symptoms could influence the absorption of substances into the body, this outcome could be interpreted as reverse causality. Thus, higher body absorption could account for a higher concentration of POPs in an asymptomatic case with abdominal discomfort, whereas lower body absorption could account for a lower concentration of POPs because of reduced gastrointestinal function. Lower POP levels are believed to result from limited gastrointestinal absorption when abdominal discomfort is present all the time. Therefore, the association with plasma POP concentrations should be considered in cases of mild abdominal discomfort of unknown cause.

This study has several limitations. The sample size was relatively small, and subjects were recruited from one general hospital. Therefore, our results cannot be generalized beyond the study sample. Additional studies with a larger sample group are crucial to further investigate the associations of plasma POP concentrations with subdivided symptoms. In addition, our cross-sectional design cannot explain causality between abdominal symptoms and POP levels.

Although there are some limitations, this study has the following merits. Functional gastrointestinal disease including IBS is one of the leading disorders associated with abdominal discomfort, diarrhea, and constipation. The exact cause of this common gastrointestinal disease has not yet been clarified. So far, functional gastrointestinal disorders are known to mainly occur due to individual factors including stress,[26] food,[27] individual lifestyle habits, and body constitution from a clinical perspective. In addition, this study suggests that these common gastrointestinal symptoms can be associated with environmental

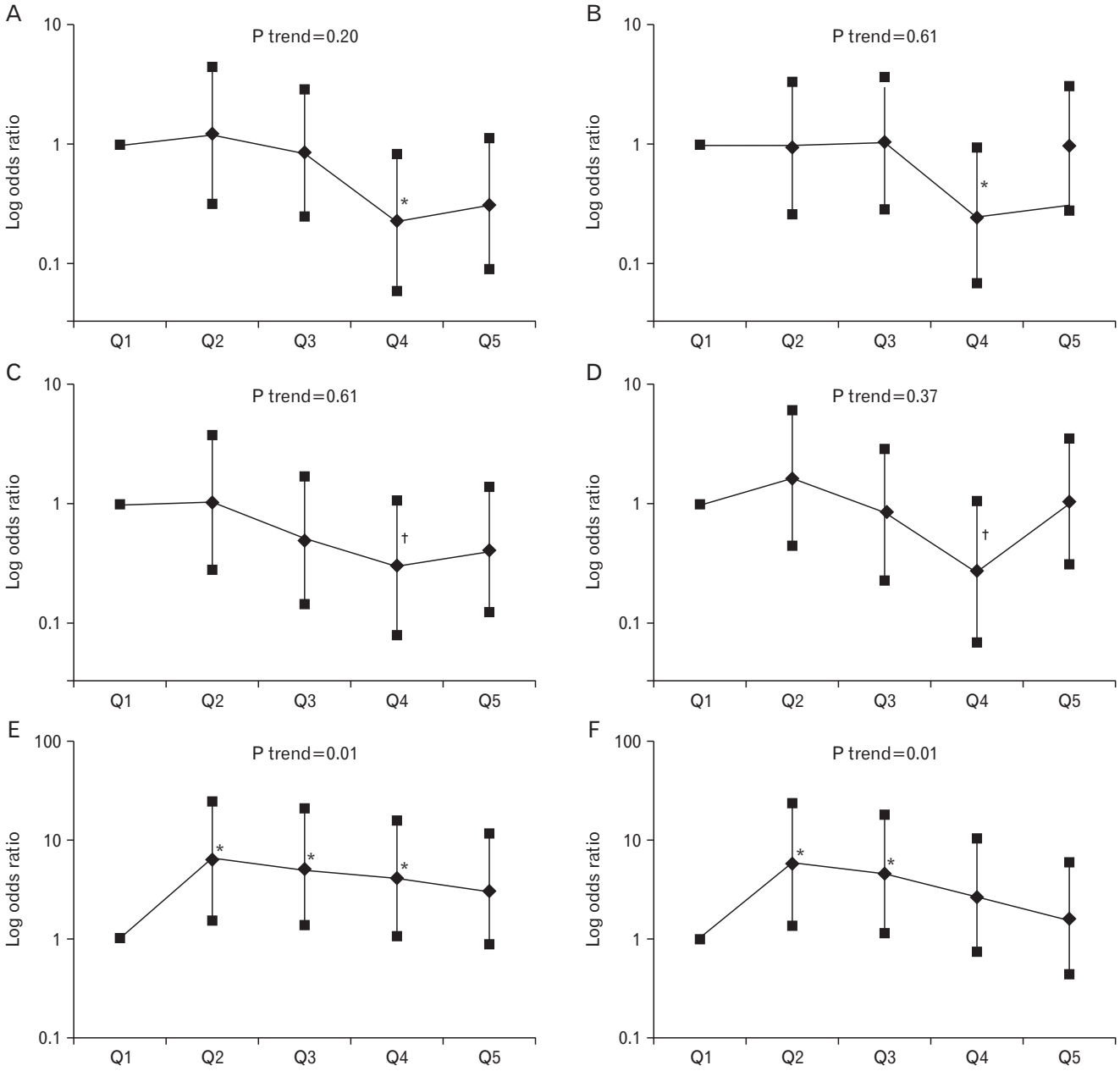

Figure 1. Effects of several POPs on abdominal discomfort. (A–D) Although not all PCBs showed any significant trend of association with abdominal discomfort, (E, F) p,p'-dichlorodiphenyldichloroethane (p,p'-DDD) and p,p'-dichlorodiphenyltrichloroethane (p,p'-DDT) had a significant inverted U-shaped relationship. In p,p'-DDD and p,p'-DDT analysis, subjects in Q2 and Q3 reported a higher prevalence of abdominal discomfort than those in Q1. The reference group is Q1 in the analysis. (A) PCB 99. (B) PCB 118. (C) PCB 138. (D) PCB 146. (E) pp-DDD. (F) pp-DDT. Q, quintile; p,p'-DDD, p,p'-dichlorodiphenyldichloroethane; p,p'-DDT, p,p'-dichlorodiphenyltrichloroethane. *P<0.05. †P<0.1.

factors such as POPs in addition to individual factors. The findings of this study are anticipated to contribute by creating a healthier environment through policy changes that prohibit the use of environmental pollutants. Moreover, this study suggests that an appropriate approach for diseases from a social perspective be taken beyond just the individual symptom-oriented diagnostic approach.

In conclusion, some POPs had a statistically significant association with gastrointestinal symptoms including abdominal discomfort, diarrhea, and constipation. OCPs had an inverted U-shaped relationship, similar to the results of previous studies. Therefore, POP concentrations should be considered when determining the etiology of gastrointestinal symptoms such as mild abdominal discomfort of unknown cause. Our results suggest that clinicians should be concerned with environmental issues including exposure to POPs, which is closely linked to public health.

http://dx.doi.org/10.4082/kjfm.2016.37.5.267

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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