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Estimation of human body concentrations of DDT from indoor residual spraying for malaria control

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ABSTRACT

Inhabitants of dwellings treated with DDT for indoor residual spraying show high DDT levels in blood and breast milk. This is of concern since mothers transfer lipid-soluble contaminants such as DDT via breastfeeding to their children. Focusing on DDT use in South Africa, we employ a pharmacokinetic model to estimate DDT levels in human lipid tissue over the lifetime of an individual to determine the amount of DDT transferred to children during breastfeeding, and to identify the dominant DDT uptake routes. In particular, the effects of breastfeeding duration, parity, and mother's age on DDT concentrations of mother and infant are investigated. Model results show that primiparous mothers have greater DDT concentrations than multiparous mothers, which causes higher DDT exposure of first-born children. DDT in the body mainly originates from diet. Generally, our modeled DDT levels reproduce levels found in South African biomonitoring data within a factor of 3.

1. Introduction

Persistent organic pollutants (POPs) are found worldwide in human tissue samples such as blood, adipose tissue, and breast milk. In Europe and elsewhere, POPs such as DDT (dichlorodiphenyltrichloroethane) and PCBs (polychlorinated biphenyls) are decreasing in humans as their production and use were banned during the 1970s and 1980s (Solomon and Weiss, 2002). However, DDT as one of the initial twelve POPs regulated under the Stockholm Convention on POPs can still be produced and used for disease-vector control (UNEP, 2009). In South Africa, during the annual indoor residual spraying (IRS), 2 g of 75% water wettable technical DDT are applied per m^2 to the inner walls of all dwellings in malaria-endemic areas, resulting in 64–128 g of DDT applied per dwelling (Bouwman et al., 2011). Technical DDT used for malaria control is typically a mixture of the isomers *p,p′*-DDT (72–75%) and *o,p′*-DDT (21%) with traces of *p,p′*-DDE and *p,p′*-DDD (Bouwman et al., 2006). People living in DDT-treated dwellings have 100 times higher DDT concentrations in blood and human milk than the general population in Europe (Ritter et al., 2011a).

Infants experience high DDT exposure through breastfeeding (Bouwman et al., 1992; Bouwman and Kylin, 2009). Pre- and postnatal exposures are especially critical because they affect the early stages of the neural and physical development (Bouwman and Kylin, 2009; Eskenazi et al., 2009; Rogan and Chen, 2005). Recent studies from South Africa found reduced retinol-binding protein and thyroid hormone concentration, urogenital malformations in newborn boys, and impaired semen quality, associated with non-occupational exposure to DDT (Aneck-Hahn et al., 2007; Bornman et al., 2010; Delport et al., 2011).

To the best of our knowledge, no study has yet combined the empirical data specific for individuals who are currently exposed to DDT for malaria control with a pharmacokinetic (PK) model which predicts the DDT concentrations in human tissue over a full lifespan and which differentiates the exposure routes (diet, inhalation). Different PK model approaches have been used to determine infants' pre- and postnatal exposure under constant or time-variant exposure (Kreuzer et al., 1997; LaKind et al., 2000; Quinn et al., 2011). Here we present a one-compartment PK model that can be employed to quantify DDT lipid concentrations derived from estimated dietary and inhalation exposures (dermal exposure was not considered due to low importance found in Ritter et al. (2011a) for highly exposed populations). We used South African datasets from malaria-endemic areas based on samples collected since 1985 because of consistency of sampling, analyses, and documentation of exposure conditions.

The objectives of our study are: i) to quantitatively determine the concentrations of DDT and its transformation product,

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dichlorodiphenyldichloroethylene (DDE), in South African women living in IRS-treated dwellings; ii) to evaluate the effects of breastfeeding duration, parity, and the mother's age at childbirth on the infant's body burden; and iii) to estimate the contribution of DDT and DDE from breast milk, diet, and inhalation at different stages of life. To this end, we defined different scenarios by varying the duration of breastfeeding, the parity as well as the mother's age and investigated the effects of these parameters on the mother's and infant's body burden.

2. Methods

It is a common approach to use PK models for lipophilic environmental contaminants and to assume that this type of contaminants partitions into the lipids of body organs, tissues, and fluids equally (Alcock et al., 2000; Lorber and Phillips, 2002; Quinn et al., 2011). This may also be applied to DDT and DDE (ATSDR, 2002; Ritter et al., 2009). In this type of model, the body is represented as one compartment containing a certain amount of lipids that changes with the age of a person (Alcock et al., 2000; Quinn et al., 2011). Consequently, lipid-normalized concentrations are assumed to be identical in different body compartments and organs. Empirical measurements support this assumption (Darnerud et al., 2010; Sapbamrer et al., 2008; Waliszewski et al., 2000, 2001).

Because individuals living in malaria-endemic regions in South Africa have experienced DDT exposure from annually performed IRS for more than 60 years (Bornman et al., 2010), we assumed that different generations experience identical exposure patterns. That is, a first-born mother would show the same DDT concentration profile as her first-born child (under the assumption that factors such as the mother's age at delivery and the duration of breastfeeding remain the same). Hence, our base case scenario is a South African woman who was the first-born of a 20-year-old woman and was breastfed for 2 years. She in turn gives birth for the first time at the age of 20 and also breastfeeds for 2 years. In addition, a nulliparous woman was included and assumed to have been breastfed for 2 years as the first-born child of a 20-year-old mother. We investigated the effect of breastfeeding duration (0.5, 1, or 2 years), parity (from one child to four children) and the mother's age (16, 20, or 25 years old) on the mother's and infant's body burden by modifying the base case scenario accordingly. We present concentration–age profiles of total DDT, which includes ΣDDT (= *p,p′*-DDT and *o,p′*-DDT) and ΣDDE (= *p,p′*-DDE and *o,p′*-DDE).

2.1. Calculation of total DDT concentration in women

Our one-compartment PK model is represented by the first-order differential equation (Eq. (1)), describing the mass balance in a South African woman, and the conversion equation (Eq. (2)) to obtain lipid-normalized concentrations:

$$\frac{dm_i(t_{age})}{dt} = U_{i,diet}(t_{age}) + U_{i,inh}(t_{age}) - \Big(k_{i,met}(t_{age}) + k_{ex}(t_{age}) + k_{i,bf}(t_{age}, t_{bf})\Big) \times m_i(t_{age}) \quad (1)$$

$$c_i(t_{age}) = \frac{m_i(t_{age})}{bw(t_{age}) \times f_{lip}(t_{age}) \times 1000} \quad (2)$$

where $m_i(t_{age})$ is the mass (ng) of substance i (i = ΣDDT or ΣDDE) in the body as a function of age, $U_{i,diet}(t_{age})$ is the uptake (ng/d) via diet, $U_{i,inh}(t_{age})$ is the uptake (ng/d) via inhalation, $k_{i,met}(t_{age})$ is the first-order rate constant (1/d) for metabolic elimination, $k_{ex}(t_{age})$ is the first-order rate constant (1/d) for non-metabolic elimination (i.e. excretion) (identical for ΣDDT and ΣDDE), $k_{i,bf}(t_{age}, t_{bf})$ is the first-order rate constant (1/d) for breastfeeding as a function of the mother's age and breastfeeding time (t_{bf}), $c_i(t_{age})$ is the lipid-normalized concentration (ng/g$_{lip}$) in the body, $bw(t_{age})$ is the body weight (kg), and $f_{lip}(t_{age})$ is the lipid fraction of the body (dimensionless).

$k_{i,met}(t_{age})$ and $k_{ex}(t_{age})$ were calculated according to Kreuzer et al. (1997) (Eqs. (3) and (4)) by using the overall intrinsic elimination half-life of DDT ($t^{1/2}_{DDT,elim}$ = 2.2 years) and DDE ($t^{1/2}_{DDE,elim}$ = 6.2 years) reported by Ritter et al. (2009):

$$k_{i,met}(t_{age}) = k^{ref}_{i,met} \times \left(\frac{V^{ref}_{lip}}{V_{lip}(t_{age})}\right) \times \left(\frac{V_{liv}(t_{age})}{V^{ref}_{liv}}\right)^{0.667} \quad (3)$$

$$k_{ex}(t_{age}) = \frac{r_{lip,feces}(t_{age})}{bw(t_{age}) \times f_{lip}(t_{age}) \times 1000} \quad (4)$$

where $k^{ref}_{i,met}$ is the first-order rate constant (1/d) for metabolic elimination of the reference subject (= 40-year-old South African woman), V^{ref}_{lip} is the lipid volume (L) and V^{ref}_{liv} is the liver volume (L) of the reference subject, $V_{lip}(t_{age})$ and $V_{liv}(t_{age})$ are the age-dependent lipid volume (L) and liver volume (L), respectively, and $r_{lip,feces}(t_{age})$ is the daily excretion rate of lipids in feces (g$_{lip}$/d). Metabolic conversion of DDT to DDE in the body was not modeled because most of the DDE present in the human body originates from uptake via diet and inhalation (Baselt and Cravey, 1989), with supporting indication from Van Dyk et al. (2010). Further, DDT is much faster degraded to DDD than to DDE (Morgan and Roan, 1971). Therefore, we concluded that the formation of DDE in the body is negligible.

When the mother starts breastfeeding, the amount of ΣDDT and ΣDDE removed via breast milk is equal to the amount taken up by her infant. The first-order rate constant for breastfeeding ($k_{i,bf}$), is described as (Eq. (5)):

$$k_{i,bf}\left(t_{age},\ t_{bf}\right) = \frac{r_{milk}(t_{bf}) \times f_{lip,milk}(t_{bf})}{bw(t_{age}) \times f_{lip}(t_{age}) \times 1000} \quad (5)$$

where $r_{milk}(t_{bf})$ is the rate of the consumed amount of breast milk (g/d) and $f_{lip,milk}(t_{bf})$ is the lipid fraction (dimensionless) of the breast milk as a function of time during the breastfeeding period. Whenever the woman is not breastfeeding, the breastfeeding term in the mass balance (Eq. (1)) is zero. All model calculations were performed in Matlab R2010b; all input parameters for this PK model are provided in the Supplemental Material (SM).

2.2. Total DDT uptake via diet and inhalation

We calculated the daily uptake of ΣDDT and ΣDDE via diet ($U_{i,diet}$) and inhalation ($U_{i,inh}$) as described by Eqs. (S1)–(S3) in the SM. Dietary uptake was calculated by using all available ΣDDT and ΣDDE concentrations measured in local food items such as chicken (muscle and fat), fish (fat) and leafy vegetables (Barnhoorn et al., 2009; Van Dyk et al., 2010). Further, we included ΣDDT and ΣDDE concentrations from recent measurements in chicken eggs in South Africa (R. Bornman, unpublished data). For concentrations of ΣDDT and ΣDDE in chicken fat, a high variability is present in the data reported by Van Dyk et al. (2010) and Barnhoorn et al. (2009). Therefore, we decided to use the median concentrations of Van Dyk et al. (2010) as the upper and the median concentrations of Barnhoorn et al. (2009) as the lower bound. The average of the medians was set as our default concentration for the chicken fat (Table S6, SM). Consumption rates of the food items considered have been reported by Nel and Steyn (2002). The reported consumption rates were extrapolated to obtain age-adjusted consumption rates according to the age-dependent calorific intake reported in Rose et al. (2002). The following age groups were used in this calculation: 0.5–3 years, 3–6 years, 6–10 years, 10–50 years, and >50 years.

Uptake via inhalation of indoor air was calculated by using age-dependent inhalation rates (U.S. EPA, 1997) with constant ΣDDT and ΣDDE concentrations in indoor air of 5.0 μg/m^3 and 0.185 μg/m^3, respectively; the ratio of ΣDDT/ΣDDE = 27 was taken from Van Dyk et al. (2010). We assumed constant concentrations in indoor air because ΣDDT and ΣDDE were still detected 84 day after an IRS intervention in South Africa (Bouwman et al., 2009; Van Dyk et al., 2010). During this period the total DDT concentration decreased quickly from initially 16.5 μg/m^3 to 3.4 μg/m^3. Further, it was assumed that the inhabitants spend 8 h/d inside their dwellings (Bouwman et al., 2009). Uptake efficiency from diet, inhalation, and breast milk was set to 100%.

2.3. Implementation of pregnancy, birth, and breastfeeding

We assumed a weight gain of 0.3 kg/week during pregnancy (Williamson, 2006). At delivery, a woman loses about 4.5 kg (= newborn baby, placenta, and amniotic fluid; ICRP (1975)) immediately and thereafter she continuously loses 0.5 kg/week until she reaches her pre-pregnancy weight (IOM, 1996). The newborn's initial ΣDDT and ΣDDE concentrations were assumed to be identical to the mother's body concentrations at the time of birth; in this way, we accounted for prenatal exposure (Sapbamrer et al., 2008; Verner et al., 2009). The amount of breast milk consumed was assumed 800 g/d for the first year and 600 g/d for the second year (Bouwman et al., 2006; Da Costa et al., 2010). Further, the lipid content of the breast milk was assumed to increase from 3.3% (month 0–4), 3.8% (month 5–8), 4.2% (month 9–12) to 5.0% (month 13–24) (Bouwman, 1990). The concentrations of ΣDDT and ΣDDE in the breast milk over the course of breastfeeding were predicted by the model itself.

2.4. Biomonitoring data

We compared our model results with biomonitoring data of non-occupationally exposed inhabitants who live in dwellings where IRS with DDT is applied once per year. Bouwman et al. (1991, 1992) and Bouwman and Schutte (1993) reported concentrations in blood or blood serum. These concentrations had to be converted to make them comparable with our modeled ΣDDT and ΣDDE concentrations. To this end, whole weight-based concentrations were doubled to yield serum-based concentrations (Bouwman et al., 1992). For the conversion of the serum-based concentrations to lipid-normalized concentrations, we used the factors proposed by the WHO (WHO, 2011), namely 200 for children under 19 years old and 160 for adults over 19 years old which were derived from the average lipid fraction of the blood serum (~0.5–0.65%). The measured total DDT concentrations consist of DDT, DDE, and DDD isomers, but DDD isomers accounted for <3% of the total DDT measured in breast milk and blood (Bouwman et al., 1990, 1992). For this reason and