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Upstream adverse effects in risk assessment: A model of polychlorinated biphenyls, thyroid hormone disruption and neurological outcomes in humans

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A R T I C L E   I N F O

A B S T R A C T

Background: Increasing data on early biological changes from chemical exposures requires new interpretation tools to support decision-making.
Objectives: To test the possibility of applying a quantitative approach using human data linking chemical exposures and upstream biological perturbations to overt downstream outcomes.
Methods: Using polychlorinated biphenyl (PCB) exposures and maternal thyroid hormone (TH) perturbations as a case study, we model three relationships: (1) prenatal PCB exposures and TH changes, using free T_4 (FT_4); (2) prenatal TH and childhood neurodevelopmental outcomes; and (3) prenatal PCB exposures and childhood neurodevelopmental outcomes (IQ). We surveyed the epidemiological literature; extracted relevant quantitative data; and developed models for each relationship, applying meta-analysis where appropriate.
Results: For relationship 1, a meta-analysis of 3 studies gives a coefficient of -0.27 pg/mL FT_4 per ln(sum of PCBs) (95% confidence interval [CI] -0.82 to 0.27). For relationship 2, regression coefficients from three studies of maternal FT_4 levels and cognitive scores ranged between 0.99 IQ points/(pg/mL FT_4) (95% CI -0.31 to 2.2) and 7.6 points/(pg/mL FT_4) (95% CI 1.2 to 16.3). For relationship 3, a meta-analysis of five studies produces a coefficient of -1.98 IQ points (95% CI -4.46 to 0.50) per unit increase in ln(sum of PCBs). Combining relationships 1 and 2 yields an estimate of -2.0 to -0.27 points of IQ per unit increase in ln(sum of PCBs).
Conclusions: Combining analysis of chemical exposures and early biological perturbations (PCBs and FT_4) with analysis of early biological perturbations and downstream overt effects (FT_4 and IQ) yields estimates within the range of studies of exposures and overt effects (PCBs and IQ). This is an example approach using upstream biological perturbations for effect prediction.

1. Introduction

Evolving science has expanded our ability to incorporate relevant and sensitive upstream markers of adverse effects into risk assessment decisions. The U.S. Environmental Protection Agency (USEPA) defines an adverse effect as "a biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism, or reduces an organism's ability to respond to an additional environmental challenge" (US Environmental Protection Agency, 2010). Thus biological perturbations that arise early in the chain of events following chemical exposure can be considered adverse effects by USEPA.

New approaches are needed to incorporate these perturbations into hazard identification and risk assessment.

A critical part of using early perturbations in hazard identification and risk assessment is an understanding of the relationship between early biological changes and subsequent downstream overt effects. Traditionally, regulatory agencies have based risk assessment decisions on the occurrence of overt effects, such as cancer and neurocognitive deficits. New approaches envisioned for toxicity testing will produce data mostly on relationships between exposures and upstream, or early, indicators (National Research Council, 2007). Further, volumes of early perturbation data are now produced in epidemiologic and toxicology studies. Understanding the quantitative links between early perturbations and downstream overt effects makes it possible to estimate the potential impact and significance of early perturbations by relating their occurrence to events, which are better understood by decision-makers.

Thyroid hormone (TH) disruption is one class of early perturbation which is linked to downstream overt effects, and is amenable to incorporation into risk assessment (Woodruff et al., 2008). Thyroid hormones, including, thyroxine (T_4) and triiodothyronine (T_3), are essential for normal brain development, particularly prenatally (Morreale de Escobar, 2001; Zoeller and Rovet, 2004). TH perturbations in pregnant mothers are associated with neurological deficits in their children, including IQ decrements (Haddow et al., 1999; Oerbeck et al., 2003; Selva et al., 2005). Moreover, numerous environmental chemicals can modulate TH levels (Crofton, 2008; Miller et al., 2009).

We have developed an approach to link early perturbations to downstream overt effects for use in risk assessment. In this paper, we evaluate exposure to TH-disrupting chemicals during the prenatal period and effects on TH disruption as a case study. We chose polychlorinated biphenyls (PCBs), which are associated with altered TH levels and neurological outcomes. We focus here on human data; similar analyses of animal data address incorporating nonhuman perturbation data in risk assessment (Bernal, 2007; Morreale de Escobar et al., 2004; Parham et al., 2012).

2. Background

2.1. PCBs

Our analysis focuses on human exposures to PCBs and circulating TH for several reasons. First, PCBs suppress circulating levels of TH in animals and humans (Langer, 2008; Yang et al., 2010). The presumed mechanism is that these chemicals induce various enzymes that metabolize TH, and thus can reduce levels of T4. (Hood et al., 2003; Liu et al., 1995; Sugatani et al., 2001; Visser et al., 1993). There is enough human data on the relationship between PCB body burden and TH levels humans for modeling. Second, many studies characterize the relationship between PCB body burden and measures of cognitive function (e.g., Stewart et al., 2008), and between TH insufficiency and measures of cognitive function (Zoeller and Rovet, 2004). The literature therefore enables us to use the chain of PCB exposures, TH perturbations, and overt effect (cognitive function) to estimate the relationship between PCB exposure and overt effect as mediated by TH insufficiency. This estimate can be compared to direct estimates of the relationships between PCB exposure and overt effect. Third, the data for other thyroid disrupting chemicals (i.e., brominated flame retardants, perfluorinated compounds, perchlorate) are insufficient to model the chemical–TH relationship, the chemical–IQ relationship, or both. One limitation of choosing PCBs for this case study is that PCBs may influence neurodevelopment through multiple mechanisms, and we do not

know the exact contribution of TH perturbations from PCB exposure to neurodevelopmental effects. However, there is a relatively robust database from which to illustrate our proposed approach, which provides data on one of the proposed mechanistic pathways between exposure and overt effects, which informs further applications.

2.2. TH function and role in development

Insufficient levels of TH during development can lead to mild to severe cognitive impairment, neurobehavioral disorders, hypomyelination, and attendant physical impairments and may predispose the individual to other conditions and disease (van der Sluijs Veer et al., 2008; Zoeller, 2005).

The thyroid system is a classic neuroendocrine axis. The hypothalamus releases thyrotropin-releasing hormone (TRH), which acts upon the pituitary gland. In response to TRH, the pituitary releases thyroid-stimulating hormone (TSH) into circulation. TSH controls the thyroid gland's production and secretion of T_4 and, to a lesser extent, T_3. TSH is regulated by the negative feedback action of T_4 on the pituitary. The feedback among the hypothalamus, pituitary, and thyroid maintains the thyroid system's activity within relatively narrow limits (Andersen et al., 2002). Although T_4 is the predominant TH found in serum, T_3 is the active form and is formed primarily by deiodination of T_4 in the target tissue.

The effects of TH on the developing brain are directly related to serum concentrations of T_4 in animal studies; even small reductions in serum TH have effects (Auso et al., 2004; Gilbert and Sui, 2006). Human studies are consistent with these animal studies. The fetus is entirely dependent on maternal THs during the first trimester (Smallridge et al., 2005). Even mild to moderately low levels of T_4 during the first trimester are associated with cognitive deficits in the children (Haddow, 2005; Haddow et al., 1999; Pop et al., 1999, 2003). Also, small deficits in circulating levels of TH are associated with decreased cognitive performance at various times during development and adulthood (Glinoer and Rovet, 2009; Heyerdahl and Oerbeck, 2003; LaFranchi and Austin, 2007; Selva et al., 2005; Simic et al., 2009).

A number of environmental chemicals can disrupt TH levels, and many decrease circulating levels of T_4 (Brucker-Davis, 1998; Howdeshell, 2002). Under normal physiological conditions, a decline in circulating levels of T_4 causes an increase in serum TSH (Burman, 2008). However, there are cases of discordant measures of T_4 and TSH, when T_4 levels can change without changes in TSH. Relying only on evaluation of changes in TSH without consideration of T_4 may underestimate effects. Various chemicals, including PCBs, lower serum total and free T_4 (TT_4 and FT_4) without causing a concomitant increase in serum TSH (Zoeller, 2007).

TH synthesis is iodine-dependent, and about one third of U.S. women have low iodine intake (Caldwell et al., 2005). This at risk population, combined with findings regarding the consequences of small decrements of T_4, and fetal dependence on maternal hormone levels indicate that small, chemically induced changes in T_4 can increase the risk of subsequent neurological events. Compensatory mechanisms may not suffice, and theories for compensation to make up for small changes in T_4 on a population-wide basis lack empirical support.

3. Methods

Fig. 1 shows a diagram of our overall approach, which is to model the relationship between the exposure and early biological perturbations (Relationship 1), and the relationship between the perturbation and overt outcome (Relationship 2), and then to combine the two relationships to determine the

relationship between exposure and overt outcome. We can compare this combined relationship to studies of exposure and overt outcome (Relationship 3) to evaluate the predicitivity of our approach. In our case study, the three quantitative epidemiological relationships are: Relationship 1, PCB exposures versus TH (FT_4) changes during pregnancy; Relationship 2, TH changes during pregnancy versus subsequent neurological deficits; Relationship 3, prenatal PCB levels versus neurocognitive deficits. For the analysis of relationship 1, we also examined studies of PCB exposures vs. TH in non-pregnant women and in men in order to increase the data available and to assess the sensitivity of the analysis to inclusion of different populations.

We focus on perturbations to serum T_4 concentration as our upstream indicator for analysis. The American Thyroid Association recommends determination of serum TSH and FT_4 concentrations as the standard measure of thyroid function, so we selected studies that include FT_4 measurements (DeVito et al., 1999). The analysis for total T_4 (TT_4) is presented in Supplementary Material.

3.1. Study selection

For each relationship, we conducted a literature search to find all relevant scientific articles. Next, we selected articles for our analysis that had each of the following:

1. Dose variables (Sum of PCBs in blood for Relationships 1 and 3, FT_4 levels for Relationship 2) (or TT_4, for inclusion in Supplementary Material).
2. Response variables (FT_4 or TT_4 levels for Relationship 1, neurocognitive test results for Relationships 2 and 3); and
3. A measure of dose-response (e.g., regression coefficient) for Relationships 1 and 3, or sufficient data to estimate such a measure for Relationship 2.

IQ as a measure of cognitive outcome was used because IQ is commonly used in epidemiological studies and in the policy process.
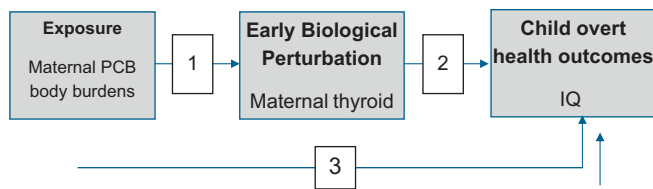

Fig. 1. Three relationships of chemical body burden to biological perturbation to downstream overt health outcome used in analysis.

3.1.1. Relationship 1: PCB body burdens and FT_4 levels

Seventeen human studies that evaluated the relationship between PCB levels and TH levels were identified (Table 1). Of these, 7 met our criteria for inclusion. Our primary analysis focuses on studies that measured PCBs and TH levels in the blood of pregnant women, as our case study is focused on childhood neurodevelopmental outcomes associated with thyroid hormone perturbations during pregnancy. Three studies were eligible for our primary analysis because they evaluated the PCB–TH relationship in maternal blood (Chevrier et al., 2008; Dallaire et al., 2009b; Lopez-Espinosa et al., 2009) Dallaire gives results for the single congener, PCB 153, but we use it in our analysis because the authors indicate results of their analysis were similar when using the sum of PCBs.

The PCB and TH measurements were obtained from different populations (maternal blood, cord blood, blood from non-pregnant women or from men). We analyzed data from the following combinations of studies: all non-cord-blood studies that included women (Chevrier, Dallaire b, Lopez-Espinosa, Dallaire a, Sala) (Dallaire et al., 2009a; Sala et al., 2001); all non-cord blood studies (Chevrier, Dallaire b, Lopez-Espinosa, Dallaire a, Sala, Meeker) (Meeker et al., 2007); all studies (Chevrier, Dallaire b, Lopez-Espinosa, Dallaire a, Sala, Meeker, Maervoet) (Maervoet et al., 2007); studies that have pregnant women or cord blood (Chevrier, Dallaire b, Lopez-Espinosa, Maervoet). Two studies included regression coefficients for only individual PCBs and were not used in the analysis (Alvarez-Pedrerol et al., 2009; Bloom et al., 2003). Two (Abdelouahab et al., 2008; Turyk et al., 2007) gave results for TT_4 only and are included in the TT_4 analysis in Supplementary Material. Further details are described in Supplementary Material.

3.1.2. Relationship 2: prenatal maternal FT_4 levels and neurocognitive outcomes

We identified six studies that evaluated the relationship between maternal TH levels during pregnancy and neurocognitive outcomes in children (Haddow et al., 1999; Klein and Mitchell, 1999; Kooistra et al., 2006; Pop et al., 1999, 2003; Vermiglio et al., 2004) (see Table 2). Four met our criteria: (Haddow et al., 1999; Pop et al., 1999, 2003; Vermiglio et al., 2004). The Pop studies reported on the same cohort and were therefore not independent. Pop 2003 found low FT_4 at 12 weeks gestation strongly associated with delays in both mental and psychomotor function of the Bayley Scales of Infant Development at 2 years of age. The earlier study found psychomotor function similarly affected at age 10 months, and did not evaluate mental function. The Pop 2003 study was chosen since the children were older, and data on mental function provided greater comparability with other studies. The Pop studies reported results for children of women who measured in the lowest 10 percent of FT_4 concentration at 12 weeks gestation. We assumed that the dose-response throughout the range of FT_4 was similar to the response for the lowest 10 percent. Haddow et al. (1999) conducted a case-control study, reporting mean IQ scores and FT_4 for cases and controls tested at ages 7 to 9 years. Vermiglio et al. (2004) studied the relationship of FT_4 and IQ at 8 to 10 years as part of a study of iodine deficiency. Although the Bayley Scales are not highly-correlated with IQ studied at older ages, we chose to include the Pop

Table 1
Studies considered for quantitative analysis of Relationship 1, between PCB body burdens and FT_4 levels in humans.

| Study | Human tissue sampled | Sex | | T_3 | TT_4 | FT_4 | TSH | Sum of PCBs | β coefficient, FT_4–PCB | Used in main meta-analysis?[a] | Used in sensitivity analysis? |
		Men	Women								
Abdelouahab et al. (2008)	Serum	X	X	X	X		X	X		N[b]	N
Alvarez-Pedrerol et al. (2009)	Serum		X (pregnant)	X		X			X	N[c]	N
Bloom et al. (2003)	Serum	X			X					N[c]	N
Chevrier et al. (2008)[d]	Serum		X (pregnant)		X	X	X	X	X	Y[b]	Y
Dallaire et al. (2009a)[d]	Plasma	X	X	X		X	X	X	X	N	Y
Dallaire et al. (2009b)	Plasma		X (pregnant)			X		X[e]	X	Y	Y
Koopman-Esseboom et al. (1994)	Plasma	X	X (pregnant)[f]	X	X					N[g]	N
Longnecker (2000)	Serum and breast milk		X (pregnant)[f]		X	X	X	X	X	N	N
Lopez-Espinosa et al. (2009)	Serum		X (pregnant)	X	X	X		X	X	Y	Y
Maervoet et al. (2007)	Cord blood		X		X		X	X	X	X	N	Y
Meeker et al. (2007)	Serum	X			X		X	X	X	X	N	Y
Nagayama et al. (1998)	Breast milk, infant blood			X	X		X			N	N
Otake et al. (2007)	Cord blood, infant blood					X	X	X		N[g]	N
Persky et al. (2001)	Serum	X	X	X	X	X	X			N	N
Sala et al. (2001)	Serum	X	X		X	X	X	X	X	N[b]	Y
Takser et al. (2005)	Plasma	X	X (pregnant)[f]	X	X	X				N	N
Turyk et al. (2007)	Serum	X	X		X		X	X		N[b]	N

[a] Included in main meta-analysis if study included pregnant women, FT4, and a beta coefficient from analysis of the sum of PCBs in blood.
[b] These studies were used for modeling the TT_4–PCBs relationship, discussed in Supplementary Material.
[c] Study gives regression coefficient for individual PCBs only (no sums).
[d] Reported PCBs on a per lipid weight basis.
[e] Dallaire et al. (2009b) reported results for PCB 153, but stated in the text that results using all PCBs were similar. This paper also included results based on measurements in cord blood and infant blood; we only used the maternal plasma results.
[f] Also measured in at least one of the following: umbilical cord, infants, and breast milk.
[g] Spearman's rank is reported, but beta is not provided in the study.

Table 2
Studies considered for quantitative analysis of Relationship 2, relationship between maternal FT$_4$ levels and neurological outcomes in children. Table includes a summary of information the studies contained: age of child, the type of IQ test administered, what thyroid hormone was monitored (T$_3$, TT$_4$, FT$_4$ or TSH), if we were able to calculate a dose/response function and if we used it in our analysis.

Study	Age of child when tested	Type of test administered	T$_3$	TT$_4$	FT$_4$	TSH	Time of measurement of FT$_4$	Ability to calculate FT$_4$ dose-response	Used in analysis?
Haddow et al. (1999)	7–9 years	Full-scale IQ, Wechsler Intelligence Scale for Children, Third Edition (WISC-III)	X	X	X		17th gestational week (mean)	X	Y
Klein et al. (2001)	8 years	Full-scale IQ, WISC-III				X	n/a	X	N
Kooistra et al. (2006)	3 weeks	Neonatal Behavioral Assessment Scale			X	X	12th gestational week		N
Pop et al. (2003)	2 years	Bayley Scales of Infant Development, Psychomotor Development Index (PDI)			X	X	12th gestational week	X	Y
Pop et al. (1999)	10 months	Bayley Scales of Infant Development, PDI and Mental Development Index			X	X	12th and 32nd gestational weeks	X	N[a]
Vermiglio et al. (2004)	8–10 years	Full-scale IQ, WISC-III			X	X	Mid-gestation	X	

[a] Same cohort as Pop 2003 which was used instead.

Table 3
Studies considered for quantitative analysis of Relationship 3, between maternal PCB body burdens and neurological outcomes in children.

Study	Age of child when tested	Location/Cohort	PCBs measured in				Measure of dose-response	Used in model?
			Cord blood	Breast milk	Maternal blood	Other		
Gray et al. (2005)	7	U.S. Collaborative. Perinatal Project			X		X	Y
Jacobson et al. (1990)	4	Michigan	X	X			X	Y
Jacobson and Jacobson (1996)	11	Michigan	X	X				N
Jacobson and Jacobson (2003)	11	Michigan	X	X				N
Patandin et al. (1999)	3.5	Dutch			X		X	Y
Stewart et al. (2003)	38 or 54 months	Oswego	X	X			X	N[a]
Stewart et al. (2008)	9	Oswego				Placenta	X	Y
Vreugdenhil et al. (2002)	6.5	Dutch	X	X	X		X	Y

[a] Reports standardized coefficients only and did not have enough data to convert to nonstandardized values.

study to incorporate a broader range of information; the alternative was to rely on the Haddow and Vermiglio studies alone for Relationship 2.

3.1.3. Relationship 3: prenatal PCB body burdens and neurocognitive outcomes

We found 8 studies that directly assessed maternal PCB body burdens and cognitive outcomes in children (Gray et al., 2005; Jacobson and Jacobson, 1996, 2003; Jacobson et al., 1990; Patandin et al., 1999; Stewart et al., 2008; Vreugdenhil et al., 2002; Stewart et al., 2003) (see Table 3). Five met our inclusion criteria (Gray et al., 2005; Jacobson et al., 1990; Patandin et al., 1999; Stewart et al., 2008; Vreugdenhil et al., 2002).

3.2. Quantitative analysis

This section outlines our mathematical modeling. Further description of quantitative methods appears in Supplementary Material.

3.2.1. Model for Relationship 1: PCB body burdens and FT$_4$ levels

We modeled dose response in each of the 7 studies used in the main meta-analysis or sensitivity analysis using a log-linear model of the form

$$FT_4 = a + b\ln(PCB)$$

where PCB = the sum of PCBs. Under ideal conditions of perfect correlation of PCB exposures, the log-linear model has the same regression coefficient no matter what PCBs are used as the dose metric—see Supplementary Material for discussion of this. Some animal studies of neurodevelopmental endpoints use total thyroxine (TT$_4$) as a measure of thyroid function disruption, and several human studies also measure TT$_4$ (see Table 1). For an analysis of TT$_4$ (instead of FT$_4$) vs. PCBs using the above model, see Supplementary Material.

Several differences in the analyses used in the seven selected papers warrant consideration when comparing the models (e.g., study population, PCB measurements). To the extent feasible, we resolved these differences by various analytic techniques, as discussed briefly below and in Supplementary Material.

All studies in the main and sensitivity analyses used measurements of PCBs in adult blood. The exception was for one study used in the sensitivity analysis Maervoet et al. (2007) measured umbilical cord blood. We used a ratio of 0.259 for cord: maternal blood PCB concentration (Covaci et al., 2002) to convert the

Maervoet PCB levels into equivalent values for maternal blood. This value is within the range reported from other studies (Jacobson et al., 1990; Patandin et al., 1999; Vreugdenhil et al., 2002). Chevrier et al. (2008) and Dallaire et al. (2009a, 2009b) reported PCBs per amount of lipid in serum or plasma, respectively. The other studies used PCBs on a wet-weight basis for their regression models. The Chevrier et al. (2008) and Dallaire et al. (2009a, 2009b) studies all used ln(PCB) as the dependent variable in their models. If the PCB concentration per amount lipid is proportional (within a study population) to the concentration per volume plasma or serum, then changes in ln(PCB) are the same whether based on PCBs/lipid or PCBs/volume. We make the approximation that the proportion holds for each study and therefore it is not necessary to convert from a per-lipid measurement in our calculations.

We used a meta-analysis to combine the slopes b from the log-linear models to obtain an overall estimate of the relationship between PCBs and FT$_4$. The studies used different sets of variables to adjust for potential confounders of a PCB effect (e.g., poor nutrition) and various PCB congeners in calculating the sum of PCBs (the independent variable in the model; we use a log-linear model, which under ideal conditions of perfect correlation of PCB exposures has the same regression coefficient whichever weighted sum of PCBs is used—see Supplementary Material). Consequently, we used a random-effects model (Dersimonian and Laird, 1986). Our main analysis uses data from the studies of pregnant women (Chevrier et al., 2008; Dallaire et al., 2009b; Lopez-Espinosa et al., 2009). Effects of including studies using cord blood or blood from men are discussed in Supplementary Material, as are all the data used in the meta-analysis.

3.2.2. Model for Relationship 2: prenatal FT$_4$ levels and neurocognitive outcomes

Pop 2003 reported data as a scatter diagram. Because the paper did not include a regression coefficient, we digitized the scatter plot and used linear regression to obtain a slope for the relationship between FT$_4$ and the neurocognitive endpoint. We used a re-sampling procedure to obtain CIs for the slopes, as discussed in Supplementary Material. The scores for the IQ tests in the Pop study have standard deviations of 16 (Pop et al. 1999). We multiplied the results by 15/16 to be on the same scale as the other results, as suggested in Axelrad et al. (2007). We converted from units pmol/L FT$_4$ to pg/mL FT$_4$ using the molecular weight of thyroxine (776.87). We obtained a slope for the relationship between FT$_4$ and IQ in Haddow et al. (1999) by simulating the population distribution of FT4 and IQ in case and control groups (see Supplementary Material for more

Table 4
Slope estimates (unscaled and scaled for equal standard deviation) for the relationship between maternal PCB concentration and neurocognitive outcomes (Relationship 3).

Study	Standard deviation of score	Slope (unscaled) (change in IQ/unit change in ln[PCB])	Standard error (unscaled)	Slope (scaled)[a] (change in IQ/unit change in ln[PCB])	Standard error (scaled)
Gray et al. (2005)	16.3	0.67	0.76	0.62	0.70
Jacobson et al. (1990)	12.6	− 1.97	1.61	− 2.35	1.91
Patandin et al. (1999)	14	− 4.56	1.62	− 4.89	1.74
Stewart et al. (2008)	12.7	− 3.58	1.55	− 4.23	1.83
Vreugdenhil et al. (2002)	12.6	− 0.14	1.58	− 0.17	1.88

[a] Slope (scaled) is the original slope scaled by 15/std. dev.

details). Vermiglio et al. (2004) also reported data as a scatter diagram, with no regression coefficient. We digitized the plot and then analyzed it using the same regression and re-sampling as we used for Pop et al. (2003), as discussed in Supplementary Material.

3.2.3. Model for Relationship 3: prenatal PCB body burdens and neurocognitive outcomes

Different IQ and cognitive tests were administered to children of different ages in the selected studies. Most of the studies found an inverse relationship between PCB concentrations and cognitive test scores. Patandin et al. (1999), Jacobson et al. (1990), and Vreugdenhil et al. (2002) used models with a log-transformed sum of PCB concentration as the independent variable. Gray et al. (2005) and Stewart et al. (2008) used linear models. We converted their slopes using log-transformed PCBs as the independent variable. The comparability of the models and selection of values from each study is given in Supplementary Material. The IQ/cognitive test results from the various studies had different standard deviations. We scaled the slopes to a common standard deviation of 15 (Axelrad et al., 2007). For results before and after scaling, see Table 4.

4. Results

4.1. Relationship 1: PCB body burdens and FT$_4$ levels

The slope of the relationship between FT$_4$ and ln(PCB level) for each of the 3 studies in pregnant women, and the meta-analysis results for those studies, is shown in Fig. 2. The beta coefficients for all seven studies and for the different meta-analyses are shown in Tables S1 and S2. Four studies found PCB levels were associated with a decrease in FT$_4$ (Chevrier, Dallaire a, Dallaire b, and Maervoet), with two of those associations being statistically significant; the other three found a positive relationship, but the confidence interval included 0. The meta-analysis of data from pregnant women yields an overall coefficient of $b = -0.27$ pg/mL FT$_4$ per unit change in ln(sum of PCBs) (95% CI of − 0.82 to 0.27). This translates into a reduction of 0.19 pg/mL (0.01871 ng/dl) FT$_4$ per twofold increase in ln(sum of PCBs). FT$_4$ levels vary from study to study. One cohort in Alvarez-Pedrerol had a median FT$_4$ concentration of 0.77 ng/dl, while Sala reported a mean concentration of 1.34 ng/dl. Using a concentration of 1 ng/dl as a value for comparison, a twofold increase in ln(sum of PCBs) gives a change in FT$_4$ concentration equal to 1.9 percent of the average value. The difference in PCB concentration between the 5th percentile and the median in Lopez-Espinosa et al. (2009) is about 2.6-fold. Longnecker et al. (2003) found that difference between the median PCB concentration in human studies and the 5th percentile was often about threefold. Using the same model, a 2.6-fold increase in the sum of PCBs would give about a 2.6 percent change in FT4 concentration and a threefold increase would give about a 3 percent change. The sensitivity analyses almost all found negative b coefficients. They were weaker than the results of the main analysis (pregnant women only), with the exception of the meta-analysis of the pregnant women and cord blood study which had a b about double the primary analysis: $b = -0.54$ pg/mL FT$_4$ per unit change in ln(sum of PCBs) (95% CI of

− 1.2 to 0.13). All results had confidence intervals including zero. See Supplementary Material for all results.

4.2. Relationship 2: prenatal FT$_4$ levels and neurocognitive outcomes

For Pop et al. (2003), the Bayley Scales mental tests versus FT$_4$ slope is 7.6 points/(pg/mL FT$_4$) (95% CI 1.2 to 16.3). The estimated regression coefficient from Haddow et al. (1999) was 0.99 IQ points/(pg/mL FT$_4$) (95% CI − 0.31 to 2.2). The estimated regression coefficient from Vermiglio 2004 was 3.4 IQ point/(pg/ml FT$_4$) (95% CI 0.81 to 6.5).

4.3. Relationship 3: prenatal PCB and neurocognitive outcomes

The slopes from the individual studies for maternal PCBs and child neurocognitive outcomes are shown in Table 4 and Fig. 3. For three studies, as PCBs increase, neurocognitive scores decrease (Patandin, Jacobson, and Stewart). The other two find slightly negative (Vreugdenhil) or slightly positive (Gray) relationships but the 95% CI includes 0. The ages of the children tested ranged from 3.5 to 9 (Table 3). Given the range of ages and study characteristics, there is relatively large uncertainty in aggregating the results through a meta-analysis (Goodman et al., 2010). Nevertheless, it is useful to apply meta-analysis to derive a single coefficient representing this literature for comparison to the combination of results from Relationships 1 and 2. A meta-analysis produces a coefficient of − 1.98 points of IQ per unit change in ln(PCB) (95% CI − 4.46 to 0.50).

4.4. Combining results from Relationships 1 and 2; comparison to Relationship 3

We found an FT$_4$ level effect of − 0.27 pg/mL per unit change in ln(sum of PCBs) from the meta-analysis for Relationship 1. We also found a 0.99 to 7.6 point decrease in neurocognitive test scores per pg/mL FT$_4$ decrease (Relationship 2). Multiplying these slope factors yields a range of estimates of the relationship between PCBs and IQ: − 2.0 to − 0.27 points of IQ per unit change in ln(sum of PCBs). This value is shown in Fig. 3 as a gray rectangle. All of these values have wide confidence limits, most including 0.

5. Discussion

We have developed a quantitative approach for using existing peer-reviewed human epidemiological studies to model the dose-response relationship between chemical exposures and between upstream biological perturbations and upstream biological perturbations and overt effects. We applied our approach to a case study on PCB-induced T$_4$ perturbation, an important upstream biological perturbation (Woodruff et al., 2008) and neurocognitive
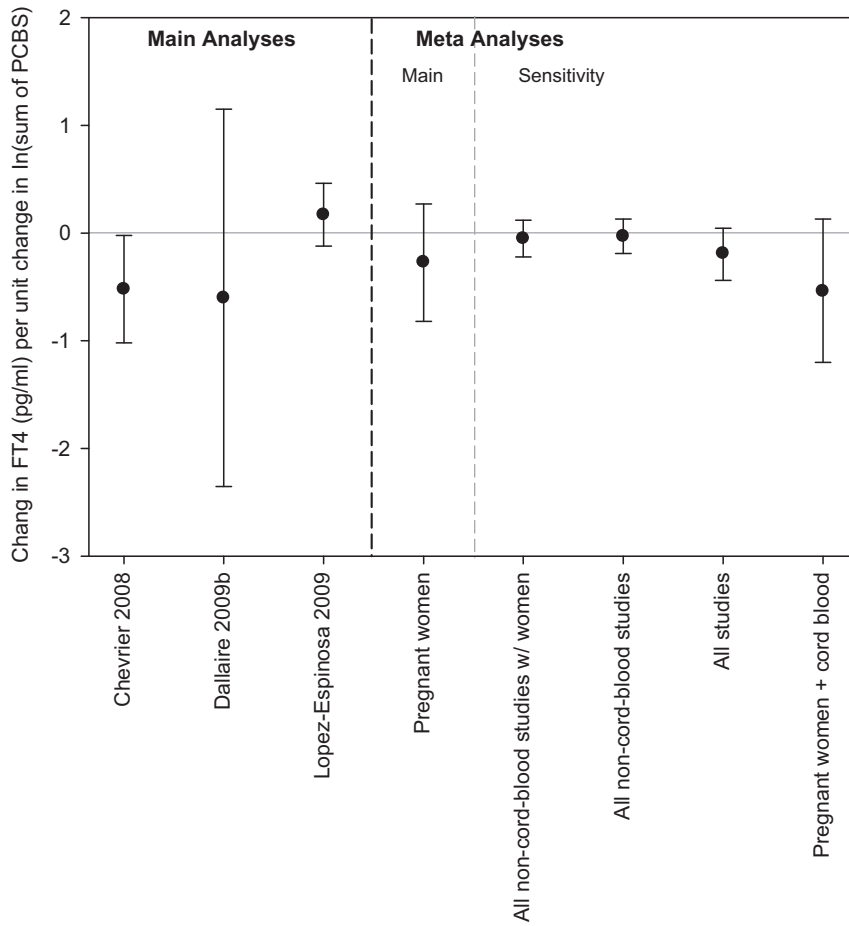
Fig. 2. Coefficient of the change in FT_4 (pg/ml) per unit change in ln(sum of PCBs). Point estimates plotted with the 95% CI range.
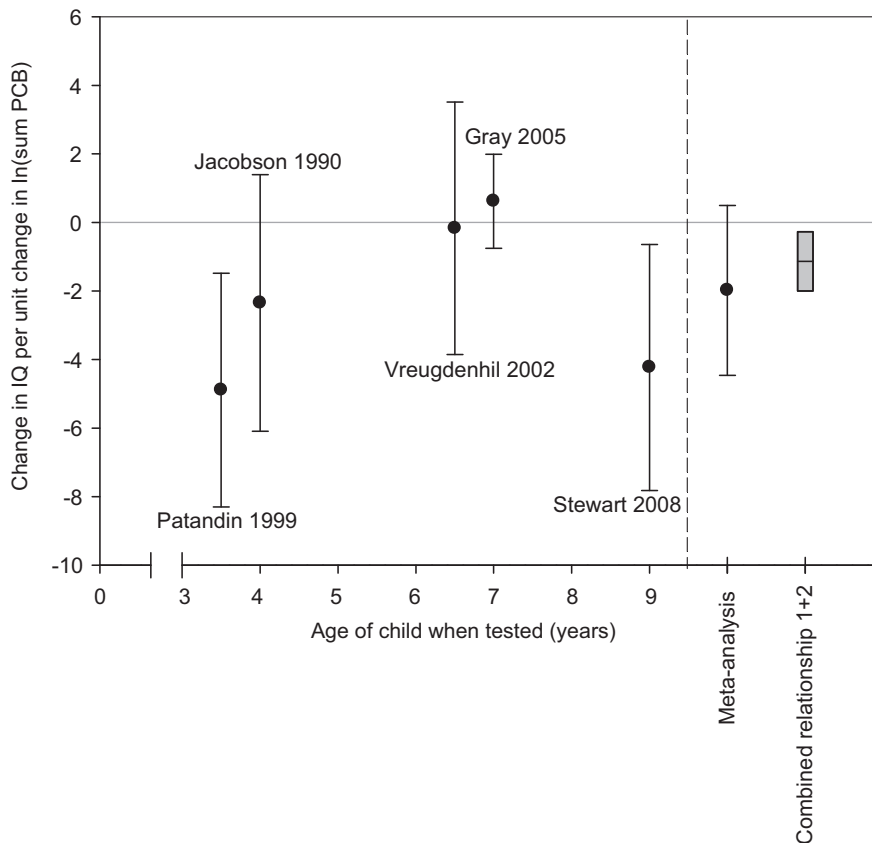

Fig. 3. Regression coefficient and 95% CIs for studies of effect of PCB exposure on IQ. Meta-analysis includes all studies shown. Error bars indicate the 95% CI. The gray box represents the range of estimates from the combined result of Relationships 1 and 2.

deficits linking epidemiological findings on exposure, early biological perturbations, and neurodevelopmental outcomes. We found that the combination of the PCB/thyroid relationship (Relationship 1) with the thyroid/IQ relationship (Relationship 2) produced results that were within the range of estimates from PCB neurodevelopmental studies (Relationship 3) despite the differences in study design. However, the confidence intervals for all results are wide. Further research would be needed to more narrowly bound estimates of effect.

The variability in the epidemiologic findings is likely in part due to variability in experimental settings (including different populations with different PCB exposures) and design. Animal studies, which have a more consistent experimental approach, consistently find increasing PCB dose associated with decreased FT_4, and as such indicate that fully assessing PCBs, THs, and neurocognitive outcomes can be informed by integrating animal and human findings (Parham et al., 2012). In addition, while our approach allows for assessing different mixtures of PCBs, it is based on the assumption that the sums of different combinations of PCBs have similar effects on THs, though they may be of varying magnitude. A study by Chevrier et al. found that the sum of individual PCB congeners that induce microsomal enzymes have a greater relationship with TSH in neonates than the sum of all PCBs (Chevrier et al., 2007), though studies by the same investigators also found the sum of PCBs produces a stronger relationship with serum T_4 in pregnant women than the sum of the enzyme inducers (Chevrier et al., 2008). They posit that if PCBs that have no or opposite effects on TH are included in the sum, it could produce more uncertainty in the relationship with serum T_4.

One of the significant challenges of integrating the epidemiology studies into a meta-analysis is variability in many aspects of study design, analysis, and reporting. Many studies have assessed the relationship between PCBs and thyroid hormones and the relationship between PCBs and neurocognitive outcomes (Salay and Garabrant, 2009). However, there are differences in selection of PCB congeners, analyses of biological matrices, exposure metrics, analytic models, and endpoint measurement and selection.

The studies evaluating the relationship between TH and IQ illustrate the challenges of variability in study design and reporting for use in these type of integrated approaches. First, only four papers provided sufficient data for quantitative analysis, with two—the Pop studies—from the same cohort. Second, the Pop studies used only a subset of the population (children born to women measuring, at gestation week 12, in the lowest 10 percent of FT_4 compared to those with mothers between the 50th to 90th percentile of FT_4). We assumed that the relationship between FT_4 and IQ is the same throughout all levels of T_4, introducing uncertainty. Third, measurements in the Haddow and Vermiglio studies occurred late in pregnancy. If early pregnancy is a more vulnerable period (Morreale de Escobar et al., 2000), using measurements from later in pregnancy could underestimate the effects. Finally, the Pop studies assessed children during infancy (up to age two years) and thus used the Bayley scales, whereas Haddow and Vermiglio tested children at school age (7 to 9 years, and 8 to 10 years, respectively) and assessed IQ. Although the correlation between the Bayley Scales and IQ is weak, we chose to use Pop as well as Haddow and Vermiglio in order to incorporate more quantitative information into our model. All three studies find a relationship with TH, though the IQ relationship from the Haddow study is smaller than the relationship for the other two studies.

Identifying studies with sufficient data to model the relationship between PCBs and THs during pregnancy was also a challenge. While there are many studies of PCBs and THs in adults,

only three provided measured of PCBs and THs in our population of interest, pregnant women. We focus on pregnant women because TH can vary and interact with exogenous disturbances uniquely during pregnancy. We conducted sensitivity analyses considering additional studies of adult women and men, including a study with measurements in cord blood. In general, sensitivity analyses that added studies in non-pregnant adults found a smaller relationship between PCBs and THs, whereas inclusion of findings from the Maervoet study that measured PCBs and TH in cord blood resulted in estimates with a greater magnitude of effect.

With regard to the PCB–IQ relationship, some researchers have found the differences in design of the studies sufficiently daunting that they have been reluctant to combine them through meta-analysis (Goodman et al., 2010). However, qualitative and selective evaluation of the literature limits the interpretation of the overall evidence. Further, there are reasonable adjustments that can be made to the exposure metrics and dose-response information to make the studies more comparable and thus increase the number of studies whose results could be used in the meta-analysis. For example, we converted the models all to a common mathematical form and used the log-linear model, which may mitigate the differences in selection of PCB congeners (see Supplementary Material). While such assumptions can increase the uncertainty of observed results, providing CIs allowed us to evaluate the degree of imprecision to some extent. However, there were still a number of studies that could not be included in this analysis because of insufficient data for quantitative modeling. An effort to encourage more standard reporting of environmental epidemiology results from studies would make them more useful for subsequent syntheses of the literature such as this.

It is challenging to standardize the studies for a meta-analysis, but meta-analysis has significant advantages. It can increase the statistical power to detect small excess risks (Grellier et al., 2010). It also provides an unbiased method for combining the results of multiple studies. The alternative is to choose individual studies to represent quantitative relationships, which could introduce bias. Studies in the clinical literature find that subjective scoring of studies can influence findings and even meta-analysis results (Juni et al., 1999).

We focus on thyroid disruption in relation to its neurotoxic effects. PCBs are well known to affect neurodevelopmental outcomes in humans (Schantz et al., 2003), and additional mechanisms may be important. For example, some PCB (and OH-PCB) congeners are estrogenic (Matthews et al., 2007; Wang et al., 2006). Some PCB congeners bind to the ryanodine receptor with high affinity and can alter calcium signaling in cells of the central nervous system (Pessah et al., 2009; Yang et al., 2009). Our Relationship 3, modeling the effect of PCBs on IQ, cannot separate out these mechanisms. Information on the relative contribution of different mechanisms to the PCB–IQ relationship is lacking. Our analysis presumes that TH is one important pathway, but it does not presume that it is the only or necessarily the most important pathway, and does not preclude a (perhaps significant) role for other mechanistic pathways.

Various factors may influence population dose-response (National Research Council, 2009), including cumulative exposures and susceptible populations. We integrate some of these concepts in our analysis. We partially accounted for multiple PCB exposures, but did not account for other exposures that can affect brain development (e.g., mercury, lead), or TH levels (e.g., PBDEs, perchlorate). Nor did we integrate other forms of population variability, such as disease status. Iodine deficient women (TH synthesis is dependent on iodine) likely have enhanced susceptibility to thyroid-disrupting chemicals, such as PCBs. About 30%

of women in the US are iodine deficient (Caldwell et al., 2005). The extent to which the relationships we observed are related to this population is unclear. The functional form used to describe the FT_4 PCB relationship may vary depending on other factors such as iodine deficiency, disease status or exposure to other thyroid disrupting chemicals. The model used here has the same (log-linear) functional form for Relationships 1 and 3, with a linear model for Relationship 2. This makes it possible to estimate Relationship 3 by multiplying the slopes found for Relationships 1 and 2. Using other functional forms would make the comparison of the relationships more difficult.

This paper explores ways to quantify IQ changes affected by chemically-induced maternal TH perturbations. IQ changes have been used to inform USEPA regulatory decisions. The 2008 revision to the National Ambient Air Quality Standard for lead was explicitly based on the estimated IQ losses in children associated with different levels of lead in ambient air (US Environmental Protection Agency, 2008b). Furthermore, the estimated benefits of recent standards to reduce childhood lead exposure from ambient air and home-renovation activities included avoided reductions in childhood IQ (US Environmental Protection Agency, 2008a, 2008c). IQ benefits have also been estimated for a standard to reduce mercury emissions (US Environmental Protection Agency, 2005). IQ decrements from changes in exposure can then be translated into monetary values. Thus, the advantage of IQ is that it can be converted into economic terms which are commonly used in decision-making. The disadvantage is that current approaches to monetizing IQ are likely an underestimate of benefits of reduced exposure to neurodevelopmental toxins. Current methods value IQ reductions based on losses in future earnings, and do not include other benefits of avoiding reduced IQ, cognitive effects not captured by IQ testing, or any other neurodevelopmental outcomes such as behavioral effects.

6. Conclusion

Given the increasing emphasis of toxicity testing on early biological markers, new methods of risk assessment that can translate the results of this testing for decision-makers is sorely needed. We present an approach for incorporating scientific studies of upstream biological perturbations from chemical exposures into estimates of risks of more overt effects, thus providing a means for facilitating the use of more efficient testing into decision-making. Our case study illustrates implementation of our approach in the context of available data for PCBs, thyroid hormone disruption, and effects of childhood IQ. Further, we identify some of the challenges and limitations to using existing data to link early biological perturbations with overt endpoints, which will likely arise in interpretation of other types of early biological perturbations. These challenges can increase the uncertainty of our findings, though further development of the literature is likely to provide improved data for each of the 3 relationships in our case study.

A larger uncertainty, however, stems from the lack of toxicological data for various endpoints and numerous chemicals. Approaches such as these will be necessary to address gaps in toxicity testing in a way that facilitate decision-making. If relationships such as these are to be used for other chemicals, pathways or endpoints, it will be necessary to have studies that report sufficient information to allow their use in these types of integrated modeling approaches.

The ultimate goal of this type of analysis is to be able to predict overt downstream effects by measuring early perturbations. This analysis showed that the reported relationships between exposure and early perturbations and between early perturbations and downstream effects are not inconsistent with the reported relationship between exposure and downstream effect..

This is an important first proof of principle and it highlights the need for further information about each of the relationships in the analysis. However, given the immediate needs of the decision-making process these types of approaches can provide useful tools for the decision-maker in interpreting early biological perturbation data.

Declaration of competing financial interests

The authors do not have any competing financial interests.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2012.05.013.

References

Abdelouahab, N., et al., 2008. Gender differences in the effects of organochlorines, mercury, and lead on thyroid hormone levels in lakeside communities of Quebec (Canada). Environ. Res. 107, 380–392.

Alvarez-Pedrerol, M., et al., 2009. Organochlorine compounds, iodine intake, and thyroid hormone levels during pregnancy. Environ. Sci. Technol. 43, 7909–7915.

Andersen, S., et al., 2002. Narrow individual variations in serum T(4) and T(3) in normal subjects: a clue to the understanding of subclinical thyroid disease. J. Clin. Endocrinol. Metab. 87, 1068–1072.

Auso, E., et al., 2004. A moderate and transient deficiency of maternal thyroid function at the beginning of fetal neocorticogenesis alters neuronal migration. Endocrinology 145, 4037–4047.

Axelrad, D.A., et al., 2007. Dose-response relationship of prenatal mercury exposure and IQ: an integrative analysis of epidemiologic data. Environ. Health Perspect. 115, 609–615.

Bernal, J., 2007. Thyroid hormone receptors in brain development and function. Nat. Clin. Pract. Endocrinol. Metab. 3, 249–259.

Bloom, M.S., et al., 2003. Exploring associations between serum levels of select organochlorines and thyroxine in a sample of New York state sportsmen: the New York State Angler Cohort Study. Environ. Res. 93, 52–66.

Brucker-Davis, F., 1998. Effects of environmental synthetic chemicals on thyroid function. Thyroid 8, 827–856.

Burman, K., 2008. Commentary: discordant measurements of serum triiodothyronine (T4), thyroxine (T3) and thyroid-stimulating hormone (TSH). Clin. Chem. 54, 1246.

Caldwell, K.L., et al., 2005. Urinary iodine concentration: United States National Health and Nutrition Examination Survey 2001–2002. Thyroid 15, 692–699.

Chevrier, J., et al., 2007. Associations between prenatal exposure to polychlorinated biphenyls and neonatal thyroid-stimulating hormone levels in a Mexican–American population, Salinas Valley, California. Environ. Health Perspect. 115, 1490–1496.

Chevrier, J., et al., 2008. Effects of exposure to polychlorinated biphenyls and organochlorine pesticides on thyroid function during pregnancy. Am. J. Epidemiol. 168, 298–310.

Covaci, A., et al., 2002. Distribution of PCBs and organochlorine pesticides in umbilical cord and maternal serum. Sci. Total Environ. 298, 45–53.

Crofton, K.M., 2008. Thyroid disrupting chemicals: mechanisms and mixtures. Int. J. Androl. 31, 209–223.

Dallaire, R., et al., 2009a. Thyroid function and plasma concentrations of polyhalogenated compounds in Inuit adults. Environ. Health Perspect. 117, 1380–1386.

Dallaire, R., et al., 2009b. Thyroid hormone levels of pregnant Inuit women and their infants exposed to environmental contaminants. Environ. Health Perspect. 117, 1014–1020.

Dersimonian, R., Laird, N., 1986. Metaanlysis in clinical-trials. Controlled Clin. Trials 7, 177–188.

DeVito, M., et al., 1999. Screening methods for thyroid hormone disruptors. Environ. Health Perspect. 107, 407–415.

Gilbert, M.E., Sui, L., 2006. Dose-dependent reductions in spatial learning and synaptic function in the dentate gyrus of adult rats following developmental thyroid hormone insufficiency. Brain Res. 1069, 10–22.

Glinoer, D., Rovet, J., 2009. Gestational hypothyroxinemia and the beneficial effects of early dietary iodine fortification. Thyroid 19, 431–434.

Goodman, M., et al., 2010. Using systematic reviews and meta-analyses to support regulatory decision-making for neurotoxicants: lessons learned from a case study of PCBs. Environ. Health Perspect. 118, 727–734.

Gray, K.A., et al., 2005. In utero exposure to background levels of polychlorinated biphenyls and cognitive functioning among school-age children. Am. J. Epidemiol. 162, 17–26.

Grellier, J., et al., 2010. Exposure to disinfection by-products, fetal growth, and prematurity a systematic review and meta-analysis. Epidemiology 21, 300–313.

Haddow, J.E., 2005. Subclinical hypothyroidism and pregnancy outcomes. Obstet. Gynecol. 106, 198. (Author reply 198–9).

Haddow, J.E., et al., 1999. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N. Engl. J. Med. 341, 549–555.

Heyerdahl, S., Oerbeck, B., 2003. Congenital hypothyroidism: developmental outcome in relation to levothyroxine treatment variables. Thyroid 13, 1029–1038.

Hood, A., et al., 2003. Induction of T(4) UDP-GT activity, serum thyroid stimulating hormone, and thyroid follicular cell proliferation in mice treated with microsomal enzyme inducers. Toxicol. Appl. Pharmacol. 188, 6–13.

Howdeshell, K.L., 2002. A model of the development of the brain as a construct of the thyroid system. Environ. Health Perspect. 110, 337–348.

Jacobson, J.L., Jacobson, S.W., 1996. Sources and implications of interstudy and interindividual variability in the developmental neurotoxicity of PCBs. Neurotoxicol. Teratol. 18, 257–264.

Jacobson, J.L., Jacobson, S.W., 2003. Prenatal exposure to polychlorinated biphenyls and attention at school age. J. Pediatr. 143, 780–788.

Jacobson, J.L., et al., 1990. Effects of in utero exposure to polychlorinated biphenyls and related contaminants on cognitive functioning in young children. J. Pediatr. 116, 38–45.

Juni, P., et al., 1999. The hazards of scoring the quality of clinical trials for meta-analysis. J. Am. Med. Assoc. 282, 1054–1060.

Klein, R.Z., Mitchell, M.L., 1999. Maternal hypothyroidism and child development. Horm. Res. 52, 55–59.

Klein, R.Z., et al., 2001. Relation of severity of maternal hypothyroidism to cognitive development of offspring. J. Med. Screen. 8, 18–20.

Koopman-Esseboom, C., et al., 1994. Effects of dioxins and polychlorinated biphenyls on thyroid hormone status of pregnant women and their infants. Pediatr. Res. 36, 468–473.

Kooistra, L., et al., 2006. Neonatal effects of maternal hypothyroxinemia during early pregnancy. Pediatrics 117, 161–167.

LaFranchi, S.H., Austin, J., 2007. How should we be treating children with congenital hypothyroidism? J. Pediatr. Endocrinol. Metab. 20, 559–578.

Langer, P., 2008. Persistent organochlorinated pollutants (PCB, DDE, HCB, dioxins, furans) and the thyroid—review part. Endocr. Regul. 42, 79–104.

Liu, J., et al., 1995. Alteration of thyroid homeostasis by UDP-glucuronosyltransferase inducers in rats: a dose-response study. J. Pharmcol. Exp. Ther. 273, 977–985.

Longnecker, M.P., et al., 2000. Polychlorinated biphenyl (PCB) exposure in relation to thyroid hormone levels in neonates. Epidemiology 11, 249–254.

Longnecker, M.P., et al., 2003. Comparison of polychlorinated biphenyl levels across studies of human neurodevelopment. Environ. Health Perspect. 111, 65–70.

Lopez-Espinosa, M.-J., et al., 2009. Association between thyroid hormone levels and 4,4′-DDE concentrations in pregnant women (Valencia, Spain). Environ. Res. 109, 479–485.

Maervoet, J., et al., 2007. Association of thyroid hormone concentrations with levels of organochlorine compounds in cord blood of neonates. Environ. Health Perspect. 115, 1780–1786.

Matthews, J., et al., 2007. Co-planar 3,3′,4,4′ 5-pentachlorinated biphenyl and non-co-planar 2,2′,4,6,6′-pentachlorinated biphenyl differentially induce recruitment of oestrogen receptor alpha to aryl hydrocarbon receptor target genes. Biochem. J. 406, 343–353.

Meeker, J.D., et al., 2007. Serum PCBs, p,p′-DDE and HCB predict thyroid hormone levels in men. Environ. Res. 104, 296–304.

Miller, M.D., et al., 2009. Thyroid-disrupting chemicals: interpreting upstream biomarkers of adverse outcomes. Environ. Health Perspect. 117, 1033–1041.

Morreale de Escobar, G., 2001. The role of thyroid hormone in fetal neurodevelopment. J. Pediatr. Endocrinol. Metab. 13, 1453–1462.

Morreale de Escobar, G., et al., 2004. Role of thyroid hormone during early brain development. Eur. J. Endocrinol. 151, U25–U37.

Morreale de Escobar, G., et al., 2000. Is neuropsychological development related to maternal hypothyroidism or to maternal hypothyroxinemia? J. Clin. Endocrinol. Metab. 85, 3975–3987.

Nagayama, J., et al., 1998. Postnatal exposure to chlorinated dioxins and related chemicals on thyroid hormone status in Japanese breast-fed infants. Chemosphere 37, 1789–1793.

National Research Council, 2007. Toxicity Testing in the 21st Century: A Vision and a Strategy. National Academies of Science, Washington D.C., p. 196.

National Research Council, 2009. Science and Decisions: Advancing Risk Assessment. National Academy of Science, (Ed.), Washington D.C.

Oerbeck, B., et al., 2003. Congenital hypothyroidism: influence of disease severity and L-thyroxine treatment on intellectual, motor, and school-associated outcomes in young adults. Pediatrics 112, 923–930.

Otake, T., et al., 2007. Thyroid hormone status of newborns in relation to in utero exposure to PCBs and hydroxylated PCB metabolites. Env. Res. 105, 240–246.

Parham, F.M., et al., 2012. Upstream Adverse Effects in Risk Assessment: Modeling Polychlorinated Biphenyls and Thyroid Hormone Disruption Outcomes in Animals and Humans Env. Res. 116, 74–84, http://dx.doi.org/10.1016/j. envres.2012.04.003.

Patandin, S., et al., 1999. Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age. J. Pediatr. 134, 33–41.

Persky, V., et al., 2001. The effects of PCB exposure and fish consumption on endocrine hormones. Env. Health. Perspect. 109, 1275–1283.

Pessah, I.N., et al., 2009. Enantiomeric specificity of (-)-2,2′,3,3′,6,6′-hexachlorobiphenyl toward ryanodine receptor types 1 and 2. Chem. Res. Toxicol. 22, 201–207.

Pop, V.J., et al., 2003. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. Clin. Endocrinol. (Oxf.) 59, 282–288.

Pop, V.J., et al., 1999. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin. Endocrinol. (Oxf.) 50, 149–155.

Sala, M., et al., 2001. Association between serum concentrations of hexachlorobenzene and polychlorobiphenyls with thyroid hormone and liver enzymes in a sample of the general population. Occup. Environ. Med. 58, 172–177.

Salay, E., Garabrant, D., 2009. Polychlorinated biphenyls and thyroid hormones in adults: a systematic review appraisal of epidemiological studies. Chemosphere 74, 1413–1419.

Schantz, S.L., et al., 2003. Effects of PCB exposure on neuropsychological function in children. Environ. Health Perspect. 111, 357–376.

Selva, K.A., et al., 2005. Neurodevelopmental outcomes in congenital hypothyroidism: comparison of initial T4 dose and time to reach target T4 and TSH. J. Pediatr. 147, 775–780.

Simic, N., et al., 2009. Impact of neonatal thyroid hormone insufficiency and medical morbidity on infant neurodevelopment and attention following preterm birth. Thyroid 19, 395–401.

Smallridge, R.C., et al., 2005. Thyroid function inside and outside of pregnancy: what do we know and what don't we know? Thyroid 15, 54–59.

Stewart, P.W., et al., 2008. The relationship between prenatal PCB exposure and intelligence (IQ) in 9-year-old children. Environ. Health Perspect. 116, 1416–1422.

Stewart, P.W., et al., 2003. Cognitive development in preschool children prenatally exposed to PCBs and MeHg. Neurotoxicol. Teratol. 25, 11–22.

Sugatani, J., et al., 2001. The phenobarbital response enhancer modelu in the human bilirubin UDP-glucuronosyltransferase UGT1A1 gene and regulation by the nuclear receptor CAR. Hepatology 33, 1232–1238.

Takser, L., et al., 2005. Thyroid hormones in pregnancy in relation to environmental exposure to organochlorine compounds and mercury. Env. Health Perspect. 113, 1039–1045.

Turyk, M.E., et al., 2007. Relationships of thyroid hormones with polychlorinated biphenyls, dioxins, furans, and DDE in adults. Environ. Health Perspect. 115, 1197–1203.

US Environmental Protection Agency, 2005. Regulatory Impact Analysis of the Clean Air Mercury Rule. Office of Air Quality Planning and Standards, Research Triangle Park, NC.

US Environmental Protection Agency, 2008a. Lead; Renovation, Repair and Painting Program; Lead Hazard information Pamphlet; Notice of Availability; Final Rule, vol. 73, Federal Register, p. 79.

US Environmental Protection Agency. 2008b, National Ambient Air Quality Standards for Lead; Final Rule, vol. 73, Federal Register, pp. 66964–67062.

US Environmental Protection Agency. 2008c, Regulatory Impact Analysis of the Proposed Revisions to the National Ambient Air Quality Standards. Office of Air Quality Planning and Standards, Health and Environmental Impact Division, Research Triangle Park, p. 177.

US Environmental Protection Agency. 2010, Integrated Risk Information System: Glossary, vol. 2010, Washington, DC.

van der Sluijs Veer, L., et al., 2008. Quality of life, developmental milestones, and self-esteem of young adults with congenital hypothyroidism diagnosed by neonatal screening. J. Clin. Endocrinol. Metab. 93, 2654–2661.

Vermiglio, F., et al., 2004. Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency: a possible novel iodine deficiency disorder in developed countries. J. Clin. Endocrinol. Metab. 89, 6054–6060.

Visser, T.J., et al., 1993. Glucuronidation of thyroid hormone in rat liver: effects of *in vivo* treatment with microsomal enzyme inducers and *in vitro* assay conditions. Endocrinology 133, 2177–2186.

Vreugdenhil, H.J.I., et al., 2002. Effects of prenatal PCB and dioxin background exposure on cognitive and motor abilities in Dutch children at school age. J. Pediatr. 140, 48–56.

Wang, S.L., et al., 2006. Body burdens of polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls and their relations to estrogen metabolism in pregnant women. Environ. Health Perspect. 114, 740–745.

Woodruff, T.J., et al., 2008. Meeting report: moving upstream-evaluating adverse upstream end points for improved risk assessment and decision-making. Environ. Health Perspect. 116, 1568–1575.

Yang, D., et al., 2009. Developmental exposure to polychlorinated biphenyls interferes with experience-dependent dendritic plasticity and ryanodine receptor expression in weanling rats. Environ. Health Perspect. 117, 426–435.

Yang, J.M., et al., 2010. Development of TEFs for PCB congeners by using an alternative biomarker-thyroid hormone levels. Regul. Toxicol. Pharmacol. 56, 225–236.

Zoeller, R.T., 2005. Environmental chemicals as thyroid hormone analogues: new studies indicate that thyroid hormone receptors are targets of industrial chemicals? Mol. Cell. Endocrinol. 242, 10–15.

Zoeller, R.T., 2007. Environmental chemicals impacting the thyroid: targets and consequences. Thyroid 17, 811–817.

Zoeller, R.T., Rovet, J., 2004. Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings. J. Neuroendocrinol. 16, 809–818.