ESTIMATED DIETARY EXPOSURE TO SELECTED INDICATOR PCBS: TOXICOKINETIC MODELING USING "INTRINSIC" ELIMINATION RATE ESTIMATES AND SERIAL SAMPLING DATA

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Introduction

Changes in measured concentrations of persistent compounds such as polychlorinated biphenyls (PCBs) reflect not only intrinsic elimination rates but also any ongoing intakes of the compounds and changes in the volume of distribution; in the case of PCBs, the volume of distribution is assumed here to be the volume of body lipids. Thus, apparent elimination rates calculated from data on changes in serum lipid-adjusted concentration may over- or under-estimate the intrinsic elimination rates for such compounds.[1-3] Ritter et al. (2011) [1] employed a physiologically-based toxicokinetic model, multiple sets of population serum sampling data, and estimates of dietary intake to estimate the intrinsic elimination rates for several PCB congeners typically used as "indicator" PCBs.

We collected serum concentration data for selected PCB congeners not related to occupational exposure at two time points approximately 5 years apart in a cohort of former trichlorophenol and pentachlorophenol manufacturing workers from Midland, Michigan, USA. [4-6] Using participant-specific information on changes in body fat volume, the paired serum sampling data, and the intrinsic elimination rates estimated by Ritter et al. (2011), we calculated estimated intake rates for five indicator PCBs.

Materials and methods

Concentrations of several PCB compounds often used as indicator PCBs were measured in serum samples collected from 43 individuals at two sampling time points approximately five years apart, 2004-2005 and 2010. Information on age, bodyweight (*BW*), height, smoking status, and other characteristics was collected at each serum sampling time point. We estimated the percent body fat, *PBF*, for each participant at each time point using an age- and gender- specific prediction formula incorporating body mass index (BMI).[7]

For five indicator PCBs (105, 118, 138, 153, and 180), we calculated the amount, *A*, of each congener, *i*, in the body from the measured concentration, C_i, assuming that the volume of distribution for each congener was equal to the volume of body fat at each time point:

$$A_i = \frac{PBF}{100} * BW * C_i \quad (1)$$

The apparent elimination rate, k_a, and corresponding half-life, HL, for each PCB congener based on change in mass in the body between the two sampling time points were calculated as follows:

$$k_a = \frac{\ln(A_{2010} / A_{2005})}{\Delta t} \quad (2)$$

$$HL = \frac{\ln(2)}{k} \quad (3)$$

For each participant, the amount of congener *i* in the body in 2010 is a function of the amount present in 2004-2005, the intrinsic elimination rate, k_i, the time elapsed between serum collection, Δt, and the ongoing dose rate, *D*:

$$A_{i,2010} = A_{i,2005} * e^{-k_i \Delta t} + \frac{D_i}{k_i}(1 - e^{-k_i \Delta t}) \quad (4)$$

Using the estimated intrinsic elimination rates for each of the five PCB congeners from Ritter et al. (2011)[1], we solved this equation for absorbed dose rate D_i in ng/yr for each individual and congener. The absorbed doses were adjusted to intake doses by assuming an absorption fraction of 0.9, as assumed by Ritter et al. (2011).[1] The calculated intake doses for each congener and individual were converted to ng/kg-d using the average bodyweight from the two time points.

We compared the resulting calculated intake doses to estimates from a 2001 total diet study in the United Kingdom[8], which is the most recent survey we could identify that provided estimates of congener-specific intake rates, and which was used by Ritter et al. (2011)[1] for the derivation of the intrinsic elimination rate estimates.

Results and Discussion

The study participants average approximately 63 years of age at the first sampling and more than 68 years of age at the second sampling. Although average BMI between the two sampling periods was nearly unchanged, individuals experienced significant changes in estimated body fat volumes between the first and second sampling period (Figures 1A and 1B).

The measured concentrations of the five PCB congeners at each time point are summarized in Table 1.

Table 2 summarizes the median apparent half-life based on the observed change in amount in the body between the two time points in this population for each congener, the estimated intrinsic half-lives from Ritter et al. (2011),[1] the estimated daily dose rates calculated from the current sampling dataset, and the estimated daily intake rates from the UKFSA 2001 diet study[8] and from a Belgian market basket study in 2005.[10] The estimated doses from this study agree well with previous estimates except for PCB 180, which is almost 10-fold higher. The general agreement in intake rates for four congeners support the estimated intrinsic half-lives from Ritter et al. (2011) as reasonable estimates of the central tendency of the true intrinsic half-lives for these congeners in this population.

The estimated intake dose for PCB 180 calculated here may be too high to be credible, given that current estimates of total intakes of summed PCBs are generally only approximately 5-8 ng/kg-d.[9,10] This suggests that the estimated intrinsic elimination half-life for PCB 180 from Ritter et al. (2011) is too low; a longer half-life would lead to lower estimated daily intakes in this population.

This conclusion is supported by the broader data from the US National Health and Nutrition Examination Survey (NHANES).[11] Concentrations of PCB 180 in the US general population remained nearly constant from 1999 to 2004 in the portion of the population aged 60+ (Figure 2), indicating a near-steady-state condition. These data suggest either that intake rates in the general US population for PCB 180 (but not the other indicator PCBs examined here) are substantially higher than in Europe, or that the intrinsic half-life for PCB 180 estimated by Ritter et al.[1] is too short for the older population examined here and in the US NHANES survey.

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References

1. Ritter R, Scheringer M, MacLeod M, Moeckel C, Jones KC & Hungerbuhler K. (2011) *Environ Health Perspect* 119: 225-231.

2. Ritter R, Scheringer M, MacLeod M, Schenker U & Hungerbuhler K. (2009) *Environ Health Perspect* 117: 1280-1286.
3. van der Molen GW, Kooijman SA, Michalek JE & Slob W. (1998) *Chemosphere* 37: 1833-1844.
4. Collins JJ, Bodner K, Aylward LL, Wilken M & Bodnar CM. (2009) *Am J Epidemiol* 170: 501-506.
5. Collins JJ, Bodner K, Aylward LL, Wilken M, Swaen G, Budinsky R *et al.* (2009) *J Occ Environ Med* 51: 1212-1219.
6. Collins JJ, Budinsky RA, Burns CJ, Lamparski LL, Carson ML, Martin GD *et al.* (2006) *J Exp Sci Environ Epidemiol* 16: 76-84.
7. Deurenberg P, Weststrate JA & Seidell JC. (1991) *Br J Nutr* 65: 105-114.
8. United Kingdom Food Standards Agency (UKFSA). (2003).
9. Tornkvist A, Glynn A, Aune M, Darnerud PO & Ankarberg EH. (2011) *Chemosphere* 83: 193-199.
10. Voorspoels S, Covaci A & Neels H. (2008) *Environ Toxicol Pharmacol* 25: 179-182.
11. Centers for Disease Control and Prevention (CDC). (2009). Fourth National Report on Human Exposure to Environmental Chemicals. Department of Health and Human Services. Atlanta, GA. Available at: http://www.cdc.gov/exposurereport/ [Accessed 5 January 2010]

Table 1: Mean measured concentrations (ng/g lipid) at two sampling time points in 43 participants. All congeners were detected and quantified at both time points in all participants.

	2004-2005 Mean (SD)	2010 Mean (SD)	% Change in means
PCB105	3.29 (3.51)	2.26 (2.57)	-31.4%
PCB118	15.86 (14.11)	11.29 (10.85)	-28.8%
PCB138	68.66 (44.00)	54.04 (33.15)	-21.3%
PCB153	85.16 (49.30)	69.71 (39.92)	-18.1%
PCB180	70.09 (51.12)	63.10 (38.23)	-10.0%

Table 2: Median apparent half-life based on change in estimated amount of congener in the body between sampling time points, estimated intrinsic half-life from Ritter et al. (2011)[1], median calculated daily dose, this study, and UKFSA congener intake rates from the 2001 Total Diet Study.[8]

Congener	Median apparent half-life, this study (yrs)	Estimated "intrinsic" half-life (yrs)[1]	Calculated daily dose, median ng/kg-d	UK 2001 daily dose estimate ng/kg-d[8]	Belgian 2005 daily dose estimate ng/kg-d[10*]
PCB 105	9.3	5.2	0.1	0.1	0.1
PCB 118	10.1	9.3	0.07	0.3	0.3
PCB 138	15.9	10.8	0.8	0.6	0.3
PCB 153	19.9	14.4	0.7	0.8	0.2
PCB 180	66.2	11.5	2.9	0.3	0.06

* Congener-specific estimates obtained by personal communication with S. Voorspoels and assume 70 kg BW.

Figure 1. A) Mean study group BMI (with standard deviations) at the two time points. B) Calculated change in body fat volume between sampling periods (2004-2005 and 2010) for the participants in the study. Percent body fat was estimated at each time point using a formula that considers age, BMI, and gender (Deurenberg et al. 1991), and body fat volume at each sampling time point was estimated as the product of the estimated percent body fat and the body weight.

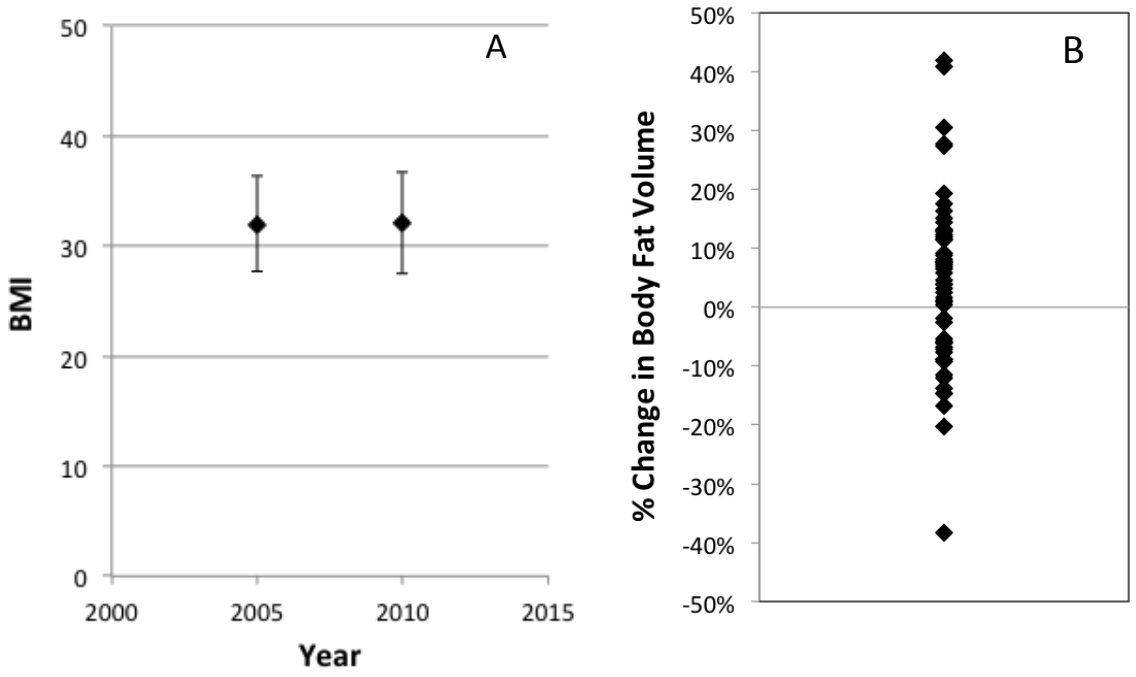

Figure 2: Distribution of lipid-adjusted concentrations of PCB 180 in the population aged 60+ in the US NHANES dataset over the years 1999 to 2004.[11] Boxes extend from the median to the 25th and 75th percentiles, while whiskers extend to the 5th and 95th percentiles.