Exposure to Polychlorinated Biphenyls and Levels of Thyroid Hormones in Children

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As part of an epidemiologic study on exposure to a toxic waste incineration plant we investigated whether blood concentrations of polychlorinated biphenyls (PCBs), lead, and cadmium, as well as concentration of mercury in 24-hr urine samples were associated with thyroid hormone status. As an indication of status, we determined levels of thyroid-stimulating hormone (TSH), free thyroxine (FT_4), and free triiodothyronine (FT_3) in children living in households where ≤ 10 cigarettes were smoked per day. Eight PCB congeners (PCBs 101, 118, 138, 153, 170, 180, 183, and 187) were measured in whole blood samples. Of these, seven congeners (PCB 101 was not detected in any sample) and the sum of all PCB congeners were analyzed as predictors for thyroid hormone status in separate linear regression models adjusted for potential confounders. In addition, the possible effects of cadmium, lead, and mercury on levels of thyroid hormones were examined. Blood concentrations and information on questionnaire data were available for 320 children 7–10 years of age. We found a statistically significant positive association between the mono-*ortho* congener PCB 118 and TSH as well as statistically significant negative relationships of PCBs 138, 153, 180, 183, and 187 to FT_3. There was no association for the PCB congeners and FT_4. Blood cadmium concentration was associated with increasing TSH and diminishing FT_4. Blood lead and urine concentration of mercury were of no importance to thyroid hormone levels. The results stress the need for future studies on the possible influences of PCB and cadmium exposure on thyroid hormones, particularly in children. These studies should also take neurologic development into account. *Key words*: cadmium, children, lead, mercury, PCB, thyroid, thyroxine, triiodothyronine, TSH, waste incinerator. *Environ Health Perspect* 107:843–849 (1999). [Online 13 September 1999]
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As part of an environmental epidemiologic study on potential exposure to a toxic waste incinerator (TWI) in the south of the Federal State of Hessen, Germany, we tested the hypothesis that blood concentrations of polychlorinated biphenyls (PCBs) are predictors of thyroid hormone status in elementary schoolchildren.

The first survey in 1994–1995 consisted of questionnaires for the parents and a medical check-up of the children, including measurements of height and weight. We performed phlebotomy and serum biochemistry, along with the measurement of thyroid hormones, cadmium, and lead in whole blood, and we collected 24-hr urine samples to assess the excretion of mercury.

Thyroid hormones are necessary for the development of brain function and cell growth; because of this, appropriate levels of peripheral thyroxine and triiodothyronine (T_3) are especially important in childhood. Deficiency of thyroid hormones can subsequently result in a serious delay in neurologic development (*1–3*).

Exposure to PCBs is suspected of altering the pituitary thyroid feedback regulation through various mechanisms. Evidence could be drawn from animal and human studies on effects of planar and nonplanar PCBs that frequently show a decrease in peripheral thyroxine, whereas thyroid-stimulating hormone (TSH) might be increased. One mechanism is hepatic microsomal induction of uridine diphosphate glucoronyl transferase (UDPGT) (*4*), possibly because of a similar molecular structure of planar and mono-*ortho* substituted PCB congeners to that of the thyroxine molecule (*5*). The induction is mediated by the nuclear aryl hydrocarbon receptor (AhR), to which only planar and coplanar PCBs have an affinity. Thus, enhanced metabolism of thyroxine (T_4) by glucoronidation could lead to reduced peripheral T_4 half-life and increased biliary excretion (*4*). Compensatory TSH secretion can follow depletion of peripheral T_4 levels unless enhanced deiodinase activity in brain results in normally local T_3 concentration (*6*).

PCB could also possibly block type I monodeiodinases. It is estimated that up to 80% of circulating T_3 results from tissue conversion of T_4 to T_3; subsequently, inhibition by PCB would lead to lower peripheral T_3 levels and to increased TSH secretion if it is not compensated for by T_4 *de novo* biosynthesis (*4*).

Disruption of thyroid hormone status can also result from competitive binding to specific transport proteins, such as transthyretin in rats and mice (*7,8*). In humans, thyroxine-binding globulin (TBG) is the main peripheral transport protein. Experimental findings show that some hydroxylated PCB congeners are not capable of displacing T_4 from TBG or if substituted in the *ortho* position only at high concentrations (*9,10*). Transthyretin (TTR) was thought to be the principal protein for thyroxine transport to the human brain, but recent observations indicate that blockage of T_4 binding to TTR or deletion of the TTR gene in mice were related to unchanged activity of deiodinase and normal levels of T_4 in plasma and brain (*11*). The significance of possible binding of hydroxylated PCB metabolites or parent PCBs to the TTR in humans remains to be elucidated.

Recently, binding to recombinant human thyroid receptor β (hTRβ) has been investigated *in vitro* by Cheek et al. (*10*). Only negligible affinity was detected for hydroxylated PCB congeners with hTRβ; therefore, little evidence is given for this mode of action.

There are also hints for direct action of nonplanar PCB on the feedback regulation that can enhance TSH release by stimulation of certain calcium channels in the pituitary or lead to a decrease in TSH secretion by inactivation of calcium channels (*12*).

The objective of this study is to analyze associations of levels of TSH, free thyroxine

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(FT_4), and free triiodothyronine (FT_3) to blood concentrations of seven PCB congeners as well as to the concentration of cadmium and lead in blood and the concentration of mercury in 24-hr urine. In human lipids and tissue, mainly higher chlorinated nonplanar PCB persist and accumulate. Consequently, congeners with a longer half-life were primarily analyzed in the blood samples.

The study region is situated around an industrial waste incinerator in the Rhine Valley approximately 30 km wide, with low mountains on both sides. The facility has a license to burn highly PCB-contaminated material. In 1990, new filters were installed in the the hazardous waste incinerator. Measurements in the flue gas of the TWI in 1992 could not detect coplanar PCBs and detected only small amounts of nonplanar PCBs (*13*). Other industries such as a chemical plant are near the incinerator. Several municipalities lie in the area that is environmentally affected by these industrial sites. The region is also heavily used for vegetable production.

The first comparison area is the Rhine Valley comparison (RVC) group. It is 20 km north of the incinerator and is also in an industrial/agricultural area. The second comparison group [Odenwald comparison (OWC) group] is located southeast of the incinerator region in an area of low mountains (approximately 400 m high).

In an initial analysis differences of thyroid hormone levels were tested with regard to the three regions (*14*). Statistically significantly reduced values for FT_3, and to a lesser extent FT_4 levels, were found in the area with the TWI.

Regional effects were controlled for putative differences in iodine intake by checking iodine excretion in 24-hr urine of the children. There were no regional differences among the three groups of children in the TSH values. However, adjusted blood concentrations of di-*ortho*-substituted congeners PCB 170 (95th percentile = 0.15 µg/L) and PCB 180 (95th percentile = 0.30 µg/L) as well as the dichotomized PCB 183 (not detected versus detected, 95th percentile = 0.04 µg/L) proved significantly higher in children who live in the TWI area as compared to the OWC group (*15*).

Methods

Study population. After obtaining permits from the Data Protection Agency of the State of Hamburg, Germany, from the Ministry of Cultural Affairs of Hessen, Germany, and from the local school committees, we approached 1,091 second-grade schoolchildren in 18 townships. Informed consent according to the requirements of the Ethical Committee of the Board of Physicians and the Data Protection Agency of the State of Hamburg were obtained from all participating parents.

Responses from a self-administered questionnaire were available for 671 children. Parents were asked if their child could participate in phlebotomy if passive smoking in the private household over the previous 12 months did not exceed 10 cigarettes/day.

Questionnaires. Three self-administered questionnaires were used in the survey: one on the living conditions and nutrition of the families; the second on occupational, demographic, and anamnestical data of the mother and father; and the third on the school situation and anamnestical data of the child. Fish consumption in the previous 12 months was assessed by questions on how often the child ate fat fish, low-fat fish, and fish from the River Rhine. For statistical analysis this information was dichotomized (two meals or more vs. none to one meal per month). Environmental tobacco smoke (ETS) was estimated first as smoking in the child's home in the previous 12 months (no cigarettes, 1–10 cigarettes, 11–20 cigarettes, or > 20 cigarettes/day). Parents were then interviewed regarding ETS exposure in general in the last 7 days preceding blood sampling (0 days, 1 to some days, or daily).

Collection of urine samples and determination of urinary mercury. During the physical examination one accompanying parent was instructed on how to collect 24-hr urine samples. We handed out a flyer and suggested collecting the urine on one weekend day. The urine samples were recollected at school, weighed, aliquoted, and frozen at -30°C. The aliquots were sent to the Institute of Toxicology, University of Kiel, Germany. For the assessment of mercury, 5-mL aliquots were processed with 0.5 mL 32% hydrochloric acid and 0.2 mL potassium bromide/potassium bromate (2 g KBr and 0.56 g $KBrO_3$ in 25 mL H_2O) and analyzed by atomic absorption spectroscopy (Perkin Elmer, Norwalk, CT). The detection limit of mercury was 0.15 µg/L.

Laboratory chemical analysis of blood samples. The vacutainer system was used for blood sampling, and approximately 25 mL blood was drawn. Serum was obtained by centrifugal fractionation and frozen at -20°C on the same day.

Serum levels of the peripheral thyroid hormones FT_4 and FT_3 as well as TSH were determined by standardized laboratory procedures (RIA and IRMA by Ciba Coming/ Chiron Diagnostics GmbH, Giessen, Germany). Coefficients of variation were calculated from three precision controls; values were 2% for TSH, 3.9% for FT_4, and 10.4% for FT_3. The analyses were performed in the Medical, Alimentary, and Veterinary Institute for Research Middle Hessen, Division of Human Medicine, Dillenburg, Germany.

From 5-mL whole blood samples we analyzed eight PCB congeners (PCBs 101, 118, 138, 153, 170, 180, 183, and 187) by high-resolution gas chromatography [HRGC; model 3400; Varian Company, Darmstadt, Germany) with a ^{63}Ni-electron-capture-detector and a detection limit of 0.02 µg/L for each congener (2-fold signal/low-noise ratio). For extraction and clean-up procedures, we used florisil and *n*-hexane [9 g florisil was deactivated with 3% H_2O and dichloromethane (80/20, v/v) in a chromatography column 22 mm in diameter and 48 mm in length for elution]. The capillary column was 30 m long and 0.25 mm in diameter and contained nitrogen as a carrier gas. The congeners were determined by retention times on the chromatograms. For identification authentic compounds were used. Additionally, reliability was tested with gas chromatography/mass spectrometry.

Cadmium and lead in whole blood samples were detected by flow injection atomic absorption spectroscopy (Perkin Elmer) after the addition of 0.1% Triton X-100-solution, 1.5 M nitric acid, and centrifugation at 3000*g*. The detection limits were 0.05 µg/L for cadmium and 9 µg/L for lead.

PCB and heavy metal analyses were performed at the Institute of Toxicology, University of Kiel, Kiel, Germany. From both laboratories certifications of successful participation in external quality assurance were available.

Statistical methods. Sample values of PCBs and heavy metals were substituted with one-half of the detection limit when they were below the detection limit.

Because the distributions of PCB congeners, cadmium, lead, and mercury were not normal, the geometric mean, median, 5th and 95th percentiles, minimum, and maximum were presented. TSH and FT_4 levels were Blom-transformed [$y_i = \Psi(r_i - 3/8)/(n + 1/4)$, with Ψ = inverse cumulative normal (Probit) function, r_i = rank, and n = number of nonmissing observations] before testing associations with possible predictors by multiple linear regression models (*16*). The distribution of the dependent variable achieves an arithmetic mean near zero and a standard deviation of ± 1. FT_3 was multivariate normally distributed without transformation after adjusting for confounding factors.

Each of the seven PCB congeners was analyzed as a predictor in separate linear regression models because all PCB congeners are highly correlated. Finally, the sum of PCBs 138, 153, and 180 and the sum of all measured congeners were used as exposure indicators, each in one model on TSH, FT_4, and FT_3.

Linear regression models were adjusted for potentially confounding factors, such as sex and age, because of differences in TSH values between boys (higher values) and girls (lower values) and because of supposed age-related changes. Exposure to ETS in the 7 days preceding phlebotomy and the consumption of fish during the previous 12 months were also controlled. Fish consumption primarily was used to control for iodine intake, whereas ETS was included because of its presumed influence on thyroid status and its association with at least some of the investigated toxic substances, e.g., cadmium. Additionally, to adjust for possible relationships of heavy metals on levels of thyroid hormones, the blood concentrations of cadmium and lead and 24-hr urine concentration of mercury were included in the models. Toxic metals were measured in the children's blood and urine to assess the exposure due to the incineration in the TWI area. Possible effects of cadmium were experimentally shown in rats and in environmentally exposed adults (*17,18*) and possible effects of mercury were shown in occupationally exposed adults (*19*).

The introduction of dummy variables indicating each one-third of the respective distribution checked the linear relationship of these metals. All values below detection limits are included in the lower third of the distribution (reference). The predictors of potentially confounding variables and of the three metals are, for the sake of brevity, only presented with the analysis of the sum of PCBs.

All statistical analyses were performed using the SAS/STAT program (*20*).

Results

The proportion of participation was 61.5% (n = 671). Twenty-four-hour urine samples were collected from 636 children; the codes and/or urine volume of nine containers could not be verified or were lost. Thus, 24-hr urine samples were available from 94.8% of the participating group. We obtained blood samples from 350 children, and complete serum and whole blood analyses could be conducted in 341 samples. Overall information (i.e., on the questionnaires) and 24-hr urine and blood samples were collected from 320 children and were statistically analyzed (TWI group n = 186, 58.1%; RVC group n = 58, 18.1%; OWC group n = 76, 23.8%).

The health status as indicated by the body mass index (BMI) varied in the normal range (BMI median 16.3 kg/m^2, range 12.6–29.8 kg/m^2). Girls had higher values than boys (BMI 95% values: girls = 23.4 kg/m^2; boys = 20.6 kg/m^2) and as compared to a British boy's cohort, the BMI of German children tended to be moderately higher (*21*). One child from the OWC group had a known goiter but was euthyreote. The parents of a few children reported the intake of additional iodine. Fewer girls than boys participated in phlebotomy (Table 1). Of those children, 96% were 7 or 8 years of age. More than one-third of the children ate fish more than twice a month. Almost 35% of all children as compared to 20% of the children with phlebotomy were exposed daily to ETS during the week preceding blood sampling. In the subgroup with phlebotomy, the prevalence of heavy cigarette smoke in the child's home was also lower than in the total group (Table 1).

Most children showed thyroid hormone levels that were within the clinical limits of TSH and FT_4 (Table 2) (*22*). For FT_3, 5.3% of children had values below the reference of 2 ng/L (TWI 7.7%, RVC 3.2%, OWC 1.2%). TSH values > 3.5 mU/L that indicate a hypothyreote function was seen in 2.5% of children (TWI 2.6%, RVC 4.8%, OWC 1.2%). Children whose thyroid hormones were outside the laboratory normal range resided more often in industrialized areas but did not exhibit a special contaminant pattern except of excessive TSH levels. They more likely have cadmium and mercury values above the respective medians.

Table 1. Descriptive characteristics of the children's cohort (potentially confounding factors).

Characteristics	All children[a] n	All children[a] %	Subgroup[b] n	Subgroup[b] %
Female	310	46.2	138	43.1
Age				
7 years	284	42.3	146	45.6
8 years	358	53.4	161	50.3
9–10 years	29	4.3	13	4.1
Fish consumption[c]	240	35.8	114	35.6
Passive smoking[d]				
No	273	56.9	172	53.8
One to some days	163	24.2	85	26.6
Daily	231	34.4	63	19.7
Passive smoking[e]				
None	346	51.6	217	67.8
1–10	155	23.1	78	24.4
11–20	95	14.2	18	5.6
> 20	67	10.0	7	2.2

[a]n = 671. [b]With phlebotomy; n = 320. [c]During the last 12 months; twice or more in a month. [d]In general; during the 7 days preceding phlebotomy. [e]In the child's home; during the last 12 months (cigarettes per day).

Table 2. Serum levels of thyroid hormones, TSH, FT_4, FT_3 in children[a] and geometric means and 95th percentiles of regional distribution.

Hormones	n	Median	Geometric mean	5% value	95% value	Minimum	Maximum
TSH (mU/L)	320	1.6	1.5	0.7	3.1	0.05	5.3
TWI	187	–	1.5	–	3.2	–	–
RVC	57	–	1.4	–	3.7	–	–
OWC	76	–	1.6	–	2.9	–	–
FT_4 (ng/L)	320	17.0	16.7	12.0	22.0	7.0	43.0
TWI	187	–	16.5	–	22.0	–	–
RVC	57	–	17.5	–	22.0	–	–
OWC	76	–	16.8	–	22.0	–	–
FT_3 (ng/L)	320	3.3	3.2	1.9	4.6	0.5	6.6
TWI	187	–	3.0	–	4.3	–	–
RVC	57	–	3.4	–	5.2	–	–
OWC	76	–	3.4	–	4.6	–	–

Abbreviations: FT_3, free triiodothyronine; FT_4, free thyroxine; OWC, Odenwald comparison group; RVC, Rhine Valley comparison group; TSH, thyroid-stimulating hormone; TWI, toxic waste incinerator.
[a]The internal laboratory reference values are 0.3–3.5 mU/L for TSH, 10–25 ng/L for FT_4, and 2.0–5.5 ng/L for FT_3 (1st–99th percentiles of children with a healthy thyroid).

Table 3. Blood concentrations of seven polychlorinated biphenyls,[a] cadmium, lead, and concentration of mercury in 24-hr urine.

Analyte	n	< dl (%)	Median	Geometric mean	5% value	95% value	Minimum	Maximum
PCB congeners (µg/L)[b]								
PCB 118	319	10.3	0.03	0.03	< dl	0.06	< dl	0.11
PCB 138	320	0	0.13	0.13	0.05	0.40	0.02	1.13
PCB 153	320	0	0.17	0.17	0.06	0.53	0.02	1.59
PCB 170	314	11.5	0.04	0.04	< dl	0.16	< dl	0.50
PCB 180	320	0.6	0.08	0.08	0.02	0.33	< dl	0.86
PCB 183	300	54.7	< dl	0.02	< dl	0.04	< dl	0.12
PCB 187	320	48.8	0.02	0.02	< dl	0.05	< dl	0.22
Σ PCB 138, 153, 180	320	0	0.38	0.39	0.14	1.24	0.06	3.58
Σ PCB (7 congeners)	298	0	0.47	0.49	0.18	1.60	0.10	4.48
Heavy metals								
Cadmium (µg/L)	320	15.9	0.23	0.18	< dl	0.65	< dl	1.80
Lead (µg/L)	320	3.1	28.5	26.8	12.3	48.0	4.5	113.7
Mercury in 24-hr urine (µg/L)	320	53.8	< dl	0.15	< dl	1.25	< dl	12.3

< dl, below detection limit.
[a]PCB 101 was not detected in any sample. [b]International Union of Pure and Applied Chemistry numbers.

Only FT_3 was significantly correlated with the two other hormones (Spearman's rank correlation coefficients: TSH and FT_4 r_s = 0.06, p = 0.28; TSH and FT_3 r_s = 0.14, p = 0.01; FT_4 and FT_3 r_s = 0.28, p = 0.0001).

PCB concentrations. PCB 101 was not detected in any of the samples. PCB 183 and PCB 187 had a higher prevalence of values below the limit of determination (Table 3). Varying numbers result from missing values for some PCB congeners. Of the eight PCB congeners, we observed a proportionately higher median blood concentration for PCBs 138, 153, and 180. PCB 153 contributed approximately 30% to the sum of all congeners.

Small regional differences for the crude values are obvious for six of the eight congeners, with the exception of PCBs 118 and 101 (Table 4).

The regression analysis revealed a statistically significant positive association of PCB 118 with TSH (Table 5). PCBs 138, 153, 180, 183, and 187 showed a statistically significant inverse relationship with FT_3. The associations of the sum of PCBs 138, 153, and 180 and the sum of all seven congeners with FT_3 gained statistical significance (Table 5). There were no relationships of PCB congeners with FT_4 of significant magnitude.

We investigated potential combined effects by stratifying the group for sex and we repeated those regression models that showed significant associations between PCBs and thyroid hormones in the total sample. The reduced sample size in each model diminished the probability to detect associations between PCBs and thyroid hormones. Between PCB 118 and TSH the associations in boys and girls did not change substantially (model with rank-transformed TSH values: parameter estimates for PCB 118, β_{boys} = 7.74, β_{girls} = 6.09, total group β = 7.13). In contrast, individual PCB congeners were significantly negative with FT_3 in girls, with regression coefficients between -0.29 for PCB 183 and -4.31 for PCB 170 (for PCB congeners 138, 153, 180, 187, β-coefficients were -1.95, -1.52, -2.71, and -0.41, respectively). Likewise, in boys there were negative but not significant associations with FT_3 (regression coefficients were between -0.19 for PCB 183 and -0.88 for PCB 170, and for PCB congeners 138, 153, 180, and 187 respective estimates were -0.48, -0.28, -0.50, and -0.20).

Neither blood concentration of lead nor the urinary concentration of mercury had a statistical influence on the levels of the thyroid hormones (Table 6). The blood concentration of cadmium, however, showed an association with increasing TSH and an association with diminishing FT_4 (Table 6). The consumption of fish more than twice in a month appeared to raise the FT_3 concentration (Table 6).

Discussion

In a group of 320 schoolchildren 7–10 years of age, we analyzed the free (not protein bound) T_3 and T_4 and TSH. We detected a statistically significantly positive association between the mono-*ortho* congener PCB 118 and TSH as well as significantly negative relationships of PCBs 138, 153, 180, 183, and 187 to FT_3. No association could be seen for PCBs and FT_4. With increasing blood cadmium concentration TSH levels rose and levels of FT_4 diminished. Blood lead and urine concentration of mercury were of no importance to thyroid hormones.

We had to select a subgroup of the total sample for blood analyses because of budget limitations. We restricted the group to those having a lower ETS exposure in their homes to reduce the potentially disturbing effect of ETS. Parents of 501 children reported an ETS exposure in the child's home in the

Table 4. Regional distribution of contaminant blood and urine concentrations in micrograms per liter.[a]

	TWI (n = 187)		RVC (n = 57)		OWC (n = 75)	
Contaminant	Geometric mean	95th percentile	Geometric mean	95th percentile	Geometric mean	95th percentile
PCB 138	0.13	0.38	0.14	0.53	0.12	0.31
PCB 153	0.17	0.52	0.19	0.61	0.16	0.40
PCB 170	0.04	0.15	0.04	0.19	0.03	0.11
PCB 180	0.09	0.32	0.10	0.36	0.07	0.24
PCB 183	0.02	0.04	0.02	0.04	< dl	0.04
PCB 187	0.02	0.05	0.02	0.06	0.02	0.04
Cadmium	0.19	0.60	0.11	0.66	0.22	0.98
Lead	2.74	4.71	2.34	4.82	2.86	5.78
Urinary mercury	0.16	1.30	0.13	0.52	0.14	1.50

Abbreviations: < dl, below detection limit; OWC, Odenwald comparison group; RVC, Rhine Valley comparison group; TWI, toxic waste incinerator.
[a]PCB 101 was not detected in any sample. PCB 118 showed no regional differences to the total group.

Table 5. Relationship between blood concentrations of PCB congeners and levels of thyroid hormones in multiple linear regression models.[a]

PCB congeners[b]		TSH		FT_4		FT_3	
(IUPAC no.)	n	β[c]	p	β[c]	p	β	p
PCB 118 (µg/L)	319	7.129	0.039	–	–	-2.933	0.342
≤ 0.02	108	–	–	0	–	–	–
0.03	90	–	–	0.005	0.710	–	–
> 0.03	121	–	–	0.005	0.971	–	–
PCB 138 (µg/L)	320	–	–	–	–	-0.999	0.017
0.02–0.10	107	0	–	0	–	–	–
0.11–0.17	111	-0.141	0.294	0.296	0.032	–	–
> 0.17	102	0.102	0.485	0.093	0.534	–	–
PCB 153 (µg/L)	320	–	–	–	–	-0.705	0.024
0.02–0.13	109	0	–	0	–	–	–
0.14–0.22	102	-0.057	0.679	0.312	0.027	–	–
> 0.22	109	0.076	0.595	0.069	0.635	–	–
PCB 170 (µg/L)	314	–	–	–	–	-1.785	0.064
≤ 0.02	92	0	–	0	–	–	–
0.03–0.05	124	0.096	0.480	0.203	0.149	–	–
> 0.05	98	0.125	0.414	0.033	0.833	–	–
PCB 180 (µg/L)	320	–	–	–	–	-1.179	0.023
≤ 0.02–0.06	117	0	–	0	–	–	–
0.07–0.11	94	0.051	0.714	0.120	0.397	–	–
> 0.11	109	0.029	0.836	0.060	0.678	–	–
PCB 183 (µg/L)	300	–	–	–	–	–	–
< 0.02	164	0	–	0	–	0	–
≥ 0.02	136	0.152	0.203	0.068	0.577	-0.236	0.022
PCB 187 (µg/L)	320	–	–	–	–	–	–
< 0.02	156	0	–	0	–	0	–
≥ 0.02	164	0.079	0.477	-0.006	0.957	-0.299	0.002
Σ PCB 138, 153, and 180 (µg/L)	320	0.102	0.503	–	–	-0.317	0.019
0.06–0.30	106	–	–	0	–	–	–
> 0.30–0.51	107	–	–	0.197	0.163	–	–
> 0.51	107	–	–	-0.007	0.961	–	–

Abbreviations: FT_3, free triiodothyronine; FT_4, free thyroxine; IUPAC, International Union of Pure and Applied Chemistry; PCB, polychlorinated biphenyl; TSH, thyroid-stimulating hormone.
[a]Each model has been adjusted for blood cadmium and lead concentrations, urinary mercury, age, sex, passive smoking, and fish consumption. [b]Predictor variables of PCB and heavy metals were ranked into two or three categories by frequency distribution if associations to thyroid hormones were not linear. [c]Parameter estimates are based on rank-transformed values to achieve normal distribution (*16*).

previous 12 months of ≤ 10 cigarettes/day. Of this group 317 participated in the phlebotomy (63%). Parents of 25 of 162 children with a higher ETS exposure (15.4%) had their children included in phlebotomy. Complete data were available for 320 children. Substantial differences were not seen for age, sex, and fish consumption between the total sample and the subgroup (n = 320) with blood samples.

When parents provided individual data on their child and on living conditions, the individual results of the blood analyses were not known to them. The information about PCB concentrations and thyroid hormones could not have been biased by the selection of the subgroup nor by questionnaire or interview data.

Thyroid hormones and concentrations of PCBs and heavy metals were analyzed in two independent laboratories that successfully participated in external quality assessments.

Cadmium. The geometric mean of blood cadmium concentration in our study (n = 320) of approximately 0.18 µg/L (Table 3) is similar to the concentration of 0.14 µg/L in the German national survey subgroup of 8–9-year-old children (n = 169) (*23*). The 95th percentile in our sample in South Hessen was 0.65 µg/L, as compared to 0.4 µg/L in the national survey.

To investigate whether the relationship between cadmium in blood and FT_4 (negative association) and TSH (positive association) depends on the influence of ETS, we restricted the analysis to the group of children who were neither exposed to passive smoking at home in the last 12 months nor in general in the 7 days preceding the phlebotomy (n = 169). In this group we detected corresponding associations of cadmium on FT_4 (p = 0.01) and on TSH (p = 0.003).

To our knowledge there is no study on cadmium and thyroid hormones in children. In adults, Nishijo et al. (*18*) showed a decrease in FT_4 levels in women from a cadmium-exposed area as compared to a nonpolluted area. In cadmium-treated pregnant rats, serum levels of total T_3 and T_4 were significantly decreased (*24*). Increased plasma levels of TSH were found in another study on rats exposed to cadmium (*17*). These reports fit with our findings of a cadmium-related increase of TSH and a decrease of FT_4.

Lead. The blood concentration of lead (Table 3) in children in South Hessen (geometric mean, 26.8 µg/L) is lower than that in children 8–9 years of age in the German national sample (geometric mean, 33.9 µg/L; n = 169) (*23*). The maximum value of 113.7 µg/L does not exceed the level of toxic effects in children, but possible long-term health effects cannot be completely ruled out (*25,26*). However, within this range we did not find a lead-related effect on thyroid hormones, which is in accordance with other studies of children (*27,28*).

Mercury. Because > 50% of the children had values below the detection limit of 0.15 µg/L, three categories (50% of the detection limit = 0.075 µg/L; 0.15–0.2 µg/L; and > 0.2 µg/L) were used in the statistical analyses. In comparison to children 6–14 years of age from the 1992 German national survey (95th percentile of mercury in spontaneous urine = 3 µg/L) (*23*), the 95th percentile in our study is almost three times lower (1.25 µg/L). A 1992–1993 study in Baden-Württemberg, Germany, a state south of the Federal State of Hessen, based on 11-year-old children found 95th percentiles of 2.75 µg/L (n = 165), 3.1 µg/L (n = 238), and 5.7 µg/L (n = 347) in spontaneous urine samples of three distinctly industrialized areas (*29*). The magnitude of differences to our values result from the particular analytic method used in our studies. We did not discover considerable associations between thyroid hormones and these low-dose concentrations of urinary mercury.

PCBs. We investigated PCB concentration in whole blood. Lipid-based concentrations are highly correlated to whole blood concentrations in our group of children. Spearman's rank correlation coefficients between whole blood and lipid-based PCB concentrations: PCB 118, r_s = 0.88; PCB 138, r_s = 0.94; PCB 153, r_s = 0.94; PCB 170, r_s = 0.96; PCB 180, r_s = 0.95; PCB 183, r_s = 0.87; PCB 187, r_s = 0.90. Thus, associations between the PCBs and thyroid hormones are not affected by the way the PCB burden is calculated.

For some PCBs, analogous analyses are available for the years 1993–1994 from the Baden-Württemberg study (*29*). The geometric mean is slightly higher in our study for PCB 138 [0.13 µg/L vs. 0.085 µg/L (n = 71), 0.117 µg/L (n = 59), and 0.117 µg/L (n = 57) in three regions from Baden-Württemberg] and PCB 153 [0.17 µg/L vs. 0.10 µg/L (n = 71), 0.151 µg/L (n = 59), and 0.134 µg/L (n = 57)]. The geometric mean shows a comparable concentration for PCB 180 [0.08 µg/L vs. 0.079 µg/L (n = 71), 0.069 µg/L (n = 59), and 0.096 µg/L (n = 57)]. However, this similarity might be biased by the procedures of different laboratories.

The observed association between mono-*ortho* PCB 118 and TSH can be explained by varying potential mechanisms. Some coplanar and mono-*ortho* PCB congeners as well as polychlorinated dibenzo-*p*-dioxin and polychlorinated dibenzofuran (PCDD/PCDF) share a similar molecular structure with thyroid hormones. Thus PCBs may interfere with endocrine function by imitating natural hormones (*30,31*). One mechanism of PCB

Table 6. Multiple linear regression models with the predictor sum of PCB congeners.

		Dependent variable					
		TSH		FT_4		FT_3	
Predictors[a]	n	β[b]	p	β[b]	p	β	p
Σ PCB (µg/L, 7 congeners)[c]	296	–	–	–	–	-0.248	0.024
0.1–0.37	95	0	–	0	–	–	–
> 0.37–0.62	104	-0.104	0.461	0.169	0.250	–	–
> 0.62	97	0.041	0.791	-0.111	0.491	–	–
Cadmium (µg/L)	296	0.712	0.003	-0.510	0.041	–	–
< 0.05–0.14	84	–	–	–	–	0	–
0.15–0.34	105	–	–	–	–	0.034	0.778
> 0.34	107	–	–	–	–	0.001	0.996
Lead (µg/L)	296	–	–	–	–	–	–
< 9 -24.8	93	0	–	0	–	0	–
25.1–31.7	102	-0.102	0.465	-0.242	0.094	-0.206	0.086
> 31.7	101	0.111	0.442	-0.129	0.384	0.082	0.500
Mercury in 24-hr urine (µg/L)	296	–	–	–	–	–	–
< 0.15	159	0	–	0	–	0	–
0.15–0.2	38	-0.246	0.171	0.111	0.443	-0.148	0.218
> 0.2	99	0.176	0.165	0.050	0.729	-0.086	0.470
Male	170	0.230	0.049	-0.206	0.087	-0.043	0.664
Age							
7 years	133	0	–	0	–	0	–
8 years	150	-0.064	0.587	0.046	0.704	-0.406	0.683
9 years	13	0.468	0.100	-0.156	0.594	-0.186	0.455
ETS (no = 0)	158	–	–	–	–	–	–
One to some days	70	0.052	0.711	-0.092	0.522	-0.072	0.545
Daily	63	-0.043	0.782	-0.224	0.161	-0.040	0.762
Consumption of fish less than twice monthly	192	0.072	0.545	0.155	0.207	0.209	0.042
Explained variance	R^2	–	8.4%	–	6.2%	–	5.9%

Abbreviations: ETS, environmental tobacco smoke; FT_3, free triiodothyronine; FT_4, free thyroxine; PCB, polychlorinated biphenyl; TSH, thyroid-stimulating hormone.
[a]Predictor variables of PCB and heavy metals were ranked into two or three categories by frequency distribution when associations to thyroid hormones were not linear. [b]Parameter estimates are based on rank-transformed values to achieve normal distribution (*16*). [c]PCBs 118, 138, 153, 170, 180, 183, and 187.

118 can be UDPGT induction mediated by the AhR. A second mode could be AhR independent; for instance, inhibition of monodeiodinase activity resulting in reduced conversion of peripheral T_4 into T_3. Third, direct acting at the pituitary via calcium channel stimulation or inhibition of FT_4 uptake is possible. We expected that FT_4 and FT_3 would diminish with increasing PCB 118, but no association of that kind was detected. In contrast, we found relationships between all of the measured nonplanar PCB congeners and FT_3. Because these congeners do not have an affinity to the AhR, only those that are AhR independent are potential mechanisms. A blockage of peripheral deiodinase activity could be responsible for our findings of depleted FT_3. Reduced FT_3 might be accompanied by a substrate increase, but we did not observe any elevation of FT_4. It is possible that FT_4 is increasingly converted to inactive reverse T_3, which was not determined in the present study.

There are clinical syndromes with selectively low T_3. For the children with FT_3 below the reference value we cannot rule out that this reduction is clinically relevant. However, for the entire group of children we would not categorize low FT_3 as a functional disorder, but as a moderate shift within the normal range of FT_3, as is expected in environmental exposure studies (*32*).

Stratification by sex showed that there is a combined effect with individual PCB and thyroid hormones. Associations between PCB 118 and TSH and individual PCB congeners and FT_3 differed in girls and boys but the direction of the regression coefficients did not change. Possible gender differences in hormone levels and metabolism need further investigation.

Although whole blood and plasma values are not equivalent because of higher values in plasma, Dutch investigations of mothers and infants found median concentrations in cord plasma (n = 373–382) comparable to those in whole blood in our sample of elementary schoolchildren (medians from cord plasma: PCB 118, 0.04 µg/L; PCB 138, 0.11 µg/L; PCB 153, 0.15 µg/L; and PCB 180, 0.08 µg/L) (*3*). Maternal plasma (n = 415) median concentrations were four times higher for PCB 118 (0.15 µg/L), PCB 138 (0.56 µg/L), PCB 153 (0.84 µg/L), and PCB 180 (0.50 µg/L) (*3*).

Koopman-Esseboom and co-workers (*33*) as well as Sauer et al. (*34*) showed a positive correlation between PCBs—planar and nonplanar—in human milk and TSH values in infants (week 2 and month 3, n = 78–82) and a negative association with FT_4 in week 2 in the high-exposure group. In this study on background levels of PCB (*33*), an effect of higher plasma levels of PCB on maternal total T_3 and total T_4 was also reported. Recently, a study on 1-year-old Japanese infants who were breast-fed showed decreased values of T_3 and T_4 depending on the levels of PCDD/PCDF and coplanar PCB in mother's milk, whereas TSH values were unaffected (*35*). Pluim et al. (*36*) found an elevation on total T_4 and TSH but not on total T_3 due to background PCDD/PCDF concentrations in newborns (n = 38), which indicates an agonistic mechanism of action. PCBs should mobilize colloid-stored T_4 in the thyroid gland, which could lead to rising T_4 levels in serum.

Our finding of an association between the mono-*ortho* congener PCB 118 and increasing TSH (Table 5) agrees with some of these results. To our knowledge there are no published investigations on schoolchildren who were exposed to background levels of PCB. A study on 12 hospitalized children aged 7–14, who had elevated blood lipid concentrations of β-hexachlorocyclohexane, DDE, and PCB, could not reveal any associations to hormone status of total T_4 and TSH (*37*).

In summary, this investigation in elementary schoolchildren supports the hypothesis that PCBs and cadmium can have a mutable or even detrimental effect on levels of thyroid hormones, with lower FT_3 and an increase in TSH. Because of possible adverse effects on growth and development (*38*) and to identify susceptible periods, there is a need for future studies to analyze the effect of PCB and cadmium on thyroid hormones in different age groups and to observe levels of thyroid hormones in connection with the neurologic development of children exposed to PCB and cadmium.

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