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Adverse effects in risk assessment: Modeling polychlorinated biphenyls and thyroid hormone disruption outcomes in animals and humans

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A B S T R A C T

There is a growing need for quantitative approaches to extrapolate relationships between chemical exposures and early biological perturbations from animals to humans given increasing use of biological assays to evaluate toxicity pathways. We have developed such an approach using polychlorinated biphenyls (PCBs) and thyroid hormone (TH) disruption as a case study. We reviewed and identified experimental animal literature from which we developed a low-dose, linear model of PCB body burdens and decrements in free thyroxine (FT4) and total thyroxine (TT4), accounting for 33 PCB congeners; extrapolated the dose–response from animals to humans; and compared the animal dose–response to the dose–response of PCB body burdens and TH changes from eleven human epidemiological studies. We estimated a range of potencies for PCB congeners (over 4 orders of magnitude), with the strongest for PCB 126. Our approach to developing toxic equivalency models produced relative potencies similar to the toxicity equivalency factors (TEFs) from the World Health Organization (WHO). We generally found that the dose–response extrapolated from the animal studies tends to under-predict the dose–response estimated from human epidemiological studies. A quantitative approach to evaluating the relationship between chemical exposures and TH perturbations, based on animal data can be used to assess human health consequences of thyroid toxicity and inform decision-making.

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1. Introduction

Assessing the potential human health hazards from exposure to chemicals in the environment has traditionally been based on the results of toxicological studies in laboratory animals (e.g., two-year carcinogenesis and two-generation reproductive toxicity assays). Animal studies are expensive and time-consuming, and many do not identify or characterize biological effects that occur earlier in the disease process. Thus, risk-assessment practices have customarily focused on using data on overt disease outcomes to characterize hazard and quantify risk, without taking into account earlier biological effects.

Abbreviations: AhR, aryl hydrocarbon receptor; FT4, free thyroxine; g, gram; LOD, limit of detection; max., maximum; µg/dL, micrograms per deciliter; µg/kg, micrograms per kilogram; mL, milliliter; NAS, National Academy of Sciences; ng/dL, nanograms per deciliter; ng/g, nanograms per gram; ng/kg, nanograms per kilogram; ng/L, nanograms per liter; NHANES, National Health and Nutrition Examination Survey; NIEHS, National Institute of Environmental Health Sciences; NTP, National Toxicology Program; OCDF, octachlorodibenzofuran; PBPK, physiologically based pharmacokinetic; PCBs, polychlorinated biphenyls; PCDD, polychlorinated dibenzo-p-dioxin; PCDF, polychlorinated dibenzofuran; pg/g, picograms per gram; pg/mL, picograms per milliliter; T3, triiodothyronine; T4, thyroxine; TCDD, tetrachlorodibenzo-p-dioxin; TCDF, tetrachlorodibenzofuran; TEF, toxicity equivalency factor; TEQ, toxic equivalent; TH, thyroid hormone; TSH, thyroid stimulating hormone, also called thyrotropin; TTH, total thyroxine; USEPA, U.S. Environmental Protection Agency; WHO, World Health Organization

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Increasingly, research is illuminating the links between environmental exposures, upstream biological perturbations, and downstream overt events. The revolution in toxicology testing of moving away from a primary focus on overt disease and towards an understanding of toxicological pathways has been recognized and endorsed by both the National Academy of Sciences (NAS), the US Environmental Protection Agency, and the National Institute of Environmental Health Sciences (NIEHS) (Collins et al., 2008; National Research Council, 2007a, 2007b). Mechanistic animal studies provide a great deal of reliable information on biological pathways that would not be ethical or practical to obtain in humans. One step necessary for making this data relevant to decision makers is to develop approaches for extrapolating dose–response relationships in animals to humans.

Research on changes in thyroid hormone (TH) serum concentrations provides relevant data to test the predictive power of mechanistic animal studies on human health effects in the area of chemical exposures. Changes in TH levels have been linked to various downstream outcomes including cognitive deficits and increased cardiovascular risks in humans (Woodruff et al., 2008). Animal studies find that numerous chemicals, including polychlorinated biphenyls (PCBs), perchlorate, and triclosan, can perturb TH levels (Crofton, 2008). A quantitative model for extrapolating the relationship between chemical exposure and TH changes from controlled animal studies to humans would advance the development of new analytic approaches for interpreting studies of chemical exposure and early biological perturbations.

We have developed a quantitative approach that links chemical exposures and effects on early endpoints in the causal chain in animals. To test whether this approach has predictive value, we compared it to findings from human epidemiological studies. We present a case study on the effects of PCB exposures on circulating TH levels, an early biological perturbation. TH perturbations have already been identified as an endpoint with sufficient data to characterize the relationship between exposure, TH changes, and downstream overt effects, making efforts to identify quantitative methods for integration into risk assessment warranted (Woodruff et al., 2008). We have also previously identified PCBs as having sufficient data to describe the relationship between exposure, early biological perturbations, and subsequent overt effects in both animals and humans (Wise et al., submitted for publication).

2. Background

2.1. PCBs

PCBs are a family of industrial compounds that are widely used in products ranging from electrical insulators and coatings to adhesives and flame retardants. They consist of two linked phenyl rings and have varying degrees of chlorination, resulting in 209 different “congeners” (Erickson, 2001; Tilson and Kodavanti, 1997). Before being banned in the 1970s, more than a billion kilograms of PCBs were produced (Erickson, 2001; Tilson and Kodavanti, 1997), an effect likely due to PCB congeners according to their dioxin-like activity (Safe, 2001), while others do not. In general, congener-specific studies demonstrate that both coplanar and non-coplanar PCB congeners can reduce circulating levels of TH (Zoeller, 2001).

Environmental chemicals can influence circulating TH levels through a variety of mechanisms, including interfering with TH synthesis and increasing TH metabolism and elimination (Crofton, 2008). Furthermore, exposure to multiple TH chemical disrupters can enhance the effects on TH levels (Crofton, 2008; Crofton et al., 2005).

3. Methods

Fig. 1 shows a diagram of our overall approach, which conceptually is to model the relationship between the exposure and early biological perturbations in animals and extrapolates the dose–response to humans. For this case study, we modeled the relationship between PCB exposures and TH levels in animals (Relationship 1) and the relationship between PCB exposures and TH levels in humans (Relationship 2). We then extrapolated the dose–response from the animal model to estimate the dose–response in humans and compared it to the dose–response estimated directly from the human epidemiological data (Relationship 3). We also compared the levels of PCBs and THs in animals and humans, as indicated by the dotted lines in Fig. 1, to assess the reliability of our extrapolation from animal to humans.

We searched the published, peer-reviewed literature and government reports for animal and human studies to use in modeling the relationship between PCBs...
and TH changes. For the animal studies, we only included papers in this analysis that had a range of doses (for dose–response modeling), sufficiently documented laboratory practices, and measurements of total TT4 (TT4 total) or FT4 levels. For the human studies, we only included studies that reported TT4 or FT4 levels, sufficient statistical information for estimating quantitative dose–response, and a PCB concentration (either an individual congener or a sum of congeners) in maternal blood, umbilical cord blood, or the blood of non-pregnant women or of men as a dose variable. We also use a meta-analysis of the relationship between PCB exposure and TH levels (Wise et al. (submitted for publication)).

3.1. Study selection

We focused on perturbations to TT4 as our upstream indicator for analysis because TT4 has already been identified as an early biological signal (Woodruff, 2008). We selected studies that included FT4 measurements because the American Thyroid Association has recommended determination of serum TSH and FT4 concentrations (but not TT4 concentration, measurements of which may be affected by changing levels of thyroxine-binding globulin) as the standard measure of thyroid function (DeVito et al., 1999). We also used studies including TT4 measurements because of the extensive animal data on TT4, and because many of the human studies measured TT4 in addition to or instead of FT4.

3.1.1. Relationship 1: animal PCB body burdens and TH levels

Based on our criteria, we selected four chronic-exposure rat-toxicity studies conducted by the National Toxicology Program (NTP) (National Toxicology Program, 2006a, b, c, d). The NTP studies evaluated the effects of a single PCB (PCB 126 or PCB 153) or a combination of two different PCB congeners (PCBs 118 and 126 or PCBs 126 and 153). Researchers administered multiple dose levels to female Sprague-Dawley rats, 10 rats per dose level, by gavage for two years, beginning when the rats were 8–9 weeks old. Blood concentrations of PCBs and of THs (TT4, FT4, TT3, and TSH) were measured at 14, 31, and 53 weeks (92, 211, and 365 day) using radioimmunoassays. For three of the studies, only summary data (group means) on the dose were available. We therefore used the group mean doses as the independent variable and the group mean TH concentration as the dependent one in our models.

There is no general PBPK model for PCBs for converting intake doses to internal doses, and no intake data for humans. The literature on human exposure to PCBs and thyroid hormone levels uses PCBs in the blood as a measure of exposure. Therefore, we developed empirical relationships between PCB serum concentrations and TH levels in animals to extrapolate to humans (Relationships 2 and 3).

The NTP studies evaluated three PCB congeners, but humans are exposed to many other PCB congeners of varying potencies (Centers for Disease Control and Prevention, 2008; Crofton et al., 2005). We searched the literature for animal studies to estimate relative potency of these other PCBs, and identified the work by Crofton et al. (2005) as sufficient for modeling. This was the only reference we found with sufficient dose–response on multiple PCBs. In this study, female Long-Evans rats were administered via gavage in a range of 7–10 doses of 12 PCBs, 2 dioxins and 4 furans individually, as well as in a mixture of all these chemicals, for 4 days. Serum TT4 was measured as a response variable (Crofton et al., 2005).

3.1.2. Relationship 2: Human PCB body burdens and TH levels

Based on our criteria, we identified eleven human studies with sufficient data to model the relationship between blood levels of PCBs and THs: Abdelouahab et al., 2008; Alvarez-Pedreiro et al., 2009; Bloom et al., 2003; Chevrier et al., 2008; Dallaire et al., 2009a, 2009b; Lopez-Espinosa et al., 2009; Maervoet et al., 2007; Martin and Klaassen, 2010; Meeker et al., 2007; Sala et al., 2001; Turyk et al., 2007).

3.2. Comparing the levels of PCBs and THs in animals and humans

Different studies measured PCBs in biological tissue in different ways. The NTP studies reported the concentration of PCBs in whole blood. The epidemiological studies reported concentrations of PCBs in plasma and serum. Because different PCBs are distributed differently between plasma and red blood cells, the concentration of a PCB in whole blood will, in general, differ from its concentration in plasma. To put the measurements on the same scale, we assumed that the concentration of PCBs in plasma is equal to the concentration of PCBs in serum (plasma minus clotting factors) and that 1 ml of blood weighs 1 g. We then used a formula from Parham et al., (1997) relating the concentration of PCBs in human plasma to concentration in human whole blood. The formula for the blood-plasma partition coefficient is $K_{BP} = (1.24 \times 0.077 \times N^{1.65} - 0.31 \times N)$, where N is the number of unsubstituted meta–para chlorine pairs in the PCB congener. Most of the PCB congeners in the studies are highly chlorinated and have N=0, which indicates that PCB blood concentration are generally 75% of the PCB plasma concentration.

The other studies gave concentrations of PCBs in units of ng/g lipids in blood (although the PCBs were measured in serum or plasma) (Alvarez-Pedreiro et al., 2009; Chevrier et al., 2008; Dallaire et al., 2009a, 2009b). The observed median concentration of lipids in the blood from five studies (Longnecker et al., 2003) was 7.9 g/L. We therefore assumed that the PCB concentration in ng/L in plasma equals 7.9 times the PCB concentration in ng/g of lipids. Turyk reported an estimate of lipid concentration in blood of 6.52 g/L, which is close to the value reported in Longnecker 2003 (Turyk et al., 2007). One study, Maervoet et al., 2007 used measurements from umbilical cord blood (Maervoet et al., 2007). We used a cord blood: maternal blood ratio of 0.259 to convert the Maervoet cord blood levels to maternal blood PCB concentration (Covaci et al., 2002). The other studies reported concentrations as PCB per volume in serum or plasma.

Rats and humans have different levels of thyroid hormones. For extrapolating from rats to humans, however, absolute TH concentrations are not relevant in this situation, since the model we used for the rat data assumed that PCBs cause a dose-dependent fractional reduction in TH concentration. In other words, we are evaluating the change in TH and not the absolute values. Therefore, comparisons between different human models and between animal and human models were expressed in terms of fractional changes in TH levels.

3.3. Quantitative analysis

3.3.1. Relationship 1: animal PCB body burdens and TH levels

3.3.1.1. Estimating relationship 1 for PCB congener in the NTP studies. The NTP studies include measurements of blood concentrations of PCBs (congeners 118, 126, and 153) and two measures of TH: TT4 and FT4. We modeled the relationship between PCBs and TH using a Michaelis–Menten model of the form:

$$T = T_0 \left(1 - \frac{\text{vmax} \cdot d_i}{K + d_i} \right)$$

where $T$ is a TH concentration (TT4 (µg/dL) or FT4 (ng/dL)), $T_0$ is the maximum reduction in serum TH that the PCBs can cause, $k$ (µg/mL) is the PCB concentration required to produce half of the maximum reduction, and $d_i$ is a weighted sum of the concentrations of the three PCB congeners used in the NTP studies. We calculated $d_i$ as $d_i = \sum_{i=1}^{3} c_i d_i$, where $c_i$ is the individual weight for each of the PCB congener ($d_i$). We fixed the weight for the most potent PCB, PCB 126, at 1 ($c_2=1$) and optimized the other weights as part of the fit to the data. We also assessed the fit of a Hill function model. The Hill function model is similar to the Michaelis–Menten model, with $d_i$ and $k$ both raised to a power, n, determined as part of the optimization. At low doses, the dose–response relationship in the Michaelis–Menten model is approximately linear, with the functional form:

$$T = T_0 \left(1 - \frac{\text{vmax} \cdot d_i}{k + d_i} \right)$$

Since $d_i$ is a linear combination of the concentrations of the three PCBs in the NTP study, the potency of each PCB can be represented by the linear equivalent $\beta_i = v_{\text{max}} \cdot c_i$, where $c_i$ is the congener weighting from the Michaelis–Menten model.

The model was fitted to the data assuming a lognormal error structure. That is, the fit minimized the sum of squared errors, where the errors are the differences between the natural logarithm of the model function and the natural logarithm of...
the data. The fitted model parameters were \( T_0 \) (a different value for each age, as the TT4 and FT4 concentrations in the control animals decreased with age), \( v_{\text{max}}, k, c_1 \) for PCB118 and \( c_3 \) for PCB153. To calculate confidence intervals for \( \beta \), we used a reparameterized version of the Michaelis–Menten model. Using the definition of \( \beta \), gives \( c_i = \beta_i \times k/v_{\text{max}} \). Substituting this value into the definition of \( d_i \), gives

\[
d_i = \frac{k}{v_{\text{max}}} \sum_{i=1}^{n} \beta_i d_i.
\]

and substituting this expression into the Michaelis–Menten model gives

\[
T = T_0 \left( 1 - \frac{v_{\text{max}} \sum_{i=1}^{n} \beta_i d_i}{v_{\text{max}} + \sum_{i=1}^{n} \beta_i d_i} \right).
\]

The standard deviations for the parameter estimates were approximated by using the inverse of the Fisher information matrix as an approximation to the covariance matrix (Armitage and Colton, 1998).

### 3.3.2. Estimating relationship 1 for PCB congeners in Crofton et al., 2005

We fitted the data from Crofton et al., 2005 using the Michaelis–Menten model (weighted for the number of animals at each dose level) to provide potency estimates for PCBs 28, 52, 101, 105, 118, 126, 138, 153, 156, 169, and 180, as well as for other compounds in Crofton et al., 2005. For these data, though, each congener was modeled with its own \( v_{\text{max}} \) and \( k \). We only used the data on individual congeners from Crofton et al., 2005. The low-dose behavior of each PCB was approximated by the function:

\[
T = T_0 (1 - \beta d)
\]

where the effective potency of each PCB congener is \( \beta = v_{\text{max}} / k \) and where \( v_{\text{max}} \) and \( k \) are estimated separately for each PCB. Standard deviations for the estimates of \( \beta \) were derived as described above.

### 3.3.2. Relationship 2: Human PCB body burdens and TH levels

The models from the human studies used different functional forms to describe the relationship between PCBs and TH levels (Table S1). The studies also evaluated different populations with different PCB body burdens. Therefore, we compared the human models to each other by comparing the fractional reduction in TH concentration in each of the human studies using the models from each study; \( f(x) = \text{concentrations in the control animals} \). Given the model parameters \( x \) and \( \beta \), the functional form, and the average PCB and thyroid hormone concentrations, it is possible to derive formulas for the fractional reduction (Table S1 in the supplemental material). When confidence limits on the slopes are available, we also calculated confidence limits on the fractional reduction, based on using the confidence limits for \( \beta \) in the formula for fractional reduction.

### 3.3.3. Relationship 3: comparing the dose–response relationships in animals and humans

We could not compare the dose–response functions directly between the animal data and the human data because of the different functional forms used in the human models. Instead, we did the following:

1. We calculated the fractional reduction in TH at the mean or median PCB concentration in each of the human studies using the models from each human study as described above;
2. We calculated the fractional reduction in TH using the dose–response model derived from the animal studies. We used the low-dose linear approximation to the Michaelis–Menten function, \( T = T_0 (1 - \beta d) \) to extrapolate the animal results to humans because the human PCB body burdens are generally low compared to those of the animals making the low-dose linear approximation appropriate. We used the observed PCB exposure concentrations in humans for \( d \);
3. We then compared the calculated fractional reduction in TH based on the human studies to the calculated fractional reduction in TH based on the animal dose–response.

We used the following assumptions and conversion to calculate the dose–response for PCBs not evaluated in the NTP animal studies, but for which we wanted to extrapolate the dose–response to humans. For congeners other than the three studied by NTP, the general approach is to derive scaling factors from Crofton et al., 2005, and to multiply each \( \beta \) on the NTP study by the most appropriate scaling factor for each congener. In the equations below, \( \beta_C \) is the slope for congener \( x \) in humans extrapolated from the rat data, \( \beta_R \) is the slope for congener \( x \) in rats in the NTP studies, and \( \beta_{CR} \) is the slope for congener \( x \) in rats in Crofton et al., 2005.

1. If the PCB congener \( x \) is one of those used in the NTP studies, then \( \beta_{CR} = \beta_R \).
2. If the PCB congener \( x \) is one of those in Crofton et al., 2005 but not in the NTP studies, then
   \[
   \beta_{CR} = \frac{\beta_{AC}}{\beta_{RC}} \beta_R.
   \]
3. If the PCB congener is not in Crofton et al., 2005, then \( \beta_{AC} = \frac{\beta_{EC}}{\beta_{RC}} \beta_R \), where congener \( z \) is the congener in Crofton et al., 2005, most structurally similar to congener \( x \), and congener \( y \) is the congener from the NTP study with \( \beta_{EC} \) nearest to \( \beta_{EC} \). The previous two cases can be expressed using this same equation, with \( z = x \) in case 2 and both \( z = x \) and \( y = x \) in case 1.

For example, PCB 52 is included in the Crofton et al., 2005 data but not in the NTP data. The congener most similar structurally to PCB 52 in the NTP data is PCB 153, so we calculated the \( \beta \) value for PCB 52 in the extrapolated model as follows:

\[
\beta_{52} = \frac{\beta_{52C}}{\beta_{153C}} \beta_{153}.
\]

We converted the \( \beta \) values from the rat studies in terms of blood concentration to values in terms of plasma concentration using the blood:plasma partition coefficient from Parham et al., 1997. This is equivalent to multiplying the concentration in the human study by the partition coefficient: \( T = T_0 (1 - \beta_R P_d) \).

This equation is used to estimate the percent reductions in THs in humans.

Several of the models in the human studies use sums of PCB congeners, rather than single congeners, as the dose. The extrapolated model \( \beta \) for these models can be calculated as a weighted sum of the \( \beta \)s for the individual congeners based on the animal data and given as

\[
\beta = \sum f_i \beta_i,
\]

where \( f_i \) is the mean or median concentration of congener \( x \) divided by the sum of all mean or median concentrations (preferring mean to median data, if both were available) from the human studies. We assume the relative concentration of each congener is constant across exposure strengths.

### 4. Results

#### 4.1. Study selection

The NTP studies are described in Table 1. Human studies used are given in Table 2.

#### 4.2. Comparing the levels of PCBs and THs in animals and humans

Table 3 compares the PCB body burdens measured in the NTP rat studies and the human studies. The concentrations for the lowest dose in the NTP studies were higher than those in the human studies.

<table>
<thead>
<tr>
<th>NTP technical report #</th>
<th>Study #</th>
<th>PCB</th>
<th>Number of doses</th>
<th>Range of doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>520</td>
<td>C96007D</td>
<td>126</td>
<td>6</td>
<td>0–1000 ng/kg</td>
</tr>
<tr>
<td>529</td>
<td>C96021D</td>
<td>153</td>
<td>8</td>
<td>0–3000 µg/kg</td>
</tr>
<tr>
<td>530</td>
<td>C96020D</td>
<td>153 &amp; 126</td>
<td>7</td>
<td>153: 0–3000 µg/kg, 126: 0–1000 ng/kg</td>
</tr>
<tr>
<td>531</td>
<td>C96022D</td>
<td>118 &amp; 126</td>
<td>6</td>
<td>118: 0–500 ug/kg, 126: 0–3110 ng/kg</td>
</tr>
</tbody>
</table>
4.2.1. Results for relationship 1: animal PCB body burdens and TH levels

4.2.1.1. Results for the PCB/TH relationship based on the NTP data. The results of fitting the Michaelis–Menten model to the NTP studies for FT4 are shown in Fig. 2; results for TT4 are in Supplemental figure S1. Parameter values for the fits are given in Table 4. The graph shows a reasonable agreement to the data. Findings for TT4 were similar in terms of fit (Figure S1). Our alternative analysis of fitting the Hill function produced values of 0.996 and 1.03 for parameter n for the fit to the TT4 and FT4 data respectively. Given that the coefficient n from the Hill model was close to 1, it supported using the Michaelis–Menten model, which is equivalent to the Hill model with n = 1.

Table 2
Studies used in the quantitative analysis of Relationship 2, PCB body burdens and whether FT4 or TT4 levels are measured in humans.

<table>
<thead>
<tr>
<th>Study</th>
<th>Human tissue sample</th>
<th>TT4</th>
<th>FT4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdelouahab et al. (2008)</td>
<td>Serum, women and men</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Alvarez-Pedrerol et al. (2009)</td>
<td>Serum, pregnant women</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Bloom et al. (2003)</td>
<td>Serum, men</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Chevrier et al. (2008)</td>
<td>Serum, pregnant women</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dallaire et al. (2009a)</td>
<td>Plasma, women and men</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Dallaire et al. (2009b)</td>
<td>Plasma, pregnant women</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Lopez-Espinosa et al. (2009)</td>
<td>Serum, pregnant women</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Meeker et al. (2007)</td>
<td>Serum, men</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Sala et al. (2001)</td>
<td>Serum, women and men</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Turyk et al. (2007)</td>
<td>Serum, women and men</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Table 3
PCB body burdens from the NTP rat studies and human epidemiological studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>PCB 118</th>
<th>PCB 126</th>
<th>PCB 153</th>
<th>Sums of PCB congeners</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Animal Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NTP studies, measurements in ng/ml in blooda</td>
<td>35.77</td>
<td>0.06391</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>NTP studies, per plasma equivalent, ng/mlb</td>
<td>47.57</td>
<td>0.085</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td><strong>Human studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdelouahab et al. (2008)</td>
<td>n/a</td>
<td>n/a</td>
<td>Maximum 2.87</td>
<td>(Mono-ortho)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median 0.48</td>
<td></td>
</tr>
<tr>
<td>Alvarez-Pedrerol et al. (2009)</td>
<td>Below LOD (0.071 ng/ml)</td>
<td>n/a</td>
<td>Median in two cohorts, 0.27 and 0.42</td>
<td>(Mono-ortho)</td>
</tr>
<tr>
<td>Bloom et al. (2003)</td>
<td>Maximum 0.642, mean 0.151</td>
<td>n/a</td>
<td>Maximum 1.891</td>
<td>(All)</td>
</tr>
<tr>
<td>Chevrier et al. (2008)d</td>
<td>Maximum 0.16, geometric mean 0.028</td>
<td>n/a</td>
<td>Maximum 0.76, geometric mean 0.045</td>
<td>(Mono-ortho)</td>
</tr>
<tr>
<td>Dallaire et al. (2009a)d</td>
<td>Maximum 3.9, geometric mean 0.18</td>
<td>n/a</td>
<td>Maximum 45.9, geometric mean 1.4</td>
<td>(Mono-ortho)</td>
</tr>
<tr>
<td>Dallaire et al. (2009b)</td>
<td>n/a</td>
<td>n/a</td>
<td>Maximum 6.12</td>
<td>Geometric mean 0.89</td>
</tr>
<tr>
<td>Lopez-Espinosa et al. (2009)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>(All) Maximum 14 Mean 1.3</td>
</tr>
<tr>
<td>Maervoet et al. (2007) e</td>
<td>95th percentile 0.27, Mean 0.12</td>
<td>n/a</td>
<td>95th percentile 0.73, Mean 0.27</td>
<td>(All) Maximum 2.65</td>
</tr>
<tr>
<td>Meeker et al. (2007)</td>
<td>95th percentile 0.18, Mean 0.06</td>
<td>n/a</td>
<td>95th percentile 0.19, Geometric mean 0.21</td>
<td>Geometric mean 1.08</td>
</tr>
<tr>
<td>Sala et al. (2001)</td>
<td>Median in two cohorts, 0.048 and 0.059</td>
<td>n/a</td>
<td>Median in two cohorts, 0.00012 and 0.00016</td>
<td>6.7 in workers</td>
</tr>
<tr>
<td>Turyk et al. (2007)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>0.23</td>
</tr>
</tbody>
</table>

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a Listed values are for the highest PCB body burden measured for the lowest administered dose.
b Concentrations in blood divided by blood:plasma partition coefficient of 0.75.
c Units are ng/ml or ng/g in plasma or serum. When data were reported for men and women separately, only data for women are listed.
d Converted from a per-lipid basis using a value of 7.9 g lipid/liter of blood.
e Converted from concentration in cord serum to concentration in maternal serum by dividing by 0.259 (see text).
We found that PCB 126 was estimated to be about two orders of magnitude times more potent in its effect on FT4 than PCB 118 and about four orders of magnitude more potent than PCB 153 (Table 4). Relative potencies were comparable, but slightly lower, in general, for TT4 than for FT4 (see Table 4). Because the relative potencies of PCBs 118 and 153 are similar for TT4 and FT4, the extrapolated values based on those PCBs will also have similar relative potencies for TT4 and FT4.

4.2.1.2. Results for the PCB/TH relationship based on the Crofton data.
The estimated relative potencies of the PCB congeners and other compounds in the Crofton et al., 2005 study are shown in Table 5. The potency of 126 was about 1,000 times greater than 118 and about 10,000 times greater than 153. The difference in potencies between PCB 126 and PCB 118 was about 100 in the NTP studies, about an order of magnitude less than the difference seen in the Crofton data. Except for PCB 28, the least potent PCB structures contained two ortho substitutions in their structure. (The ortho positions are positions 2, 2', 6, and 6' in the ring structure.). The coplanar PCBs, with no position 2 or 2' substitutions (sometimes referred to as “dioxin-like PCBs”), were generally most potent. However, the coplanar PCB 77 was less potent than some of the mono-ortho PCBs. We found that the relative potency of the compounds in this study was somewhat similar to TEFs for dioxin-like activity used by the WHO (Table 5 and Supplemental Figure S2).

We found that PCB 126 was estimated to be about two orders of magnitude times more potent in its effect on FT4 than PCB 118 and about four orders of magnitude more potent than PCB 153 (Table 4). Relative potencies were comparable, but slightly lower, in general, for TT4 than for FT4 (see Table 4). Because the relative potencies of PCBs 118 and 153 are similar for TT4 and FT4, the extrapolated values based on those PCBs will also have similar relative potencies for TT4 and FT4.

4.2.2. Results for relationship 2: Human PCB body burdens and TH measurements
The formulas for fractional reduction in thyroid hormone level, depending on the functional form of the model, are given in Table S1. The data used for the calculation of the fractional

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**Table 4**

Model parameters from the fit of the Michaelis–Menten model to the NTP data. Model parameters $c$ and $k$ are from the first model; parameters $b$ are from the reparameterized model; $V$ and the Ts are in both models.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Values for FT4 (95% confidence limits)</th>
<th>Values for TT4 (95% confidence limits)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V$ (unitless)</td>
<td>1 (0.88, 1.12)</td>
<td>1.0 (0.95, 1.05)</td>
</tr>
<tr>
<td>$K$ (pg/ml)</td>
<td>899 pg/ml (435,1363)</td>
<td>663 pg/ml (301, 1026)</td>
</tr>
<tr>
<td>$c_1$ (for PCB 118)</td>
<td>0.013 (4.5 × 10^{-5}, 2.1 × 10^{-2})</td>
<td>0.024 (0.0087, 0.039)</td>
</tr>
<tr>
<td>$c_2$ (for PCB 126)</td>
<td>1 (fixed)</td>
<td>1 (fixed)</td>
</tr>
<tr>
<td>$c_3$ (for PCB 153)</td>
<td>0.00013 (4.2 × 10^{-5}, 2.2 × 10^{-4})</td>
<td>0.00021 (7.2 × 10^{-5}, 3.5 × 10^{-4})</td>
</tr>
<tr>
<td>$T_s$ for 14 weeks</td>
<td>2.1 ng/dL (1.9,2.3)</td>
<td>5.1 µg/dL (4.6,5.7)</td>
</tr>
<tr>
<td>$T_s$ for 31 weeks</td>
<td>2.2 ng/dL (2.0,2.3)</td>
<td>4.0 µg/dL (3.6,4.5)</td>
</tr>
<tr>
<td>$T_s$ for 53 weeks</td>
<td>1.8 ng/dL (1.7,2.0)</td>
<td>3.5 µg/dL (3.1,3.9)</td>
</tr>
<tr>
<td>$b$ for 118 (pg/mL)^{-1}</td>
<td>1.4 × 10^{-3} (7.0 × 10^{-5}, 2.1 × 10^{-3})</td>
<td>3.6 × 10^{-5} (2.0 × 10^{-5}, 5.1 × 10^{-5})</td>
</tr>
<tr>
<td>$b$ for 126 (pg/mL)^{-1}</td>
<td>1.1 × 10^{-3} (5.8 × 10^{-4}, 1.6 × 10^{-3})</td>
<td>1.5 × 10^{-3} (7.0 × 10^{-4}, 2.3 × 10^{-3})</td>
</tr>
<tr>
<td>$b$ for 153 (pg/mL)^{-1}</td>
<td>1.4 × 10^{-7} (7.5 × 10^{-8}, 2.1 × 10^{-7})</td>
<td>3.2 × 10^{-7} (1.9 × 10^{-7}, 4.5 × 10^{-7})</td>
</tr>
</tbody>
</table>

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Fig. 2. PCB body burden (weighted sum of concentrations in pg/mL) and measured FT4 levels in the blood of rats at different ages of the rat. The line represents the fitted value from the Michaelis–Menten model.
reduction in thyroid hormones predicted by the models in the human studies are given in Table S2. PCB congeners 118, 138, 180 (also in Crofton et al., 2005, with 118 and 153 in the NTP studies as well) were modeled in at least four human studies each. Abdelouahab et al., 2008 reported results based on ‘non-ortho-substituted (dioxin-like)’ congeners; however, the congeners they listed as being used in the model do not fit that description, so we did not use those results. For calculation of results using the meta-analysis results from Wise et al. (submitted for publication), it was necessary to choose a nominal value for the average thyroid hormone level \( T_h \) (see Table S1). Average \( T_{45} \) concentrations in the studies range from 0.77 ng/dl for one cohort from Alvarez-Pedrero et al., 2009 to 1.32 ng/dl for Maervoet et al., 2007. Average \( T_{45} \) concentrations range from 74.5 ng/ml for male subjects in Abdelouahab et al., 2008 to 107 ng/ml in Chevrier et al., 2008. For the calculations using the meta-analysis results, we chose values of \( T_{45} = 0.8 \) ng/dl for \( T_4 \) and \( T_{45} = 80 \) ng/ml for \( T_4 \).

The estimated percent reduction in \( F_T \) and \( T_{45} \) levels at the average PCB concentrations, for the single congeners 118, 138, 153, and 180, and for the sums of mono-ortho congeners or of all congeners, is given in Fig. 3 (all calculations are in Table S2). The percent reduction in \( F_T \) for the individual PCB congeners ranged from −3.1% to 7.6%. We found a 3.6% (95% CI = 3.9 to 10.1%) reduction in \( F_T \) based on the meta-analysis for the sum of PCBs. For the other models of the sum of PCBs, fractional reductions in \( F_T \) ranged from −2.2% to 7.9%. Results were similar for \( T_{45} \). For individual congeners, fractions ranged from −1.2% to 4.2%, with 0.037% increase (95% CI = 0.16% to 0.082%) based on the meta-analysis for the sum of PCBs, and results for sums of all PCBs from the other models ranging from −1.8% to 7.8%.

### 4.2.3. Results for relationship 3: extrapolating relationship 1 from animals to humans

#### 4.2.3.1. Comparing congeners for extrapolation.

There are 33 congeners in the human studies used in this paper (summarized in Supplemental Table S3). Of those, 11 are in Crofton et al., 2005, of which 3 are also in the NTP studies. The other 22 are not in the animal studies. Selection of the congener \( y \) in the extrapolation equation (Section 3.3.3), which determines the scaling between the PCB in the NTP study and the other PCBs in the Crofton study was based on the potencies of the congeners in the Crofton results as shown in Table 5. PCB 153 has a potency of about an order of magnitude lower than PCB 118. Congeners with potency less than PCB 153 were scaled to 153. Only one congener, 101, has potency between 118 and 153. It was scaled to 153 because its potency was closer to that of 153. All of the other congeners other than 126 were scaled to 118. Three congeners (157, 167, and 189) were included in the sum of mono-ortho congeners in Chevrier et al., 2008, but their concentrations were not given because of their low detection frequency. Therefore, they are not included in the calculations.

Eleven of the congeners from the human studies are found in Crofton et al., 2005. The other 22 congeners need to be assigned to congeners from the Crofton studies that are most similar to each of the 22 for purposes of extrapolation (this is congener \( x \) in the extrapolation equation, Section 3.3.3). We based the extrapolation on structural similarity, as determined by the pattern of chlorine substitution considering the number of chlorines and the position of the chlorines. Twelve of the 22 congeners have at least 7 chlorines, with at least 2 in ortho positions; their extrapolation is based on PCB 180. Two congeners, PCBs 146 and 163, are hexachloro congeners with 2 ortho chlorines; their extrapolation is based on PCB 153. Five congeners (18, 19, 44, 47, and 49), all with at least two ortho chlorines and 3 or 4 chlorines total, are extrapolated based on 52. The remaining 3 congeners are two mono-ortho-substituted tetrachloro congeners (66 and 74) and a di-ortho pentachloro congener, 99. These are extrapolated based on 101. It is not clear that this extrapolation is the best one for 66 and 74. The di-ortho tetrachloro congener 52 has a potency nearly two orders of magnitude lower than the mono-ortho penta congener 105 in the Crofton data (Table 5); the potency of 101 is intermediate between those of 52 and 105. However, these congeners make only a small contribution to the summed potencies (Table S4) for the studies in which they occur, Chevrier et al., 2008; Turyk et al., 2007.

Calculations of the extrapolated slopes for sums of congeners in the human studies are shown in Table S4. For the mono-ortho congeners (PCBs 105, 118, and 156) in Abdelouahab et al., 2008,
there were no data on the relative concentrations of individual congeners to use in the weighted sum of potencies, so we assumed equal concentrations of all three, which is equivalent to using the mean potency of the three congeners (the extrapolated potency values are similar (see Table S3), so this is a reasonable assumption). Turyk et al., 2007 gave median congener concentrations for two sets of subjects, from 1999 to 2000 and from 2001 to 2002. We used the 2001–2002 values for the weighting, because those data include measurements of more congeners. The lowest reported median concentration was 0.13 pg/g. We assumed a median concentration of 0.1 pg/g for congeners where no median was reported (because more than half of the observations were below the limit of detection, which varied from subject to subject); results are not highly sensitive to this choice.

We did not use the Sala et al., 2001 or Lopez-Espinosa et al., 2009 results for the sum of PCBs when comparing the human results to the extrapolated animal results because these studies did not provide the relative amounts of the congeners in the sum of PCBs (Lopez-Espinosa et al., 2009; Sala et al., 2001). We also did not use the results for the sum of all PCBs from Abdelouahab et al., 2008 since concentrations were available for only some of the PCBs in that study. Since the meta-analysis of Wise et al. is not based on any specific combination of congeners, we also do not use those results in the extrapolation.

Differences in the extrapolated β values for the sums of all PCBs or sums of mono-ortho congeners are due to the different congeners included in the sum in different studies. The β values for the sums of all PCB congeners are similar across studies (Table S4). The β value calculated for the sum of mono-ortho congeners in Chevrier et al., 2008 is much smaller than the other sum of mono-ortho congener values. This is because the sum of mono-ortho congeners in Chevrier et al., 2008 is dominated by congener 28, which is the least potent of all the congeners in Crofton et al., 2005 but of relatively high concentration in the Chevrier et al., 2008 data.

The Michaelis–Menten function approaches linearity as dose approaches 0. The degree to which a linear approximation to the function is valid can be examined by calculating the fractional reduction in FT₄ using the original Michaelis–Menten function and comparing it to the fractional reduction in FT₄ calculated from the extrapolated linear model both at the same maximum PCB concentrations observed in humans. The maximum concentrations of PCBs 118 and 153 measured in the human studies are in Dallaire et al., 2009a (Table 3), so the Dallaire data on the sum of PCBs will be used for the comparison of the two functional forms (extrapolated linear and Michaelis–Menten). The maximum measured concentration of the sum of all PCBs is 14,261 mg/kg lipid, which becomes 14,261 × 7.9 = 112.7 ng/ml on a wet-weight basis. The slope β for the extrapolated linear model for the
fractional reduction of FT₄ for the sum of all PCB congeners in this study is (see Table S4) 0.000711 (ng/ml)⁻¹. The fractional reduction in FT₄ for the extrapolated linear function, 1 − β₀d, gives a value of 0.920. The fractional reduction in FT₄ from calculated from the Michaelis–Menten function with the same low-dose slope β (like the reparameterized function in Section 3.3.1.1 above), and with Vₐₚₙₓ = 1, is 1 − β₀d/(1 + β₀d), which gives a value of 0.926, very close to the result of the linear model.

The fractional reduction in TH predicted by the extrapolated animal model is given in Table S5. Fractional reductions in TT₄ for the extrapolated rat model, applied to the human data sets used for models of the sum of all PCBs, range from 0.0007 to 0.0025 (0.07–0.25%). The values for FT₄ range from 0.0003 to 0.0024 (0.03–0.24%). Fig. 4 shows the values of the extrapolated percent reduction of FT₄ and TT₄ from rats (Relationship 1) for different individual PCBs or sums of PCBs, compared to the percent reduction predicted by the models from the human studies (Relationship 2). Because the data are plotted on a log-log scale, the figure shows only results for which the human models predict reduction in TH level with increasing PCB concentration (79 out of 112 models from the human studies). The predicted dose–responses for individual PCB congeners from the extrapolated rat model are generally orders of magnitude lower than the dose–responses derived from the human data that also find a reduction in TH with increasing PCBs.

Fig. 4 does not include comparisons for the human studies that find that increasing PCBs exposures are associated with increasing TH. The rat studies, and the subsequent models, find a reduction in TH from PCB exposures, and the confidence bounds for these results do not include zero. Thus, all the extrapolated rat values for different individual PCBs or sums of PCBs can only predict reductions in TH when PCB levels increase. We can assess how often the TH reductions estimated from the extrapolated rat models for individual and sum of PCBs are within the confidence intervals of the models based on the human studies (See Table S5). Of the 112 human models with corresponding extrapolated rat models, 81 had the extrapolated rat model prediction within the confidence limits of the human model. 62 of those 81 human models predicted reductions in TH with increasing PCBs and 19 predicted increases in TH with increasing PCBs. (This includes all of the models with negative slopes and no confidence limits. Those models reported as having nonsignificant results, so their confidence limits for the slope must include 0.) Two of the models of FT₄ from Alvarez-Pedrerol et al., 2009 had significant positive slopes (TH increasing with PCBs) and therefore had the rat predictions greater than the upper confidence limit of the human model. 15 of the human models had significant negative slopes (TH decreasing with PCBs), with the extrapolated rat values lower than the lower confidence limit for the human models. These 15 models include all 6 models of FT₄ from Maervoet et al., 2007 (5 models of single congeners, and 1 of the sum of congeners), one of the models of TT₄ from Turyk et al., 2007 (for the sum of PCBs from one set of subjects), and 8 models from Chevrier et al., 2006 (6 for FT₄ and single congeners, 1 for TT₄ and a single congener, and 1 for FT₄ and the sum of all congeners). For 14 of the 112 models, it was not possible to tell whether the rat model results were within the confidence limits of the human model (see Table S5 for details).

Extrapolating the dose–response based on the animal data for different metrics of the sum of PCBs yields results closer to the dose–response derived from the human data. There also appear to be patterns in the dose–response based on the type of congener (mono-ortho substituted congeners vs. congeners with more than one ortho substitution) and on the thyroid endpoint (TT₄ vs. FT₄). Because of the high correlation generally observed between levels of different PCB congeners, the modeled effects of less potent PCB congeners are probably partly due to confounding with those of stronger congeners.

5. Discussion

We have developed a quantitative approach for using existing animal and human peer-reviewed data to model the dose–response relationship between chemical exposures and upstream biological perturbations. We applied our approach to a case study of PCBs and TH in animals and humans. For this case study, we found that extrapolating the relationship between PCB body burdens and serum TH levels in animals to humans underestimate the dose–response relationship found in the human studies. Table 4 shows that upper confidence limits for the potency estimates (β) from the NTP data are no greater than about 1.5 times the point estimate. So even using the upper limits of potency from the rat data for extrapolating to humans would still produce calculated TH fractions that are well below those based on the human data. In fact, even increasing the potency values extrapolated from the rat by an order of magnitude would still produce TH fractions less than the fractions calculated from the human data. However, the difference between the human model and the extrapolated rat model is largest for the single-congener models; the difference is much less for the models of sums of congeners. Our analysis of the NTP studies consistently finds an inverse relationship between PCBs and FT₄, which is further supported by other animal studies (Zoeller, 2007). However, we found more variation in the dose–response among the human studies. A meta-analysis of the human studies shows an inverse
relationship between PCBs and FT₄, but the 95% CI includes 0 (Wise et al., submitted for publication). The variability in the epidemiologic findings is likely in part due to variability in settings and design, such as differences in selections of PCB congeners, biological matrices analyzed, exposure metrics, analytic models, and endpoint measurement and selection.

The use of PCBs in this case study has several strengths. First, there is a robust database of peer-reviewed research exploring the health consequences of PCB exposure and the capacity of PCBs to alter circulating levels of TH. Moreover, although our analysis uses data from NTP studies, other research supports the NTP findings and lends confidence to our conclusion that PCBs can affect TH levels (Martin and Klaassen, 2010). Second, PCBs represent a complex chemical mixture. One challenge in risk assessment is accounting for risks from exposure to multiple chemicals that have a similar adverse effect (National Research Council, 2008). Our approach accounts for multiple PCB exposures, many of which act on the thyroid system, and we found that aggregate measures of PCBs in animals generally predicted the results in humans better than the dose–response for individual PCBs. We aggregate the PCB body burdens empirically, which does not account for their individual mechanisms of action. This is consistent with recommendations from the NAS to consider together chemicals that can affect the same common adverse outcome (National Research Council, 2008). Given this recommendation, a limitation is that we could not account for exposures to other chemicals that can disrupt THs, such as dioxins, furans, triclosan, and perchlorate, all of which are common contaminants in the population (Centers for Disease Control and Prevention, 2008).

We found the ranking of the potencies of PCB congeners in association with reduced TH is similar to that observed for some non-thyroid effects (Yang et al., 2010) and is also similar to the assignment of TEFs to represent the potency of dioxin-like compounds (Van den Berg et al., 2006). Since the relative potency of the PCBs for thyroid endpoints is similar to the TEFs, the TEFs may be important to consider when accounting for other PCB related effects.

Our case study allows us to illustrate the application of a proposed approach for integrating experimental data on environmental chemical exposures and early biological perturbations into outcomes that can be more meaningful for decision-making. The advantage of using animal studies is that, due to the experimental setting, many of the factors that can influence findings in human studies, such as co-exposures and variation in susceptibilities and populations studied, are absent. However, the disadvantage of using animal studies is that these very factors, including age-related susceptibilities, are not accounted for, and thus, animal studies may underrepresent population-level effects in humans. This effect may be in part due to the specific animal strains or species used for modeling. These types of factors may explain the higher sensitivity of response in humans versus animals for this outcome.

6. Conclusion

We have developed an approach for quantitatively assessing the dose–response relationship between chemical exposures and TH perturbations using PCBs as a case study. Numerous chemicals have been shown to disrupt TH levels, which have been previously identified as an adverse endpoint (Woodruff et al., 2008). A shift to assessing risks based on upstream endpoints is likely to provide more sensitive indicators of adverse health effects and improve our ability to protect against harmful exposures. However, there is a challenge in using the dose–response for chemical exposures and TH changes in the decision-making context, where more overt endpoints are more typically used, often more easily understood, and can be integrated into other decision-making tools such as cost-benefit analysis. Thus, analytic approaches that link upstream perturbations to more apical endpoints will be important for using upstream data to inform decision-makers. Our focus on the thyroid system is supported by a well-developed literature characterizing the relationship between changes in serum TH levels and adverse outcomes. This analysis may also provide a rational, structured, and quantitative approach to evaluating the health consequences of exposures to multiple chemicals that exert thyroid toxicity.

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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.2012.04.003.

References


