https://doi.org/10.4082/kjfm.2017.38.4.233 • Korean J Fam Med 2017;38:233-238

KJFM
Korean Journal of Family Medicine

eISSN: 2092-6715

■ Brief Communication

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 uncover the effects of POPs on the endocrine and nervous systems and on cancer, few focus on the relationship between low-dose POPs and public health. Here, we attempt to determine the 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 Medical Center for health screening. Plasma concentrations were evaluated for 40 kinds of POPs including 17 types of polychlorinated biphenyls (PCBs) and 23 types of organochlorine pesticides (OCP). Furthermore, the Korean version of the Rome III criteria was used to identify gastrointestinal symptoms.
Results: Based on our results, abdominal discomfort showed an inverse relationship with several PCBs and an inverted U-shaped relationship with several other OCPs including pp-DDD and pp-DDT. The effects of pp-DDD and pp-DDT on abdominal discomfort were similar to those of OCPs on obesity and metabolic syndrome.
Conclusion: Our results suggest that mild and unspecified gastrointestinal symptoms with no clear causes could be related to POP levels.

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

Received: August 24, 2016, Accepted: September 1, 2016
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INTRODUCTION

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

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 with gastric problems in humans.[18-20]

Abdominal discomfort is one of the most common digestive symptoms these days. A study reported that a statistically significant decrease was observed in the quality of life as the severity of abdominal discomfort increased.[18] Another study demonstrated 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 a low level of PCBs 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 did not clearly state the relationship of the subjective symptoms with 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 included 121 healthy subjects who visited Kyungpook National University Medical Center for 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 provided written informed consent. According to a study on the correlation of POP concentrations with the onset of obesity,[15] the body mass index (BMI) of subjects were taken into consideration during the recruitment process. Fifty-one subjects with BMI >25.0 kg/m^2 were included in the study. All subjects were asked to complete the survey questionnaire. The study was approved by the Ethics Committee of the Kyungpook National University Medical Center (KNUH 2012-02-018).

2. Physical Measurements

Weight, height, waist, hip, and thigh circumferences, the thickness of subcutaneous fat at the triceps muscles, blood pressure, and pulse were measured. Using the measured values, BMI (kg/m^2) was calculated.

Smoking status was divided into non-smoker, former smoker, and current smoker. Drinking status was divided into non-drinker, former drinker, and current drinker. Drinkers were asked about their average frequency of alcohol consumption and the mean dose of alcohol consumed per drinking session in the past year prior to their visit.

3. Questionnaire

The presence of symptoms including gastrointestinal symptoms such as diarrhea, constipation, and abdominal discomfort were evaluated with 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, namely PCB74, PCB99, PCB105, PCB118, PCB138, PCB146, PCB153, PCB156, PCB157, PCB164, PCB167, PCB172, PCB177, PCB178, PCB180, PCB183, and PCB187 and 23 types of OCPs including hexachlorobenzene (HCBz), 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'-DDT, 4,4'-DDE, 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, us-

ing solid phase extraction. For instrumental analyses, we used high resolution gas chromatography and mass spectrometry with high resolution tandem MS 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. We also conducted additional analysis using IBS diagnosis as a dependent variable. Chi-square 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 Corp., 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 with a mean age of 49.5 years (range, 38 to 66 years). Sixty-nine subjects were current

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	24.74±3.37
Male	24.91±0.40
Female	24.56±0.47
Fat percent	28.87±8.09
Male	23.29±0.96
Female	33.67±0.75
Smoking	
Current-smoker	20 (16.5)
Non-smoker	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)
Past history	
Hypertension	20 (16.5)
Diabetes	12 (9.9)
Dyslipidemia	17 (14)

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

Table 2. Adjusted odds ratios (95% confidence interval) for the frequency of abdominal discomfort, diarrhea, constipation, and fatigue 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 for 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
pp-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
pp-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
b-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
b-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

Values are presented as odds ratio (95% confidence interval). Adjusted for age, sex, smoking, alcohol, and body mass index.
PCB, polychlorinated biphenyl.

https://doi.org/10.4082/kjfm.2017.38.4.233

smokers, and the others were non-smokers (N=20) or former smokers (N=32). Ninety-two subjects were alcohol drinkers: 25 subjects consumed less than 70 g/wk and the others consumed 70 g/wk or more. The mean±standard deviation BMI score was 24.74±3.37. The number of subjects that reported constipation, diarrhea, and abdominal discomfort was 58, 72, and 57, respectively. Detailed information on the general characteristics is provided in Table 1.

2. Adjusted Odds Ratios (95% Confidence Interval) for the Frequency of Abdominal Discomfort, Diarrhea, and Constipation according to Quintiles of Plasma Concentrations of Persistent Organic Pollutants

Subjects were divided into five groups based on the quintiles of plasma concentrations of POPs, and the odds ratios for every quintile were obtained for each symptom. Logistic regression analysis adjusting for age, sex, smoking, alcohol and BMI[15] was performed to identify the correlation between the POPs and the severity of the 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 odd ratios of the 4th quintile decreased to 0.23–0.30, compared with those of the 1st quintile of PCBs. Statistical significance was observed for PCB99 and PCB118 (P<0.05), indicating an inverse association. In contrast, the odd ratios of the 2nd and 3rd quintiles increased to about 5 on average, compared with those of the 1st quintile for OCPs including pp-DDD and pp-DDT (P<0.05), and then showed a gradually decreasing tendency, indicating an inverted U-shaped association. A P for trend of 0.01 was considered statistically significant. The resulting graph represents the odds ratios for the quintiles of the plasma concentrations of POPs that cause abdominal discomfort (Figure 1).

In the case of diarrhea, the odds ratios of the 2nd quintile were greater than those of the 1st quintile for PCB183 (P<0.05), and a gradually decreasing tendency was observed in the odd ratios of the 4th and 5th quintiles. PCB183 had statistical significance with a P for 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 gastrointestinal symptoms. The odds ratios of PCBs (PCB74, PCB146, PCB153, and PCB164) that caused constipation decreased to 0.13–0.23 in the 3rd quintile compared to the 1st quintile (all Ps<0.05), and were maintained between approximately 0.3–0.5 in the 4th and 5th quintiles. The odds ratios of b-HCH (OCPs), which caused constipation, decreased to 0.6 on average in the 2nd-4th quintiles compared to the 1st quintile, and were maintained for a while. Moreover, the odds ratios decreased to 0.26 in the 5th quintile, with statistical significance.

However, in subsequent analysis using the diagnosis of IBS as a dependent variable, there was no significant association between the levels of POPs and the frequency of IBS diagnosis (all Ps>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 pp-DDD and pp-DDT. This association is similar to the association identified between POPs and obesity as well as metabolic syndrome in previous investigations.[14,15,25] Even though BMI was modified to reduce the effects of obesity and metabolic syndrome, similar association patterns for POPs were observed 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 subjects working in buildings exposed to POPs when the severity of gastric complaints was compared with that of the control group.[22] Although the number of POPs included in this study is small,[22] the outcomes are predicted to be drawn from the non-linear association proposed in a previous study with subjects under low-dose exposure to POPs.

This investigation provides stronger evidence than 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 (quintile 2 and quintile 4) than in higher plasma concentrations (quintile 4 and quintile 5). Taking into consideration the fact that gastrointestinal symptoms can influence the absorption of substances into the body, the outcome could be interpreted with reverse causality. Thus, higher absorption could be attributed to a higher concentration of POPs in an asymptotic case with abdominal discomfort, while lower absorption could be attributed to a lower concentration of POPs because of reduced gastrointestinal function. Lower POP levels are believed to be due to limited gastrointestinal absorption with constant abdominal discomfort. Therefore, the association with plasma POP concentrations should be considered in cases of mild abdominal discomfort with unknown causes.

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 samples. Additional studies with a larger sample group are crucial to further investigate the associations of plasma concentrations of POPs with subdivided symptoms. In addition, our cross-sectional design cannot confirm 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

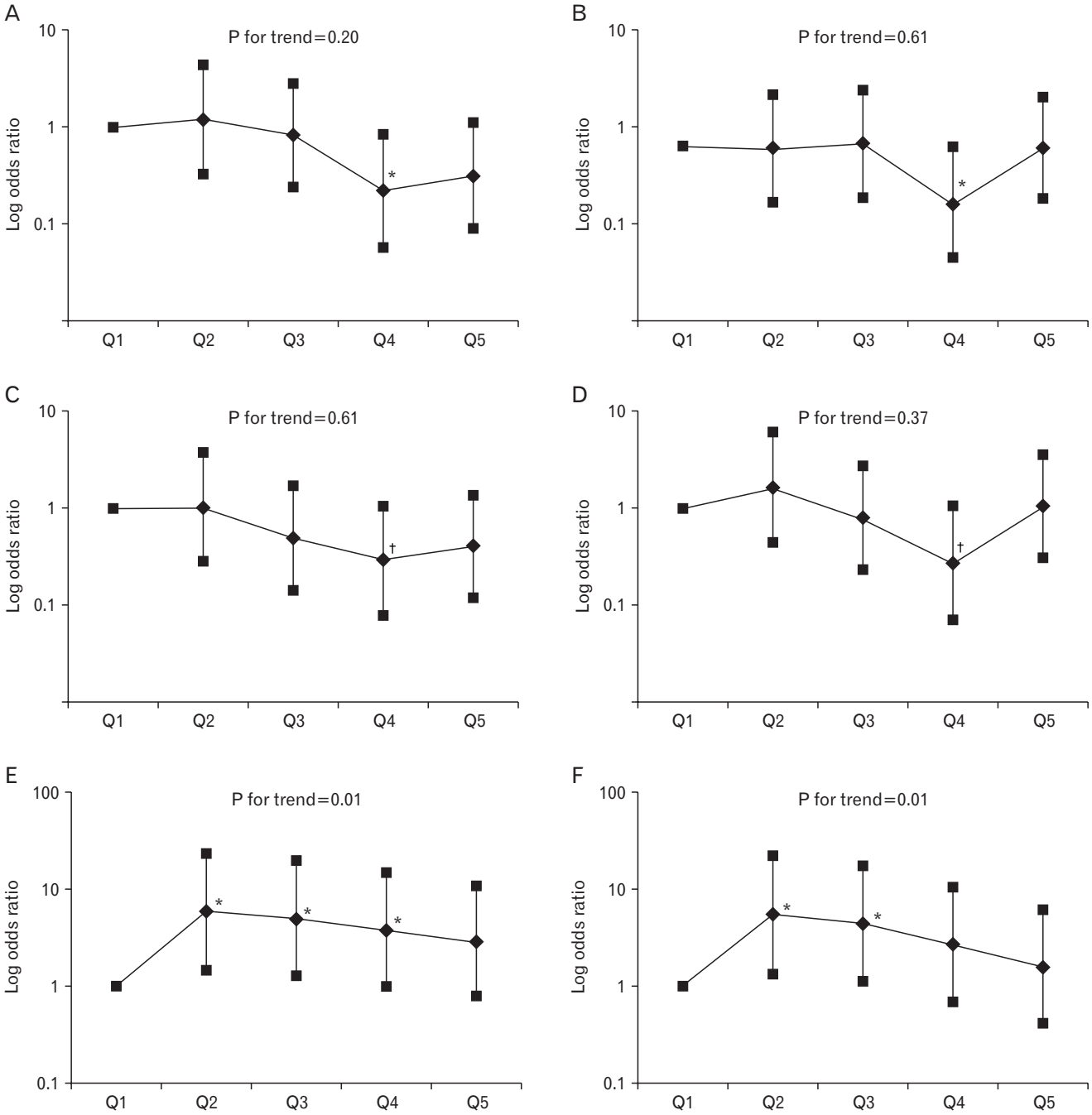

Figure 1. Effects of several persistent organic pollutants on abdominal discomfort. Although none of the PCBs showed any significant trends (A–D), pp-DDD and pp-DDT have a significant inverted U-shaped relationship (E, F). (A) PCB99; (B) PCB118; (C) PCB138; (D) PCB146; (E) pp-DDD; (F) pp-DDT. In pp-DDD and pp-DDT analysis, groups Q2 and Q3 reported higher abdominal discomforts than group Q1. Reference group is Q1 in the analysis. PCB, polychlorinated biphenyl. *P<0.05. †P<0.1.

a clinical perspective. In addition, this study suggests that these common gastrointestinal symptoms can be associated with environmental factors such as POPs, in addition to individual factors. The findings of this study are anticipated to contribute to the creation of a healthier environment through policy change that prohibits the use of environmental pollutants. Moreover, this study suggests that an appropriate approach for diseases from a social perspective be taken beyond 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, the concentrations of POPs should be considered when determining the association of gastrointestinal symptoms with unknown causes such as mild ab-

https://doi.org/10.4082/kjfm.2017.38.4.233

dominal discomfort. Our results indicate that clinicians should be concerned with environmental issues including the use of POPs, which is closely linked to public health.

CONFLICT OF INTEREST

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

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