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ARTICLE *in* ENVIRONMENTAL SCIENCE & TECHNOLOGY · JUNE 2011

Impact Factor: 5.33 · DOI: 10.1021/es1043563 · Source: PubMed

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Global Trends and Diversity in Pentachlorophenol Levels in the Environment and in Humans: A Meta-Analysis

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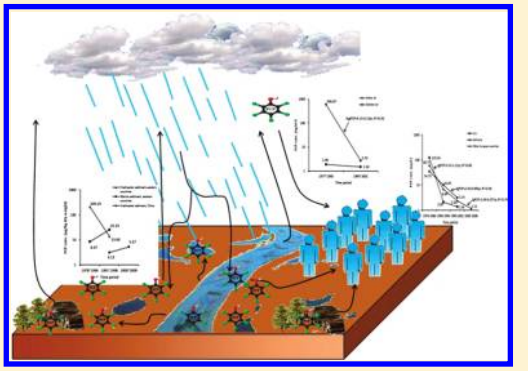
Supporting Information

ABSTRACT: Pentachlorophenol (PCP) was banned or restricted in many countries worldwide because of its adverse effects on the ecological environment and humans. However, the endocrine disrupting effects caused by low environmental PCP exposure levels has warranted more analysis. We reviewed 80 studies conducted in 21 countries and published between 1967 and 2010, using meta-regression analysis to examine the time trends and regional differences in PCP levels. The results suggested that in indoor air, bodies of water, freshwater sediments in western countries, invertebrates and freshwater vertebrates, PCP levels had declined over time, with half-lives ranging from 2.0 years to 11.1 years. However, in marine sediments/vertebrates and Chinese surface water/sediments, PCP levels increased over time. PCP levels in human blood and urine had decreased since the 1970s, with population half-lives of 3.6 years and 5.7 years, respectively. The intervals for global population blood and urine reference values decreased to 1.1−6.3 μg/L (2002−2008) and 2.5−7 μg/L (1995−2003), respectively. The possible thyroid disrupting effects and other health risks correlated with low environmental PCP exposure should be concerning. This study can help to ascertain the effects of the banning/restriction policy, providing data for cost-benefit analysis in policy-making and further control of health risks caused by low environmental exposure to PCP.



INTRODUCTION

Since the 1930s, pentachlorophenol (PCP) and its sodium salt have been widely used as herbicide, algaecide, defoliant, wood preservative, germicide, fungicide or molluskacide because of its bactericidal and fungicidal properties.[1−3] Due to its widespread use for these purposes, PCP can now be detected in the air, water, and soil throughout the world[4−6] as well as in the blood, urine, seminal fluid, breast milk, and adipose tissue of humans.[3]

PCP's adverse health effects were first reported in the 1940s.[4] In the 1970s, the liver and kidney toxicities of PCP were confirmed, and its reproductive and developmental toxicities were reported.[4] The first literature about PCP exposure and human cancer was published in 1978.[7] PCP was classified as a group 2B possible human carcinogen by the IARC [8] and as a probable human carcinogen by the U.S. EPA.[6] Both the IARC and the EPA based their similar classifications on inadequate evidence in humans but sufficient evidence in rodent studies.[6,8] In 1990s, the endocrine disrupting effects of PCP were reported.[9,10] Research suggested that PCP might interfere with thyroid hormones, which play important roles in the growth and development of fetuses.[9,11,12]

Because of the possible adverse effects of PCP on humans, many countries have restricted or banned the production and use of PCP. For example, in 1978, Sweden did so at the outset of the progress for global PCP control.[13] Use of PCP was restricted or banned in Indonesia (1981), Belize (1985), Switzerland (1988), Germany (1989), Austria (1991), India (1991), New Zealand (1991), and the whole of Europe (1992).[1,2,5,13] In the U.S., PCP has been restricted to use as a wood preservative in specified outdoor applications since 1984; China did the same in 1997.[2,5,6]

After these restrictive measures, the production and consumption of PCP and its salts and esters decreased rapidly around the globe. In Europe, consumption of PCP dramatically decreased from 2500 tons in the mid-1980s to 426 tons in 1996.[5] But in some countries (e.g., France and Spain), PCP is still being used. In China, with the re-emergence of schistosomiasis in the traditionally epidemic areas,[14] the production and use of PCP for snail elimination and schistosomiasis control

Received: December 28, 2010
Accepted: April 22, 2011
Revised: April 19, 2011
Published: April 29, 2011

Table 1. Trends and Variations in Pentachlorophenol Levels in Different Environmental Media and in Human, by Region, and Sample Type

			regression function						
	sample type	region/country	rate (β)	S.E. [a]	p value	sample size [b]	R^2	average annual decrease (%)[c]	decreasing half-life (yr)[c]
air	indoor air	Globe	−0.154	0.013	<0.001	14(5)	0.92	30(26−34)	2.0(1.7−2.3)
	outdoor air		−0.051[d]	0.069	0.477	13(3)	0.07	--[e]	--[e]
water	all	globe	−0.029	0.011	0.007	83(23)	0.09	6(2−11)	10.4(6.0−37.6)
	known contaminated water	western countries	0.053[d,f]	0.124	0.686	7(4)	0.04	--[e]	--[e]
	fresh water		−0.051	0.013	0.001	28(7)	0.38	11(6−16)	5.9(3.9−12.2)
	marine		−0.094	0.026	0.004	13(3)	0.54	19(8−29)	3.2(2.0−8.4)
	surface water	China	0.039[f]	0.016	0.018	35(11)	0.16	9(2−17)[d]	7.7(4.3−43.0)[d]
sediment	all	Globe	−0.043[d]	0.022	0.054	42(17)	0.09	--[e]	--[e]
	fresh water sediment	western countries	−0.110	0.033	0.006	13(3)	0.48	22(8−34)	2.7(1.7−7.8)
	marine sediment		−0.027[d]	0.175	0.886	6(5)	0.01	--[e]	--[e]
	fresh water sediment	China	0.024[d,f]	0.032	0.460	23(11)	0.03	--[e]	--[e]
aquatic organism	all	Globe	−0.027	0.011	0.024	33(6)	0.15	6(1−11)	11.1(6.0−79.5)
	invertebrates		−0.035	0.014	0.026	15(4)	0.33	8(1−14)	8.6(4.6−60.2)
	fresh water vertebrates		−0.067	0.030	0.048	12(3)	0.34	14(0.2−26)	4.5(2.3−346)
	marine vertebrates		0.062[d,f]	0.024	0.061	6(3)	0.63	--[e]	--[e]
human	blood	Globe	−0.084	0.006	<0.001	54(22)	0.78	18(15−20)	3.6(3.1−4.2)
		North America	−0.131	0.019	<0.001	15(7)	0.80	26(19−33)	2.3(1.7−3.4)
		Germany	−0.095	0.008	<0.001	9(3)	0.96	20(16−23)	3.2(2.6−4.0)
		Other EUR countries	−0.077	0.009	<0.001	21(9)	0.79	16(12−20)	3.9(3.1−5.2)
		China	0.068[d,f]	0.059	0.313	7(2)	0.25	--[e]	--[e]
	urine	Globe	−0.053	0.006	<0.001	57(25)	0.62	11(9−14)	5.7(4.6−7.6)
		U.S.	−0.037	0.007	<0.001	26(13)	0.52	8(5−11)	8.1(5.8−13.7)
		Germany	−0.088	0.008	<0.001	12(3)	0.93	18(15−22)	3.4(2.8−4.4)
	lipid	Globe	−0.067	0.030	0.039	18(12)	0.25	14(9−26)	4.5(2.3−77.2)
		Sweden	−0.130	0.016	0.004	5(2)	0.96	26(17−34)	2.3(1.7−3.8)

[a] SE, standard error of estimated β value. [b] Sample size represents numbers of data used in the regression analysis. Values in the bracket indicate numbers of studies included. [c] Values in the bracket indicate 95% CI. [d] $p \geq 0.05$ for the null hypothesis that $\beta = 0$; all others, $p < 0.05$. [e] No statistic significant values were shown. [f] The positive β value indicates average annual increase and half-life of increase.

were warranted once again, and the annual output reached about 3000 tons in 2000.[15]

The criteria and standards for PCP exposure have been established. Both in the second and third edition (1993 and 2003) of the *Guidelines for Drinking Water Quality* (WHO), the provisional guideline value of PCP in drinking water was 9 μg/L.[16] The U.S. EPA's Maximum Contaminant Level (MCL) and Maximum Contaminant Level Goal (MCLG) for PCP in drinking water was 1 μg/L and zero,[6] respectively. The state of California in the U.S. even set the Drinking Water Public Health Goal level of PCP at 0.4 μg/L in 1997.[6] But the *Standards for Drinking Water Quality* in China (2006) still adopted 9 μg/L as the limit value of PCP, as recommended by the WHO.[16]

Although these standards have played an important role in protecting human health, they do not apply to other environmental media such as air and sediment. These reference values were based on PCP's carcinogenic effects,[6,16] but endocrine disrupting effects (e.g., thyroid disrupting effects) of PCP and environmental exposures to PCP were not taken into account.

To evaluate the variation of PCP levels and time-lapsed exposure to PCP throughout the world, we analyzed worldwide trends in PCP levels in different environmental media and in human samples. We also examined the region and sample type variability and the distribution of PCP body burden in specific populations.[17] Finally, we assessed the efficiency, reliability, and accuracy of the linear regression model used for trends analysis and PCP levels estimation.

METHODS

1. Literature Search Strategies. We searched databases including Pubmed, Medline, Web of Knowledge, ACS, and Springer for studies published between January 1, 1967, and October 1, 2010, regarding PCP in the environment or in humans. In our search, keywords were "PCP" (or "pentachlorophenol") combined with environment, water, sediment, air, human, blood, urine, lipid, detection, and so on. Additional publications were retrieved from the literature reference list. Some early studies and those published in other languages (e.g., Japanese and German) were acquired from EHC 71 [4] and from the review paper by House et al.[5]

Study inclusion criteria for our meta-analysis were as follows: 1) studies that were designed to evaluate the environmental exposure of PCP instead of occupational exposures and 2) studies that provided explicit averages or ranges of PCP levels.

Our research resulted in 80 studies being included in our meta-analysis.

2. Data Synthesis. Different units in different studies were transformed into the same type of unit for analysis purpose.[18−20]

Information on the year of data collection for each study was estimated based on the following: (1) such information being reported in the paper; (2) the midpoint of the data collection, if the paper only provided the interval (≥2 years) of sampling time; and (3) the year of the publication, if there was no information on the sampling year.[18,21−23] PCP banning or restriction dates in different countries were also collected.

Because of the log-normal distribution of the environmental concentration data,[18] geometric means were preferred as measures of central tendency. If a paper did not provide geometric mean (GM), then the median or arithmetic mean (AM) was collected.[18] For studies that only provided the concentration range, we used the medians to indicate the means.

3. Regression Analysis. In total, we fitted 25 linear regression models for PCP trends and diversities in various environmental media and humans in different regions.

Weighted least-squares models[24] were used to estimate the linear regression function of PCP levels (using the logarithm of the mean concentration: GM, AM, or median) on the date of the samples. When available, the sample sizes were used as weight; otherwise, an unweighted least-squares method was used.[24] To identify the change of PCP in environment and human samples, the half-life was calculated according to the formula of half-life = log 2 ÷ slope of the regression on log concentration. Analysis of covariance was used to compare mean PCP levels between different demographic subgroups in the population.

4. Regression Diagnosis. To determine whether the established regression function adequately fit the data, an *F* test was used if repeating observations at one or more X levels existed. The Brown-Forsythe test and the Breusch-Pagan test were employed to ascertain whether the error terms of the regression models had a constant variance. Graphical methods were used to analyze the linearity of regression function and constancy as well as the normality of error terms of the regression models.[24] The leverage-versus-residual-squared plot and Cooks' distance plot were graphed to identify outliers and analyze concerned and influential cases.[24]

5. Population Reference Levels Estimation. For PCP levels in human (blood and urine) samples, the reference levels of global populations and the time point when PCP levels dropped to human biological monitoring values (HBM values) were also calculated. Reference values represented the upper margin (usually the 90th or 95th percentiles of the concentration values determined from studies) of the current background exposure of the general population to a given environmental toxin at a given time. If possible, the 95% confidence interval of these percentile values was calculated, and a reference value was calculated within this interval. HBM values were derived from toxicological and epidemiological studies and may indicate health-related biological exposure limits.[1,25,26] Both HBMI and HBMII represented the concentrations of an environmental toxin in human biological material. The former represented an altered value; the latter, an action level.[26]

All of the statistical analysis was conducted using STATA version 10.0.[27]

RESULTS

The overview of PCP levels in different environmental media and human samples, including regional and sample type diversities, is listed in Table 1. Detailed information including location, study year, exposure type, sample size, and PCP conditions from each study is provided in Supplemental Tables (Tables SI 1−9).

1. Air. Table SI-1 shows the PCP concentrations in air samples, grouped by air type (indoor air, outdoor air, and air in occupational settings) and sorted by year.

Trends/Air Type Disparities. PCP concentrations in indoor air have decreased rapidly, and the weighted regression function formula was log (PCP) = 4.15−0.15 yr., with a R^2 of 0.92 (Table 1, Figure 1a). The 95% confidence interval (CI) for the slope ranged between −0.18 and −0.13 log PCP/yr., translating into a 26% to 34% per year reduction in logarithm of average PCP in indoor air ($1-10^{[slope]}$). Another way to look at this decline was to calculate a half-life, for which the slope gives an estimated population half-life of 2.0 yrs. (95% CI: 1.7 yrs.-2.3 yrs.). Among all media, the decline of PCP levels in indoor air was fastest (Table 1). This may be related to restriction in the use of PCP as an indoor wood preservative in western countries. It is noteworthy that PCP levels in outdoor air demonstrated no significant decreasing trend (R^2 = 0.07, p = 0.477, Table 1), suggesting that there were no obvious changes in PCP levels during the last three decades. Despite the decreasing trend, in various periods indoor air had a higher GM of PCP levels than outdoor air (Figure 1a).

2. Aquatic Environments. *2.1. Water.* PCP data in different water samples are summarized in Table SI-2 and Table SI-3. Water samples collected from known contaminated areas (within, near, and around factories or sawmills) or downstream from bodies of water receiving discharges from these sources were classified as "known contaminated water". The other samples were labeled as "reference water (unknown contamination)," including freshwater and marine water samples.

Trends/Water Type Disparities. These data showed a clear decrease in PCP concentrations in both "contaminated water" and "reference water" in western countries. The freshwater samples had a somewhat slower decreasing rate than the marine samples (half-life of 5.9 yrs., p = 0.001 vs 3.2 yrs., p = 0.004, Table 1). PCP concentrations from the "contaminated water" samples were obviously higher than the other samples in the U.S. This suggested that before 1984, the year the U.S. government began to restrict the production and use of PCP, its levels in American contaminated water were much higher than in other countries' freshwater and marine because of the severe industrial drainage from PCP-applying factories.

Regional Disparities. Compared to western countries in various periods, water samples from China between 1986 and 1998 had lower PCP levels than known contaminated water in the U.S. and reference water in North America and Europe during 1980s (Table SI-2). Except for the outliers, in the 1990s, China and European countries had similar PCP levels in water (Table SI-3). Compared to the decreasing PCP levels in other countries, China had a slightly increasing trend in PCP contamination in water from the 1990s to the 2000s (GM: 0.05 μg/L vs 0.16 μg/L; p = 0.018, R^2 = 0.16; Table 1).

2.2. Sediments. Sediment samples collected from rivers, lakes, and marine environments were reported in western countries and China (Table SI-4, Table SI-5). We tested the time trends in PCP levels in freshwater, marine environments, and Chinese water using linear regression models (Table 1).

Trends/Sediment Type Disparities. The limited available data indicated a decrease (p = 0.006, R^2 = 0.48) in PCP levels in freshwater sediment, with a half-life of 2.7 yrs. (Table 1,

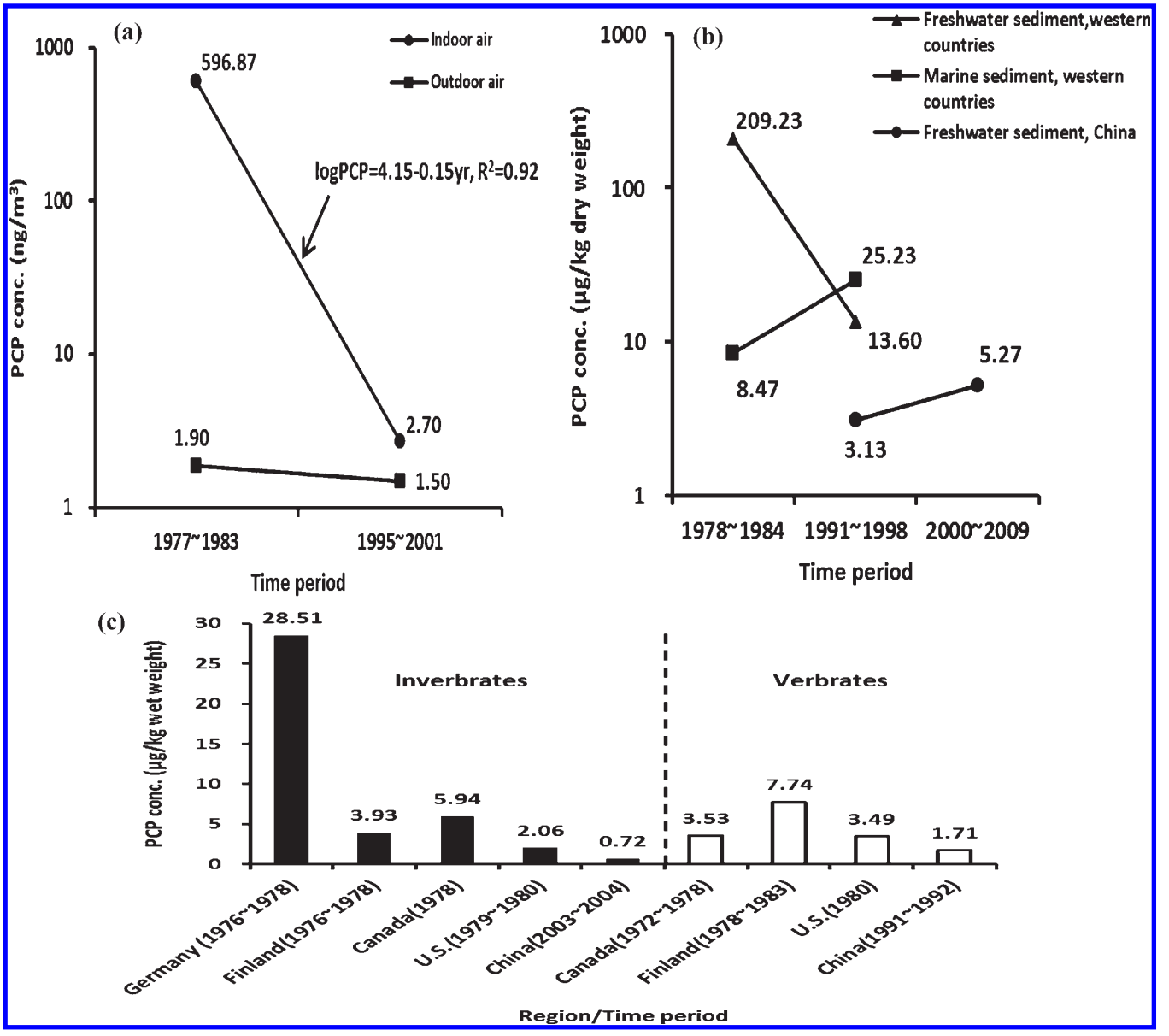


Figure 1. Trends and diversities of PCP levels in different environmental media including air, sediment, and aquatic organism. a. Trends of PCP levels in air (ng/m^3) of western countries, by sample type, see Table SI-1. The bottom line with square symbols represents outdoor air samples. The top line with circle symbos is for indoor air samples; and the trend is shown as a regression function of the year in which the samples were taken, see Table SI-1. b. Trends of PCP levels in sediments (μg/kg dry weight), by sample type; see Table SI-4 and Table SI-5. The bottom line with circle symbols represents freshwater sediment samples from China; the median line with square symbols is for marine sediment samples from western countries; and the top line with triangle symbols is for freshwater sediment samples from western countries. c. PCP levels in aquatic organisms (μg/kg dry weight), by region and sample type; see Table SI-6. The shaded and open bars represent PCP average levels in inverbrates and verbrates, respectively.

Figure 1b). Of interest, PCP levels had been increasing in sediment samples from marine environments (Figure 1b), although it was not statistically significant (p = 0.886, Table 1). Before 1990, PCP levels in freshwater sediments were higher than in marine sediments (GM: 209.23 μg/kg vs 8.47 μg/kg), while the situation has reversed since 1990 (GM: 13.60 μg/kg vs 25.23 μg/kg).

Regional Disparities. In China, compared to the generally decreasing trend in PCP levels in freshwater sediments during 1990s, the PCP levels in freshwater sediments during 2000s indicated a rising trend (Figure 1c, 3.13 μg/kg during 1990s vs 5.27 μg/kg during 2000s; p = 0.460, Table 1). However, Chinese samples were all below the line of marine sediment samples, mostly those from Netherlands, suggesting that PCP levels may be lower in Chinese freshwater sediments than in North European marine environments (Table SI-4, Table SI-5).

2.3. Aquatic Organisms. Analysis for PCP levels in aquatic organisms was based on the data from the studies shown in Table SI-6. The data were classified as invertebrate samples and vertebrate samples (mostly fish), and the concentrations were summarized by sampling years.

Trends/Organism Type Disparities. There was no statistically significant difference of PCP levels between invertebrates and vertebrates (GM [95% CI]: 2.98 μg/kg [1.24−7.16] vs

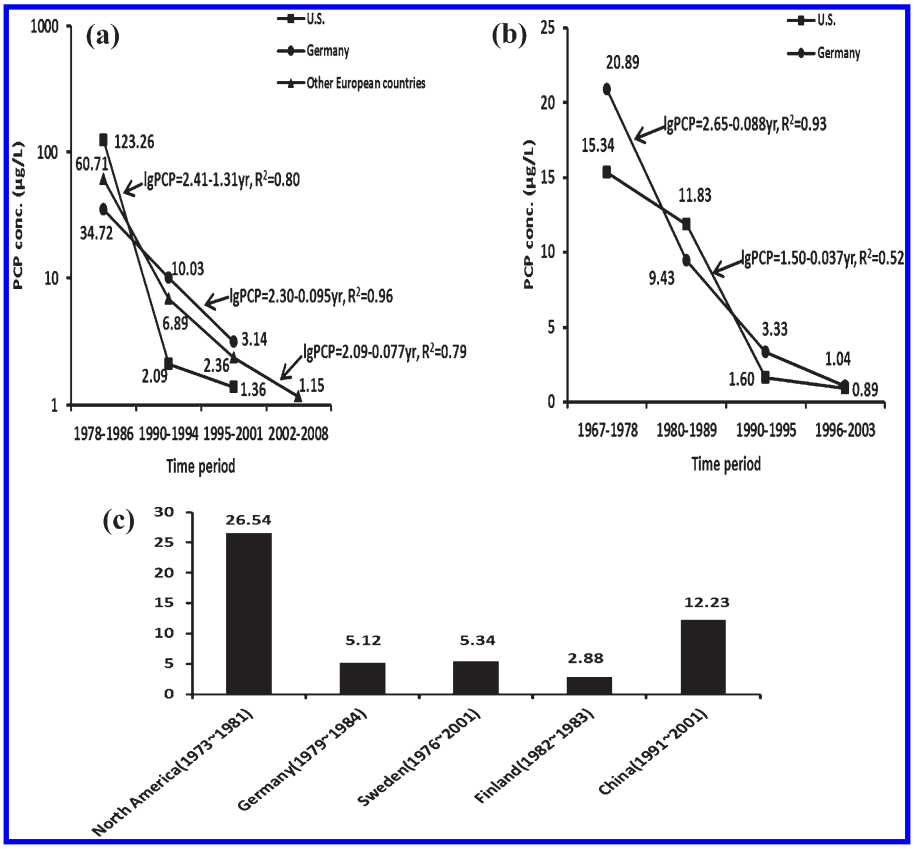


Figure 2. Trends and diversities of PCP levels in different human samples including blood, urine, and lipid. a. Trends of PCP levels in human blood (μg/L) shown as a function of the year in which the samples were taken, by region, see Table SI-7. The line with square symbols represents samples from U.S.; the line with circle symbols is for samples from Germany; and the line with triangle symbols is for samples from other European countries. The regressions for the three data sets are shown separately. b. Trends of PCP levels in human urine (μg/L) shown as a function of the year in which the samples were taken, by region, see Table SI-8. The line with square symbols represents samples from U.S.; and the line with circle symbols is for samples from Germany. The regressions for the two data sets are shown separately. c. PCP levels in human lipid (μg/kg), by region; see Table SI-9. The shaded bars represent PCP average levels in samples from different regions during various periods.

4.24 μg/kg [2.26−7.97]). Invertebrates showed a declining trend in PCP levels with a half-life of 8.6 yrs. (p = 0.026, R^2 = 0.38; Table 1). However, PCP concentrations in freshwater vertebrates and in marine vertebrates had different time trends (Table 1). PCP levels in freshwater vertebrates declined with a half-life of 4.5 yrs. (p = 0.048, R^2 = 0.34), while those in marine vertebrates in a similar period demonstrated a weak increasing trend (p = 0.061, R^2 = 0.63).

Regional Disparities. Figure 1c and Table SI-6 showed considerable regional differences. Germany had the highest GM of PCP levels (28.51 μg/kg) in invertebrates in the 1970s, while China had the lowest PCP levels in 1991−2004 (0.72 μg/kg). Both in vertebrate and invertebrate samples, Finland, Canada, and the U.S. had similar PCP levels (about 2−8 μg/kg) during 1976−1983.

3. Humans. *3.1. Human Blood.* PCP concentrations in ambient human blood (serum, plasma, whole blood) are shown in Table SI-7, with data sorted by sample years. In this analysis, "ambient" means samples from people who were not known to have been occupationally exposed.[19]

Trends/Regional Differences. An exponential decrease of PCP levels in human blood was observed from 1978 to 2008, with the population half-life of 3.6 yrs. (p < 0.001, R^2 = 0.78; Table 1).

The decreasing trends in PCP levels in human blood demonstrated regional differences (Figure 2a). In the 1980s, North America showed the highest PCP body burden (GM, 123.26 μg/L). With the restriction and ban of PCP use, this region experienced a sharp decline in PCP blood levels, with a half-life of 2.3 yrs. Germany and other European countries had a similar decline, with half-lives of 3.2 yrs. and 3.9 yrs., respectively, which were similar to the global trend. After 1995, populations in North America and Europe had similar PCP body burdens. The mean PCP blood levels decreased to 1.15−3.14 μg/L, significantly lower than those in the 1980s (Figure 2a).

Gender/Age/Population Disparities. Cline et al. (1989) reported no statistically significant gender difference in PCP levels from serum samples of normal populations (p = 0.88) and residents in PCP-treated homes (p = 0.67) (U.S. 1980−1986).[28] Sandau et al. (2000) measured PCP and other contaminants in whole blood from Canadian Inuit with the exposure route of sea mammal consumption and found that women had significantly lower geometric mean levels of PCP than men.[29] Serum PCP levels may decrease with age, with the 2−7-year age group having higher levels of PCP than the over-15-year age group (p = 0.019).[29] Data from PCP-treated homes containing both children and adults suggested that children of all ages had a serum level of PCP double that of their parents. In Germany, in 1998, monitoring data from a population with neither occupational contact nor indoor exposure also showed higher plasma PCP levels in children than in adults.[1]

Reference Levels/HBM Values. The worldwide intervals for reference levels calculated from mean PCP levels in blood samples were as follows: 234−1126 μg/L (1978−1986), 9.8−171 μg/L (1990−1994), 2.1−4.1 μg/L (1995−2001), 1.1−6.3 μg/L (2002−2008). In 1982 and 1985, the mean concentrations of PCP in blood declined to 70 μg/L (HBMIIvalue) and 40 μg/L (HBMIvalue), respectively. As the PCP blood levels in the North America population had the fastest declining trend, the mean PCP blood levels there dropped to HBM values before 1980. In Europe, the PCP blood levels declined to HBM values during 1981−1984.

3.2. Human Urine. Table SI-8 focused on PCP levels in human excrement (mostly urine).

Trends/Regional Disparities. Similar to the concentrations in human blood, levels of PCP in ambient urine of the global population showed an exponential decrease, with a half-life of 5.7 yrs. ($p < 0.001$, $R^2 = 0.62$; Table 1), suggesting that the decline of PCP levels in human urine might be slower than the decline in human blood. Figure 2 b indicated that PCP levels in urine had a different rate of decline in Germany (3.4 yrs.) and the U.S. (8.1 yrs.).

Reference Levels/HBM Values. The worldwide intervals for reference levels calculated from mean PCP levels in blood samples were as follows: 39.20−90 μg/L (1967−1979), 25.16−84 μg/L (1980−1989), 2.08−51 μg/L (1990−1995), and 2.50−7 μg/L (1995−2003).

The two special time points relevant to the 40 μg/L (HBM II) and 25 μg/L (HBM I) values for the global population were 1972 and 1976, respectively. These dates were both earlier than the corresponding dates for the blood samples. In Germany, the two time points were 1978 and 1981; but in the U.S., they were 1965 and 1970, earlier than the dates in Germany.

Gender/Age Disparities. The mean PCP level in adult urine samples was higher than children's, for both sexes. Male urine samples had higher PCP concentrations than female samples; however, there were no significant differences (data were not shown).

3.3. Human Lipid. Table SI-9 lists studies about PCP levels in human lipid sorted by years.

Trends. Table 1 suggests a weak decreasing trend in PCP levels in lipid samples in the global population ($p = 0.039$, $R^2 = 0.25$). However, PCP lipid levels of Sweden's population demonstrated a significant decreasing trend ($p = 0.004$, $R^2 = 0.96$), with an estimated population half-life of 2.3 yrs. (95% CI: 1.7 yrs.- 3.8 yrs).

Regional Disparities. Figure 2 c shows the GM of PCP levels in lipid samples from different regions during various periods. In the 1970s and 1980s, North America had the highest PCP lipid levels (GM = 26.54 μg/kg), which was much higher than those in Germany (GM = 5.12 μg/kg) and Finland (GM = 2.88 μg/kg). The GM for Sweden during 1976−2001 was only 5.34 μg/kg, reduced 80% compared to the 1970s and 1980s (21.7 μg/kg), which was similar to that of North America during the same period.

Sample Type Disparities. The GM of PCP levels in breast milk and adipose samples were 14.39 μg/kg and 11.03 μg/kg, respectively, with no significant difference ($p = 0.465$).

Gender/Age Disparities. Williams et al. (1984) found no significant gender differences in PCP lipid levels.[30] Mussalo-Rauhamma (1989) also reported that PCP residues in human lipid samples did not correlate with gender or age ($p > 0.05$).[31]

DISCUSSION

With the global restrictions and bans of PCP production and use since the 1980s, PCP concentrations had declined in human blood and urine samples, and in water, freshwater sediment, indoor air, invertebrates, and freshwater vertebrates, as measured by their respective half-lives. However, our study with regression analysis demonstrated that PCP levels presented potentially increasing trends in some environmental media and regions, based on data from recent studies. The results from linear regression analysis provided an easy, effective, and reliable estimation for the trends and variation of PCP levels in various environmental media and humans in different regions.

1. Relationship between Low Environmental Exposure and Health Risk. In this decade, the human burden of PCP has been decreasing to low levels along with declining trends in PCP levels in the environmental media. The intervals for global population blood reference values were 1.1−6.3 μg/L (2002−2008), and for urine reference values were 2.50−7 μg/L (1995−2003). Early in the 1970s and 1980s, PCP levels in human urine and blood had decreased to their HBM values. Therefore, cancer risk related to long-term exposure to high levels of PCP in specific sites had been reduced due to the global restriction or ban of the productions and use of PCP.

However, some investigations suggest that exposure to low levels of PCP in the environment could cause a decrease in thyroid hormone levels and may have adverse effects on motor, cognitive, and behavioral outcomes in children.[32,33] The negative association between maternal plasma PCP levels (mean, 0.93 μg/kg; range, 0.77−1.12 μg/kg) and cord free thyroxine (fT_4) concentrations in neonates ($p = 0.02$) was reported.[32] Sandau et al. (2002) revealed that PCP concentrations (range, 0.63−7.68 μg/kg) in cord plasma of neonates from coastal populations in Canada were inversely correlated with iodothyronine (T_3) ($p = 0.01$), thyroxine-binding globulin (TGB), and fT_4 levels.[33] Roze et al. (2009) reported that PCP in children's blood serum (range, 0.30−8.53 μg/kg) was correlated with worse outcomes such as coordination ($p = 0.004$), sensory integrity ($p = 0.03$), attention ($p = 0.02$), and visuomotor integration ($p = 0.04$).[34]

The population data on the relationship between low environmental PCP exposure and thyroid-disrupting effects and other health risks were limited. The differences in the population sampled make it important to take care when extrapolating the results to the global population. However, the health risks induced by low environmental PCP exposure of global populations was not negligible. In particular, the potential impacts of PCP exposure on children's growth and development give rise to concerns and require further studies.

2. Potentially Increasing Trends in Some Media and Regions. Notably, PCP levels in marine sediments, Chinese surface water and sediments and marine vertebrates demonstrated potentially and slightly increasing trends. The observed increased PCP levels in China were consistent with the rising trends in Na-PCP consumption in those areas due to the re-emergence of schistosomiasis.[35] As indicated by the limited data on PCP levels in marine sediment and vertebrates during recent decades, the trends in PCP levels in these environmental media warrant further study.

3. Diagnosis of Regression Function. Table SI-10 shows the statistical test results of regression diagnosis to judge whether the error terms of constant variance and a linear regression function are a good fit for the data. For the Breusch-Pagan test, only the

regression function of PCP concentration in human blood in Germany shows a statistical difference (p = 0.031). For the Brown-Forsythe test, the regression models of PCP levels in human blood in North America (p = 0.018), indoor and outdoor air (p < 0.01) show significant statistical differences. Based on both test results, the error variances for most of the regression models established in this study are constant. Except for the regression function of PCP concentration in human blood in European countries without Germany (p = 0.037) and in freshwater vertebrates (p = 0.035), all models show no significant statistical difference so that they are linear, and there is not any evidence of lack of fit according to the F-test for lack of fit.

Figure SI-1 displays some typical examples of different kinds of graphic diagnosis results for error terms, outliers, and influential cases. Studentized residual plots against *Year* show that most regression functions are appropriate and the error variances are constant (Figure SI-1a), which corresponds to the statistical test results. For normal probability plots of residuals, though many plots have one outlier, the remaining points are not far from the linear and show no evidence of trend (Figure SI-1b). No strong indications of substantial departures from normality are indicated by these plots.

For outliers, leverage-versus-residual-squared plots in Figure SI-1c show the average values of leverage and the (normalized) residuals squared. Points above the horizontal line have higher-than-average leverage, while points to the right of the vertical line have larger-than-average residuals. Cook's distance measure can also identify outliers and ascertain whether or not these outlying cases are influential (Figure SI-1d).

These graphic results indicate that the established regression functions are apt to the data acquired from different studies and that the inferences based on those regression models are reliable.

4. Assessment of Regression Model for Trends Analysis. Linear regression is widely used as the method to examine time trends in many studies[18,19] including this one. Since the data from different studies typically follow a geometric distribution, the linear regression line can be acquired after a logarithmic transformation. In this study, some regression functions have high R^2; however, the slopes are not significantly different from zero (Table 1). Therefore, other assistant analytical or qualitative methods were used in this quantitative meta-analysis, including symbol-line plot, box plot (data not shown), and comparison of average PCP concentrations among different regions, sample types and periods and so on. These methods can help reveal the true trends. Our study also found that the goodness of fit of the regression function for human samples was obviously higher than that for environmental media. And the trends in PCP levels in human samples were more significantly apparent than those of environmental media. This indicates that the regression analysis method, based on the integration of data from literature, has much higher validity and reliability for estimating trends in PCP levels in humans than in environmental media.

Linear functions were fitted because of their simple, clear, and intuitive characteristics. Carlsen et al. used this method to reach an important conclusion about "the decreasing quality of semen during the past 50 years"[21] and raised wide concerns about environmental quality and health. Although some studies have debated the feasibility of the linear model,[22,23] similar conclusions about the trend in semen quality were obtained using nonlinear models. As the curvilinear function is more complicated and difficult to explain than the linear function, linear functions are used in this study.

Since the data used in this meta-analysis have involved different countries, races, ages, and sexes, it is very important to determine whether the data from different studies are homogeneous, whether samples in various locations are from identical populations, and whether the data can be fitted by the linear regression model. The gender and age disparity analysis revealed that there were no significant differences of PCP levels in human samples from population with different ages and sexes. As disparities exist in the region and sample types, the regression analysis for the overall data may cover or distort the real trends and diversities of PCP levels. We analyzed various disparities among different regions and types of environmental samples and used separate regression functions for them, to minimize and even remove bias from these disparities.

CONCLUSIONS

Findings from our meta-analysis will help scientists and governments better understand the trends and variations in global PCP levels based on the 80 studies from 21 countries published between January 1, 1967, and October 1, 2010. We found that PCP levels in water, in freshwater sediments, and in humans have declined globally since the 1970s. Although the global population reference values of PCP body burden have decreased to low environmental levels thanks to restrictions and bans on PCP production and use, there are still possible thyroid disrupting effects, adverse effects on motor, cognitive, and behavioral outcomes and other health risks correlated to PCP exposure even at lower levels. In some countries, such as China, PCP levels may be increasing in some environmental media due to the re-emergence of schistosomiasis.[35]

Linear regression models can provide easy, effective, and reliable estimations of the trends and variations in PCP levels in various environmental media and humans in different regions based on data from literature reviews, although firmer projections for the future can be affected by many uncertainties.

By helping to ascertain the effects of the restriction and banning of PCP, our study may assist in guiding the future control of this possibly carcinogenic and endocrine-disrupting compound and pave the way for future health effect analysis.

ASSOCIATED CONTENT

Supporting Information. Details of data of PCP levels in various environmental media and in human from the literature collected (Table SI-1-Table SI-9). The statistic test results of regression diagnosis for the representative regression functions are listed in Table SI-10, and some typical examples of different kinds of graphic diagnosis results are shown in Figure SI-1. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

Competing Interests: The authors declare they have no competing financial interests.

■ ACKNOWLEDGMENT

This project was supported by National Key Technology R&D Program in the 11th Five Year Plan (No. 2006BAI19B02 & 2008ZX07421-004), Discipline Pioneer Plan for Bureau of Health in Shanghai (08GWD) and "Dawn" Scholar Plan in Shanghai (07SG01), National Natural Science Foundation of China (30972438&30771770), and 863 Key Project of National High-tech R&D Program of China (2008AA062501).

The authors gratefully appreciated Professor Suihen Lyn (Department of Biostatics of Fudan University) for his crucial reviewer and association in statistics.

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