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Review

Polychlorinated biphenyls and thyroid hormones in adults: A systematic review appraisal of epidemiological studies ☆

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ABSTRACT

Reported evidence regarding relationships between polychlorinated biphenlys (PCBs) and thyroid homeostasis in adults has been considered contradictory. The objective of this systematic review is to determine a possible association between PCB exposure and the circulating thyroid hormones and thyrotropin (TSH) levels in adults, by analyzing the quality of published studies. A systematic review of epidemiological papers was conducted using PubMed. An evaluation of the quality of 22 studies was performed, and the papers were classified into two tiers: Tier I for studies with higher quality scores (eight) and Tier II for studies with lower quality scores (14). It appears that PCBs can interfere with thyroid hormone homeostasis; however epidemiological evidence is not entirely clear. For triiodothyronine (T3) and thyroxine (T4), Tier I studies showed either an inverse (four cases for T3; five cases for T4) or no significant association (two cases for T3; five cases for T4) with PCBs. In the case of free thyroxine and TSH, the Tier I papers observed no clear association with PCB levels. Rigorous study design, assessment of potential confounding factors, and fuller reporting of methods and results in future studies will facilitate understanding of whether PCB exposure is associated with changes in thyroid function.

Contents

1. Introduction

Thyroid hormones (THs), thyroxine (T4) and triiodothyronine (T3), are essential for normal development and for physiology (Zoeller et al., 2007). The synthesis of THs is regulated by the pituitary gland hormone thyrotropin (TSH). The regulation of TH delivery to cells and tissues is controlled by feedback systems, and potential thyroid toxicants including polychlorinated biphenyls (PCBs) may disturb this system at different points, inducing various responses (DeVito et al., 1999; Gauger et al., 2008).

PCBs are a group of 209 synthetic polychlorinated biphenyl congeners that have different numbers and positions of chlorine atoms in the biphenyl structure. Aroclor is a trade name for some PCB mixtures that have had widespread industrial uses, such as in capacitors, transformers, hydraulic fluids, flame retardants, adhesives, inks, metal coatings, pesticide extenders, etc, but were banned in the US in the 1970s. The general population, however, continues to be exposed to PCBs, primarily through the ingestion of food, especially from fish, meat and dairy products (Agency for Toxic Substances and Disease Registry – ATSDR, 2000).

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Previous reviews on the effects of persistent organohalogen pollutants, including PCBs, on TH status in adults have highlighted that the results of studies are inconsistent (Barsano, 1981; Hagmar, 2003; Langer, 2005, 2008; Boas et al., 2006). No previous reviews have focused specifically on epidemiological studies related to PCBs in adults. In addition, none performed a standardized assessment of the quality of the studies, calculating an overall quality score.

The objective of this review is to evaluate, with a systematic and standardized approach, the tenability of a causal association between PCB exposure and the circulating TH and TSH levels in adults, by analyzing the quality of published studies.

2. Methods

A systematic review of epidemiological papers was conducted using PubMed. Different combinations of key words were used: PCBs, thyroid, thyroid hormones, thyroid function, human health, and breast milk. The only limit applied in Pubmed was human study. Studies published until May 2008 were collected. Reference lists of the retrieved articles and published reviews were consulted to find additional studies. All of the 22 retrieved studies, written in English, that presented the measurement of PCB levels in biologic matrices and of TH and TSH levels from adult individuals (18 years and older) were included in this review.

A formal evaluation allowed the assignment of a quality score to each study, as published. The approach used was to designate a positive point (1) for each methodological strength and a negative point (−1) for each evident limitation, based on a method used by Goodman et al. (2004). Agreement between the co-authors was reached after discussion of all uncertain or conflicting points raised by the co-authors reviewing the papers.

Two criteria were elaborated related to the study design, based on Elwood (1998). The first was related to the type of sampling system selected on exposure (cohort), or outcome (case control), or for total or sample of a defined population (survey). Cohorts and case control studies were considered more adequate designs than surveys. The second criteria, time relationship of a cross-sectional nature, was considered limited.

The estimation of PCBs can be performed as total PCBs, as homolog groups or as specific congeners, in accordance with ATSDR (2000). Originally, assays quantified total or homolog PCBs. Recently, capillary or high resolution gas chromatography has led to lower detection limits and improved separation of PCB congeners for quantification (ATSDR, 2000). According to Brouwer et al. (1999), the quantitative comparison across laboratories of PCB measurements resulting from the earliest techniques is unreliable. It is possible to quantitatively compare PCB measurements resulting from congener-specific methods. However, this remains difficult due to variations across laboratories in procedures, data handling and presentation (Brouwer et al., 1999; Longnecker et al., 2003). Despite the limitations noted above, the congener-specific analytical technique to measure PCBs was considered adequate for the purposes of the quality criteria. The techniques that estimate total or PCB homologs were considered less accurate.

Regarding the outcome, two criteria were used: (1) the type of outcome, and (2) the technique's sensitivity to estimate TSH. The TSH test is considered a first strategy to diagnose thyroid dysfunction in adults by the American Thyroid Association (Landenson et al., 2000). Besides the fact that a TSH measurement can be used to detect both hypo- and hyperthyroidism, FT4 measurement can detect other conditions, such as central hypothyrodism (Landenson et al., 2000; Demers and Spencer, 2002). In this way, the measurement of both TSH and FT4 levels was considered an adequate outcome, as previously recommended by Surks et al. (1990) and DeVito et al. (1999).

The American Thyroid Association considers that the TSH assay sensitivity must be 0.02 mIU L^{-1} or less, and if this assay is not available, a serum FT4 or FT3 or T3 should be performed (Landenson et al., 2000). The assays to measure TSH are usually categorized in three generations, according to their sensitivity. The first generation, radioimmunoassay, presents a functional sensitivity of 1 to 2 mIU L^{-1}; for the second generation, immunoradiometric assays, the functional sensitivity is in the range of 0.1–0.2 mIU L^{-1}; and for the third generation, the nonisotopic immunometric assays, the functional sensitivity is in the range of 0.01–0.02 mIU L^{-1} (Spencer, 1996). However, Spencer et al. (1996) point out that commercial marketing practices and intermediary sensitivities have made the distinctions between generations less clear. In general, published studies do not report assay sensitivity. As a consequence, a mixed criterion to analyze assays that includes the notion of technique generation and reported sensitivity for TSH has been developed. If the assay was not specified, this was also considered a limitation.

Potential confounders should be considered in the design and analysis of the study. In general, confounding can be controlled by restriction, randomization, or matching in the study design, or by multivariate methods in the analysis (Elwood, 1998). To study the association of PCB levels and THs and TSH, we considered whether confounding by the following variables had been addressed: age, gender, smoking, body mass index (BMI), and medications (Osius et al., 1999; Demers and Spencer, 2002; Crofton, 2008). An item related to the analysis of other potential endocrine disrupting chemicals, such as organochlorine compounds and metals (Bloom et al., 2003; Crofton, 2008) was also included in the quality criteria.

Information regarding the subject selection process was considered adequate when the paper provided data on the target and source populations, eligible subjects and study participants (definitions provided by Elwood (1998)).

The items related to the selection of subjects, external and internal validity, were elaborated based on Elwood (1998) and Goodman et al. (2004). The final criteria for the quality scoring are described below:

1. Study design – sampling system: cohort and case control, score = 0; survey, score = −1.
2. Study design – time relationship: retrospective, prospective, score = 0; cross sectional, score = −1.
3. Determination of PCB levels: congener-specific technique, score = 0; else, score = −1.
4. Estimation of TSH and FT4, score = 0; no TSH or FT4, score = −1.
5. Assay for TSH: radioimmunoassay, reported sensitivity of more than 0.2 mIU L^{-1}, no specification of the method, score = −1; reported assay sensitivity of 0.02 mIU L^{-1} or less, score = 1; else, score = 0.
6. Exposure–response analysis: no, score = 0; yes, score = 1.
7. Age adjustment: no, score = −1; yes, score = 0.
8. Gender adjustment: no, score = −1; yes, score = 0.
9. Medication adjustment: no, score = −1; yes, score = 0.
10. Smoking adjustment: no, score = −1, yes; score = 0.
11. BMI adjustment: no, score = −1, yes; score = 0.
12. Analysis of other potential endocrine disruptor chemical exposure: not addressed, score = −1; not clear, addressed at least one, score = 0; other potential endocrine disruptor chemical exposure unlikely, addressed at least two, score = 1.
13. Information about the subject selection process: limited, score = −1; sufficient score = 0.

14. Selection issues affecting external validity: likely (restricted target population), score = −1; possible but not clearly evident (hospital-based studies), score = 0; unlikely /addressed (cohort studies or other population-based studies), score = 1.
15. Selection bias affecting internal validity: likely (systematic differences in case and control recruitment or inadequate control) score = −1, possible but not clearly evident, score = 0; unlikely/addressed, score = 1.

Five outcome variables were considered: T3, FT3, T4, FT4, and TSH. The studies were classified into two tiers: Tier I papers had a summary score $\geqslant 0$, and Tier II papers had a summary score < 0.

3. Results

Table 1 shows each criterion and the total quality score for the papers. Of the 22 studies analyzed, 8 obtained a zero quality or higher quality score and were classified as Tier I papers. The results for the analysis of an association between T3, FT3, T4, FT4, and TSH and PCB levels and details of the studies' designs are presented in Tables 2 and 3 for Tier I and II papers, respectively. The principal strengths, limitations and results of each paper will be highlighted below. We noted that all papers presented a cross-sectional design.

3.1. Tier I papers

A total of 20 PCBs as well as T4 and TSH data from the National Health and Nutrition Examination Survey were studied by Turyk et al. (2007). Strengths of the paper included reliance on a random and nationally representative sample (1166 males and 1279 females), assessment of confounders (age, gender, medication, smoking and BMI), and quantification of TSH with a sensitive technique (Centers for Disease Control and Prevention, 2007). A significant inverse association ($p < 0.05$) was observed only for serum PCBs and TSH levels for men older than 60 years.

A sample of Great Lakes fish eaters (179 males and 51 females) was studied by Persky et al. (2001). This cohort study addressed important confounders (age, gender, medication, smoking and BMI). The authors found a significant inverse association ($p < 0.05$) between serum PCB levels and serum T4 and free T4 index among women and between PCBs and serum T4 among men.

A sample of 56 males from the Great Lakes cohort study was analyzed by Turyk et al. (2006). Serum concentration of the sum of 89 PCBs was significantly inversely associated with serum levels of T3 ($p = 0.03$), T4 ($p = 0.009$), and TSH ($p = 0.01$). Advantages of the research were the assessment of confounding and the techniques for measurements of PCBs and TSH.

Abdelouahab et al. (2008) studied a sample of 124 male and 87 female fish-eaters from Québec. The strengths of the paper were the TSH assay (Forest et al., 1998) and the analysis of confounding. The population selection process was only partially reported. For males, the authors observed a significant inverse association ($p < 0.05$) between the sum of 16 PCBs and serum T4 and positive for TSH; for females, an inverse significant association was observed for T3.

An exploratory study within a cohort of 66 New York State Anglers was conducted by Bloom et al. (2003). Confounders were taken into consideration in the analysis of association. No significant associations between 10 PCB congeners and T4 serum levels were observed.

Rylander et al. (2006) analyzed a cohort sample of 196 Swedish fishermen, selected as described by Wallin et al. (2005). Different potential confounders were considered. No significant association was observed between PCB-153 and serum levels of FT4 and TSH.

Meeker et al. (2007) analyzed the association between 57 PCBs with serum levels of T3, FT4, and TSH in a sample of 341 males from sub-fertile couples. The main strength of this research was the control of important confounding factors (age, medication, smoking and BMI). However, the study target population was limited. An inverse, significant association ($p < 0.05$) was observed between T3 and PCB-153 concentration.

Sala et al. (1999, 2001) studied subjects from the general population who lived near an electrochemical factory. The technique used to determine TSH level was not specified. For the multiple regression analysis, confounders (age, gender, smoking and BMI), were taken into consideration. No significant association ($p > 0.05$) was observed between plasma concentration of the sum of 186 PCBs and the hormone levels studied.

3.2. Tier II papers

Langer et al. (2007a,b) examined a large convenience sample of 2046 individuals stratified by age and sex. Incomplete information was given regarding the selection of subjects for the study. A significant positive association ($p < 0.05$) between the levels of PCB and FT4 was observed (Langer et al., 2007a,b). For T3, there was a significant inverse association among subjects with serum PCB levels below 530 ng g lipid^{-1}. However, among subjects with serum PCB levels of 531–3000 ng g lipid^{-1}, there was a significant positive association (Langer et al., 2007a).

Takser et al. (2005) studied samples of pregnant women recruited in a centre for community services in Québec. Limited information about the study participants selection process was provided. The study addressed confounding by age, smoking, and other contaminants. The serum T3 level was significantly associated ($p < 0.05$) with plasma PCBs.

Hagmar et al. (2001b) studied a sample of 110 men who had a wide range of fish consumption. The blood of the exposed and control groups were analyzed two years apart. Incomplete information was provided regarding subject selection. Confounding by age and drugs was addressed. No significant association ($p > 0.05$) was observed between the plasma levels of T3, Ft, T4, FT4, and TSH and the levels of the sum of 18 PCBs.

Hagmar et al. (2001a) studied a restricted target population consisting of 182 wives of Swedish fishermen who had previously been selected to participate in a low birth weight case control study (Rylander et al., 1998). A multiple linear regression model, controlling for age, was used. A significant inverse association ($p < 0.05$) was observed between PCB-153 and T3.

Langer et al. (2007c) did not find a significant association between PCB and TSH serum levels. The relationship between FT4 and the sum of 15 PCB levels was not studied. Other information on this study was provided above (Langer et al., 2007a,b).

Langer et al. (2003, 2005, 2006) analyzed data from a cohort of former employees of a PCB producing factory. Scant information on the selection procedures for the study participants was provided. No potential confounders were considered. In Langer et al. (2003), another methodological weakness was the selection of the control group, which presented high levels of PCB. For the relationship between TSH and the sum of 15 PCB serum levels, Langer et al. (2006) observed a significant inverse association ($p < 0.05$).

Emmett et al. (1988a,b) studied a sample of transformer repair workers by analyzing T4 and total PCBs. The adjusted regression model controlled for age. No significant associations were observed. A non-congener-specific technique for PCBs estimation was used.

Koopman-Esseboom et al. (1994) studied the association between the sum of 26 PCBs in breast milk and plasma levels of T3 in pregnancy and T3 and T4 after delivery. No covariates were analyzed. PCDD and PCDF congeners in milk were also addressed. It

Table 1
Quality scores of studies assessing the association between polychlorinated biphenyl (PCB) exposure and thyroid hormones and thyrotropin in adults.

Studies	Quality Criteria															
	Study design – sampling	Study design – time relationship	PCBs assay	TSH and FT4	TSH assay	Exposure / response	Age	Gender	Medication	Smoking	Body mass index	Other contaminants	Information – subject selection	Study participants – external validity	Study participants – internal validity	Total quality score
Abdelouahab et al. (2008)	0	−1	0	−1	1	1	0	0	0	0	0	1	−1	1	1	2
Langer et al. (2007a)	0	−1	0	0	0	1	0	0	−1	−1	−1	1	−1	1	1	−1
Langer et al. (2007b)	0	−1	0	0	0	1	0	0	−1	−1	−1	1	−1	1	1	−1
Langer et al. (2007c)	0	−1	0	−1	0	1	0	0	−1	−1	−1	1	−1	1	1	−2
Meeker et al. (2007)	−1	−1	0	0	0	1	0	NA	0	0	0	1	0	−1	1	0
Turyk et al. (2007)	−1	−1	0	−1	1	1	0	0	0	0	0	1	0	1	1	2
Bloom et al. (2003)	0	−1	0	−1	NA	1	0	NA	−1	0	0	1	0	1	1	1
Langer et al. (2006)	0	−1	0	−1	0	1	−1	0	−1	−1	−1	1	−1	1	1	−3
Turyk et al. (2006)	0	−1	0	0	0	1	0	NA	0	0	0	0	0	1	1	2
Rylander et al. (2006)	0	−1	0	0	0	1	0	NA	−1	0	0	0	0	1	1	1
Langer et al. (2005)	0	−1	0	0	0	0	0	0	−1	−1	−1	1	−1	1	1	−2
Takser et al. (2005)	−1	−1	0	0	1	1	0	NA	−1	0	−1	1	−1	0	1	−1
Langer et al. (2003)	0	−1	0	−1	0	0	−1	0	−1	0	0	1	−1	1	−1	−4
Pelletier et al. (2002)	−1	−1	0	−1	NA	1	−1	NA	−1	−1	0	1	−1	−1	1	−5
Hagmar et al. (2001a)	−1	−1	0	0	0	1	0	NA	−1	−1	−1	1	0	−1	1	−3
Hagmar et al. (2001b)	0	−1	0	0	0	1	0	NA	0	−1	−1	1	−1	1	0	−1
Persky et al. (2001)	0	−1	0	0	0	1	0	0	0	0	0	0	0	1	1	2
Sala et al. (2001)	0	−1	0	0	−1	1	0	0	−1	0	0	0	0	1	1	0
Steuerwald et al. (2000)	0	−1	0	0	0	1	−1	NA	−1	−1	−1	−1	0	0	1	−4
Koopman-Esseboom et al. (1994)	−1	−1	0	0	0	1	−1	NA	−1	−1	−1	1	−1	0	1	−4
Murai et al. (1987)	0	−1	−1	0	0	1	0	0	−1	−1	−1	−1	−1	0	1	−5
Emmett et al. (1988a)	0	−1	−1	−1	NA	1	0	NA	−1	0	−1	−1	0	1	1	−3

NA – not applicable.

Table 2
Associations in adults between serum or plasma PCBs and blood concentrations of thyrotropin and thyroid hormones observed by the Tier I papers (quality score ⩾ 0).

Study	Total quality score	Exposure matrix	Number of PCBs congeners	Gender (N)	∑PCBs (ng/g lipid)	T3	FT3	T4	FT4	TSH
Turyk et al. (2007)	2	Serum	20 PCBs	Males (1166)	Geometric mean = 200.3	–	–	↔	–	↓[a]
				Females (1279)		–	–	↔	–	↔[b]
Persky et al. (2001)	2	Serum	89 PCBs	Males (179)	Exposed mean = 822.2 Referents mean = 201.1	↓	–	↓	↔[c]	↔
				Females (51)	Exposed mean = 304.9 Referents mean = 157.1	↔	–	↓	↓[c]	↔[d]
Turyk et al. (2006)	2	Serum	89 PCBs	Males (56)	Exposed mean = 806 Referents mean = 204	↓	–	↓	↔[c]	↓
Abdelouahab et al. (2008)	2	Serum	16 PCBs	Males (124)	Median = 269	↔	–	↓	–	↑
				Females (87)	Median = 237	↓	–	↔	–	↔
Bloom et al. (2003)	1	Serum	10 PCBs	Males (66)	Mean = 234.6[e]	–	–	↔	–	–
Rylander et al. (2006)	1	Serum	PCB 153	Males (196)	Median = 370	–	–	–	↔	↔[f]
Meeker et al. (2007)	0	Serum	57 PCBs	Males from infertile couples (341)	Geometric mean = 222	↓	–	–	↔	↔
Sala et al. (2001)	0	Plasma	186 PCBs	Males and females 608(TSH), 192 (FT4, T4))	Exposed mean (SD)[e] = 848.1 (1582.3) Referents = 405.1 (397.4)	–	–	↓[g]↔	↔	↔[h]

↔ no significant association ; ↓ significant inverse association ($p < 0.05$); ↑ significant positive association ($p < 0.05$); – hormone parameter not assessed; SD = standard deviation; T3 = triiodothyronine, FT3 = free triiodothyronine, T4 = thyroxine, FT4 = free thyroxine , TSH = thyrotropin.

[a] Significant for men > 60 years of age in two NHANES cycles.
[b] Significant for women > 60 years of age only in one NHANES cycle.
[c] Measured as FTI (free thyroxine index).
[d] Association significantly positive after the elimination of a female with high TSH.
[e] The PCB levels were converted to a lipid basis using the concentration of serum lipid of 7.9 g/L as applied by Longnecker et al. (2003).
[f] Age adjusted model. In the crude analysis the relationship was significant and positive.
[g] Negative significant association for the first quartile of PCB level – (1.3–2.6 ng/ml); no association in the analysis of PCB as a continuous variable.
[h] The association between PCBs and TSH was significantly negative in the crude analysis.

was not stated how the study participants were selected. Statistically significant inverse associations ($p < 0.05$) were observed between serum levels of T3 and T4 and planar PCBs, and between T3 and nonplanar PCBs.

Steuerwald et al. (2000) analyzed a sample of 182 pregnant women. No potential confounders were taken into consideration. No significant association was found between the sum of 28 PCBs and serum levels of FT3, T4, FT4, and TSH.

Pelletier et al. (2002) studied 16 obese men who were a subset of participants in a larger study. No important potential confounders were analyzed. They found a significant inverse association ($p < 0.05$) between T3 and Aroclor 1260.

Murai et al. (1987) analyzed Yusho patients in a case control study with 167 subjects. Because this study dates from the 1980s, it relied on less reliable methods for PCB and TSH estimation. Confounding by gender and age were addressed. No association was observed between PCB and T3, T4, and TSH levels.

4. Discussion

In the papers analyzed, the most frequent methodological limitation was the cross-sectional design of the studies. In addition, in many studies important confounders were not addressed in the research design or analysis. For example, only 10 of 22 studies took into account BMI, 11 of 22 took into account smoking practices and 6 of 22 took into account medication use. A limited description of the subject selection process, was also identified. Few studies provided any specific justification for the choice of THs studied.

In general, most of the Tier II papers, which included studies with methodological limitations, noted no significant associations between PCBs and TSH or THs, with the exception of T3. For T3 and T4, the Tier I papers observed inverse or null associations with PCB levels. This data supports a conclusion that serum PCB levels are inversely associated with both T3 and T4; however the epidemiological evidence is not entirely consistent. There was no relationship between PCB levels and TSH or FT4.

Inconsistent results regarding the association between PCB and TH and TSH levels might be due not only to the methodological limitations in the research papers, but also to different factors such as, serum PCB levels, the congeners analyzed, the demographic characteristics of the populations studied, and exposure to other environmental thyroid toxicants, among others.

The studies measured and reported PCBs in ways that made comparisons of exposure levels across them difficult. This is a major shortcoming of this body of literature. However, to allow a reasonable discussion of the results, we transformed the exposure level to a lipid basis using the concentration of serum lipid of 7.9 g L^{-1} (Longnecker et al., 2003) for the Tier I studies. In this way, for the exposure in the context of the general population or fish consumers to different PCB mixtures varying from 222 ng g $lipid^{-1}$ to 822.2 ng g $lipid^{-1}$, some papers observed a significant inverse association for the relationship between PCB and T3 serum levels (Persky et al. (2001); Turyk et al. (2006) and Meeker et al. (2007) for males; Abdelouahab et al. (2008) for females). However, among fish consumers (sum of PCBs in the range of 269–304.9 ng g $lipid^{-1}$), no significant association between PCB and T3 levels was observed by Persky et al. (2001) for females, as well as for Abdelouahab et al. (2008) for males.

For the general population, only one Tier I paper analyzed T4 for a national sample of males and females with a serum geometric mean of the sum of 20 PCBs = 200.3 ng g $lipid^{-1}$ and found no association with the sum of 20 PCBs (Turyk et al., 2007). For fish consumers, a significant inverse association was observed between PCB levels and T4 in some of the Tier I papers (Persky et al. (2001) for males and females; and Turyk et al. (2006) and Abdelouahab et al. (2008) for males). However, no association between T4 and PCBs was observed by Bloom et al. (2003) for males; Sala et al. (2001) for a population with plasma PCB mean levels of 848.1 ng g $lipid^{-1}$; and Abdelouahab et al. (2008) for females.

Table 3
Associations in adults between PCBs in different biologic matrices and blood concentrations of thyrotropin and thyroid hormones observed by the Tier II papers (negative quality score).

Study	Total quality score	Exposure matrix	Number of PCB congeners	Gender (N)	∑PCBs	T3	FT3	T4	FT4	TSH
Langer et al. (2007a)	−1	Serum	15 PCBs	Males and females (2046)	Median = 1087 ng/g lipid	↓↑[a]		–	↓[b]	↔
Langer et al. (2007b)	−1	Serum	15 PCBs	Males and females (2045)	Exposed Mean (SD) = 3146 (238) Referents Mean (SD) = 971 (68) ng/g lipid	–	–	–	↑	–[c]
Takser et al. (2005)	−1	Plasma	14 PCBs	Pregnant women (39, 145, 101, 92)	Median = 0.33 μg/L	↓	–	–	↔	↔[d]
Hagmar et al. (2001a)	−1	Plasma	18 PCBs	Males (110)	Median = 1137 ng/g lipid	↔	↔	↔	↔	↔
Langer et al. (2007c)	−2	Serum	15 PCBS	Males and females (2046)	Mean (SD) = 485 (5)–5772 (387) ng/g lipid	–	–	–	–	↔
Langer et al. (2005)	−2	Serum	9 PCBs	Males and females (461)	Mean (SD) = 1205 (53)–7300 (871) ng/g lipid	–	–	–	–	∼[e]
Langer et al. (2006)	−3	Serum	15 PCBs	Males and females (454)	Median = 1750 ng/g lipid	–	–	–	–	↓
Hagmar et al. (2001b)	−3	Plasma	PCB-153	Females (182)	Median = 159 ng/g lipid	↓	↔	↔	↔	↔
Emmett et al. (1988a)	−3	Serum	Total PCBs	Males (111)	Current exposed median = 12 ppb	–	–	↔	–	–
Langer et al. (2003)	−4	Serum	9 PCBs	Males (239)	Mean (SD) (ng/g lipid) Exposed = 9097 (1396) Referent = 2250 (147)	–	–	–	–	∼[f]
				Females (222)	Mean (SD) (ng/g lipid) Exposed = 6207 (957) Referent = 2336 (485)	–	–	–	–	∼[f]
Steuerwald et al. (2000)	−4	Serum	28 PCBs	Pregnant women (182)	Geometric mean = 1.12 μg/g	–	↔	↔	↔	↔
Koopman-Esseboom et al. (1994)	−4	Breast milk/ Plasma	26 PCBs	Pregnant women (78)	Mean (SD)planar –PCB TEQ = 19.95 (8.54) pg TEQ/g fat	↓[g]	–	↓	↔	↔
Pelletier et al. (2002)	−5	Plasma	Aroclor 1260	Males (16)	Mean (SD) = 515.5 (217.4) ng/g lipid	↓	–	–	↔	–
Murai et al. (1987)	−5	Blood	Total PCBs	Males and females (167)	Mean (SD) Exposed = 4.2 (2.6) ppb	↔[h]	–	↔[h]	–	↔[h]

↔no significant association ; ↓ significant inverse association ($p < 0.05$); ↑ significant positive association ($p < 0.05$); – hormone parameter not assessed, ∼ no conclusive result; SD = standard deviation; TEQ = toxic equivalent ; T3 = triiodothyronine, FT3 = free triiodothyronine, T4 = thyroxine, FT4 = free thyroxine , TSH = thyrotropin.

[a] Negative significant association for subjects with serum PCBs < 530 ng/g lipid and positive significant association for serum PCBs in the range of 531–2000 ng/g lipid.

[b] Positive significant association for subjects with serum PCBs ⩾ 531 ng/g lipid.

[c] For TSH the association was not measured.

[d] Association significant only with PCB – 180 and TSH.

[e] TSH and PCB level relationship was analyzed considering only the abnormal high levels of TSH. No difference was observed.

[f] TSH levels were analyzed considering abnormal (high and low) range levels.

[g] Associations measured during pregnancy and after delivery for T3.

[h] No significant association was observed between PCB and TH levels. However, the mean value of T4 and T3 were significantly higher in Yusho patients than in controls; this was not observed for TSH.

Most of the results for FT4 and for TSH show no association with PCBs in the Tier I papers. In the case of FT4, no association was found in the general population (Meeker et al. (2007) for males), or among fish consumers (Persky et al. (2001), Rylander et al. (2006) and Turyk et al. (2006) for males; and Abdelouahab et al. (2008) for females), or for occupational exposures (Sala et al. (2001) for males and females). However, Persky et al. (2001) observed a significant inverse association for females. In the case of TSH, a significant inverse association with the sum of PCB levels was observed by Turyk et al. (2006, 2007) for men, in addition to a significant positive association by Abdelouahab et al. (2008) for men. However, in seven other reported results there were no associations between PCB and TSH levels.

Most of the epidemiological studies examined analyzed at least two environmental contaminants other than PCBs. However, part of the inconsistency of the epidemiological study results may also be explained by the fact that study participants were exposed to other possible endocrine disrupting chemicals. Different mechanisms of action were reported to explain the interference of environmental chemicals in thyroid homeostasis at the receptor level, in biding to transport proteins, in cellular uptake mechanisms or in modifying the metabolism of THs, as reviewed by Boas et al. (2006). However, uncertainties still exist relative to the potential additive, antagonistic or synergistic effects of exposure to endocrine disrupter mixtures (Crofton, 2008).

Inconsistencies in results, even in higher quality epidemiological studies, might signal the necessity of improvements of the definition and estimation of thyroid function markers. Zoeller (2003) suggested that changes in circulating levels of TH and/or TSH are not the most sensitive measure of PCB actions on thyroid toxicity and that measures of hormone action are more sensitive. However, the same author pointed out that there are still no validated markers of TH action independent of circulating levels of hormones.

For some studies reviewed, the power to find an association between PCBs and measures of thyroid function was likely low (Pelletier et al., 20012; Bloom et al., 2003; Turkey et al., 2006). However, none of the studies provided any estimate of their power to find the associations between PCBs and thyroid hormone serum levels. This deficiency limits the utility of some of the existing studies for addressing whether PCBs are associated with perturbations of thyroid function.

Longitudinal study designs are recommended for further epidemiological study on PCBs, thyroid hormones, and TSH. In addition, the research should include a careful analysis and inclusion of potential confounders. In particular, it is important to identify and control for other potential environmental thyroid disruptors. In addition, the selection of outcomes for the thyroid homeostasis should be carefully justified. The publications should also provide a more accurate description of the study population selection, assays used for exposure and outcome and power of the study. There is a need to standardize what PCB congeners are measured and reported in future studies. Many studies report only total PCBs, or selected congeners, or different groups of congeners, which precludes meaningful comparisons of findings across studies.

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