TIME TRENDS OF PERSISTENT CHEMICALS IN HUMANS – QUANTIFIYING EXPOSURE TRENDS AND ELIMINATION HALF-LIVES FROM POPULATION BIOMONITORING DATA

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Abstract
Population time trends of persistent chemicals are assembled by building time series of different sets of cross-sectional monitoring data (CSD). We refer to such time trends as cross sectional trend data (CSTD). We developed a multi-individual pharmacokinetic framework that quantifies the influence of the exposure trend (i.e. long-term change in daily intake) and the elimination half-life (i.e. the clearance from the human body). Under post-ban conditions (i.e. if only individuals having spent their lifetime in a post-ban phase are included in CSTD), the framework provides analytically explicit pharmacokinetic equations describing CSD and CSTD. It is current practice to use log-linear regression to quantify declining trends observed in CSTD. However, results from log-linear regressions have been interpreted in various, sometimes inconsistent ways. Here, we employ a multi-individual pharmacokinetic framework to (i) show that exponential fits of CSTD are a direct quantitative measure of exposure and independent from elimination kinetics if all individuals included in the trend study have spent their lifetime under post ban conditions, and (ii) to establish a method to estimate human elimination half-lives for persistent chemicals under background exposure conditions that uses CSTD instead of sequential measurements in individuals.

Introduction

Measurements of persistent organic pollutants (POPs) in human milk or blood are used to detect time trends and as indicators for exposure of human populations. Human tissues facilitate a standardized global comparison of data and therefore have been chosen as core sampling media for the effectiveness evaluation of the Stockholm Convention on POPs.

So far, time-trends have often been assembled retrospectively by forming time-series of averaged cross-sectional monitoring studies, i.e. measurements in different individuals at one point in time, repeatedly performed in different years.[1,2] We refer to time-trends of cross-sectional data (CSD) as cross-sectional trend data (CSTD). For declining time trends, it is current practice to use log-linear regression (i.e. exponential fitting) to obtain quantitative indicators for the decline in the form of a half-life.[1,2] In the literature, results from log-linear regressions have been interpreted in various, sometimes inconsistent ways. In particular, there is uncertainty about the influence of elimination kinetics and the exposure trend (i.e. long-term change in daily intake) on CSTD.

We developed a multi-individual pharmacokinetic framework to (i) describe the relationship between the exposure trend, elimination kinetics and the trend observed in CSTD and (ii) to establish a method that uses CSTD together with daily intake estimates from total diet studies to estimate human elimination half-lives for persistent chemicals.

The standard method to estimate human elimination half-lives uses sequential measurements in individuals, so-called longitudinal data (LD). For non-persistent chemicals, with human elimination half-lives in the range of hours or days this method is powerful since individuals can be followed easily over a sufficient time period and background exposure can be eliminated through fasting.[3] In contrast, for persistent chemicals, which have long elimination half-lives in the range of many years up to decades, LD studies are more difficult to perform. This is because individuals have to be followed over many years and confounding effects of background exposure cannot be eliminated by fasting. In consequence, estimates are often based on only two measurements and show high variability.[4] For

instance, a review of PCB elimination half-lives reveals that estimates can range from less than one year to virtual infinity even for one specific PCB congener.[5]

Materials and Methods

We present a multi-individual pharmacokinetic framework that quantitatively describes time-trends of human body burdens observed in a population. The population is represented by individuals with common average characteristics but born at different years. The framework can be applied to arbitrary exposure functions and exposure routes. In the particular case of a post-ban situation, in which all individuals included in the CSTD have spent their lifetime under post-ban exposure conditions, the model can be solved analytically and provides explicit equations describing CSTD and CSD as given in equations 1 and 2:

$$C^{\mathrm{CSTD}}(t^{\mathrm{birth}}) = \frac{U \cdot E_{\mathrm{a}}}{\left(k_{\mathrm{elim}} - k_{\mathrm{dec}}\right) \cdot bw \cdot f_{\mathrm{lipid}}} \cdot I_0 \cdot e^{-k_{\mathrm{dec}} \cdot t^{\mathrm{birth}}} \cdot \left(e^{-k_{\mathrm{dec}} \cdot t_{\mathrm{c}}^{\mathrm{age}}} - e^{-k_{\mathrm{elim}} \cdot t_{\mathrm{c}}^{\mathrm{age}}}\right) = K_{\mathrm{CSTD}} \cdot e^{-k_{\mathrm{dec}} \cdot t^{\mathrm{birth}}} \quad [1]$$

$$C^{\mathrm{CSD}}(t^{\mathrm{age}}) = \frac{U \cdot E_{\mathrm{a}}}{\left(k_{\mathrm{elim}} - k_{\mathrm{dec}}\right) \cdot bw \cdot f_{\mathrm{lipid}}} \cdot I_0 \cdot e^{-k_{\mathrm{dec}} \cdot t_{\mathrm{m}}} \cdot \left(1 - e^{-(k_{\mathrm{elim}} - k_{\mathrm{dec}}) \cdot t^{\mathrm{age}}}\right) = K_{\mathrm{CSD}} \cdot \left(1 - e^{-(k_{\mathrm{elim}} - k_{\mathrm{dec}}) \cdot t^{\mathrm{age}}}\right) \quad [2]$$

Where $C^{\mathrm{CSTD}}(t^{\mathrm{birth}})$ [ng/g lipid] is the concentration observed in CSTD as a function of birth year of the individuals sampled; $C^{\mathrm{CSD}}(t^{\mathrm{age}})$ [ng/g lipid] is the concentration observed in one cross-sectional study as a function of age; $t_{\mathrm{c}}^{\mathrm{age}}$ [years] is the characteristic age of the individuals sampled, which is constant and representative for the whole modeled CSTD set; U [days·year^{-1}·kg·g^{-1}] is a unit conversion factor; E_{a} [dimensionless] is the absorption efficiency in the gastrointestinal tract; k_{elim} [years^{-1}] is the first-order rate constant for elimination of contaminant from the human body; k_{dec} [years^{-1}] is the first-order rate constant for decline in exposure of a chemical in a post-ban phase; bw [kg] is body weight; f_{lipid} [dimensionless] is the lipid fraction of the human body; I_0 [ng/person/day] is the intake at t_0, t_{m} [year] is the year the cross-sectional study was performed; and K_{CSTD} and K_{CSD} are constants independent of the birth year or age, respectively. Details and derivation of the equations are given elsewhere.[6]

We use empirical data for DDTs from the UK and Sweden to demonstrate the applicability of the framework.[6] The method to estimate human elimination half-lives from CSTD consists in the application of a five step procedure using eq. 1 and empirical CSTD as well as daily intake estimates. The procedure is based on empirical intake data (Figure 1A) and empirical CSTD (Figure 1B) and yields k_{elim} as a result of fitting eq. 1 to the empirical CSTD. Figure 1 represents a more general application of the framework that is not only including intake data and CSTD but also modeled (eq. 2) and empirical CSD which are not necessarily needed to estimate elimination kinetics.

Results and Discussion

The empirical biomonitoring and daily intake data from the UK were not prospectively planned to assess time trends. As a result, inconsistencies concerning age structure and other study features are inevitable. Despite of these limitations, Figure 1 reveals a relative good consistency between empirical and modeled data including exposure trends (Figure 1A), CSTD (Figure 1B) and CSD (Figure 1C). A key point is that, under post-ban conditions, the time trend in the CSTD (Figure 1B) is identical to the time trend in exposure (Figure 1A). Estimates for human elimination half-lives derived for p,p'-DDE and p,p'-DDT from the UK data are 7.6 years and 2.1 years, respectively. They are in good agreement with results from CSTD from Sweden and additional elimination half-life estimates based on LD.[6]

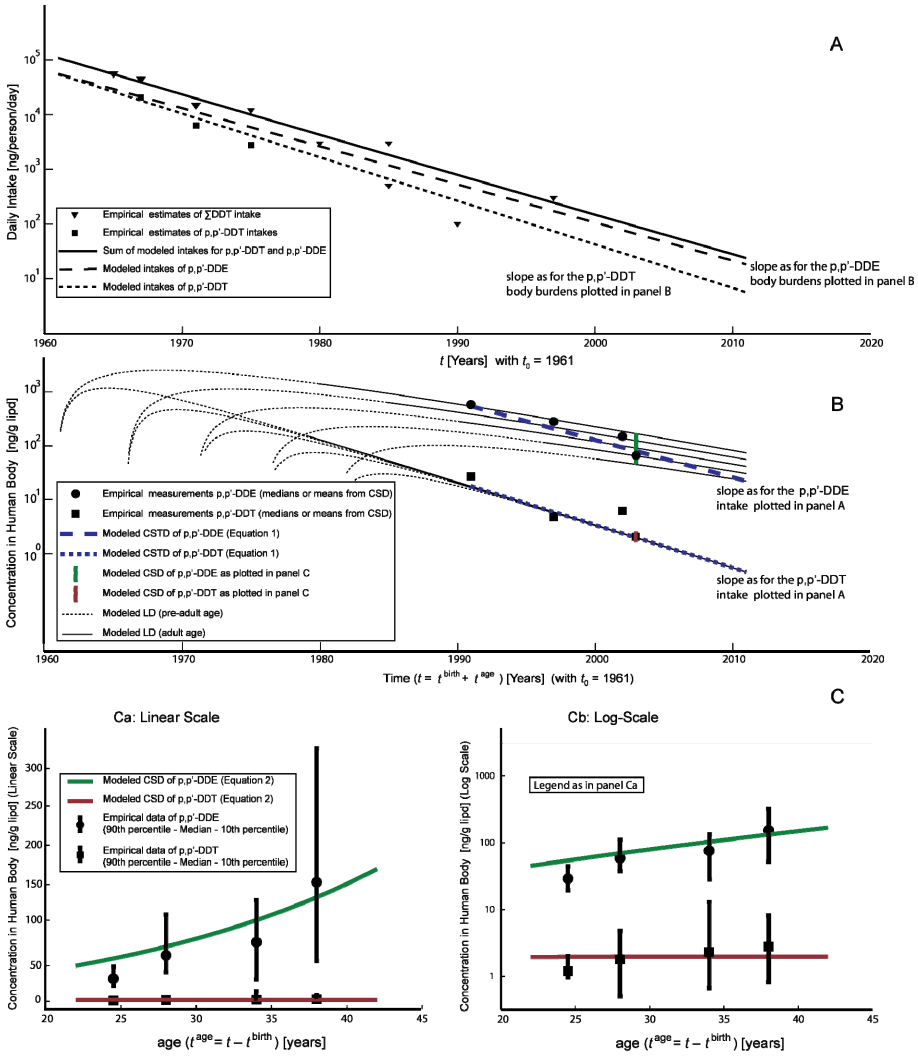

Figure 1. A: Empirical and modeled daily intake of DDTs in the UK; B: Empirical and modeled body burden of DDTs observed in the population (CSTD) and longitudinal data (LD) of representative individuals (LD plotted for illustrative reasons only); C: Empirical and modeled cross-sectional data (CSD) from 2003.[7] plotted on linear scale (panel Ca) and logarithmic scale (panel Cb).

Figure 1C shows that for the more slowly eliminating chemical p,p'-DDE a correlation between body-burden and age can be observed whereas for the faster eliminating chemical p,p'-DDT no significant relationship is detectable. This can also be observed in Figure 1B where LD curves appear to be more separated for p,p'-DDE as compared to LD curves for p,p'-DDT. This highlights that a consistent age-structure becomes especially important when assembling CSTD for slowly eliminating chemicals since including sets of CSD with different age-structure would have a stronger influence on the detected trend for the slowly eliminating chemicals. This requires prospective design of biomonitoring studies aiming to detect time trends.

In 2009, first results of the global monitoring campaign performed in the context of the effectiveness evaluation of the Stockholm Convention are presented. One major goal of this global monitoring campaign is the detection of time trends to assess the effectiveness of measures taken to reduce and finally eliminate POPs from the environment. The prospective character of this long-term monitoring campaign provides unique opportunities to collect consistent biomonitoring trend data. Based on our results, we propose the three main design and coordination criteria for human biomonitoring and exposure studies for persistent chemicals (Figure 2).

The first criterion is the availability of adult individuals that have spent their lifetime under post-ban conditions. If this is the case, it is possible to sample CSD that will form CSTD that directly reflect the trend in exposure and eq. 1 can be applied. If not, eq. 1 cannot be applied. Such data may still be interpreted with the multi-individual pharmacokinetic framework; in this case, however, numerical integration and more detailed empirical knowledge about the exposure trend will be required.

A second aspect is the consistency in age structure and other characteristics of the individuals from which CSTD are derived. Ideally, all CSD sets included in CSTD have the same mean or median age which corresponds to the assumption of a constant characteristic age, t_c^{age}, in eq. 1. In addition, individuals sampled should be as similar as possible in parity (if a woman), and physiological and lifestyle factors such as BMI or smoking habits.

As a third criterion we recommend to coordinate total diet studies, that are already performed in many countries, with the biomonitoring trend studies for two main reasons: First because intake estimates should reflect the same population as in the CSTD and second, to assure optimal use of resources. The frequency of total diet studies can be lower in the post-ban context since in this case they mainly serve to calibrate the absolute level of intake rather than the trend which can be detected in CSTD. Figure 2 summarizes these recommendations.

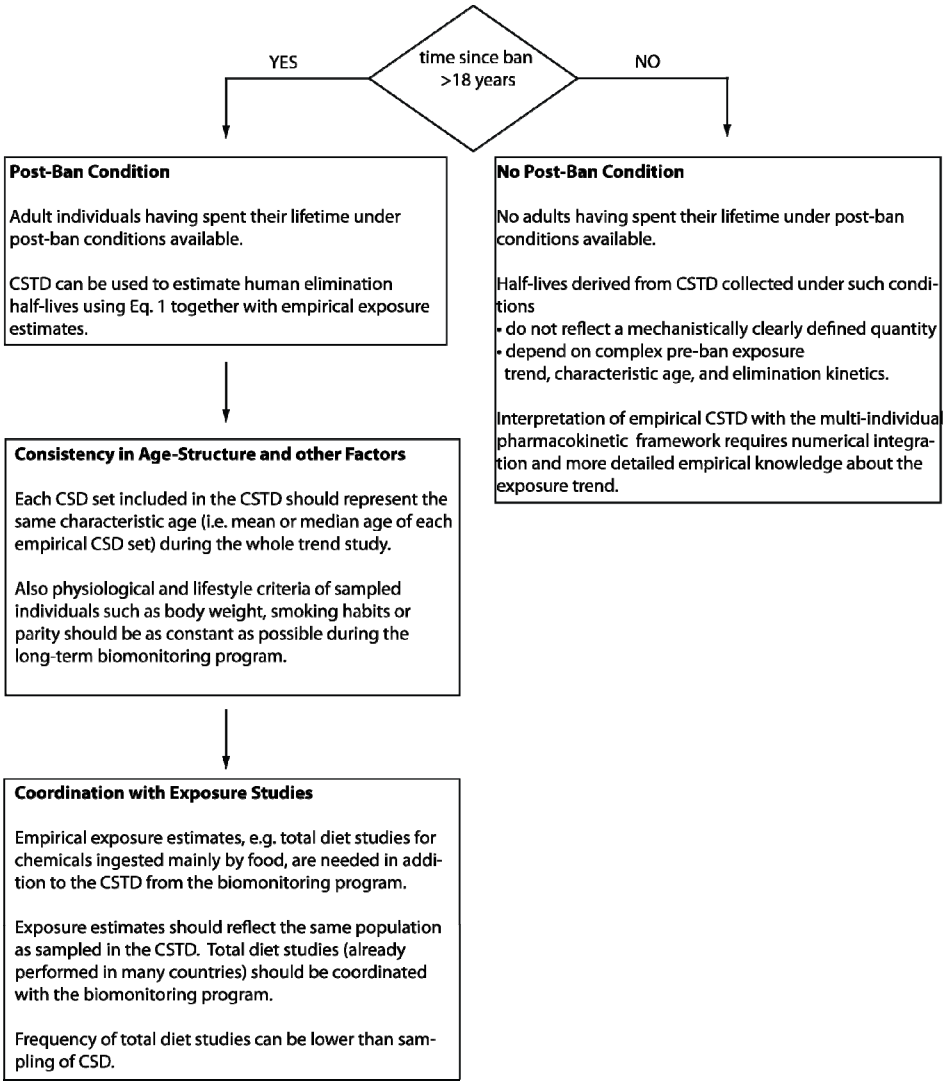

Figure 2. Proposed design and coordination criteria for biomonitoring programs and exposure studies to estimate population exposure and elimination half-lives. The criterion of 18 years is based on the fact that large variability and peaks in body burden as they occur in early child hood (i.e. formula fed vs. breast-fed) have been shown to be leveled out at early adult age (i.e. > 18 years).[8,9]

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