Estimation of Human Body Concentrations of DDT from Indoor Residual Spraying for Malaria Control

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Abstract

Blood and breast milk samples from inhabitants living in dwellings treated with DDT in indoor residual spraying show high DDT levels. This is of concern since mothers transfer lipid-soluble contaminants such as DDT via breastfeeding to their children. We focused on DDT use in South Africa and used a pharmacokinetic model to identify the dominant DDT uptake routes (food vs. inhalation), to estimate DDT levels in human lipid tissue over the full lifetime of an individual, and to determine the amount of DDT transferred to children during pregnancy and breastfeeding. In particular, the effects of breastfeeding duration, parity, and the mother's age on the DDT concentrations of mother and infant were estimated. The model results suggest that primiparous mothers have greater DDT concentrations than multiparous mothers which lead to higher DDT exposure for their first-born children. Furthermore, DDT in the body mainly originates from diet (92-95%). Our modeled DDT levels reproduce the levels found in South African biomonitoring data within a factor of five or less.

1 Introduction

Persistent organic pollutants (POPs) are found worldwide in human tissue samples such as blood, adipose tissue, and breast milk. In Europe, POPs such as DDT (dichlorodiphenyltrichloroethane) and PCBs (polychlorinated biphenyls) are decreasing in humans as their production and use was 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. 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 these dwellings that are treated with 64g DDT or more every year have high DDT concentrations in blood and human milk due to continuous exposure through diet, inhalation, and dermal contact (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 due to the early stages of the brain 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 (food uptake, inhalation). Different PK model approaches have been used to determine infants' pre- and postnatal exposure under constant exposure or time-variant exposure (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 inhalation and diet exposures. 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 ΣDDT (= *p,p'*-DDT and *o,p'*-DDT) and ΣDDE (= *p,p'*-DDE and *o,p'*-DDE) in individuals living in IRS-treated dwellings; ii) to evaluate the effect of the mother's age, breastfeeding duration, and parity on the infant body burden; and iii) to estimate the contribution of breast milk, inhalation and diet 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

Model set-up and assumptions

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 will be similar between different body compartments. 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, assuming that factors such as the mother's age at delivery and the duration of breastfeeding remained the same (Quinn et al., 2011). From published and unpublished data from South Africa, these assumptions are warranted.

We assumed a woman who was the first-born child of a 20.75-year-old mother and who was breastfed for 2 years as our base-case scenario. When investigating the effect of breastfeeding duration, parity, and mother's age, we modified the base-case scenario assuming the woman gave birth to her first-born child at the age of 20.75 and breastfed her child for 2 years. All model calculations were performed in Matlab R2010b; input data for this PK model are provided in the Supplemental Material.

Calculation of ΣDDT and ΣDDE uptake via diet

The daily uptake of ΣDDT (=*p,p'*-DDT and *o,p'*-DDT) and ΣDDE (=*p,p'*-DDE and *o,p'*-DDE) from each food item individually, namely chicken muscle, chicken fat, chicken egg, fish fat, and leafy vegetables, was estimated according to

$$U_{i,\mathrm{diet}}(t_{\mathrm{age}}) = E_{\mathrm{diet}} * \sum_{\mathrm{j}} (r_{i,j}(t_{\mathrm{age}}) * c_{i,j}) \quad (1)$$

where $U_{i,\text{diet}}(t_{\text{age}})$ is the overall daily uptake of ΣDDT or ΣDDE (ng/d) from all food items j, E_{diet} is the dietary uptake efficiency (–), estimated at 0.9 (Moser and McLachlan, 2001), $r_{i,j}(t_{\text{age}})$ is the daily average consumption rate per capita (g/d) of the food item j, and $c_{i,j}$ is the ΣDDT or ΣDDE concentration (ng/g) in each food item j on wet weight basis. Food consumption rates of the different food products for rural populations in South Africa were derived from Nel and Steyn (2002). We assumed that chicken meat consists of 90% chicken muscle and 10% chicken fat (see Supplemental Material). Reported consumption rates were extrapolated to obtain age-adjusted consumption rates according the age-dependent calorie intake reported by Rose et al. (2002). The following age groups were used: 0.5-3 years, 4-6 years, 7-10 years, and >10 years. ΣDDT and ΣDDE concentrations in chicken muscle and leafy vegetables were obtained from van Dyk et al. (2010), the concentrations in fish fat from Barnhoorn et al. (2009). 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 Barnhorn et al. (2009). Therefore, we decided to set a range for the model concentrations applying the median concentrations of van Dyk et al. (2010) as the upper bound 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. The concentrations in chicken eggs were taken from recent measurements (Bornman, unpublished data).

Calculation of ΣDDT and ΣDDE uptake via inhalation

The daily uptake via inhalation ($U_{i,\text{inh}}(t_{\text{age}})$) was calculated as

$$U_{i,\text{inh}}(t_{\text{age}}) = E_{\text{inh}} * f_{\text{indoor}} * r_{\text{air}}(t_{\text{age}}) * c_{i,\text{air}} \quad (2)$$

where $U_{i,\text{inh}}(t_{\text{age}})$ is the daily uptake of ΣDDT or ΣDDE (ng/g) from indoor air, E_{inh} is the uptake efficiency (–), estimated at 0.75 (European Commission, 1996), f_{indoor} is the fraction of time (–) spent indoors, estimated at 8 h/d (Bouwman et al., 2009), $r_{\text{air}}(t_{\text{age}})$ is the inhalation rate (m^3/d), $c_{i,\text{air}}$ is the sum of gas and particulate-phase concentration of ΣDDT or ΣDDE (ng/m^3) in indoor air. Recommended age-dependent values for inhalation rates were used from the U.S. EPA exposure factors handbook (U.S. EPA, 1997). Ritter et al. (2011a) showed that for adults dermal exposure was of minor importance whereas inhalation significantly contributed to the overall uptake of total DDT (=ΣDDT and ΣDDE). Therefore, we did not consider dermal exposure in our estimated overall uptake. ΣDDT and ΣDDE concentrations in indoor air were measured after IRS interventions in South Africa (Bouwman et al., 2009; van Dyk et al., 2010); total DDT could still be detected after 84 days. During this period the total DDT

concentration decreased quickly from 16.5μg/m^3 initially to 3.4μg/m^3 (Bouwman et al., 2009; van Dyk et al., 2010). We used constant concentrations of ΣDDT and ΣDDE of 5 μg/m^3 and 0.37 μg/m^3, respectively; the ratio of ΣDDE/ ΣDDT was taken from van Dyk et al. (2010).

Calculation of total DDT concentration in women

The one-compartment PK model is represented by the first-order differential equation (3), describing the mass balance in lipids, and the conversion equation (4) to obtain lipid-normalized concentrations:

$$\frac{dm_i(t_{\text{age}})}{dt} = U_{i,\text{tot}}(t_{\text{age}}) - k_{i,\text{elim}} * m_i(t_{\text{age}}) \quad (3)$$

$$c_i(t_{\text{age}}) = \frac{m_i(t_{\text{age}})}{bw(t_{\text{age}}) * f_{\text{lip}}(t_{\text{age}}) * 1000} \quad (4)$$

where $m_i(t_{\text{age}})$ is the mass (ng) of ΣDDT or ΣDDE in lipids as a function of age, $U_{i,\text{tot}}(t_{\text{age}})$ is the total uptake (ng/d) via diet ($U_{i,\text{diet}}(t_{\text{age}})$) and inhalation ($U_{i,\text{inh}}(t_{\text{age}})$), $k_{i,\text{elim}}$ is the first-order rate constant (1/d) for the elimination of the ΣDDT or ΣDDE from the human body, $c_i(t_{\text{age}})$ is the lipid-normalized ΣDDT or ΣDDE concentration (ng/g$_{\text{lip}}$) as function of age, $bw(t_{\text{age}})$ is the body mass (kg), and $f_{\text{lip}}(t_{\text{age}})$ is the lipid fraction (–).

The elimination rate constants ($k_{i,\text{elim}}$) were derived from the intrinsic elimination half-lives reported by Ritter et al. (2009), which are 2.2 years for ΣDDT and 6.2 years for ΣDDE. Metabolic conversion of DDT to DDE in the body was not modeled because it is slow (Morgan and Roan, 1971).

Body mass for rural areas in South Africa have been reported in various nutritional studies (Cameron and Kgamphe, 1993; Mamabolo et al., 2004, 2005; Monyeki et al., 2000; Mostert et al., 2005; Nel and Steyn, 2002; Steyn et al., 1992). For the PK model, we linearly interpolated the data to obtain a growth curve for a woman (see Supplemental Material, Figure S1). We used the age-dependent lipid fractions for girls from Veldhuis et al. (2005) for the age of 0-17; the final lipid fraction was assumed to be 30% for the age of 20 and above (Levitt et al., 2005). On average, until the age of 18, male body development does not differ greatly from that of females, so even though they may be slightly heavier (Cameron and Kgamphe, 1993), a slightly smaller lipid fraction (Monyeki et al., 2005) would result in a similar lipid mass. Therefore, lipid-normalized concentrations were assumed to be similar between girls and boys until the age of 18.

Implementation of pregnancy, birth, and breastfeeding

We assumed a mass gain of 0.3kg/week during pregnancy (Williamson, 2006). At delivery, a woman loses 5 kg (= newborn baby, placenta, and amniotic fluid) immediately and thereafter she continues losing 0.5kg/week until she reaches her pre-pregnancy weight (Institute of Medicine (IOM), 1996). The newborn's initial body concentrations of ΣDDT and ΣDDE were assumed to be identical to the mother's body concentrations at the time of birth thereby accounting for prenatal exposure to ΣDDT and ΣDDE (Sapbamrer et al., 2008; Verner et al., 2009). We assumed a breastfeeding period of 2 years as our base-case. The lipid-normalized ΣDDT and ΣDDE concentrations in the breast milk were modeled to decrease over the course of breastfeeding (see Supplemental Material Equation S1 for mathematical description). The uptake efficiency of ΣDDT and ΣDDE from breast milk was assumed to be 95% (LaKind et al., 2000). The breast milk consumption rate was assumed to be 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, we set the lipid content of the breast milk constant at 3.5% (Bouwman et al., 2006).

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 results for the ΣDDT and ΣDDE concentrations. To this end, blood-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 below 19 years and 160 for adults above 19 years.

Hypothetical complete postban situation

To describe a possible ban of DDT in the future, we calculated ΣDDT and ΣDDE concentrations in 20.75-year-old mothers until 2100. In this calculation, the half-life of ΣDDT and ΣDDE was set at 10 years for soils (ATSDR, 2002). The dietary exposure was assumed to decline according to a first-order exponential decrease with the same environmental half-life (Ritter et al., 2009).

3. Results

1. Total DDT concentration profile over lifetime of a nulliparous woman

Figure 1 shows the modeled age-dependent lipid-normalized concentrations of total DDT (=ΣDDT + ΣDDE) for a nulliparous woman who was breastfed for two years. The sharp increase in total DDT concentrations after birth is due to the lactational transfer of ΣDDT and ΣDDE, which was assumed to be greater than the rate of growth during the first two years of life. The peak concentration of total DDT is reached at the age of 2 and is 131$\mu g/g_{lip}$, which consists of 20% ΣDDT and 80% ΣDDE. After weaning, the total DDT concentration declines due to the mass gain during childhood and adolescence until it stabilizes around the age of 20. During this period, growth dilution is the dominant process and exceeds the rate of contaminant uptake via diet and inhalation. At the age of 20, the woman's body mass and lipid fraction stabilizes, resulting in a total DDT steady state concentration of approximately 32$\mu g/g_{lip}$.

We compared the modeled predictions with measured concentrations in blood serum of both genders living in DDT-sprayed areas derived from Bouwman et al. (1991). These model results agree with the measurements within a factor of 5.

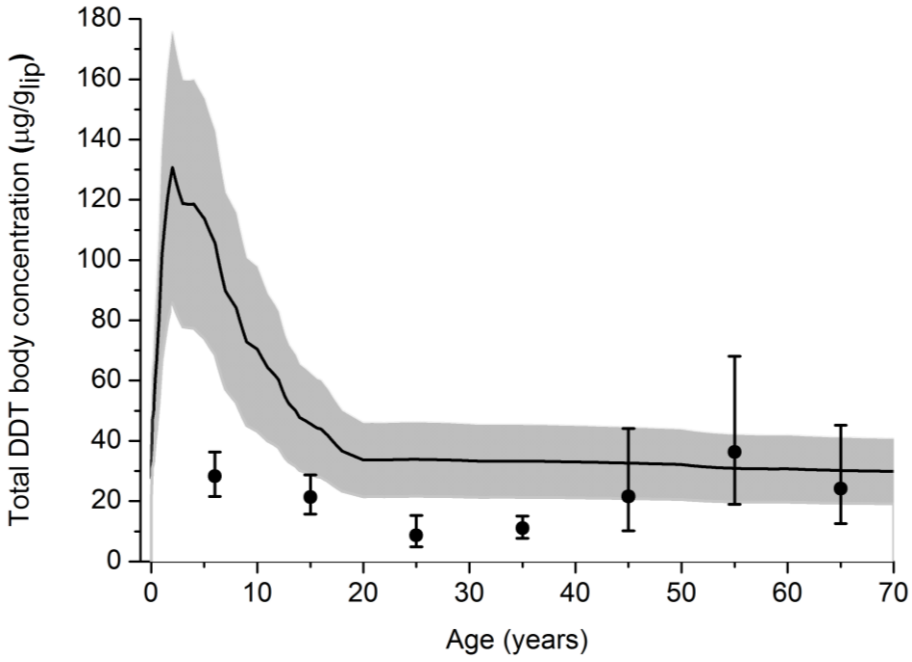

Figure 1: Total DDT lipid-normalized concentration profile of a nulliparous woman with 2 years of breastfeeding (black line: base case). The shaded area represents the variability caused by the range of median ΣDDT and ΣDDE concentrations measured in chicken fat (van Dyk et al., 2010; Barnhoorn et al., 2009) (see sensitivity analysis in Supplemental Material). The biomonitoring data (dots) are the converted total DDT lipid-normalized mean concentrations with 95% confidence interval reported in Bouwman et al. (1991).

2. Effect of duration of lactation, parity, and mother's age at childbirth on the infant's body burden

Fig. 2A shows the total DDT concentration of a nulliparous woman and a mother of a single child with different breastfeeding periods (6 months, 1 year, 2 years). When the woman becomes pregnant at the age of 20, her body lipid mass starts to increase causing a drop in the total DDT concentration from the beginning of her pregnancy (duration 270 days), see Figure 2A. After giving birth, the steep decrease in maternal total DDT concentration is caused by the transfer of contaminants to the child, which exceeds the mother's contaminant uptake via diet and inhalation. The longer the breastfeeding lasts, the more the total DDT concentration decreases in the mother. After weaning, the mother's total DDT concentration rises again until it reaches almost the same level as for the nulliparous woman in Figure 1.

The corresponding postnatal exposure of the first-born child is shown in Figure 2B. We assumed that the infant is exclusively breastfed for 6 months, 1 year, or 2 years and then receives a normal diet. For the 1-year and 2-year scenario, the total DDT concentration in the infant peaks at 101µg/g_{lip} and 131µg/g_{lip}, respectively, just at the end of the breastfeeding period. For the 6-month scenario, the concentration further increases after weaning and reaches its maximum around the age of 5. The amounts of ΣDDT, ΣDDE, and total DDT that are transferred during breastfeeding are shown in Table 1.

Bouwman et al. (1992) investigated the transfer of total DDT to infants via breast milk and reported concentrations in infant blood (µg/L). Figure 2B shows that the adjusted total DDT concentrations of 22 infants investigated (green circles) and our modeled concentrations (lines) are in the same range.

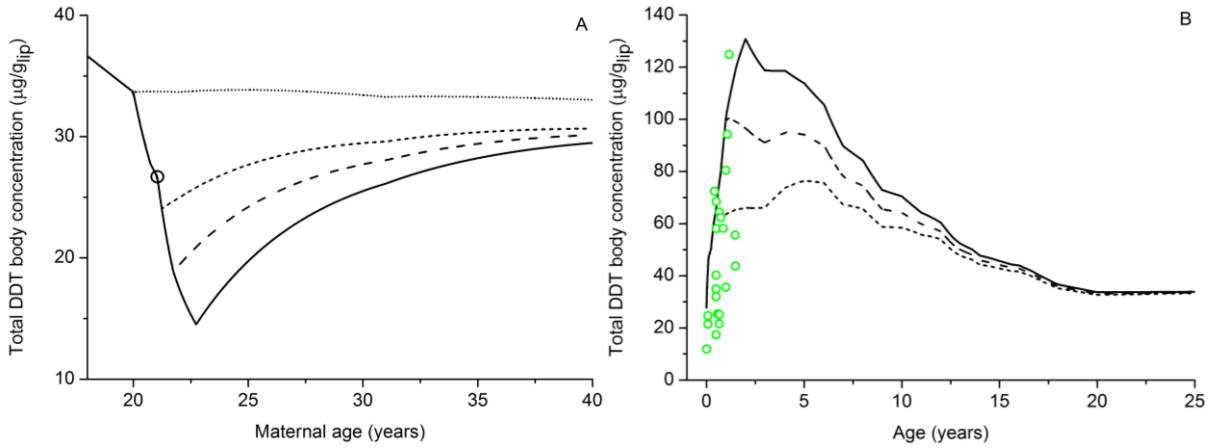

Figure 2: Effect of duration of breastfeeding on the total DDT body concentration of the mother (A) and her first-born child (B). The duration of breastfeeding was varied between 6 months (---), 1 year (– – –), and 2 years (—). In A, the mother becomes pregnant at the age of 20 and gives birth after 270 days (**o**). As reference, a nulliparous woman is shown (· · ·). In B, the comparison of modeled total DDT concentrations between first-born children with different duration of breastfeeding is shown. The biomonitoring data (**o**) are the converted total DDT lipid-normalized concentrations of 22 infants aged 5-540 days who were still breastfed at the time of sampling (Bouwman et al., 1991).

Figure 3 shows the effect of parity on both the mother's and her child's total DDT concentrations. In this case, the woman was assumed to give birth to four consecutive children who are born in 3-year intervals at ages 20.75, 23.75, 26.75, and 29.75 years. Each child is breastfed for 2 years. During these reproductive years, the total DDT

concentration profile of the mother is determined by the interplay of different processes, namely mass gain during pregnancy, mass loss after pregnancy, breastfeeding, and contaminant uptake via diet and inhalation.

Bouwman et al. (1990) examined 132 breast milk samples of women living in IRS-treated dwellings to identify possible factors (i.e. parity, infant's age, and maternal age) affecting the levels of total DDT in breast milk. They found that mothers aged 17-20 years had higher total DDT concentrations than older mothers (red triangles in Figure 3A) and that primiparous mothers had significantly higher total DDT concentrations than multiparous mothers (green triangles in Figure 3A). Our model results agree with these findings (solid line in Figure 3A).

As revealed by Figure 3A and 3B, the first-born child experiences the highest load of contaminants: the steep decrease in the mother's concentration corresponds with the steep increase in the first-born's concentration (identical case as the 2-year breastfeeding scenario in Figure 2A and 2B). The subsequent children receive considerably smaller amounts of contaminants via breastfeeding (Table 1). With increasing number of children, the mean level of total DDT contamination in the breast milk decreases from 20$\mu g/g_{lip}$ to 12$\mu g/g_{lip}$, 10$\mu g/g_{lip}$ and 9$\mu g/g_{lip}$. The first-born child experiences the maximum concentration at the age of 2, while the others reach the maximum 3 years later (Figure 3B).

The effect of parity on the total DDT concentrations among siblings was investigated by Bouwman and Schutte (1993) in eight families by measuring total DDT in blood serum. The converted lipid-normalized total DDT concentrations of girls and boys aged 3-19 years are shown in Figure 3B. The model results are within a factor of 4 of the measured concentrations, but are systematically higher. The agreement improves with increasing age of the children.

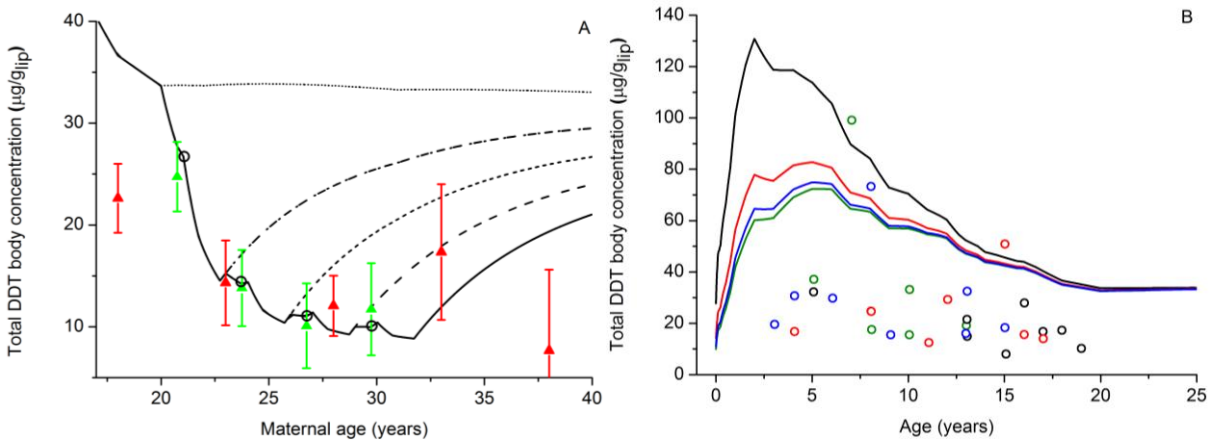

Figure 3: Effect of parity on the total DDT body concentration of the mother (A) and her corresponding children (B) compared with biomonitoring data. A: The total DDT concentration of women with different numbers of children: 1 (– · –), 2 (- --), 3 (– —), 4 children (—). As reference, a nulliparous woman is shown (· · ·). 132 breast milk measurements grouped according to the mother's age (red triangles) and to parity (green triangles) with 95% confidence intervals were taken from Bouwman et al. (1990). The parity data were assigned according to the age of the model mother. B: Total DDT concentration profiles of four siblings: first-born (black), second-born (red), third-born (blue), and fourth-born child (green). The total DDT concentrations of the first four children of eight families are shown (each symbol represents one family) (Bouwman and Schutte, 1993).

Table 1: Mass transfer of ΣDDT and ΣDDE from mother to child depends on the duration of breastfeeding and the order of children born. The duration of breastfeeding was varied for the first-born child in A, and a 2-year breastfeeding period was assumed for each child in B.

A: Duration of breastfeeding	**ΣDDT (mg)**	**ΣDDE (mg)**	**Total DDT (mg)**
6 months	29	106	135
1 year	52	192	244
2 years	81	289	370
B: Parity	**ΣDDT (mg)**	**ΣDDE (mg)**	**Total DDT (mg)**
first-born child	81	289	370
second-born child	57	162	219
third-born child	52	130	182
fourth-born child	50	119	169

Quinn et al. (2011) discussed the influence of the mother's age at her first delivery on the prenatal exposure of the fetus. For the South African conditions assumed here, we found that at birth the total DDT concentration in the first child of a 16.75-years-old mother is higher by 20% than in the first child of a 20.75-years-old mother. On the other hand, an infant born to a 25.75-year-old mother shows almost the same initial total DDT concentration compared to the 20.75-year-old mother. The lactational transfer of total DDT to the first-born child is not greatly influenced by the mother's age.

3. Contribution of diet and inhalation to the overall uptake of total DDT

The overall uptake of total DDT was calculated as the sum of ΣDDT and ΣDDE uptake via diet and inhalation (see Equation 3). For children below 2 years, the contributions of ΣDDT and ΣDDE to this uptake are 23% and 77%, respectively. In this age group, 6% of ΣDDT originate from inhalation and 94% from breast milk, while ΣDDE comes mainly from breast milk (>99.9%). Also in older age groups, more than 99% of ΣDDE stem from food (this is because technical DDT consists of mainly DDT isomers). For the age 2-11 years, ΣDDT contributes 41% and ΣDDE 59% to the total DDT uptake, and the contribution of inhalation to the ΣDDT uptake is 20% (diet: 80%). For the age > 11 years, the fractions of ΣDDT and ΣDDE are the same, but only 13% of ΣDDT originate from inhalation and 87% from diet. While the inhalation route is important for ΣDDT uptake, it is less important for the total DDT uptake (5-8%) because firstly, the contribution of ΣDDT to total DDT uptake is smaller than the contribution of ΣDDE and, secondly, even for ΣDDT uptake from diet is more important than inhalation.

4. Hypothetical post-ban situation from 2020

A hypothetical situation in which DDT use in IRS would be terminated was modeled in order to predict the evolution of the total DDT concentration of future generations. Figure 4 illustrates the initial concentrations in breast milk of 20.75-year old primiparous mothers under the assumption that IRS with DDT was abandoned in 2020. Swedish levels (below 0.1μg/g_{lip}) were reached after 80 years (Norén and Meironté, 2000).

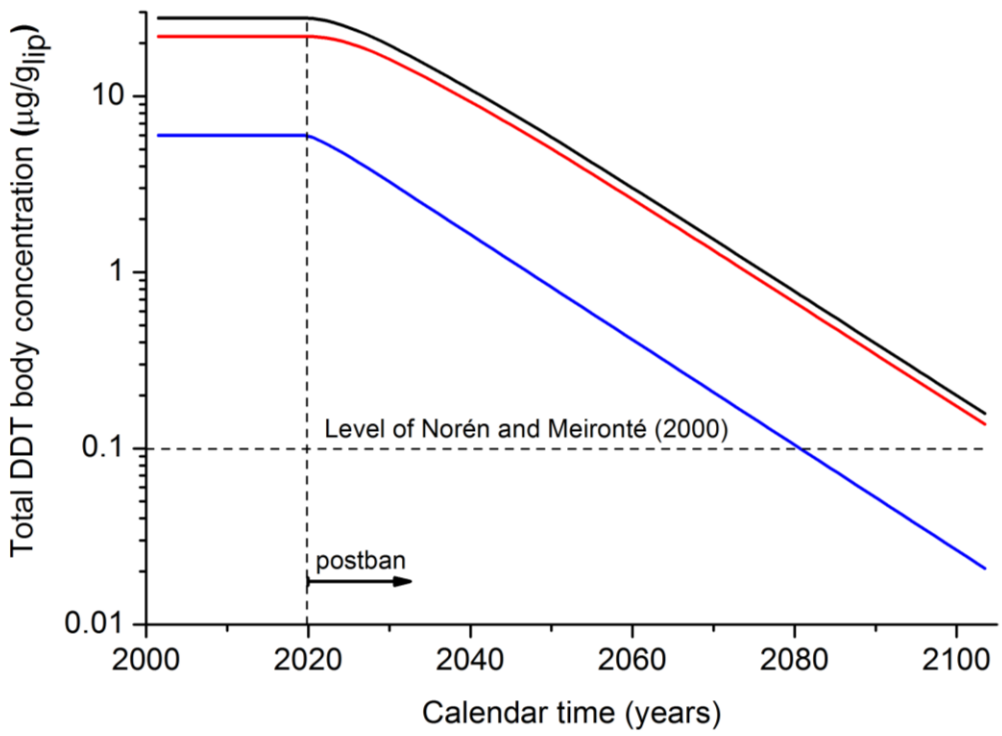

Figure 4: Modeled cross-sectional trend data of ΣDDT (blue), ΣDDE (red) and total DDT (black) in 20.75-year-old primiparous women in a hypothetical postban scenario after 2020.

4. Discussion

We used a one-compartment PK model to predict the lipid-normalized total DDT (= ΣDDT and ΣDDE) concentrations in mothers and in their children living in IRS-treated areas in South Africa. This approach yields total DDT concentrations in women and in their children that are in good agreement with the biomonitoring data reported by Bouwman et al. (1990, 1991, 1992) and Bouwman and Schutte (1993). However, the comparison between the predicted and the measured data warrants closer attention: Firstly, the measured total DDT concentrations consist of DDT, DDE, and DDD isomers, but DDD isomers accounted for less than 3% of the total DDT measured in breast milk and blood (Bouwman et al., 1990, 1992). For this reason and also because DDD is less persistent in humans than DDT and DDE (Kirman et al., 2011), we only modeled ΣDDT and ΣDDE uptake. Secondly, confounding factors may exist for the measured concentrations of Bouwman et al. (1990, 1991, 1992). For the age group of 20-40 years shown in Figure 1, the drop in the total DDT concentration could be caused by including women who already

had children, whereas we present model results for a nulliparous woman. In Figure 3A, the breast milk samples were shown according to parity and mother's age as presented in Bouwman et al. (1990). Yet, the breast milk samples labeled for parity are not labeled for age, and vice versa. Here, we assumed that parity is positively correlated with the mother's age, especially in the case of rural areas in South Africa where women have four children on average (Department of Health, 2007) and arranged the data points (green triangles) accordingly in Figure 3A. Finally, since some of the biomonitoring data were presented on a blood or blood serum basis, we had to apply conversion factors to obtain lipid-normalized concentrations (Bouwman et al., 1992; WHO, 2011).

We identified first-born children to experience both the highest pre- and postnatal exposure compared to later-born children (Figure 3B). Breastfeeding caused elevated concentrations in infants which were up to 4 times higher than the concentrations in adults. This model result is also confirmed by empirical measurements (Figure 2B). Additionally, the average concentration of total DDT in primiparous mothers was found to be twice as high as that of the multiparous mothers (Figure 3A). These finding agrees with the outcomes of the biomonitoring studies by Bouwman et al. (1990, 2006). They also found that primiparous mothers have higher concentrations than multiparous mothers and considered first-born children as a possible high-risk group. Both the birth interval (3 years) and the breastfeeding duration (2 years) are realistic values for the rural population in South Africa (Bouwman et al., 1992, 2006; Bouwman and Schutte, 1993; Department of Health, 2007). The estimated average daily intake of total DDT from breast milk is 66μg/kg/d for the first-born child and 29-38μg/kg/d for the successive children. These values are above the provisional tolerable daily intake (PTDI) for total DDT of 10μg/kg/d (FAO and WHO, 2001).

Also the total amount transferred during breastfeeding depends on parity and duration of breastfeeding (Table 1). Bouwman et al. (1990) calculated 559 mg of total DDT that was transferred to the first-born child during a breastfeeding period of 2 years. Our estimate is lower by a factor of 0.67. However, according to the model the concentration in the breast milk decreases over the course of breastfeeding (see Figures 2A and 3A), which was not assumed by Bouwman et al. (1990). In some special cases, the breast milk concentration have been found to be exceptionally high, namely a 21-year-old primiparous mother from KwaZulu-Natal, South Africa, whose total DDT (= ΣDDT and ΣDDE) concentration was measured to be 117 $\mu g/g_{lip}$ (Bouwman et al., in prep). This case was

calculated separately, and throughout her 381 days of breastfeeding almost 1 g of total DDT was transferred which is almost 4 times higher than the average infant exposure (Table 1).

According to our results, dietary uptake is the dominant exposure route for both ΣDDT and ΣDDE. Among the food items considered, chicken muscle and chicken fat were highly contaminated (van Dyk et al., 2010; Barnhoorn et al., 2009). Moreover, van Dyk et al. (2010) observed high variability in the *p,p'*-isomers differing by six orders of magnitudes. The domestic chickens were highly contaminated probably due to uptake of contaminated dust and soil particles with their feed (van Dyk et al., 2010). The high variability in chicken levels might also be caused by their age, sex, husbandry conditions, and import from non-sprayed areas. Since we identified the concentration in chicken fat as a highly influential model input parameter that also exhibits the highest actual variability (see Supplemental Material Figure S2), we chose this parameter to estimate the variability in the concentrations in the human body (Figure 1). The dietary uptakes of ΣDDT and ΣDDE were obtained with the estimated consumption rates per capita found in Nel and Steyn (2002) for populations in rural areas of South Africa. These daily consumption amounts were in the same range as the food availability study by Rose et al. (2002) for the same population.

We used a constant indoor air concentration since total DDT could be measured in indoor air long after its application (Bouwman et al., 2009; Singh et al., 1992; van Dyk et al., 2010). In our calculations, the contribution of inhalation to the overall uptake of total DDT is small (2-8%). Ritter et al. (2011a), in contrast, estimated that inhalation contributes 70% to the overall uptake of total DDT for adults in regions with IRS. This discrepancy probably originates from the different concentrations used for the dietary uptake: Ritter et al. (2011a), in their compilation of data before 2009, found typical concentrations in various food groups on the order of 100 ng/g_{lip}, whereas the chicken fat concentrations according to van Dyk et al. (2010) and Barnhoorn et al. (2009) are on the order of 10^4 ng/g_{lip}.

If DDT is ever completely phased out, the exposure to total DDT via diet would exponentially decrease as it has done in developed countries in the last 40 years (Ritter et al., 2009). The cross-sectional trend concentration profile displayed in Figure 4 is governed by the slower one of two processes, intrinsic elimination from the body vs. decrease of exposure (Ritter et al., 2011b). With our assumption of an environmental half-life of 10 years, the decrease of exposure is slower than intrinsic elimination (half-lives of 2.2 and 6.2 years). The model results suggest

that it would take more than 80 years until the body concentration of women living in formerly IRS-treated regions are in the similar range as today's women (below 0.1μg/g_{lip}) in Sweden (Norén and Meironyté, 2000).

5. Conclusion

The finding that diet contributes significantly to DDT body burden indicates that exposure reduction efforts should target this uptake route. Domesticated animals kept near the homestead are a plausible DDT source because they are kept in the same vicinity where DDT is applied. It seems that chickens (and possibly other domesticated food animals such as pigs and goats where they occur) that reside on or near homestead premises act as a major vector of DDT to humans. A better understanding of the Total Homestead Environment (THE) as advanced by van Dyk et al. (2010), and modeled here, may therefore support the design of exposure reduction strategies leading to reduced impacts on human and environmental health.

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