A NOVEL APPROACH TO ESTIMATING INTRINSIC ELIMINATION HALF-LIVES OF PERSISTENT ORGANIC POLLUTANTS IN HUMANS – NEW HALF-LIFE DATA FOR POLYCHLORINATED BIPHENYLS

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Introduction

The elimination of persistent organic pollutants (POPs) from the human body at background exposure levels is difficult to quantify because of several confounding factors. A first factor is the continuous uptake of POPs from food (ongoing exposure), which cannot be avoided because the elimination half-lives of POPs in the human body are so long (on the order of years) that interruption of exposure by fasting is not possible. A second factor is changes in body weight, e.g. by growth during childhood, which leads to an increasing volume of body lipids and, thereby, to a reduction in lipid-based POP concentrations in the body ("growth dilution"). If the POP concentration in the tissue of an individual is recorded as a function of time, the resulting data (called "longitudinal data", LD) reflect the combined effects of intake (ongoing exposure), elimination, and changes in body weight. By means of regression between concentration and time, a half-life can be derived from LD. However, a half-life derived from LD without correction for ongoing exposure and body-weight changes does not indicate the time scale of elimination from the body, but is an "apparent" half-life reflecting the combination of ongoing intake, elimination and body-weight changes[1]. For polychlorinated biphenyls (PCBs), apparent half-lives derived from LD have been reported in the literature[2,3,4,5]; they show a very wide range, which reflects the effect of the confounding factors: from less than 1 yr to more than 25 yr or even infinity for PCB-153. If the presence of confounding factors is well characterized in a set of LD, it can be corrected for and half-lives of "true" or "intrinsic" elimination can be derived[1,6]. However, often this information is not available. Another approach is to take LD from individuals that were accidentally exposed to very high doses so that the effect of intrinsic elimination is much stronger than effects of confounding factors. However, in such cases the elimination kinetics is often considerably faster than in individuals exposed at background levels and the half-life estimates cannot be directly applied to the general population. Instead of LD, it is also possible to use POP concentrations in the human body that are derived from samples taken in population sub-groups of different ages (cross-sectional data, CSD). The simplest approach based on CSD is to derive the population average of the measured concentration and to employ a single-individual pharmacokinetic (PK) model. Model inputs are the average POP concentration in human tissue and average POP intake via food; on this basis, the model yields an estimate of the elimination half-life[1]. The information present in the CSD can be exploited to a fuller extent if, instead of a single-individual PK model, a population PK model is used, i.e. if each age group present in the CSD is represented by a separate model run with a corresponding POP intake function. In this case, the time trend of the POP concentration across the population can be reflected by the model. The elimination half-life is used as an adjustable parameter and by adjusting this parameter, the agreement between measured CSD and model results is optimized[7,8,9]. However, this approach exploiting the temporal trend of POPs concentrations measured in CSD has not been used frequently. Here we significantly expand the approach by using not just one, but two sets of CSD measured at different times; using the example of PCBs, we demonstrate the potential of the approach for deriving reliable intrinsic elimination half-lives[9]. This is of high importance for the analysis of human biomonitoring data measured under the Global Monitoring Plan of the Stockholm Convention on Persistent Organic Pollutants.

Materials and methods

Our approach is based on four components: (i) CSD for nine PCB congeners measured in cohorts from the UK in two different years, 1993 and 2000[10,11]; (ii) PCB intake data (in ng/(kg·d)) from several total diet studies from the UK[12,13,14]; (iii) a population PK model that calculates PCB concentrations in human lipid tissue based on initial estimates of the PCB intake and the elimination rate constant, k_{elim} ($k_{elim} = \ln 2/t_{1/2}$); (iv) a simultaneous fit of the PCB intake function used as model input to the empirical PCB intake data from (ii) and of model-derived PCB concentrations to PCB concentrations measured in humans of different age in the years 1991 and 2003, i.e.

the CSD sets from (i). The fit was performed by adjustment of the elimination half-life and the PCB intake in the years 1970 and 2000; for the fit, the deviations of intake data and modeled concentrations from empirical data were minimized by least-squares optimization.

The first CSD set was derived from adipose tissue samples collected in Wales, UK, in 1990–1991 from 75 individuals aged 14 to 79 years[10]. The second set consists of 154 human blood samples taken at 13 locations in the UK in 2003 from individuals aged 22 to 80 years[11]. PCB intake data were derived from total diet studies conducted in the UK[12,13,14]. The PK model describes the concentration of PCBs in a compartment representing the total body lipids of a representative person. The concentration is derived from a mass balance equation according to:

$$\frac{dc(t)}{dt} = -\left(k_{\text{elim}} + \frac{1}{m_{\text{lipid}}(t)} \times \frac{dm_{\text{lipid}}(t)}{dt} \right) \times c(t) + \frac{I(t, t_0)}{m_{\text{lipid}}(t)}, \qquad (1)$$

where $c(t)$ in ng/g lipid is the lipid-normalized PCB concentration in an individual of age t and born in the year t_0; note that t (years) is variable, t_0 is constant; $m_{\text{lipid}}(t)$ in kg is the mass of total body lipid as function of age; k_{elim} in yr^{-1} is the intrinsic elimination rate constant; and $I(t, t_0)$ in ng/yr is the PCB intake of an individual born in the year t_0. The term $dm_{\text{lipid}}(t)/dt$ describes the increase in body lipids during growth. The intake function, $I(t, t_0)$, is a function of t (age), but also depends on the calender time, $t + t_0$, because the intake of PCBs increased until approximately 1970 and then decreased. It is determined as

$$I(t, t_0) = E_{\text{abs}} \times m_{\text{bw}}(t) \times I_{\text{ref}}(t + t_0) \times a(t), \qquad (2)$$

where E_{abs} is the net absorption of PCBs in the gastrointestinal tract and is assumed to be 0.9; $m_{\text{bw}}(t)$ in kg is the body weight as function of age; $I_{\text{ref}}(t + t_0)$ in ng/(kg·d) is the reference daily intake of an adult in the calender year $t + t_0$, and $a(t)$ is an adjustment factor that adjusts the adult reference daily intake, $I_{\text{ref}}(t + t_0)$, to younger ages and is based on total diet studies. The reference daily intake of adults at calender time $t + t_0$, $I_{\text{ref}}(t + t_0)$, is determined according to the following assumptions: peak intake occurred in 1970, intake increased exponentially before and decreased exponentially after 1970 so that intakes in 1950 and 1990 are equal, intake before 1950 increased more slowly than between 1950 and 1970, as is indicated by PCB emission inventories. With this course of $I_{\text{ref}}(t + t_0)$ as a function of calendar time, the model was run from 1910 to 2020. As stated above, the intakes in 1970 and 2000 were used as adjustable parameters in the least-square optimization to fit the intake function to empirical intake data.

Results and discussion

Our estimates of the intrinsic elimination half-lives for nine PCB congeners are shown in Table 1 along with results from a study that used one set of CSD in combination with a population PK model[8] and a study that derived intrinsic elimination half-lives from LD by accounting for changes in body weight and ongoing exposure[6].

Table 1: Intrinsic elimination half-lives of nine PCB congeners, derived from cross-sectional data (CSD) covering ages 25 to 34 and from longitudinal data (LD) in children corrected for growth dilution and ongoing exposure.

data used; reference	PCB-28	PCB-52	PCB-105	PCB-118	PCB-138	PCB-153	PCB-170	PCB-180	PCB-187
2 sets of CSD, ages 14–80 (this study[9])	5.5	2.6	5.2	9.3	10.8	14.4	15.5	11.5	10.5
1 set of CSD, ages 25–34[8]			5.2	6.3					
LD, corrected, children[6]			5.4	5.7	3.7	8.4	7.6	9.1	8

Table 2: Apparent elimination half-lives of eight PCB congeners, derived from longitudinal data (LD) in adults.

data used; reference	PCB-28	PCB-52	PCB-105	PCB-118	PCB-138	PCB-153	PCB-170	PCB-180
LD[2]				0.27–0.82	0.88	0.93		0.34
LD[3]	4.8	5.5	infinite	9.6	16.7	infinite		9.9
LD[4]			0.51	0.77	20	26	71	infinite
LD[5] (0–15 years after poisoning)				1.6	4.5	4.2	5.9	6.0
LD[5] (14–29 years after poisoning)				17.6	12.8	9.1	18.4	16.7

Our estimates of the intrinsic elimination half-lives of the nine PCB congeners range from 2.6 yr (PCB-52) to 15.5 yr (PCB-170). They are largely consistent with the intrinsic elimination half-lives that were reported earlier[6,8] although one of these sets was obtained from LD instead of CSD and with an entirely different method[6]. The three sets of intrinsic elimination half-lives in Table 1 show that intrinsic elimination of PCBs from the human body occurs on time scales of several years. As suggested earlier[15], it is likely that there is an upper limit of intrinsic elimination half-lives even for chemicals that are not metabolized; this is caused by slow non-metabolic excretion and is around 10–15 yr. Our results for the longest intrinsic elimination half-lives are consistent with this hypothesis.

The apparent elimination half-lives in Table 2, in contrast, show much wider ranges and include very short (< 1 yr) and very long (several decades, infinity) values. Apparent elimination half-lives are directly derived from the trend of concentration vs. time and it is likely that the values in Table 2 reflect other factors than intrinsic elimination alone. The very long half-lives of several decades or even infinity are probably caused by ongoing intake of PCBs from food. When the concentrations in the individuals investigated approach background levels, ongoing exposure from background contamination of food is sufficient to cause very shallow concentration-time trends. The results reported by Masuda[5] illustrate another important aspect: apparent half-lives derived from individuals who were accidentally exposed to very high PCB concentrations reflect the fact that elimination may be faster when PCB levels are much higher than background levels. Masuda reported apparent half-lives separately for the first and second 15 years after the poisoning event. In the later period, have increased by factors 2 to 10. However, from the observed increase in the apparent half-lives it cannot be told how much of the change is due to (i) an increased influence from ongoing exposure or (ii) due to a slowdown in intrinsic elimination, because both effects are possible to occur when concentrations become lower years after the poisoning event.

From a methodological point of view it is important to note that our approach demonstrates how the empirical basis for estimating intrinsic elimination half-lives of persistent chemicals in humans can be improved. The two sets of CSD each span several decades of age and are 13 years apart. This extensive body of empirical information constrains k_{elim} considerably. The uncertainty of our half-life estimates is around a factor of 1.5. These methodological considerations are relevant to the quantitative analysis of biomonitoring data that will be obtained in the coming years under the Global Monitoring Plan of the Stockholm Convention on POPs. Whenever possible, two or even more sets of CSD spanning a wide age range and collected at least five years apart should be used to derive intrinsic elimination half-lives of POPs in humans. This strategy of less frequent sampling of CSD with a wide age range could be coordinated with the more frequent collection of pool samples with a narrow age-range.

In conclusion, intrinsic elimination half-lives at background concentration levels can be derived with high accuracy if a sufficient number of empirical data are available and if a method is used that eliminates the effects of ongoing exposure and growth dilution. Intrinsic elimination half-lives at background concentration levels are essential for reliably back-calculating exposure from levels measured in humans in the general population.

Uncertainty in elimination half-lives directly and considerably affects estimates of past exposure[1]. Estimates of exposure trends are highly important in the effectiveness evaluation of the Stockholm Convention on POPs.

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