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UPTAKE, BODY CONCENTRATION, AND ELIMINATION OF PERSISTENT ORGANIC POLLUTANTS IN HUMANS: INSIGHTS GAINED FROM BIOMONITORING DATA AND POPULATION PHARMACOKINETIC MODELING

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Today, the number of synthetic organic chemicals that humans are exposed to is ever increasing. While the majority of these chemicals are (probably) harmless to humans and the environment, a specific group of chemicals with distinct physical and chemical properties, namely the Persistent Organic Pollutants (POPs), are of global concern. POPs bioaccumulate in fatty tissues of living organisms and cause toxic effects in wildlife and humans. Additionally, because they degrade very slowly in the environment, they are transported through air and water to remote regions on earth. Thus, POPs are found ubiquitously in the environment and in every human being. National laws and regulations have proved insufficient in eliminating these chemicals, and hence a global agreement and action was necessary. Thus, in 2004 the Stockholm Convention on POPs entered into force, with 128 countries committed to the goal to eliminate the use and production of acknowledged POPs and thereby protecting the environment and humans from POPs. Today, 179 out of 195 countries are parties to the Stockholm Convention.

In order to evaluate whether national and international regulations on POP restrictions are effective, biomonitoring data of POPs are collected. These human biomonitoring data include longitudinal data (LD, repeated measurements in the same individuals as they age), cross-sectional data (CSD, many individuals of different ages are sampled once at one point in time), and cross-sectional trend data (CSTD, changes of the POP concentration in individuals of similar age but sampled in different years). The best example for CSTD are temporal trends of POPs observed in breast milk. However, the interpretation of temporal trends of POPs observed in LD, CSD, and CSTD is not straightforward for several reasons: (i) the intake of POPs cannot be stopped from one moment to the other (as for example with pharmaceuticals); (ii) because elimination half-lives are expected to be on the order of years, past exposure as well as changes in body weight affect the current observed levels in the bodies; (iii) because of (i) and (ii) elimination half-lives are difficult to obtain from LD, and thus they offer a wide range of estimated elimination half-lives for the same POP.

In this situation, population pharmacokinetic (PK) models that account for all confounding effects influencing the biomonitoring data (exposure, change of body
weight, time) have been demonstrated to be a suitable tool for investigating temporal trends in LD, CSD, and CSTD. A population PK model estimates the lifetime body concentrations of many representative individuals who were born at different times and have therefore experienced different lifetime exposure to POPs. Hence, it is a suitable choice of model design for exploiting the biomonitoring data along the three temporal perspectives of time: (i) age, (ii) birth year, and (iii) sampling time period. The objective of this thesis is to expand the existing knowledge of the interpretation of temporal trends of POPs observed in LD, CSD, and CSTD. To this end, population PK models are employed in order to retrieve the maximum information contained in biomonitoring data.

In the first study (Chapter 2), the levels of dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyl dichloroethylene (DDE) in South African mothers were investigated. These mothers lived in dwellings treated with DDT during the annual indoor residual spraying (IRS) to prevent Malaria outbreaks. This is of concern since mothers transfer hydrophobic contaminants such as DDT and DDE via breastfeeding to their children. A PK model was used in a forward approach, i.e. all input parameters were previously known or estimated from similar studies. It was found that local contamination in some food items (chicken products) is the predominant source of the measured DDT and DDE levels found in the bodies. Good agreement between measured and modeled concentrations in mothers and their children was obtained when reproductive characteristics such as the mother’s age at childbirth (16, 20, 25 years), the duration of breastfeeding (6, 12, 24 months) and the number of children (up to four) were varied. The total amount of DDT and DDE transferred from mothers to their first-born children was quantified to be 350 mg over the course of two years of breastfeeding. Later-born children receive “only” about half of this amount. These results support the previous indications from biomonitoring data that first-born children receive the highest load of contaminants through breastfeeding and are thus most vulnerable to adverse health effects caused by DDT and DDE. Because of the constant exposure to these chemicals over several decades due to the regular IRS, the modeled LD can be validated with measured CSD because the age-concentration trends as well as the absolute levels are the same in both LD and CSD. Further, in such a setting, the body concentrations of DDT and DDE reach steady-state once the body is outgrown. Therefore, in both LD and CSD, the concentrations do not increase with increasing age.

In the second study (Chapter 3), a population PK model was employed to identify the PBDE uptake rates of Australians which would explain the concentrations of polybrominated diphenyl ethers (PBDEs) measured in five cross-sectional studies between 2002 and 2011, i.e. shortly after the import stop of these chemicals. The CSD
sets cover a wide age range with five to six age groups from toddlers to elderly. A time-variant intake of PBDEs was considered and the focus was set on the uptake rates for the different age groups (uptake = intake multiplied by absorption fraction). Thus, for each of three sets of intrinsic elimination half-lives of PBDE congeners (BDE-47, BDE-99, BDE-100, and BDE-153), the PK model was fitted to the five CSD sets in order to back-calculate the PBDE uptake for the Australian population (top-down approach). These uptake rates were then compared to uptake rates calculated from dietary intake estimates of PBDEs and PBDE concentrations in dust (bottom-up approach). Top-down uptake rates were in most cases higher than the bottom-up uptake rates independently of the intrinsic elimination half-life for all PBDE congeners. Hence, this study provided more and new evidence that known pathways were not sufficient to explain the measured PBDE concentrations, especially in young children (top-down uptake of ∑4BDEs = 8–19 ng/kg/d; bottom-up uptake of ∑4BDEs = 2 ng/kg/d). Although there was a large body of biomonitoring data available, the timing of the sampling campaigns prevented the estimation of the intrinsic elimination half-lives of the PBDE congeners. During the transition period (i.e. the period shortly after the peak exposure), the age-concentration trends of hydrophobic POPs resemble each other independently of the chemical’s elimination half-lives. Thus, the PK model cannot discriminate between short and long elimination half-lives and thus highly underestimates the elimination half-lives of POPs that truly have slow elimination kinetics. Another characteristic of the transition period is that CSD sets of hydrophobic POPs collected during this period do not show increasing concentrations with increasing age.

In the third study (Chapter 4), the temporal course in CSTD of different POPs observed in breast milk was investigated. The focus was set on the interpretation of the CSTD since, from this type of data, many temporal trends have been estimated and will increasingly be estimated all over the world in order to evaluate the effectiveness of the measures taken under the Stockholm Convention to reduce human exposure to these POPs. The aim of this study was to clarify the interpretation of the CSTD from the preban, transition, and postban period and provide recommendations for future interpretations of CSTD sets. To this end, CSTD of two contrasting chemicals, i.e. BDE-47 (peak exposure around late 1990s, short intrinsic elimination half-life) and the polychlorinated biphenyl congener PCB-153 (peak exposure in the 1970s, long intrinsic elimination half-life), were evaluated using the same population PK model as in Chapter 3 as well as a publicly available CSTD half-life tool. While increasing slopes in CSTD of both chemicals directly reflect the increase in intake, the decreasing slopes in CSTD reflects directly the decrease in intake only for BDE-47. The analysis of trends of short-lived POPs is rather straightforward and facilitates additionally the extraction
of the intrinsic elimination half-lives from the breast milk data by means of the CSTD half-life tool. This tool yields an intrinsic elimination half-life of BDE-47 of 2.2 years, which fits very well in the range of previously reported values. For PCB-153, the decrease in CSTD is slower than the decrease in intake because of the mother-child transfer of PCB-153 during breastfeeding. Past exposure to slowly-eliminated POPs slows down the observed decline in CSTD during the postban phase. Consequently, trends of slowly-eliminated POPs in breast milk only provide an indication for the upper bound of exposure time trend because the decrease in CSTD is slower than the decrease in the intake. Temporal trends of slowly-eliminated POPs are more complicated to interpret and the extraction of the elimination half-lives requires CSD sets covering several decades.
Zusammenfassung


Die Länder haben sich damit verpflichtet, die Herstellung und den Gebrauch von anerkannten POPs in ihren Ländern zu verbieten, um so die Menschen und die Umwelt vor den POPs zu schützen. Heute sind schon 179 von weltweit 195 Ländern Teil des Stockholmer Übereinkommens.

Um zu entscheiden, ob die nationalen und internationalen Regulationen wirksam sind, werden Biomonitoring-Daten von POPs erhoben. Man unterscheidet zwischen drei Arten von Biomonitoring-Daten: Längsschnittdaten (auf Englisch „longitudinal data“, LD) werden in denselben Menschen, aber zu unterschiedlichen Zeiten erhoben; Querschnittsdaten (auf Englisch „cross-sectional data“, CSD) sind Messungen in mehreren Personen unterschiedlichen Alters zum selben Zeitpunkt; und Zeitreihen von Messungen bei gleichaltrigen Personen (auf Englisch „cross-sectional trend data“, CSTD). Das beste Beispiel von CSTD ist die Analyse der Muttermilchbelastung aus verschiedenen Jahren. Jedoch ist die Interpretation von LD, CSD und CSTD von POPs aus den folgenden Gründen nicht ganz einfach: a) die Aufnahme von POPs kann nicht plötzlich gestoppt werden (wie es z. B. bei den Medikamenten der Fall wäre), so dass man danach die ungestörte Ausscheidung untersuchen kann; b) die aktuell ge-
messene Konzentration im Körper widerspiegelt sowohl die Aufnahme von POPs aus vergangenen Jahren als auch Veränderungen im Körpergewicht, weil POPs sehr lange Eliminationshalbwertszeiten (mehrere Jahre) haben; und c), wegen a) und b) ist es besonders schwierig die Eliminationshalbwertszeit aus LD abzuleiten. Deshalb findet man teils sehr unterschiedliche Eliminationshalbwertszeit für dieselbe Substanz in der Literatur.


Zusammenfassung


In der zweiten Studie (Kapitel 3) wurde das populationsbasierte PK-Modell angewandt, um die Aufnahmeraten von polybromierten Diphenylethern (PBDEs) aus fünf Australischen Querschnittsstudien, welche zwischen 2002 und 2011 durchgeführt wurden, abzuleiten. Diese Studien wurden kurz nach dem Einführungsstopp dieser Chemikalien durchgeführt. Die Querschnittsdaten decken einen grossen Altersbereich mit fünf bis sechs Altersgruppen vom Kleinkind bis zu älteren Menschen ab. Im Modell wurde eine zeitabhängige Aufnahme von PBDEs angenommen, und der Fokus lag auf der Bestimmung der Aufnahmeraten für die verschiedenen Altersgruppen (Aufnahme bedeutet hier Aufnahme in den Körper, z.B. mit der Nahrung, multipliziert mit einem Absorptionsfaktor). Die Aufnahmeraten von PBDEs (BDE-47, BDE-99, BDE-100 und BDE-153) wurden mit Hilfe des Modells aus den Konzentrationsdaten abgeleitet, indem drei verschiedene Sätze von intrinsischen Eliminationshalbwertszeiten von PBDE-Kongeneren verwendet wurden (Top-down-Ansatz; aus gemessener Konzentration kann in Verbindung mit gegebenen Eliminationshalbwertszeiten auf die Aufnahme geschlossen werden). Diese Aufnahmeraten wurden anschliessend mit solchen Aufnahmeraten verglichen, welche sich aus der Nahrungsmittel- und Staubaufnahme ergeben (Bottom-up-Ansatz). Die Top-Down-Aufnahmeraten waren in den meisten Fällen unabhängig von den gewählten Eliminationshalbwertszeiten deutlich höher als die Bottom-up-Aufnahmeraten. Folglich hat diese Untersuchung weitere und neue Belege dafür geliefert, dass die bekannten Aufnahmewege nicht ausreichend sind, um die gemessenen PBDE-Konzentrationen zu erklären, und dies vor allem bei kleinen Kindern (Top-Down-Aufnahmerate von $\sum_4 \text{BDEs} = 8–19$ ng/kg/d; Bottom-up-Aufnahmeraten von $\sum_4 \text{BDEs} = 2$ ng/kg/d). Obwohl eine grosse Menge von Biomonitoring-Daten zur Verfügung stand, waren die Zeitpunkte der Messkampagnen nicht dafür geeignet, die Eliminationshalbwertszeit der PBDE-Kongeneren aus diesen Daten zu extrahieren. Dies hat folgenden Grund: Während der Übergangszeit (d.h. gleich nach dem Zeitpunkt der höchsten Aufnahme, auf Englisch „transition period“) gleichen sich die Trends in den CSD-Sätzen von hydrophoben POPs unabhängig von

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General introduction
1.1 Persistent organic pollutants

The standard of living in modern societies would not be as high as it is without the use of many thousands of synthetic chemicals. As a result, the general population is continuously exposed in their everyday life to an increasing number of chemicals. It has become virtually impossible to avoid the exposure to these chemicals as they are (intentionally and unintentionally) part of many products that consumers are in contact with on a daily basis: pesticides in food, ultraviolet (UV) filters in personal care products and cosmetics, surfactants in clothing and food packaging, plasticizers in bottles and food containers, and flame retardants in furniture and computers (Carpenter 2013). While the majority of these synthetic organic chemicals are probably harmless for the environment and humans, regulations and actions are required for those chemicals that are persistent and bioaccumulate in humans (e.g., chemicals found in blood and breast milk) (Sonawane 1995; Schlumpf et al. 2010).

1.1.1 History, definition, and regulation

A group of synthetic organic chemicals that are of global concern because of their distinct physical and chemical properties are known as persistent organic pollutants (POPs). POPs are characterized as follows:

“They possess a particular combination of physical and chemical properties such that, once released into the environment, they remain intact for exceptionally long periods of time (many years); become widely distributed throughout the environment as a result of natural processes involving soil, water and, most notably, air; accumulate in the fatty tissue of living organisms including humans, and are found at higher concentrations at higher levels in the food chain; and are toxic to both humans and wildlife.” (www.pops.int)

Because of their persistence, POPs are widely distributed all over the world and can be detected in every single human being today (Tan et al. 2008; Fiedler et al. 2013). The most well-known POPs are dichlorodiphenyltrichloroethane (DDT), polychlorinated biphenyls (PCBs) and polychlorinated dibenzo-p-dioxins and dibenzo-furans (PCDD/Fs). The use of PCBs, DDT and other POPs started in the 1930s and their large-scale production increased rapidly because they proved beneficial to industry and pest and disease control (AMAP 2004). However, signs for negative impacts of those persistent chemicals on the environment and human health were observed early. In her book Silent Spring, which was published in 1962, Rachel Carson describes the bioaccumulation and biomagnification potential of DDT and related pesticides and their impact on wildlife and human health (Carson 1962). Soon after she brought the
uncontrolled and massive use of pesticides and their consequences to public attention, first countries banned or restricted the use of DDT, related pesticides, and PCBs as early as in the beginning of the 1970s (Glynn et al. 2012; O’Sullivan and Megson 2014). Since then, POP concentrations have been decreasing in the environment (Bignert et al. 1998) and humans (Zietz et al. 2008) but have not yet fully disappeared. Due to their environmental persistence and global distribution as well as the detection of increasing concentrations of new persistent chemicals, a global joint action and binding agreement for the elimination and regulation of such chemicals was needed. In 2004, the Stockholm Convention on POPs came into force with 128 countries (= parties). Today, there are 179 countries committed to the objectives of the Stockholm Convention (there are 195 countries in the world today). The Stockholm Convention pursues the goal to protect the environment and human health from POPs on a global level. POPs included in the Stockholm Convention are divided into three categories: Annex A lists POPs for which the intentional production and use has to be eliminated. Annex B lists those for which the production and use are only allowed for exempted purposes, such as DDT use for vector-disease control. Finally, POPs for which measures have to be implemented to reduce and eliminate their unintentional production are listed under Annex C. While the initial twelve POPs included in the Stockholm Convention were all organochlorine chemicals, the list of acknowledged POPs was updated with brominated and fluorinated chemicals in the later rounds (2009–2013) (UNEP 2015). Currently, 23 chemicals and groups of chemicals are regulated and six more chemicals are proposed for listing. However, a screening of 93,000 industrial chemicals according to the criteria defined in Annex D identified approximately 500 chemicals as potential POPs (Scheringer et al. 2012).

1.1.2 Human exposure and chronic effects

The general population experiences chronic exposure to low levels of POPs from different sources. This is because POPs are found in all environmental compartments (air, water, soil, and vegetation). Once in the environment, POPs find their way back to humans through biomagnification up the food chains. In fact, food intake is the predominant pathway of human exposure to POPs (Trudel et al. 2008; Törnqvist et al. 2011). For some POPs, other sources and pathways are also relevant, e.g. drinking water for fluorinated POPs (Skutlarek et al. 2006) and dust particles for brominated POPs (Jones-Otazo et al. 2005). Since the latter two types for POPs are also incorporated in consumer products, hand-to-mouth and object-to-mouth contact are non-negligible exposure pathways, especially for small children (Trudel et al. 2008; Stapleton et al. 2012).
Today, there is a large body of evidence that low-level exposure to POPs earlier in life can lead to adverse effects and non-communicable diseases later in life (Carpenter 2013). The most critical stages of POP exposure are early-life exposures, i.e. in-utero exposure and postnatal exposure through breastfeeding because of the critical stage of the individual’s development (Makri et al. 2004; Eskenazi et al. 2013). Numerous studies have associated POPs with increased risk of cancers (Engel et al. 2007), diabetes (Lee et al. 2011), mental and motoric deficiencies (Herbstman et al. 2010), cardiovascular disease and hypertension (Zeliger 2013). POPs are also known endocrine disrupting chemicals (EDCs) because they interfere with the normal functions of estrogens, androgens and thyroid hormones in the body due to their structural similarity with these hormones (Bergman et al. 2013). EDCs are characterized by low-dose effects and non-monotonic dose-response relationship (Vandenberg et al. 2012; Bergman et al. 2013). Observed consequences of these interactions are e.g., childhood obesity (La Merrill and Birnbaum 2011), early onset of puberty (Chen et al. 2011), or reduced cognitive functions (Patandin et al. 1999). Another mode of action of POPs, especially that of PCDD/Fs, and dioxin-like PCBs, is the binding to the aryl hydrocarbon receptor (AhR), and thus interference with the AhR signaling cascade. AhR is involved in the regulation of gene expression. Disturbance by POPs leads to changes in the gene transcription and the normal development is impaired (Mandal 2005).

Epidemiologic studies use biomonitoring data to investigate these cause-and-effect relationship of POPs in humans. In these studies, measured POP concentrations in blood or breast milk are related to the investigated effect (Patandin et al. 1999; Lee et al. 2011). However, human biomonitoring is also a method proposed by the Stockholm Convention to monitor changes in POP concentrations over time.

1.2 Human biomonitoring

Human biomonitoring studies report the level of chemical concentration in different body fluids (blood, urine, breast milk) or tissues (fat, hair, organs) in a large number of individuals. This method was first applied in pharmaceutical science, where drugs (or drug metabolites) were measured in humans after intentional administration, as well as in occupational exposure science, where employees were monitored for workplace related (and potentially harmful) chemicals (Sexton et al. 2004; Angerer et al. 2007). However, over the past fifty years, human biomonitoring has also become a fundamental tool for assessing occupational and background exposure to POPs (Needham et al. 2007; Patterson Jr et al. 2014).
1.2.1 Biomonitoring of POPs
Biomonitoring studies are performed to measure to which POPs humans are exposed and what the magnitude of this exposure is. The strength of biomonitoring is that it is a direct method for assessing the internal exposure to POPs via all exposure routes (ingestion, inhalation, and skin contact) and from all sources. Further, biomonitoring data are used to characterize background levels of individual POPs in the general population and to identify subpopulation(s) with above-background levels (Toms et al. 2009c). With repeated measurements, changes of the POP concentrations in the population can be tracked over time. This makes it possible to evaluate how effective regulatory measures are in reducing human exposure to regulated POPs. Biomonitoring can also be used as a tool for identifying emerging persistent chemicals. Once new contaminants are detected in the environment, archived samples can be re-analyzed for those new chemicals and thus the extent of past exposure and changes in exposure can be assessed. An example for emerging contaminants was the detection of PBDEs in breast milk samples from Sweden. Once PBDEs had been detected in the environment, breast milk samples were re-analyzed for PBDEs and increasing concentrations in breast milk were observed with a doubling time of around five years in the Swedish population during 1972 and 1997 (Meironyté et al. 1999). This first publication on PBDE in humans triggered many other biomonitoring studies on PBDEs all over the world (Frederiksen et al. 2009). These biomonitoring studies contributed to the listing of the technical mixtures of pentaBDE and octaBDE to the Stockholm Convention in 2009 as they provided additional evidence for persistence, bio-accumulation and toxic effects.

1.2.2 Types of biomonitoring data
There are three types of biomonitoring data which present temporal trends of POPs in humans: Firstly, longitudinal data (LD) are collected in biomonitoring studies that investigate the change of the POP concentration in the same group of (aging) people with repeated measurements over a period of time. An example for this type of data are LD from individuals involved in poisoning incidents with POPs who were followed over several years or even decades to monitor the POP concentrations (Masuda 2001; Sorg et al. 2009). Secondly, cross-sectional data (CSD) are collected if a large number of individuals of different ages is sampled at one point in time. CSD represent a snapshot of the contaminant level in the whole population for the particular sampling time. In combination with questionnaires, CSD are used to associate concentrations not only to age but also to additional information such as life-style factors (e.g. smoking), physical parameters (e.g. body mass index), socio-economic parameters (e.g. educational level), and ethnicity (Becker et al. 2002; Sjödin et al. 2008b; Den Hond et al. 2009).
Thirdly, sequential cross-sectional studies generate cross-sectional trend data (CSTD). In CSTD, the changes of POP concentration in groups with similar age but sampled in different years can be observed. This type of biomonitoring data are generally used to identify new chemicals in humans and/or to evaluate the effectiveness of regulatory exposure reduction measures to regulated chemicals. The best example for CSTD are trends observed in breast milk samples over time (Nörén and Meironyté 2000; Wilhelm et al. 2007).

LD, CSD, and CSTD of POPs have been quantitatively evaluated using log-linear or linear regression analysis (Noegrohati et al. 1992; Wolff et al. 2000; Wittsiepe et al. 2008). However, this method reduces too much the inherent complexity of the biomonitoring data of POPs. Consequently, the results from these regression analysis neglect important process-driven factors and thus clear interpretation is often not feasible. An improved understanding is needed to differentiate between apparent and process-driven time trends in POP concentration data. Pharmacokinetic models which quantify the body concentration in relation to intake and elimination in different individuals from different time periods are powerful tools for investigating temporal trends of POPs observed in human biomonitoring data.

1.3 Population-based pharmacokinetic modeling

Like human biomonitoring studies, pharmacokinetic (PK) models were first applied in the field of pharmaceutical science in order to understand, interpret, and predict time-concentration profiles after drug administration. A PK model mathematically describes the relationship between intake of a drug, its elimination from the body and its resulting body concentration (Wagner 1981). However, the principles of the PK model can be applied to understand the time course of any synthetic chemical, not only drugs, in the human body. In the field of POPs, such PK models are also referred to as toxicokinetic models to emphasize their application for non-pharmaceutical compounds. However, both terms are used equivalently in both fields.

Numerous PK models of different complexity have been developed to conceptualize the processes of intake and elimination of POPs and the resulting POP concentrations in the human body, either on an individual or a population level. The most comprehensive individual PK models are physiologically based PK (PBPK) models. PBPK models are multi-compartment models with each compartment corresponding to an organ such as lungs, liver, and kidney or to a certain type of body tissue such as adipose tissue and muscles. The chemical is transferred to the different compartments via blood flow. An important limitation of these models is the need for a large amount
of data (information on organ and tissue volumes, blood flow rate, and partition coefficients) for model parameterization (Verner et al. 2008).

A more simplified approach is the one-compartment PK model to represent the lifetime concentration of an individual (Aylward and Hays 2002; Lorber and Phillips 2002). In this type of PK models, the human body is represented as one lipid compartment that changes its volume with age. Less data are needed for the model set-up. Further, this simplified approach is supported by the fact that lipid-normalized POP concentrations in different body compartment are similar (Waliszewski et al. 2001; Toms et al. 2007). For the investigation of temporal trends of POPs, a population PK model is more suitable because the measured biomonitoring data often cover a large time and/or age span which promotes the consideration of different individuals from different generations. This type of PK models represents a multiplication of the single-individual one-compartment model. That is, the population PK model estimates the lifetime body concentrations of many representative individuals born at different times and who have therefore experienced different lifetime exposure to POPs (Ritter et al. 2011b; Quinn and Wania 2012).

In the past 20 years, model development for the evaluation of temporal trends of POPs in humans has greatly advanced. Two processes which have been neglected for a long time, but have to be considered for an accurate interpretation of biomonitoring data of POPs, are (i) the (inevitable) ongoing exposure to POPs and (ii) the changes in the storage volume of POPs which is related to an increase (or decrease) in body weight. These two processes particularly mask the intrinsic elimination of POPs from the human body, which is the elimination by metabolic and non-metabolic processes. This is because POPs are very slowly eliminated from the human body. Since elimination half-lives of POPs are mostly derived from decreasing LD from individuals over several years (Masuda 2001; Olsen et al. 2007), the observed changes of the body concentrations are easily confounded by ongoing exposure and changes in body weight (Shirai and Kissel 1996; Milbrath et al. 2009). Consequently, many estimated elimination half-lives from LD are “apparent” instead of “intrinsic” elimination half-lives because ongoing exposure and changes in the body weight were not considered. Apparent elimination half-lives are not suitable for understanding the interplay between intake and elimination of POPs in the general population. However, the rate of a chemical’s intrinsic elimination from the body is an important parameter with respect to the toxicodynamics. The longer chemical remains in the body, the more harm it can cause.
Ritter et al. (2011b) developed a time-variant population PK model which reflects all the important aspects of interpretation of LD, CSD and CSTD of POPs: ongoing exposure, physical growth, time-variant exposure, multiple representative individuals, and generational timespan. Accounting for all these factors, Ritter et al. (2011b) estimated the intrinsic elimination half-lives of PCBs based on two CSD set collected in 1990 and 2003 in the UK population. In doing so, they applied a new approach to exploiting the biomonitoring data along the three temporal perspectives of time: (i) age, (ii) birth year, and (iii) sampling period. Figure 1.1 presents the model design of the population PK model with the chemical concentrations over the full lifespan of multiple representative individuals of the model population who were born in different years (first row). Based on the model population, any type of biomonitoring data can be extracted for comparison with measured biomonitoring data. Illustrative examples of modelled LD, CSD, and CSTD are shown in the second row of Figure 1.1.

**Figure 1.1.** Model design of the population pharmacokinetic model according to Ritter et al. (2011b) and used in this thesis. Representation of different modeled biomonitoring data of a chemical with an intrinsic elimination half-life of 10 years and a time-variant exposure regime. Frist row: Body concentrations of representative individuals born in different years. Second row: Longitudinal data (LD) of an individual born in 1960; cross-sectional data (CSD) of the population sampled in 2010; and cross-sectional trend data (CSTD) of 30-year-old individuals sampled in different years.
1.4 Motivation and thesis outline

On a national level, such as in the United States, Germany or Australia, biomonitoring programs measure POP concentrations across all age groups in regular intervals (Schulz et al. 2007; Toms et al. 2012; Sjödin et al. 2013). On a global level, parties of the Stockholm Convention are encouraged to participate in the Global Monitoring Plan, i.e. the monitoring of POP concentrations in ambient air, blood or breast milk in their country. Well-defined methods for sampling collection and analysis are used, thus, consistent data are collected all over the world. The monitoring of breast milk is especially important because infants experience high exposure to POPs through breastfeeding. In addition, pre- and postnatal exposure to POPs coincides with the critical window of the individual’s neural and physical development.

Human biomonitoring studies require ethical approvals and are expensive to conduct. Therefore, the interest should not only focus on the measured concentrations of chemicals as such but also on exploiting these data to the maximum extent. Only in the recent years, the effects of age, birth year, and sampling period in the area of human exposure to POPs has been methodologically evaluated (Ritter et al. 2009; Ritter et al. 2011b; Quinn and Wania 2012; Nøst et al. 2013). Thus, the objective of this thesis is to contribute to this field of research and hence expand the existing knowledge of the interpretation of temporal trends of POPs in humans.

In the first study (Chapter 2), the body concentrations of total DDT (DDT + dichlorodiphenyldichloroethylene (DDE)) in South African mothers and their children were investigated. These women and their family represent a highly non-occupationally-exposed subpopulation because they lived in dwellings treated annually with DDT to prevent Malaria outbreaks. For the first time, the empirical data of DDT contamination specific for this region were combined. These are measurements in exposure media (i.e. food items and indoor air) as well as biomonitoring data (measurements in mothers, children, and infants). By means of a PK model, the aims were to investigate whether the total DDT contamination in the exposure media are plausible to explain the total DDT concentrations found in the population and to determine which exposure route dominates the uptake of total DDT at different stages of life. Further, postnatal exposure to total DDT via breastfeeding was quantified by varying reproductive characteristics such as the breastfeeding duration (6, 12, 24 months), the number of children (up to four) and the mother’s age at childbirth (16, 20, 25 years).
Whereas the human exposure to organochlorine POPs occurs primarily through diet and the triad of uptake, body concentration and elimination has been shown to be in agreement, the contribution of each exposure pathways of polybrominated diphenyl ethers (PBDEs) has not yet been fully elucidated and varies additionally with age and geography. Therefore, in the second study (Chapter 3), a population PK model was employed to back-calculate the PBDE uptake rates of the Australian population which would result in the PBDE concentrations measured in biomonitoring studies. The focus was set on four PBDE congeners: BDE-47, BDE-99, BDE-100, and BDE-153. Using five CSD sets collected between 2002 and 2011, i.e. shortly after the import stop of these chemicals, as well as three sets of elimination half-lives as model inputs, PBDE uptake rates were fitted and then compared to PBDE uptake rates estimated from dietary intake and dust ingestion.

In few countries, long-term monitoring data of POPs in breast milk are available. However, in context of the Global Monitoring Plan by the Stockholm Convention temporal trends in breast milk will increasingly be estimated all over the world and available for quantitative analysis of levels and time trends. Currently, increasing and decreasing CSTD of POPs from breast milk are interpreted by applying log-linear regression to calculate doubling and halving times of the POP concentrations based on the temporal trend observed in breast milk. However, different interpretation exists of what the doubling and halving times represent. Therefore, the aim of the third study (Chapter 4) was provide recommendations for future evaluations of temporal trends of POPs in breast milk during three distinct periods (preban, transition, postban period) based on the insights gained from the population PK model.
2

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

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2.1 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.
2.2 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 m² 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 breast 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 (Rogan and Chen 2005; Bouwman and Kylin 2009; Eskenazi et al. 2009). 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 data sets 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: 

a) to quantitatively determine the concentrations of DDT and its transformation product, dichlorodiphenyldichloroethylene (DDE), in South African women living in IRS-treated dwellings; 

b) to evaluate the effects of breastfeeding duration, parity, and the mother’s age at childbirth on the infant’s body burden; and 

c) 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.

### 2.3 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 (Waliszewski et al. 2000; Waliszewski et al. 2001; Sapbamrer et al. 2008; Darnerud et al. 2010). 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 age-concentration profiles of total DDT, which includes $\Sigma$DDT (= $p,p'$-DDT and $o,p'$-DDT) and $\Sigma$DDE (= $p,p'$-DDE and $o,p'$-DDE).

#### 2.3.1 Calculation of total DDT concentration in women

Our one-compartment PK model is represented by the first-order differential equation (Equation 2.1), describing the mass balance in a South African woman, and the conversion equation (Equation 2.2) to obtain lipid-normalized concentrations:
\[
\frac{dm_i(t_{\text{age}})}{dt} = U_{i,\text{diet}}(t_{\text{age}}) + U_{i,\text{inh}}(t_{\text{age}}) \\
- (k_{i,\text{met}}(t_{\text{age}}) + k_{\text{ex}}(t_{\text{age}}) + k_{i,\text{bf}}(t_{\text{age}}, t_{\text{bf}})) \times m_i(t_{\text{age}}) 
\]

Eq. 2.1

\[
c_i(t_{\text{age}}) = \frac{m_i(t_{\text{age}})}{bw(t_{\text{age}}) \times f_{\text{lip}}(t_{\text{age}}) \times 1000} 
\]

Eq. 2.2

where \(m_i(t_{\text{age}})\) is the mass (ng) of substance \(i\) \((i = \sum \text{DDT or } \sum \text{DDE})\) in the body as a function of age, \(U_{i,\text{diet}}(t_{\text{age}})\) is the uptake (ng/d) via diet, \(U_{i,\text{inh}}(t_{\text{age}})\) is the uptake (ng/d) via inhalation, \(k_{i,\text{met}}(t_{\text{age}})\) is the first-order rate constant (1/d) for metabolic elimination, \(k_{\text{ex}}(t_{\text{age}})\) is the first-order rate constant (1/d) for non-metabolic elimination (i.e. excretion) (identical for \(\sum \text{DDT}\) and \(\sum \text{DDE}\)), \(k_{i,\text{bf}}(t_{\text{age}}, t_{\text{bf}})\) is the first-order rate constant (1/d) for breastfeeding as a function of the mother’s age and breastfeeding time \(t_{\text{bf}}\). \(c_i(t_{\text{age}})\) is the lipid-normalized concentration (ng/g lipid) in the body, \(bw(t_{\text{age}})\) is the body weight (kg), and \(f_{\text{lip}}(t_{\text{age}})\) is the lipid fraction of the body (dimensionless). \(k_{i,\text{met}}(t_{\text{age}})\) and \(k_{\text{ex}}(t_{\text{age}})\) were calculated according to Kreuzer et al. (1997) (Equations 2.3 and 2.4) by using the overall intrinsic elimination half-life of DDT \(t_{1/2}^{\text{elim,DDT}} = 2.2\) years\) and DDE \(t_{1/2}^{\text{elim,DDE}} = 6.2\) years\) reported by Ritter et al. (2009):

\[
k_{i,\text{met}}(t_{\text{age}}) = k_{i,\text{met}}^{\text{ref}} \times \left(\frac{V_{\text{lip}}^{\text{ref}}}{V_{\text{lip}}(t_{\text{age}})}\right) \times \left(\frac{V_{\text{liv}}(t_{\text{age}})}{V_{\text{liv}}^{\text{ref}}}\right)^{0.667} 
\]

Eq. 2.3

\[
k_{\text{ex}}(t_{\text{age}}) = \frac{r_{\text{lip,feces}}(t_{\text{age}})}{bw(t_{\text{age}}) \times f_{\text{lip}}(t_{\text{age}}) \times 1000} 
\]

Eq. 2.4

where \(k_{i,\text{met}}^{\text{ref}}\) is the first-order rate constant (1/d) for metabolic elimination of the reference subject (= 40-year-old South African woman), \(V_{\text{lip}}^{\text{ref}}\) is the lipid volume (L) and \(V_{\text{liv}}^{\text{ref}}\) is the liver volume (L) of the reference subject, \(V_{\text{lip}}(t_{\text{age}})\) and \(V_{\text{liv}}(t_{\text{age}})\) are the age-dependent lipid volume (L) and liver volume (L), respectively, and \(r_{\text{lip,feces}}(t_{\text{age}})\) is the daily excretion rate of lipids in feces (g lipid/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 $\Sigma$DDT and $\Sigma$DDE removed via breast milk is equal to the amount taken up by her infant. The first-order rate constant for breastfeeding, $k_{i, \text{bf}}$, is described as (Equation 2.5):

$$k_{i, \text{bf}}(\text{age}) = \frac{r_{\text{milk}}(\text{bf}) \times f_{\text{lip,milk}}(\text{bf})}{\text{bw}(\text{age}) \times f_{\text{lip}}(\text{age}) \times 1000}$$  \hspace{1cm} \text{Eq. 2.5}$$

where $r_{\text{milk}}(\text{bf})$ is the rate of the consumed amount of breast milk (g/d) and $f_{\text{lip,milk}}(\text{bf})$ 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 (Equation 2.1) is zero. All model calculations were performed in Matlab R2010b; all input parameters for this PK model are provided in the Appendix A1.

### 2.3.2 Total DDT uptake via diet and inhalation

We calculated the daily uptake of $\Sigma$DDT and $\Sigma$DDE via diet $U_{i, \text{diet}}(\text{age})$ and inhalation $U_{i, \text{inh}}(\text{age})$ as described by Equations A1.1–A1.3 in the Appendix A1. Dietary uptake was calculated by using all available $\Sigma$DDT and $\Sigma$DDE 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 $\Sigma$DDT and $\Sigma$DDE concentrations from recent measurements in chicken eggs in South Africa (R. Bornman, unpublished data). For concentrations of $\Sigma$DDT and $\Sigma$DDE 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 (Appendix A1, Table A1.6). 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 $\Sigma$DDT and $\Sigma$DDE concentrations in indoor air of 5.0 mg/m$^3$ and 0.185 mg/m$^3$, respectively; the ratio of $\Sigma$DDT/$\Sigma$DDE = 27 was taken from Van Dyk et al. (2010). We assumed constant concentrations in indoor air because $\Sigma$DDT and $\Sigma$DDE were still detected 84 day after an IRS intervention in South Africa (Bouwman and Kylin 2009; Van Dyk et al. 2010). During this period the total DDT concentration decreased quickly from initially 16.5 mg/m$^3$ to 3.4 mg/m$^3$. 
Further, it was assumed that the inhabitants spend 8 h/d inside their dwellings (Bouwman and Kylin 2009). Uptake efficiency from diet, inhalation, and breast milk was set to 100%.

### 2.3.3 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 $\Sigma$DDT and $\Sigma$DDE 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 $\Sigma$DDT and $\Sigma$DDE in the breast milk over the course of breastfeeding were predicted by the model itself.

### 2.3.4 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 $\Sigma$DDT and $\Sigma$DDE 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; Bouwman et al. 1992). For this reason and also because DDD is less persistent in humans than DDT and DDE (Kirman et al. 2011), we only included $\Sigma$DDT and $\Sigma$DDE in our investigation.

### 2.3.5 Hypothetical complete postban situation

To describe a scenario of a total ban of DDT in 2020, we calculated $\Sigma$DDT and $\Sigma$DDE concentrations in 20-year-old primiparous mothers until 2100. In this calculation, the half-life of $\Sigma$DDT and $\Sigma$DDE 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 half-life of 10 years (Ritter et al. 2009).

2.4 Results

2.4.1 Total DDT concentration profile over lifetime of a nulliparous woman

Figure 2.1 shows the modeled age-dependent lipid-normalized concentration of total DDT (= \( \Sigma \text{DDT} + \Sigma \text{DDE} \)) for a nulliparous woman who was breastfed for two years. The sharp increase in total DDT concentration after birth is due to the lactational transfer of \( \Sigma \text{DDT} \) and \( \Sigma \text{DDE} \), which is greater than the rate of growth during the first two years of life according to the model. The peak concentration of total DDT is reached at the age of 1.7 and is 75 mg/g lipid, which consists of 21% \( \Sigma \text{DDT} \) and 79% \( \Sigma \text{DDE} \). After the age of 2, the total DDT concentration in the child declines due to the weight gain during childhood until the age of 10. During this period, growth dilution is the dominant process and exceeds the rate of contaminant uptake via diet and inhalation. After the age of 10, the uptake exceeds growth dilution resulting in an increase of total DDT concentration until it stabilizes around the age of 20. After this age, the woman’s body weight and lipid fraction stabilizes, resulting in a total DDT steady state concentration of approximately 30 mg/g lipid.

We compared our modeled concentrations of total DDT with measured concentrations in blood serum of both genders living in DDT-sprayed areas (Bouwman et al. 1991; Bouwman et al. 1992). Our model results agree with the measurements within a factor of 1.5 except for the ages of 25 and 35, which fit within a factor of 3.3. The drop in the measured concentration for the age group of 20–40 years might have been caused by including women who already had children, whereas we present model results for a nulliparous woman.
Interpretation of longitudinal data

Figure 2.1. Total DDT lipid-normalized concentration profile of a nulliparous woman who was breastfed for 2 years as the first-born child of a 20-year-old mother. The shaded area represents the variability caused by the range of median ∑DDT and ∑DDE concentrations measured in chicken fat (Barnhoorn et al. 2009; Van Dyk et al. 2010) (see section 2.3.2 and sensitivity analysis in Appendix A1). The biomonitoring data are the lipid-normalized total DDT concentrations converted from mean serum and blood concentrations with 95% confidence intervals reported in Bouwman et al. (1991; 1992).

2.4.2 Effect of breastfeeding duration, parity, and mother’s age at childbirth

Figure 2.2a shows the total DDT concentration of a nulliparous woman in contrast to a primiparous mother with different durations of breastfeeding (6 months, 1 year or 2 years). When the woman becomes pregnant at the age of 20, her body lipid weight starts to increase causing a drop in the total DDT concentration from the beginning of her pregnancy (gestation of 270 days). After giving birth, the steep decrease in maternal total DDT concentration is caused by the transfer of contaminants to the infant, 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. When the breastfeeding ends, the mother’s total DDT concentration rises again approaching finally the level of the nulliparous woman.

The corresponding postnatal exposure of the first-born child is shown in Figure 2.2b. We assumed that the infant is exclusively breastfed for 6 months, 1 year, or 2 years and then receives a normal diet. In each case the maximum of total DDT concentration is reached at the end of the breastfeeding period and increases with its duration from
54 to 66 and 75 mg/g lipid, respectively. The amounts of $\sum$DDT, $\sum$DDE, and total DDT that are transferred during breastfeeding are shown in Table 2.1. Bouwman et al. (1992) investigated the transfer of total DDT to infants via breast milk and reported concentrations in infant blood (mg/L). Figure 2.2b shows additionally the adjusted total DDT concentrations in infants investigated by Bouwman et al. (1992). Most measured concentrations differ by a factor of less than 2, few by a factor of less than 3 from the model results.

Figure 2.2c and 2.2d show the effect of parity on the total DDT concentration of the mother as well as on her children. In this case, the woman was assumed to give birth to four consecutive children who are born in 3-year intervals when the mother is 20, 23, 26, and 29 years old. 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 weight gain during pregnancy, weight loss after pregnancy, breastfeeding, and contaminant uptake via diet and inhalation. According to Figure 2.2c, the model predicts a fast decrease in the mother’s body burden with the first child and a further decrease in total DDT concentration with subsequent births.

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 mother’s 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 (blue triangles in Figure 2.2c) and that primiparous mothers had significantly higher total DDT concentrations than multiparous mothers (green dots in Figure 2.2c). Although the breast milk samples labeled for parity are not labeled for age, we here assumed that parity is positively correlated with the mother’s age. Especially in the case of rural areas in South Africa this assumption is valid where women have four children on average (DoH 2007). Therefore, we arranged these data points (green dots) accordingly. Our model results agree well with these findings.

As revealed by Figure 2.2d, 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 firstborn’s concentration (identical case as the 2-year breastfeeding scenario in Figure 2.2b). The subsequent children receive considerably less contaminant via breastfeeding (Figure 2.2d and Table 2.1).
Figure 2.2. Effect of breastfeeding duration and parity on the total DDT concentration of the mother (a, c) and her children (b, d); see Equation A1.5 in the Appendix A1 for the mass balance equation for infants. Births are indicated with black dots. The biomonitoring data presented in panel c are the mean concentrations (with 95% confidence interval) of total DDT in breast milk of mothers at different ages (blue triangles) and with different parity (green dots) reported by Bouwman et al. (1990). The parity data were assigned according to the age of the model mother. Biomonitoring data in panel b and d represent measurements from individual children (Bouwman et al. 1992; Bouwman and Schutte 1993).

With increasing number of children, the mean level of total DDT contamination in the breast milk decreases from 16 mg/g lipid to 10 mg/g lipid, 9.2 mg/g lipid and 8.8 mg/g lipid. The maximum concentrations in the children are reached around the age of 2 with the first-born child showing almost twice the maximum concentration of the subsequent children. 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 total DDT concentrations measured in girls and boys aged 3–19 years are shown in Figure 2.2d. The model results differ by a factor of less than 4.3 from these measured concentrations.
Table 2.1. Transfer of ΣDDT and ΣDDE from mother to child over the full duration of breastfeeding; shown is the effect of the duration of breastfeeding (A), the order of children born (B), and the mother’s age (C).

<table>
<thead>
<tr>
<th>A: duration of breastfeeding</th>
<th>ΣDDT (mg)</th>
<th>ΣDDE (mg)</th>
<th>total DDT (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>26</td>
<td>81</td>
<td>107</td>
</tr>
<tr>
<td>1 year</td>
<td>51</td>
<td>159</td>
<td>210</td>
</tr>
<tr>
<td>2 years (base case)</td>
<td>88</td>
<td>265</td>
<td>352</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B: parity</th>
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<tbody>
<tr>
<td>first-born child (base case)</td>
<td>88</td>
<td>265</td>
<td>352</td>
</tr>
<tr>
<td>second-born child</td>
<td>66</td>
<td>162</td>
<td>228</td>
</tr>
<tr>
<td>third-born child</td>
<td>62</td>
<td>139</td>
<td>202</td>
</tr>
<tr>
<td>fourth-born child</td>
<td>61</td>
<td>134</td>
<td>194</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C: mother’s age</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>16 years</td>
<td>82</td>
<td>229</td>
<td>310</td>
</tr>
<tr>
<td>20 years</td>
<td>88</td>
<td>265</td>
<td>352</td>
</tr>
<tr>
<td>25 years (base case)</td>
<td>91</td>
<td>302</td>
<td>393</td>
</tr>
</tbody>
</table>

Finally, the difference in the mother’s age at childbirth has a smaller effect on the infant’s chemical burden than breastfeeding duration and parity (Table 2.1). This difference in lactational transfer is caused by the age-dependent total DDT concentration of the mother prior to pregnancy (Figure 2.1). The latter is a direct result of the fluctuation of the body lipid volume at this age.

2.4.3 Contribution of breast milk, 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 breast milk, diet and inhalation. For children under 2 years, the contributions of ΣDDT and ΣDDE to this uptake are 26% and 74%, respectively. In this age group, 7% of ΣDDT originate from inhalation and 93% from breast milk, while ΣDDE comes mainly from breast milk (>99%). 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 2–10 years, ΣDDT contributes 43% and ΣDDE 57% to the total DDT uptake, and 24% of the ΣDDT uptake originates from inhalation (diet: 76%). For the age >10 years, the contribution of ΣDDT and ΣDDE is similar as in the younger age group but the fraction of ΣDDT from inhalation is only 15% (diet: 85%). In conclusion, the inhalation route is important for ΣDDT uptake (7–24%), but is less relevant for the total DDT uptake (2–10%) because, firstly, the contribution of ΣDDT to total DDT uptake is smaller than the contribution of ΣDDE, and secondly, uptake via diet is more important than via inhalation even for ΣDDT.
2.4.4 Hypothetical postban 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 2.3 illustrates the initial concentrations in breast milk of 20-year-old primiparous mothers under the assumption that IRS with DDT was abandoned in 2020. Swedish levels (total DDT below 0.15 mg/g lipid) were reached after more than 80 years (Norén and Meironyté 2000).

![Figure 2.3](image)

**Figure 2.3.** Model prediction of cross-sectional trend data of $\sum$DDT, $\sum$DDE, and total DDT in 20-year-old primiparous women in a hypothetical postban scenario after 2020.

2.5 Discussion
We used a one-compartment PK model to predict the lipid-normalized total DDT (=$\sum$DDT + $\sum$DDE) 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 agree within a factor of less than 3.3 and less than 4.3 with the biomonitoring data reported by Bouwman et al. (1990; 1991; 1992) and Bouwman and Schutte (1993), respectively. The factor of 4.3 is due to siblings of two families who had much higher levels compared to the other children. Different exposure level and/or pharmacokinetic elimination pattern might have caused this variability in children (Bouwman and Schutte 1993).

We identified first-born children to experience both the highest pre- and postnatal exposure compared to later-born children. Breastfeeding caused elevated
concentrations in infants that are twice as much as the concentrations in adults. Additionally, the mean concentration of total DDT in primiparous mothers was found to be 36–45% higher than that of multiparous mothers (Figure 2.2c). These findings agree with the outcomes of the biomonitoring studies by Bouwman et al. (1990; 2006) who 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 2 years of breastfeeding (our base case) are realistic values for the rural population in South Africa (Bouwman et al. 1992; Bouwman and Schutte 1993; Bouwman et al. 2006; DoH 2007).

Infant exposure to TCDD was investigated by using differential elimination half-life of TCDD based on age-dependent liver volume, lipid volume, and fecal lipid excretion (Kreuzer et al. 1997; LaKind et al. 2000; Lorber and Phillips 2002). In our investigation of infant exposure to total DDT, this approach also yields a better agreement with the biomonitoring data in infants and children than using constant elimination half-lives. The overall intrinsic half-life of ∑DDT and ∑DDE increased from 0.2 to 0.6 years and from 0.3 to 1.2 years, respectively, during the first two years after birth. In adults (>20 years old), the elimination half-lives correspond to those reported in Ritter et al. (2009). Due to the very short half-lives in infants and children (Appendix A1, Figure A1.6) the maximum modeled concentrations in infants differ only by a factor of less than 2.

In addition, the total amount of total DDT transferred during breastfeeding depends on the duration of breastfeeding, parity, and mother’s age at delivery (Table 2.1). 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 0.63. However, according to the model the concentration in the breast milk decreases over the course of breastfeeding (see Figure 2.2a and 2.2c), which was not taken into consideration by Bouwman et al. (1990). Exceptionally high concentrations can be found in breast milk such as of a 21-year-old primiparous mother from KwaZulu-Natal, South Africa, whose total DDT (= ∑DDT + ∑DDE, ∑DDD was not considered) concentration was measured to be 117 mg/g lipid (H. Bouwman, personal communication) after 381 days of breastfeeding. In this case, at least 2 g of total DDT was transferred from mother to child throughout the 381 days of breastfeeding that was not finished at the time of sampling. This high amount of DDT transferred during the postnatal phase together with the prenatal exposure indicates serious risk of long-lasting adverse health effects. Evidence for adverse health effects has been discussed elsewhere (Longnecker et al. 2001; Bouwman et al. 2006; Eskenazi et al. 2009; Bouwman et al. 2011).
According to our results, dietary uptake is the dominant exposure route for both ∑DDT and ∑DDE. Among the food items considered, chicken muscle and chicken fat were highly contaminated (Barnhoorn et al. 2009; Van Dyk et al. 2010). Further, a high variability in the p,p’-isomers of DDT and DDE concentrations differing by four orders of magnitude were observed, probably caused by uptake of contaminated dust and soil particles with their feed (Van Dyk et al. 2010). This variability in chicken levels might also be caused by different 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 (Appendix A1, Figure A1.4), we chose this parameter for estimating the variability in the concentrations in the human body (Figure 2.1).

For inhalation exposure, we used a constant indoor air concentration since total DDT was detected in indoor air long after its application (Singh et al. 1992; Bouwman and Kylin 2009; Van Dyk et al. 2010). In our calculations, the contribution of inhalation to the overall uptake of total DDT is small (2–10%). 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 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 lipid, while the chicken fat concentrations, according to Van Dyk et al. (2010) and Barnhoorn et al. (2009), are on the order of 10⁴ ng/g lipid. Further, the influence of the constant indoor concentration chosen on the model results is low (Appendix A1, Table A1.9).

If DDT were 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 2.3 is governed by the slower one of two processes, namely intrinsic elimination from the body and decrease in exposure (Ritter et al. 2011b). With our assumption of an environmental half-life of 10 years, the decrease in exposure is slower than intrinsic elimination (half-lives of 2.2 and 6.2 years for ∑DDT and ∑DDE, respectively). The model results suggest that it would take more than 80 years until the total DDT concentration of women living in formerly IRS treated regions are in the similar range as those of today’s women (below 0.15 ng/g lipid) in Sweden (Norén and Meironyté 2000).
2.6 Conclusion

The finding that diet contributes significantly to the 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 chicken (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. Finally, it is of high importance to not only continue the regular biomonitoring of DDT in breast milk, but also to focus on determining actual health effects from DDT, especially in infants and children.
Insights into PBDE uptake, body burden, and elimination gained from Australian age–concentration trends observed shortly after peak exposure

Tenzing Gyalpo, Leisa-Maree Toms, Jochen F. Mueller, Fiona A. Harden, Martin Scheringer, Konrad Hungerbühler

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(Reproduced from Environmental Health Perspectives)
3.1 Abstract

**Background:** Population pharmacokinetic models combined with multiple sets of age–concentration biomonitoring data facilitate back-calculation of chemical uptake rates from biomonitoring data.

**Objectives:** We back-calculated uptake rates of PBDEs for the Australian population from multiple biomonitoring surveys (top-down) and compared them with uptake rates calculated from dietary intake estimates of PBDEs and PBDE concentrations in dust (bottom-up).

**Methods:** Using three sets of PBDE elimination half-lives, we applied a population pharmacokinetic model to the PBDE biomonitoring data measured between 2002–2003 and 2010–2011 to derive the top-down uptake rates of four key PBDE congeners and six age groups. For the bottom-up approach, we used PBDE concentrations measured around 2005.

**Results:** Top-down uptake rates of Σ4BDE (the sum of BDEs 47, 99, 100, and 153) varied from 7.9 to 19 ng/kg/d for toddlers and from 1.2 to 3.0 ng/kg/d for adults; in most cases, they were – for all age groups – higher than the bottom-up uptake rates. The discrepancy was largest for toddlers with factors up to 7–15 depending on the congener. Despite different elimination half-lives of the four congeners, the age–concentration trends showed no increase in concentration with age and were similar for all congeners.

**Conclusions:** In the bottom-up approach, PBDE uptake is underestimated; currently known pathways are not sufficient to explain measured PBDE concentrations, especially in young children. Although PBDE exposure of toddlers has declined in the past years, pre- and postnatal exposure to PBDEs has remained almost constant because the mothers’ PBDE body burden has not yet decreased substantially.
3.2 Introduction

At present, there are comprehensive empirical data sets showing the levels of legacy persistent organic pollutants (POPs), such as polychlorinated biphenyls (PCBs) and dichlorodiphenyltrichloroethane (DDT), in human tissue. In combination with time-variant population pharmacokinetic (PK) models, these data have been used to estimate the human intrinsic elimination half-lives of these chemicals and to reproduce cross-sectional age–concentration profiles for the past and future (Ritter et al. 2009; Ritter et al. 2011b, Quinn and Wania 2012).

For polybrominated diphenyl ethers (PBDEs), the situation differs in several respects. First, most PBDE measurements in humans and in the environment were initiated after 2000 and, therefore, the temporal range of the empirical data is rather short (< 15 years). Second, the timing of these measurements coincides with regulatory efforts to reduce human exposure to PBDEs in different countries and the eventual ban of the commercial mixtures of penta- and octaBDE in the European Union (EU) as well as the voluntary withdrawal from the U.S. market, both in 2004 (EU 2003; U.S. EPA 2009). Third, non-dietary exposure, such as ingestion of residential dust and mouthing behavior, has been found to be as important as or even more important than dietary intake for the total human exposure to PBDEs (Jones-Otazo et al. 2005; Lorber 2008; Stapleton et al. 2012). In contrast, the human exposure to legacy POPs occurs primarily through consumption of fish, meat, and dairy products. However, the contribution of each PBDE exposure pathway has not yet been fully elucidated and, in addition, varies with age and geography (Jones-Otazo et al. 2005; Besis and Samara 2012). Further, in contrast to legacy POPs, no increase in concentration has been observed with increasing age in cross-sectional biomonitoring data; on the contrary, children show higher PBDE concentration than adults (Mueller and Toms 2010). Finally, whereas for legacy POPs a good agreement between measured and modeled concentrations in humans has been observed (Ritter et al. 2009; Ritter et al. 2011b), this is not the case for PBDEs in the United States (Wong et al. 2013) and in Australia (Toms et al. 2008).

In Australia, the first biomonitoring survey of PBDE levels in the general population that accounted for regional differences, age, and sex was conducted in 2002–2003. Subsequently, four more surveys were conducted in approximately two-year intervals (Toms et al. 2008; Toms et al. 2009c; Toms et al. 2012; unpublished data). In this period of nearly 10 years, the PBDE concentrations were rather stable in the adult population (age groups 16–30, 31–45, 46–60, >60 years) from survey to survey [the sum of BDE-47, -99, -100, and -153 ($\Sigma_4$BDE) was around 10 ng/g lipid in serum]
samples] whereas in children in the 0–4 years age group, PBDE concentrations declined by two-thirds from 2004–2005 to 2010–2011.

In a first attempt to explain these body concentrations, Toms et al. (2008) compared predicted PBDE body concentrations with the biomonitoring data from the survey of 2004–2005 and discovered a mismatch with the measured levels, the latter being significantly higher than the predicted concentrations. The measured levels could not be explained by the uptake rates calculated by Toms et al. (2008) from PBDE concentrations in contact media and corresponding contact rates. The authors suggested that exposure pathways and/or sources might be missing in the prediction or that the intrinsic elimination half-lives of PBDEs in humans are underestimated.

The intrinsic elimination half-life in the body plays an important role in the balance between intake and body burden. However, until now there have been only three sets of PBDE half-life estimates for the general human population (Geyer et al. 2004; Trudel et al. 2011). In earlier studies, steady-state calculations were performed with either of the two sets of elimination half-lives presented by Geyer et al. (2004) (Table 3.1) in order to compare predicted with measured PBDE concentration in adults (Lorber 2008; Toms et al. 2008; Fromme et al. 2009; Abdallah and Harrad 2014).

Table 3.1. Intrinsic elimination half-lives (years) estimated for adults with background exposure (general population) as they are used in different scenarios investigated in this study.

<table>
<thead>
<tr>
<th>congener</th>
<th>scenario A</th>
<th>scenario B</th>
<th>scenario C</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDE-47</td>
<td>1.4</td>
<td>1.8</td>
<td>3.0</td>
</tr>
<tr>
<td>BDE-99</td>
<td>0.8</td>
<td>2.9</td>
<td>5.4</td>
</tr>
<tr>
<td>BDE-100</td>
<td>1.8</td>
<td>1.6</td>
<td>2.9</td>
</tr>
<tr>
<td>BDE-153</td>
<td>7.4</td>
<td>6.5</td>
<td>11.7</td>
</tr>
</tbody>
</table>


In the present study, we systematically investigated the gap between PBDE uptake rates derived from PBDE levels measured in the Australian population and PBDE uptake rates derived from exposure to PBDEs in food, air, and dust. To that end, we employed a time-variant population PK model using the data sets of five biomonitoring surveys performed between 2002–2003 and 2010–2011. Our goals were to back-calculate the total daily uptake of four key PBDE congeners (BDE-47, -99, -100, and -153) for different age groups (0–3 months, 3–12 months, 1–6 years, 6–12 years, 12–20 years, and >20 years) of the Australian population based on the biomonitoring surveys using different elimination half-lives (“top-down” approach);
b) to calculate “bottom-up” uptake rates from diet, dust ingestion, dermal absorption, and inhalation, and compare these uptake rates to those derived from the top-down approach; and c) to provide guidance on the interpretation of cross-sectional biomonitoring data of lipophilic POPs regarding accumulation with age and derivation of the chemical’s elimination half-life.

3.3 Methods

3.3.1 Biomonitoring data
We used congener-specific cross-sectional data of four key PBDE congeners, BDE-47, -99, -100, and -153, sampled in the following biomonitoring surveys in Australia: 2002–2003 [60 pooled samples (p.s.)], 2004–2005 (12 p.s.), 2006–2007 (81 p.s.), 2008–2009 (12 p.s.) and 2010–2011 (12 p.s.). Blood serum samples of >15,000 residents were collected and pooled for the analysis of individual PBDE congeners (in nanograms per gram lipid). The pools were stratified by age and sex; each pool represents the average concentration of 30 serum samples (survey in 2006–2007) or up to 100 serum samples (all other surveys). Age groups common to all surveys were 16–30, 31–45, 46–60, and >60 years. In addition, age groups of 0–4 and 5–15 years were available for the surveys in 2004–2005, 2008–2009, and 2010–2011; in 2002–2003, the youngest age group was <16 years. In 2006–2007, the age groups covered 6-month periods from newborn to 4 years of age, and were followed by 3-year periods for ages 4–15 years. A detailed description of the analytical method is provided elsewhere (Toms et al. 2008; Toms et al. 2009c; Toms et al. 2012; unpublished data).

For the present analysis, we used the concentrations of the following age groups for the back-calculation of PBDE exposure: 0–4, 5–15, <16, 16–30, 31–45, 46–60, and >60 years. For the sake of consistency and equal weighting, the eight age groups of 6-month periods and the four age groups of 3-year periods in the survey of 2006–2007 were randomly combined to represent the age groups of 0–4 and 5–15 years, respectively.

3.3.2 Part 1. Top-down approach for uptake
The time-variant population PK model originally presented by Ritter et al. (2011b) was applied (step 1 in Figure 3.1). All model equations are provided in Appendix A2 (Equations A2.1–A2.4). Briefly, single individuals are represented as a single well-mixed lipid compartment that receives PBDEs via uptake and loses PBDEs via elimination (excretion and/or metabolism). The size of the lipid compartment varies as a function of age and reflects age-dependent changes in body weight and lipid fraction (ABS 1998; ICRP 2002; WHO 2006). The PK model calculates longitudinal concentrations of chemicals as a function of age for representative females and males.
born in 1-year intervals from 1921 until 2020. Uptake rates (step 2) are age- and time-
dependent and represent the internal dose, (i.e. the amount of chemical that passes
absorption barriers such as skin, lung tissue, and gastrointestinal tract wall), whereas
the chemicals’ intrinsic elimination half-lives are age-independent (step 3). These two
parameters define the longitudinal PBDE concentration profile in each individual.

**Figure 3.1.** Overview of the approach employed in this work.

For comparison with empirical data, cross-sectional concentrations (step 4 in Figure
3.1) were extracted from the PK model representing concentrations of individuals of
different ages at the same calendar time. These model-derived cross-sectional trends
were then compared (step 5) with a subset of the biomonitoring data (step 6), which
is a random sample (step 7) from the full set of biomonitoring data. As long as the
agreement can be improved, the uptake rate was adjusted (step 8) and the PK model
was re-run.

**Time-dependent uptake.** Few data are available for the parameterization of a time-
variant uptake of PBDEs in Australia. The time-variant adult reference uptake was
described by an exponential increase during the phase of production and use followed
by an exponential decrease after import stop or ban of the chemicals. We assumed that
the transition happened in 2001 (prior to the actual ban in 2005) because the
importation of penta- and octaBDE mixtures in Australia dropped significantly after
1998–1999, from 72 to 10–30 metric tons/year for pentaBDE and from 47 to <10
metric tons/year for octaBDE in 2003–2004 (NICNAS 2005). The exposure half-life
(i.e., halving time) after 2001 was derived from the declining trend in PBDE
concentrations in dust samples in Australia; in quantifying this trend, we included
only studies with ≥10 investigated homes (Sjödin et al. 2008a; Toms et al. 2009b;
Stasinska et al. 2013). No trend data of other exposure-related parameters were
available for Australia. Between 2004 and 2010, the concentrations in dust declined
with half-lives varying between 5.9 and 9.0 years for the four PBDE congeners. On the
basis of these data, we used the average of 7 years to represent the half-life of declining PBDE exposure for all congeners. Because no data on increases in PBDE exposure prior to 2001 in Australia are available, we applied the approach by Wong et al. (2013) and mirrored the trend in decline, that is, we used an exposure doubling time of 7 years for all congeners.

*Age-dependent uptake.* The initial PBDE concentration of newborns was set to be equal to the maternal concentration. Newborns were assumed to be exclusively breastfed for three months (AIHW 2011), and transfer of chemical from the mother to the newborn was modeled as shown by Verner et al. (2013). Because all PBDE concentrations are lipid-normalized, the mother's concentration of PBDEs was used as the PBDE concentration in breast milk. For the age groups older than newborns, uptake rates were obtained by multiplying the adult reference uptake by a proportionality factor derived from PBDE intake reported by Lorber (2008) (Appendix A2, Figures A2.1 and Table A2.1).

*Optimization process.* In the optimization, the only adjustable parameter was the adult reference uptake rate in 2001. It was varied in a least-squares optimization until the difference between modeled PBDE levels and measured levels was minimal (Appendix A2, Equation A2.4). The modeled PBDE concentrations are the average concentrations of groups of modeled individuals that include the same number of individuals and the same average age as the pools from which the measured PBDE concentrations were obtained in the biomonitoring surveys.

*Bootstrapping.* To preserve the empirical variability in the biomonitoring data, we ran the optimization process 100 times with 100 different biomonitoring data subsets for each PBDE congener and each elimination half-life (scenarios A, B, and C in Table 3.1). Each subset was bootstrapped (step 7 in Figure 3.1) from the full set of biomonitoring data; we randomly selected 1 pool per age group and survey (throughout the five surveys, the number of pools per age group varied from 2 to 9). Each subset consisted of 29 pools (five age groups from survey 2002–2003, six age groups from the other surveys). The variability in body concentrations originating from the 100 simulations is shown as shaded areas for the female population in Figure 3.2. The 100 simulations resulted in 100 optimized uptake rates; the average uptake rates for each age group for the year 2005 are shown in Figure 3.3. We refer to the uptake rates from the model fit as “top-down” uptake rates.
3.3.3 Part 2. Bottom-up approach for uptake
For comparison with the top-down uptake rates (Part 3 in Figure 3.1), we calculated uptake rates using the bottom-up approach. Estimates of PBDE dietary intake and PBDE concentrations in office dust were only available for 2005 (FSANZ 2007; Toms et al. 2009a). In combination with generic contact rates and absorption factors (step 9 in Figure 3.1), we estimated total uptake rates (step 10) from diet (including breast milk), dust ingestion (home and office), dermal uptake from dust, and indoor air inhalation (home and office) (Appendix A2, Table A2.2 and A2.3).

3.3.4 Sensitivity and uncertainty analysis
We examined the effect of four model parameters that potentially influence the optimized uptake rates. First, the variability in the intrinsic elimination half-lives was accounted for by running the PK model for each congener with three different elimination half-lives (scenarios A, B, and C in Table 3.1). Further, we tested a) the influence of the year of peak exposure (by moving it from 2001 to 1998 and 2004), b) the exposure doubling and halving time (by changing it from 7 to 4.5 years), and c) the proportionality factor for age-dependent uptake rates by using a different PBDE exposure study for its derivation (Appendix A2, Figure A2.1 and Table A2.1).

3.4 Results
Figure 3.2 presents the fitted PBDE body burdens of the female population for scenarios A, B, and C and for each PBDE congener and sampling year. The shaded areas represent the variability of the 100 bootstrapping runs. Results for the male population are shown in the Appendix A2, Figure A2.2.

For all congeners and all elimination half-lives, there is the same course of concentration versus age within each survey: The modeled cross-sectional concentration in the population increases from birth until the age of 4–6 years for BDE-47, -99, and -100, and until 5–8 years for BDE-153 and thereafter decreases and levels off during adulthood. Further, from year to year the peak concentration in children decreases because, in contrast to adults, children have no exposure from earlier years and thus their body burden is directly determined by the current uptake rate. This means that decreasing exposure following the peak in 2001 has a greater effect on PBDE concentrations in children than in adults.
Figure 3.2. Modeled age-concentration profiles (blue: scenario A; green: scenario B; red: scenario C) fitted to the biomonitoring data (dots) of BDE-47, BDE-99, BDE-100, and BDE-153 in the female population. To increase the visibility of the data for the younger age groups, the x-axis ends at 50 years and the two oldest age groups are not shown. The concentrations in adults >50 years of age equal to the concentrations of adults <50 years of age and therefore do not contribute additional information.
Figure 3.3 presents the average fitted top-down uptake rates derived from the different model scenarios A, B and C, as well as the uptake rates from the bottom-up approach for the different age groups of the Australian population for the year 2005. The exact values are presented in the Appendix A2, Table A2.4.

### 3.4.1 Top-down uptake

The highest fitted uptake rates for all age groups are present in the scenarios with the shortest elimination half-lives, that is, BDE-47 and BDE-99 in scenario A, and BDE-100 and BDE-153 in scenario B (Figure 3.3). The fitted uptake rates decrease with increasing elimination half-lives. For BDE-47, uptake rates in scenarios B and C are 75% and 50%, respectively, of those in scenario A for all age groups. For BDE-99, they are 30% and 20%. For BDE-100, scenario B yields 115% and scenario C 65% of the uptake rate in scenario A. The same trend is seen for BDE-153, where uptake rates in scenario B and scenario C are 110% and 80%, respectively, of those in scenario A. However, there is virtually no difference in the uptake rates of breastfed infants among all scenarios (Figure 3.3, Table 3.2), which is due to the fact that the modeled PBDE concentration in the breast milk of the 25-year old mothers is very similar in all three scenarios (Figure 3.2).

**Age groups.** Due to exclusive breastfeeding, infants younger than 3 months of age have the highest PBDE uptake rate in all scenarios (Figure 3.3). For infants older than 3 months, the uptake rate decreases rapidly by a factor of 3–15, 5–14, and 9–18, respectively, depending on the PBDE congener in scenarios A, B, and C, with BDE-153 showing the largest differences (Appendix A2, Table A2.4). With increasing age, the uptake rates continue to decline to levels of 3.0, 2.0, and 1.2 ng/kg/d of $\Sigma_4$BDE for adults in scenarios A, B, and C, respectively (Table 3.2).

<table>
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<th>scenario B</th>
<th>scenario C</th>
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<td>2.0</td>
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</tr>
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</table>
Interpretatio
n of cross-
sectional data

Figure 3.3. PBDE uptake rates of different age groups in 2005 derived from both the top-down approach with different elimination half-lives (blue: scenario A; green: scenario B; red: scenario C) and the bottom-up approach (white). Note the different scale on the y-axis for infants aged 0–3 months of age.

3.4.2 Bottom-up uptake
A similar age trend is visible in the uptake rates from the bottom-up approach (Figure 3.3). Breastfed infants have the highest uptake rates (Table 3.2); for the different PBDE congeners, they are 8–84 times higher than the uptake rate of infants above 3 months (Appendix A2, Table A2.4). Again, the difference is highest for BDE-153. Σ BDE uptake rates of toddlers, children and teens range from 1.2 to 2.3 ng/kg/d with toddlers having the highest exposure (Table 3.2). Adults have the lowest Σ BDE uptake rate of 0.89 ng/kg/d.

For the top-down approach, it is not possible to break down PBDE uptake rates in terms of different exposure pathways, but this can be done for the bottom-up approach. For all age groups, dietary uptake is by far the most important exposure pathway, representing 85–95% of total uptake for all age groups. Dust ingestion is
responsible for the remaining uptake; inhalation and dermal uptake are negligible (data not shown).

### 3.4.3 Bottom-up vs. top-down approach

In general, the top-down uptake rates are higher than the bottom-up uptake rates (Figure 3.3, Table 3.2). For all age groups except breastfed infants, the top-down uptake rates are higher than the bottom-up uptake rates by factors of 2–8, 2–7, 2–15, and 2–12 for BDE-47 (scenarios A and B), -99 (A only), -100, and -153, respectively, depending on the age group and scenario (Appendix A2, Table A2.4). The largest differences, on the order of a factor of 10, are found for toddlers. In terms of PBDE congeners, the differences in uptake rates are higher for BDE-100 and BDE-153 than for BDE-47 and BDE-99. Even with the longest set of elimination half-lives (scenario C), the top-down uptake rates of BDE-100 and BDE-153 for adults are still four times higher than their corresponding bottom-up uptake rates.

It is important to note that in cases where top-down and bottom-up uptake rates are similar (i.e., BDE-99 in scenarios B and C, and BDE-47 in scenario C), the modeled concentrations are clearly lower than the measured concentrations for children (Figure 3.2; Appendix A2, Figure A2.2). This suggests that the top-down uptake rates are too low in these cases and that the actual uptake rates are higher than indicated by both top-down and bottom-up uptake rates.

### 3.5 Discussion

Ideally, there would be agreement between modeled and measured cross-sectional concentrations for all biomonitoring surveys, as well as agreement between top-down and bottom-up uptake rates. Because this is not the case for the investigated PBDE congeners and any of the scenarios, we conclude that either some exposure sources and/or pathways are missing or underestimated in the bottom-up approach, or that the current intrinsic PBDE elimination half-lives are underestimated, or a combination of both. This is in agreement with the findings by Toms et al. (2008).

#### 3.5.1 Top-down approach: Sensitivity and uncertainty analysis

Overall, the elimination half-lives of the four key PBDE congeners had the largest effect on the uptake rates for 2005 (Figure 3.3). In contrast, the choice of the exposure doubling and halving time had little effect on the uptake rates for 2005 (a deviation of only ±3%) (data not shown). Next, moving the year of maximum uptake from 2001 to 1998 resulted in a reduction in uptake rates of 7–15% depending on the scenario, whereas a shift from 2001 to 2004 resulted in an increase of 18–29% (data not shown). Finally, by using a different PBDE exposure study (Trudel et al. 2011) for the
derivation of the proportionality factor, the uptake rates of toddlers were most affected among the different age groups. Their uptake rates decreased by 37% because the average proportionality factor was reduced from 6.4 to 3.8 for this age group; at the same time, the adult uptake rates increased by 7% (data not shown). Altogether, we altered influential model parameters within reasonable ranges. The highest effects on the top-down uptake rates across all model scenarios were a factor of 1.4–6 caused by the changes in elimination half-lives (Appendix A2, scenarios A to C in Table A2.4) and a factor of 0.6 (decrease by 37%) to 1.3 (increase by 30%) caused by changes in other parameters (data not shown). In contrast, the difference between top-down and bottom-up uptake rates are up to a factor of 15 (Appendix A2, Table A2.4).

3.5.2 Bottom-up approach: Uncertainties
In our bottom-up approach, the predominant exposure pathway is diet, which in all age groups contributes 85–95% of the $\Sigma_4$BDE uptake (calculated as described in section 3.3.3). According to FSANZ (2007), bread and boiled eggs are the most important food items, together contributing approximately 30% to the total dietary intake, independently of the age group. Fish, in contrast, contributes only 1–2% (FSANZ 2007). Also in many European and Asian countries, dietary intake is the main PBDE exposure pathway for the general population, but the largest contribution, up to 67% of the total dietary intake, stems from fish and shellfish (Domingo 2012; Na et al. 2013). Thus, this particular food category might be substantially underestimated in Australia. Strong evidence that this might be the case is given by the similar fish and seafood consumption rates in Australia and Western Europe (NOAA 2012) and even higher PBDE contamination in fish consumed in Australia than in Europe (Domingo 2012).

The contribution of PBDE exposure from dust to the total uptake for the Australian population is low (16% for toddlers, 6% for adults; calculated as described in section 3.3.3). A possible explanation of the discrepancy between top-down and bottom-up uptake rates could be a large underestimation of the PBDE concentrations in the dust samples from Australia. However, the dust samples ($n = 5–30$) measured between 2004 and 2012 in homes, offices, and schools (Sjödin et al. 2008a; Toms et al. 2009a; Toms et al. 2009b; Toms et al. 2012; Stasinska et al. 2013; Toms et al. 2015) show similar mean and median concentrations of the key congeners and are much closer to the PBDE concentrations found in Europe than to those in North America (Whitehead et al. 2011). It is unlikely that all of these measurements systematically underestimated the actual PBDE levels in dust in Australia.
Had we used concentrations of 2,000, 1,000, 500, and 150 ng/g dust for BDE-47, -99, -100, and -153 in dust samples, respectively, which are in the range of the U.S. data, the total $\sum_4$BDE uptake rates would increase from 2.3 to 6.8 ng/kg/d for toddlers and from 0.89 to 1.5 ng/kg/d for adults. This approximately 10-fold increase in hypothetical average PBDE concentrations in dust samples would produce good agreement between top-down and bottom-up uptake rates for all age groups except for toddlers. However, as noted above, such elevated average PBDE concentrations in dust samples are not supported by the PBDE measurements in dust from Australia.

Our bottom-up uptake rates are more uncertain than the top-down uptake rates, because the underlying sample sizes are small. Dietary intake is, according to our analysis, the dominant exposure pathway, but dietary intake estimates were determined only once (in 2005) (FSANZ 2007). In addition, dust ingestion rates are very uncertain parameters and vary substantially between exposure studies; specifically, values used for toddlers vary from 50 to 200 mg/d (here 60 mg/d) and for adults from 4.16 to 100 mg/d (here 30 mg/d) (Jones-Otazo et al. 2005; Toms et al. 2009a).

### 3.5.3 Why the PBDE concentrations do not increase with age

The present situation with PBDEs is similar to the situation with PCBs shortly after 1970, for which Quinn and Wania (2012) modeled the cross-sectional age-concentration trends. For the transition period after the peak exposure in 1974, the course of the modeled cross-sectional data of PCB-153 (elimination half-life, 15 years) looks like the current course of the PBDE concentrations in the Australian population, as shown in Figure 3.2. This is the case although the time trends of the PBDEs shown in Figure 3.2 are based on elimination half-lives considerably shorter than 15 years. That is, cross-sectional biomonitoring data of lipophilic chemicals (independently of a chemical’s elimination half-life) exhibit age-concentration profiles as presented in Figure 3.2 if they are sampled during the transition period, that is, within 10 years after peak exposure (Quinn and Wania 2012).

It is not until at least 20 years after the year of peak exposure that the age-concentration profile of chemicals with long elimination half-lives starts to differentiate from that of rapidly eliminated chemicals (Ritter et al. 2011b; Quinn and Wania 2012). In this later stage, the concentrations of chemicals with long elimination half-lives increase with increasing age, which is not the case for chemicals with rapid elimination. Thus, now we observe chemical concentrations increasing with age in cross-sectional biomonitoring data for legacy POPs such as most PCBs, dioxins and dichlorodiphenyldichloroethylene (DDE) (Mueller and Toms 2010), but not (yet) for
Interpretation of cross-sectional data

PBDEs (Thomsen et al. 2002; Toms et al. 2012; Garí and Grimalt 2013; Sjödin et al. 2013).

3.5.4 Why we cannot fit the elimination half-lives of PBDEs

It is important to note that the currently available PBDE biomonitoring data from 2002–2003 to 2010–2011 cannot be used to accurately estimate the PBDE elimination half-lives because these data were collected in the transition phase around the time of maximum exposure. As stated above, in this phase, age-concentration profiles show the same trend independently of the chemical’s elimination half-life.

This is different from the analysis performed by Ritter et al. (2011b), who used PCB biomonitoring data to estimate PCB elimination half-lives in humans by fitting a population PK model to the biomonitoring data. In their case, the data were from 1990 and 2003, but the ban of PCBs took place already in the 1970s. Both PCB data sets were sampled in the postban phase two and three decades after the ban. Under these conditions, the data were sufficient to constrain congener-specific elimination half-lives for different PCBs because, in the long term, the age-concentration profile shows an increase in concentrations with increasing age if the chemical's elimination half-life is longer than the exposure half-life. If not, the age-concentration profiles are the same as they are observed today for PBDEs; that is, there is no increase with age, as it was found for PCB-52 (Ritter et al. 2011b).

Therefore, derivation of the elimination half-life from the current PBDE biomonitoring data would result in an underestimation of the elimination half-life of those chemicals that truly have long elimination half-lives because the PK model is not constrained by long-term biomonitoring data, as was the case for PCBs (Ritter et al. 2011b).

3.6 Conclusions

We have provided new evidence for the inconsistency between uptake rates derived from the biomonitoring data and uptakes rates calculated from dietary intake of PBDEs and PBDE concentrations in dust. Especially the contribution from fish and shellfish might currently be highly underestimated in Australia. Therefore, long-term continuation of biomonitoring surveys of identical design and complemented with measurements of PBDE concentrations in contact media are vital for identifying the cause of the mismatch between modeled and measured PBDE concentrations and also as a basis of potential measures for risk reduction and risk management.

Beyond the case of PBDEs, insights gained from this study suggest that cross-sectional biomonitoring data of emerging lipophilic chemicals such as alternative brominated
flame retardants [e.g. bis-(tribromophenoxy)ethane (BTBPE), or decabromodiphenyl ethane (DBDPE)], will show the same age-concentration profile as observed in the current biomonitoring data of PBDEs, that is, no increase in concentration with increasing age (Figure 3.2).

Further, it is important to note that as a result of the declining exposure, the PBDE body burden of toddlers and children has declined during the past 10 years, whereas the PBDE exposure of fetuses and breast-fed infants (the most sensitive groups) has remained rather constant. This is because the PBDE body burden of the mothers has not reacted as fast as that of young children to the decreasing exposure (Figure 3.2).
Recommendations for evaluating temporal trends of persistent organic pollutants in breast milk

Tenzing Gyalpo, Martin Scheringer, Konrad Hungerbühler

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4.1 Abstract

**Background:** Biomonitoring data of persistent organic pollutants (POPs) in breast milk are increasingly collected and available for quantitative analysis of levels and time trends. A common approach is to apply log-linear regression to calculate doubling and halving times of the POP concentrations based on the temporal trend observed in breast milk. However, there are different, sometimes conflicting interpretations of these doubling and halving times.

**Objectives:** We provide a mechanistic understanding of doubling and halving times where possible. Five recommendations are proposed for dealing with POP concentration trends in breast milk during three distinct periods (preban, transition, postban period).

**Discussion:** Using temporal trends of BDE-47 and PCB-153 in breast milk data, we show which information can be gained from the time-trend data. To this end, we analyze time trends of hypothetical POPs for different periods with time-variant exposure and different intrinsic elimination half-lives, using a dynamic population-based pharmacokinetic model. Different pieces of information can be extracted from time-trend data from different periods. The analysis of trends of short-lived POPs is rather straightforward and facilitates extraction of the intrinsic elimination half-lives from the breast milk data. However, trends of slowly-eliminated POPs only provide indications for the exposure time trend.

**Conclusions:** Time-trend data of rapidly-eliminated POPs provide information on exposure time trends and elimination half-lives. Temporal trends of slowly-eliminated POPs are more complicated to interpret, and the extraction of exposure time trends and elimination half-lives require data sets covering several decades.
4.2 Introduction

The Stockholm Convention on Persistent Organic Pollutants (POPs) entered into force in 2004 and aims at protecting humans and the environment from POPs (UNEP 2009). To evaluate the effectiveness of measures taken under this Convention, time trends of POPs in human samples, mostly milk, are investigated. Today, many long-term data sets of POPs, such as dichlorodiphenyltrichloroethane (DDT), polychlorinated biphenyls (PCBs), hexachlorobenzene (HCB) and polybrominated diphenyl ethers (PBDEs), are available that cover periods of 20–40 years (Wilhelm et al. 2007; Glynn et al. 2012; Fång et al. 2013).

Here we call these time-concentration trends taken from groups of individuals with similar characteristics, but sampled in different years, “cross-sectional trend data” (CSTD). Declining CSTD are often fitted with exponential functions (Craan and Haines 1998; Norén and Meironyté 2000; Minh et al. 2004; Glynn et al. 2012). The slope of these fits provides the CSTD-based half-life, $t_{1/2}^{\text{CSTD}}$. Generally, depending on the time period of data collection in relation to the introduction of the ban (or voluntary phase-out) of a chemical, and the physicochemical properties of the chemical and age of the population, the time-concentration plot may be subdivided into three different periods: preban (constant positive slope), transition (gradual change in slope from positive to negative), and postban (constant negative slope). For example, the CSTD for BDE-47 in Figure 4.1 increase up until the mid-1990s, when the phase-out of technical mixture of pentaBDE was implemented in Sweden (Alcock and Busby 2006), then flattens out during the transition period, and eventually shows a negative slope during the postban period.

In the literature, different terms have been used to describe $t_{1/2}^{\text{CSTD}}$ and various interpretations of $t_{1/2}^{\text{CSTD}}$ have been proposed (Ritter et al. 2009). Technically, it is straightforward to derive $t_{1/2}^{\text{CSTD}}$ from data of the postban period, but there is considerable confusion about the meaning of these CSTD-based half-lives. They were interpreted to be related to either the intrinsic elimination half-life, $t_{1/2}^{\text{elim}}$, which indicates how fast the chemical is metabolized and excreted (= elimination) from the human body (Noegrohati et al. 1992; Wolff et al. 2000), or to the trend in exposure characterized by the half-life of decline in intake, $t_{1/2}^{\text{in}}$, which indicates how fast the total human exposure to the chemical is declining (e.g. time trend derived from total diet studies) (Minh et al. 2004; Glynn et al. 2012), or to both (Sjödin et al. 2004).

To resolve this confusion, Ritter et al. (2009) have provided a tool to disentangle these different half-lives. They developed a static population-based pharmacokinetic (PPK) model, called “CSTD half-life tool” (available on http://www.sust-chem.ethz.ch/downloads) specifically for the postban period that explains the relationships between $t_{1/2}^{\text{in}}$, $t_{1/2}^{\text{elim}}$, and $t_{1/2}^{\text{CSTD}}$. “Static” here refers to the assumptions there is no transfer of chemical from mother to child (i.e. in-utero transfer or via breastfeeding), and that there is no change in body weight or lipid weight of any individual (Table 4.1, Static PPK model). Because of these assumptions, the mass-balance equation of the model can be solved analytically, see Ritter et al. (2009). This tool first derives $t_{1/2}^{\text{CSTD}}$ from the exponential fit of a set of CSTD, but then, in addition, uses the relationships between $t_{1/2}^{\text{in}}$, $t_{1/2}^{\text{elim}}$, and $t_{1/2}^{\text{CSTD}}$ to extract also $t_{1/2}^{\text{elim}}$ from the data, which is another important metric for the assessment of human exposure to POP-like chemicals. This is a novel approach to estimating $t_{1/2}^{\text{elim}}$ of a persistent chemical based on human data. However, limitations of the CSTD half-life tool due to the assumptions of the static PPK
model were not specifically discussed in the original publication (Ritter et al. 2009) and will, therefore, be presented in this commentary.

Table 4.1. Comparison between static PPK and dynamic PPK models.

<table>
<thead>
<tr>
<th>processes</th>
<th>static PPK modela</th>
<th>dynamic PPK modelb</th>
</tr>
</thead>
<tbody>
<tr>
<td>in-utero transfer</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>transfer via breastfeeding</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>change of body weight</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>change of lipid weight</td>
<td>no</td>
<td>yes</td>
</tr>
</tbody>
</table>

a The CSTD half-life tool as developed by Ritter et al. (2009) is one example of a static PPK model. The tool is available on http://www.sust-chem.ethz.ch/downloads. b The PPK model as developed by Ritter et al. (2011b) is one example of a dynamic PPK model.

Meanwhile, dynamic PPK models that accommodate changes in individual characteristics with age and transgenerational transfer of chemicals (in-utero exposure and via breastfeeding), such as the “CoZMoMAN model” or the “Ritter model”, have been developed and used to evaluate POP concentrations in longitudinal (Nøst et al. 2013) or cross-sectional biomonitoring data (Ritter et al. 2011b; Wong et al. 2013; Gyalpo et al. 2015). CSTD collected under the Global Monitoring Plan of the Stockholm Convention can also be evaluated with these models, which (unlike the CSTD half-life tool) can accommodate transgenerational transfer and changes in body weight and lipid weight with age (Table 4.1, Dynamic PPK model) and are not restricted to biomonitoring data from the postban period.

Here, our objective is to combine the knowledge gained from these previously published dynamic and static PPK models for the evaluation of CSTD. This is important because in the context of the Global Monitoring Plan of the Stockholm Convention extensive data sets have been collected and will be generated in the future, which calls for a common approach to interpreting the measured CSTD. To this end, we present five recommendations for the evaluation of CSTD sampled during the preban and transition periods as observed for e.g. BDE-47 (Figure 4.1). In addition, we explain the limitations of the CSTD half-life tool and clarify its applicability domain, which is important for future applications of this tool. Hence, our overarching goal is to illustrate which model framework can be used in which situation to fully exploit the information that is contained in CSTD.

4.3 Recommendations for the evaluation of CSTD from different periods

We differentiate between two categories of POPs: (1) POPs whose intrinsic elimination half-lives \( t_{1/2}^{\text{elim}} \) are shorter than their intake doubling times \( t_{2}^{\text{in}} \) and
intake half-lives ($t_{\text{in}}^{1/2}$) (e.g. BDE-47), and (2) POPs whose $t_{\text{elim}}^{1/2}$ values are longer than $t_{\text{in}}^{2}$ and $t_{\text{in}}^{1/2}$ (e.g. PCB-153). Thus, POPs similar to BDE-47 are referred to as “rapidly-eliminated” or “short-lived” POPs whereas POPs similar to PCB-153 are referred to as “slowly-eliminated” POPs. In the following sections we illustrate with the examples of BDE-47 and PCB-153 (Figure 4.1) and other POPs how the trends in CSTD from different periods are to be interpreted based on the insights gained from the dynamic PPK model. Five recommendations for the interpretation of CSTD sets are derived in the following sections. They are listed in Table 4.2.

Table 4.2. Recommendations for evaluation of CSTD.

<table>
<thead>
<tr>
<th>recommendations</th>
<th>relevant time period</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The doubling time in intake prior to the phase-out of the chemical can directly be derived from the slope of the exponential increase in CSTD, i.e. $t_{\text{CSTD}}^{2} = t_{\text{in}}^{2}$, and is completely independent of $t_{\text{in}}^{1/2}$</td>
<td>preban period</td>
</tr>
<tr>
<td>2. It does not make sense to estimate a $t_{\text{in}}^{1/2}$ during the transition period, even though it is technically possible.</td>
<td>transition period</td>
</tr>
<tr>
<td>3. If there are indications that $t_{\text{elim}}^{1/2} &lt; t_{\text{in}}^{1/2}$, CSTD can be used to identify the half-life of decline in intake ($t_{\text{CSTD}}^{1/2} = t_{\text{in}}^{1/2}$) already after ten years into the transition period.</td>
<td>transition period</td>
</tr>
<tr>
<td>4. The CSTD half-life tool is applicable not only to the postban period but also during the transition period if the chemical fulfills the condition of $t_{\text{in}}^{1/2} &lt; t_{\text{in}}^{1/2}$, and CSTD are available for the later stage of the transition period.</td>
<td>transition period</td>
</tr>
<tr>
<td>5. If there are indications for $t_{\text{elim}}^{1/2} &gt; t_{\text{in}}^{1/2}$ or long $t_{\text{elim}}^{1/2}$ values in general (roughly ten and more years), the CSTD half-life tool should not be applied.</td>
<td>postban period</td>
</tr>
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</table>

**Preban period.** For newer POPs which were introduced to the market in the past 20 years, an exponential increase in CSTD is found in the population prior to the ban, e.g. for PBDEs (Meironyté et al. 1999). Dynamic PPK models, as developed by Ritter et al. (2011b) and also used by others (Wong et al. 2013), have shown that the doubling time of CSTD ($t_{\text{CSTD}}^{2}$) directly reflects the doubling time of the intake ($t_{\text{in}}^{2}$), i.e. $t_{\text{CSTD}}^{2} = t_{\text{in}}^{2}$. Importantly, the value of $t_{\text{CSTD}}^{2} = t_{\text{in}}^{2}$ is not affected by the intrinsic elimination half-life, $t_{\text{in}}^{1/2}$. That is, if intake estimates of BDE-47 prior to 1995 had been reported for the Swedish population, for example from total diet studies, they would have increased with the same slope as the CSTD measured in the preban period (Figure 4.1).
Sampling from breast milk is restricted to lactating women of a certain age (mostly 20–40 years). CSTD from blood samples are, however, equally valid and appropriate for elucidating time trends. For instance, the preban CSTD of serum samples of 40–50-year-old Norwegian men provide a good estimate of the doubling time of PBDE intake by the Norwegian population (Thomsen et al. 2002). Thus, our first recommendation is: The doubling time in intake prior to the phase-out of the chemical can directly be derived from the slope of the exponential increase in CSTD, i.e. \( t_{2}^{\text{CSTD}} = t_{2}^{\text{in}} \), and is completely independent of \( t_{1/2}^{\text{elim}} \). That is, in the preban period, all individuals of a population experience the same doubling time of their exposure vs. calendar time. Note that the absolute intake rate (e.g. in ng/kg/d) is age-dependent.

Transition period. In this period, calculation of \( t_{1/2}^{\text{CSTD}} \) always results in a very long \( t_{1/2}^{\text{CSTD}} \). For instance, \( t_{1/2}^{\text{CSTD}} \) for BDE-47 is 26.7 years for the period of 1996–2003 (Lignell et al. 2014) or 16.5 years for 1996–2006 (Lignell et al. 2009). In both cases \( t_{1/2}^{\text{CSTD}} \) was calculated for the first ten years of the transition period, when concentrations are rather stable. Similarly, the CSTD of hexabromocyclododecane (HBCDD) from Swedish mothers can also be allocated to the end of the preban and the beginning of the transition period (Fångström et al. 2005; Covaci et al. 2006). Consequently, very long \( t_{1/2}^{\text{CSTD}} \) values (i.e. 15–27.7 years) were estimated for 1996–2010 and 2002–2012, respectively (Lignell et al. 2012, 2014). Hence, our second recommendation is: It does not make sense to estimate \( t_{1/2}^{\text{CSTD}} \) during the transition period, even though it is technically possible. For rapidly-eliminated chemicals this restriction applies only to the beginning of the transition period (see below), but for slowly-eliminated chemicals the derivation of \( t_{1/2}^{\text{CSTD}} \) should be avoided for the whole transition period. The longer \( t_{1/2}^{\text{elim}} \) is, the slower is the change from increasing to decreasing CSTD during the transition period (Figure 4.2).

However, for rapidly-eliminated chemicals, it is possible to calculate a meaningful value of \( t_{1/2}^{\text{CSTD}} \) already at the end of the transition period because \( t_{1/2}^{\text{CSTD}} \) is then already equal to \( t_{1/2}^{\text{in}} \) for these chemicals. For example, after approximately ten years into the transition period, the \( t_{1/2}^{\text{CSTD}} \) of BDE-47 reduces to 6.4 years for the period of 2004–2012 (see Appendix A3, Table A3.1, for empirical CSTD and fitted \( t_{1/2}^{\text{CSTD}} \)). Estimates for \( t_{1/2}^{\text{in}} \) from Swedish food baskets reveal a \( t_{1/2}^{\text{in}} \) value of 6.8 years for the period of 1999–2010 (Darnerud et al. 2006; Törnkvist et al. 2011; National Food Agency 2012), which is very close to the 6.4 years found for \( t_{1/2}^{\text{CSTD}} \). The reason why we find this result already around ten years into the transition period is that, for BDE-47, \( t_{1/2}^{\text{elim}} < t_{1/2}^{\text{in}} \):
estimates of $t_{1/2}^{\text{elim}}$ of BDE-47 are rather short, i.e. between 1.4 and 3.0 years (Geyer et al. 2004; Trudel et al. 2011), and clearly shorter than the $t_{1/2}^\text{in}$ of 6.4 years. Thus, our **third recommendation** is: If there are indications that $t_{1/2}^{\text{elim}} < t_{1/2}^\text{in}$, CSTD can be used to identify the half-life of decline in intake ($t_{1/2}^{\text{CSTD}} = t_{1/2}^\text{in}$) already after ten years into the transition period. Ritter et al. (2009) stated that if only CSTD from the postban period are considered, $t_{1/2}^{\text{CSTD}}$ is equal to $t_{1/2}^\text{in}$. For chemicals like BDE-47, this is true already after around ten years into the transition period.

If we now apply the CSTD half-life tool to derive $t_{1/2}^{\text{elim}}$ from the CSTD of BDE-47 from the period of 2004–2012, we obtain a $t_{1/2}^{\text{elim}}$ value of 2.2 years for BDE-47 (see Appendix A3, Table A3.1, for input data used and model output), which agrees very well with estimates from previous studies, specifically, 1.4 and 3.0 years from Geyer et al. (2004) and Trudel et al. (2011), respectively. Consequently, our **fourth recommendation** is: The CSTD half-life tool is applicable not only to the postban period but also during the transition period if the chemical fulfills the condition of $t_{1/2}^{\text{elim}} < t_{1/2}^\text{in}$, and CSTD are available for the later stage of the transition period.

The CSTD of DDT from studies of Swedish mothers (Norén and Meironytė 2000; Glynn et al. 2012; Lignell et al. 2014) (see Appendix A3, Table A3.2) illustrate our fourth recommendation. Based on CSTD of DDT from the postban period (1996–2006), the CSTD half-life tool estimates a $t_{1/2}^{\text{elim}}$ of 2.2 years (Ritter et al. 2009). When we apply the half-life tool to CSTD from the later stage of the transition period (1980–2006, leaving out the first decade of the transition period from 1970 to 1980), we obtain a $t_{1/2}^{\text{elim}}$ of 1.9 years (see Appendix A3, Table A3.2, for input data used and model output), which is very close to the estimate of 2.2 years derived from the postban data.

The same will probably apply to HBCDD in the near future. Efforts to reduce HBCDD emissions to the environment were initiated around 2004 in Sweden (Remberger et al. 2004). Estimates of $t_{1/2}^{\text{elim}}$ of HBCDD in humans are only a few months (Geyer et al. 2004), which is most likely shorter than $t_{1/2}^\text{in}$ of HBCDD. Therefore, as soon as HBCDD intake decreases due to reductions in emission, the CSTD half-life tool will be suitable for estimating $t_{1/2}^{\text{elim}}$ based on future CSTD of HBCDD from the general population.

**Postban period.** Ritter et al. (2009) demonstrated by using a static PPK model that in the postban period $t_{1/2}^{\text{CSTD}} = t_{1/2}^\text{in}$ is valid. Under the assumption of “static” individuals, i.e. no chemical transfer via *in-utero* exposure or via breastfeeding and no change in body weight and lipid weight, this result is true without any qualifications. However,
as soon as there is transfer of chemical from mother to child, this result is only true if $t_{1/2}^{\text{elim}} < t_{1/2}^{\text{in}}$. If this condition is not fulfilled because $t_{1/2}^{\text{elim}}$ is very long, the measured CSTD violate the assumptions of the CSTD half-life tool, and estimates derived with this tool will be incorrect. For example, when CSTD for PCB-153 (see Appendix A3, Table A3.3) are inputted into the CSTD half-life tool, the estimated $t_{1/2}^{\text{CSTD}}$ value is 9.8 years, and the estimated $t_{1/2}^{\text{elim}}$ is 7.0 years. This value of $t_{1/2}^{\text{elim}}$ for PCB-153 is considerably shorter than previous estimates of 14.4–17 years (Ritter et al. 2011b; Aylward et al. 2014; Bu et al. 2015), and thus appears to be incorrect. Additionally, PCB-153 concentrations during the postban period (25–30 years after the highest concentrations had occurred, i.e. since around 1995) have been reported to increase with age within cross-sectional populations (Ritter et al. 2011b; Quinn and Wania 2012), which is possible only if $t_{1/2}^{\text{elim}} > t_{1/2}^{\text{in}}$ (Ritter et al. 2011b). Therefore, our fifth recommendation is: If there are indications for $t_{1/2}^{\text{elim}} > t_{1/2}^{\text{in}}$ or long $t_{1/2}^{\text{elim}}$ values in general (roughly ten and more years), the CSTD half-life tool should not be applied.

The reason why the CSTD half-life tool is not applicable to PCB-153 and other chemicals with long $t_{1/2}^{\text{elim}}$ is that due to the long $t_{1/2}^{\text{elim}}$ of the chemical the body burden later in life is still influenced by the exposure to the chemical much earlier in life (i.e. from in-utero exposure and transfer via breastfeeding). This fact is not considered in the assumptions made in the CSTD half-life tool (Table 4.1, Static PPK model). A more realistic model is a dynamic PPK model. Such a model is not restricted to the postban period but includes the preban and transition periods, and longitudinal POP concentrations are estimated for each individual, including transgenerational transfer of chemical from mother to child (Table 4.1, Dynamic PPK model). Figure 4.2 compares modeled CSTD with the assumptions of the CSTD half-life tool (A) and under more realistic assumptions (B) for two hypothetical chemicals. Importantly, as illustrated in Figure 4.2B, for chemicals whose $t_{1/2}^{\text{elim}}$ exceeds $t_{1/2}^{\text{in}}$ (circles), the slope in CSTD is not equal to the slope in intake of the chemical at any time in the postban period, that is $t_{1/2}^{\text{CSTD}} \neq t_{1/2}^{\text{in}}$. In contrast, for chemicals with $t_{1/2}^{\text{elim}} \leq t_{1/2}^{\text{in}}$, $t_{1/2}^{\text{CSTD}} = t_{1/2}^{\text{in}}$ is true (diamonds). This shift in the slope for slowly-eliminated chemicals in Figure 4.2B (red line) is due to the non-zero initial concentration at birth and intake via breastfeeding. The effect of transgenerational input is pronounced in the postban period, when intake is declining and therefore the contribution from a “contaminated” mother is important.
Figure 4.2. Modeled CSTD of two hypothetical chemicals in 30-year old individuals with identical intake trend (black line, $t_{1/2}^{in} = t_{1/2}^{out} = 7$ years) for the period 1940–2080. Circles: slow elimination, $t_{1/2}^{elim} = 14$ years; diamonds: rapid elimination, $t_{1/2}^{elim} = 3$ years. Ban of chemicals took place in 1970. (A) If the static PPK model is applied, the slopes of the CSTD of both chemicals (slopes indicated by green lines) are parallel to the intake trend in the postban period. (B) If the dynamic PPK model is applied, only the slope of the CSTD of the rapidly-eliminated chemical (slope indicated by green line) is parallel to the intake trend in the postban period. The slope of the CSTD of the slowly-eliminated chemical (slope indicated by red line) deviates from the others.

Another case that illustrates the limitations of the CSTD half-life tool is HCB. Two studies have reported a $t_{1/2}^{elim}$ of HCB of around six years (To-Figueras et al. 2000; Bu et al. 2015) and the $t_{1/2}^{in}$ is 12.0 years for the period of 1975–2010 in Sweden (Vaz 1995; Darnerud et al. 2006; Törnkvist et al. 2011; National Food Agency 2012). When the CSTD and the intake data from the Table A3.4 of Appendix A3 are inputted, the CSTD half-life tool estimates a $t_{1/2}^{CSTD}$ value of 14.9 years, and a $t_{1/2}^{elim}$ value of only 2.4 years, which is considerably shorter than previous $t_{1/2}^{elim}$ estimates of approximately six years (To-Figueras et al. 2000; Bu et al. 2015). As for PCB-153, cross-sectional age-concentration trends should be evaluated to confirm the model outputs of the CSTD half-life tool. However, this cross-check can only be performed with cross-sectional data from the postban period, since age-concentration trends will not differ between slowly- and rapidly-eliminated POPs during the preban and transition periods (Quinn and Wania 2012; Gyalpo et al. 2015). If $t_{1/2}^{elim}$ is substantially shorter than $t_{1/2}^{in}$, as suggested by the CSTD half-life tool estimates for HCB, HCB concentrations should not increase with age in cross-sectional populations. However, cross-sectional biomonitoring data from Australia (Bu et al. 2015), Spain (Zubero et al. 2015), and Germany (Becker et al. 2002) do show increasing HCB concentration with increasing age, indicating $t_{1/2}^{elim}$ is underestimated by the CSTD half-life tool. Hence it is advised not to use this tool for evaluating CSTD of HCB.
4.3 Conclusions

In evaluating decreasing CSTD, it is important to distinguish between three half-lives: the CSTD-based half-life \( t_{1/2}^{\text{CSTD}} \), the half-life of decline in intake \( t_{1/2}^{\text{in}} \), and the intrinsic elimination half-life \( t_{1/2}^{\text{elim}} \). During the preban period, the doubling time of CSTD \( t_{2}^{\text{CSTD}} \) is equal to the doubling time of intake \( t_{2}^{\text{in}} \); during the transition period, calculation of \( t_{1/2}^{\text{CSTD}} \) yields nonsensical results; and in the postban period, \( t_{1/2}^{\text{CSTD}} \) is equal to \( t_{1/2}^{\text{in}} \) only for chemicals that are rapidly eliminated, whereas for slowly-eliminated chemicals, \( t_{1/2}^{\text{CSTD}} \) only represents the upper limit of \( t_{1/2}^{\text{in}} \). Importantly, \( t_{1/2}^{\text{CSTD}} \) never equals \( t_{1/2}^{\text{elim}} \).

For chemicals for which estimates of short \( t_{1/2}^{\text{elim}} \) exist (e.g. extrapolated from animal studies or derived from highly exposed individuals), the CSTD half-life tool will provide a good estimate of \( t_{1/2}^{\text{in}} \) based on CSTD from the later stage of the transition period. In contrast, for chemicals that may have long \( t_{1/2}^{\text{elim}} \) values, \( t_{1/2}^{\text{elim}} \) can only be derived with dynamic PPK models combined with sequential sets of cross-sectional data. This approach requires long-term planning since cross-sectional data sets are needed from at least 20 years after the ban of the chemical.

As pointed out by Ritter et al. (2009), the \( t_{1/2}^{\text{CSTD}} \) is specific to the sampled population. Different countries can have different \( t_{1/2}^{\text{CSTD}} \) values for the same chemicals because \( t_{1/2}^{\text{CSTD}} \) is a measure of the degree of the reduction in exposure to a chemical, which is governed by the country’s amount in production and use and the time of a phase-out. It is an “apparent” property that is specific to the environmental conditions in the country and therefore not something that has to be globally identical.
5

Overall conclusions and outlook
5.1 Conclusions

The overall objective of this thesis was to contribute to the scientific understanding of temporal trends observed in different types of biomonitoring data of POPs from the general human population. Five overall conclusions can be drawn from the three studies presented in this thesis:

Firstly, new biomonitoring and exposure data are constantly generated and thus earlier findings and interpretations might be changed or supported by these new data sets. In Chapter 2, it was shown that dietary uptake (= intake multiplied by absorption factor) of total DDT is the main source of the total DDT concentrations found in South African women living in Malaria-endemic areas. This result opposes an earlier finding for a similar (but larger) population group (= all adults living in regions with IRS) where inhalation exposure was found to be the main exposure route. When this first study was conducted, this finding was valid based on the current state of the available data at that time. While the conclusions from the first study might still be correct when averaged for all individuals exposed to IRS globally, it is not true anymore for the subpopulation in South Africa. This is because new data on local DDT contamination in domesticated animals were available by the time the study presented in Chapter 2 was conducted.

Secondly, the PK model is a tool that helps to understand the biomonitoring data of POPs by putting the body concentrations in context with available data on uptake and elimination. For the first time, all available DDT concentrations in food items and indoor air were related to the DDT concentrations in individuals of different ages by means of a PK model for a South African environment with IRS. A good agreement between measured and modeled concentrations of total DDT in mothers and their children was found when the PK model was run in a forward approach (i.e. all model input parameters were previously known or estimated from similar studies). Reproductive characteristics such as the mother’s age at childbirth, the duration of lactation and the number of children were varied. Modeled concentrations differed only by a factor of 2 (for mothers) and 3 (for children) from the measured concentrations if the most realistic assumptions (first child at the age of 20, 2 years of breastfeeding, and 3-year intervals between siblings) were considered as the default scenario. By means of the PK model the amount of lactational transfer of total DDT from mothers to their children was quantified with an inclusion of changing breast milk consumption and varying lipid content of the breast milk throughout the lactation period. Thus, as biomonitoring data already suggested, the PK model supports the fact that first-born children receive the highest load of contaminants...
through breastfeeding and are thus most vulnerable to adverse health effects caused by DDT.

Thirdly, since the PK model quantitatively describes the relationship between uptake, body concentration, and elimination, it can be used to fit any one of these if the other two are known and/or predefined. However, the fitted parameters should be validated with other techniques. In Chapter 3, it was shown that unlike the case study on DDT (Chapter 2) the triad of uptake, body concentration, and elimination did not match in the case of PBDEs for the Australian population. The top-down and bottom-up uptakes rates did not agree with each other, independently of the range of possible elimination half-lives based on existing studies that were used as predefined input parameters. Hence, this study provided more and new evidence that that current information on intake/uptake and elimination is not sufficient to explain the body concentrations of PBDEs in the Australian population. Therefore, more investigations of exposure media are needed in regular intervals and continuation of the biomonitoring campaigns is important to detect any changing trends in the population.

Fourthly, publicly available models which are used in a fitting mode have to be applied within their application domain and assumptions behind those models have to be checked and re-evaluated for the investigated data set. In Chapter 3, it was shown that although a large body of empirical data was available, i.e. the five sets of cross-sectional data of PBDEs and estimated PBDE intake rates from diet and dust ingestion, it was not possible to fit the modeled to the measured body concentrations of PBDEs in order to extract the intrinsic elimination half-lives of the different PBDE congeners. This is because the biomonitoring data were sampled during the transition period during which all cross-sectional data of POPs show the same age-concentration trend independently of the chemical’s elimination half-life. Therefore, the PK model cannot discriminate between short and long elimination half-lives. Thus, for chemicals which truly have slow elimination kinetics the model fit would have produced a solution that (strongly) underestimated their elimination half-lives. This is because a possible memory effect in older individuals due to the slow elimination can only be observed in the postban period. In other words, the PK model was not sufficiently constrained for PBDEs in contrast to the case of PCBs where the intrinsic elimination half-lives if different congeners could be estimated based on two CSD sets (Ritter et al. 2011 b). In Chapter 4, it was shown that the assumptions behind the CSTD half-life tool were too simplistic for slowly-eliminated POPs and thus application of this tool should be avoided for POPs with slow elimination from the human body (i.e. elimination half-life longer than halving-time of the intake trend). However, the assumptions of the half-life tool are valid for faster-eliminated POPs (i.e. elimination half-life shorter than
Overall conclusions and outlook

The halving time of the intake trend. Furthermore, it is also justified to use this tool not only for the postban period but also in the later part of the transition period for POPs with short elimination half-lives. In summary, publicly available fitting models should be applied carefully and necessary conditions for their application should be given, otherwise the solutions found might be arbitrary and therefore meaningless.

Finally, when temporal trends of biomonitoring data of any kind (i.e. LD, CSD, or CSTD) of hydrophobic POPs with time-variant emissions are investigated, the timing of the sample collection relative to peak in exposure to POPs strongly determines the observed temporal trends. That is, the calendar time (i.e. preban, transition, postban period) is the most important temporal perspective of time; birth cohort and age are of lower importance. Concentrations of hydrophobic POP in the adult body increase with age in longitudinal studies when the sampling is performed during the preban phase and they decrease with age when the sampling is performed during the postban phase, independently of the intrinsic elimination half-lives of the investigated POPs. This also implies that the general statement of “POPs accumulate in the body with age” is not correct. In CSD collected during the preban and transition periods, POP concentrations are rather stable for the whole adult population, independently of the intrinsic elimination half-life of the POPs (i.e. no increase with increasing age). Only when the cross-sectional study is performed at least twenty years after the peak in exposure of the chemical (i.e. in the postban period), the age-concentration profiles of slowly-eliminated chemicals differ significantly from those of faster-eliminated chemicals. An increase with increasing age in the CSD can then be observed because the slower of the two exponentially driven processes (i.e. elimination half-life in the human body is longer than the halving time in intake trend) governs the temporal trend in CSD. Finally, CSTD follow the exposure trend independently of age, with a smoothing time lag in the concentrations during the transition period. In contrast, in a situation with constant emissions (as presented in Chapter 2), modeled LD can be validated with measured CSD because in such a situation, the age-concentration profile is identical in LD and CSD. If CSTD had been available, these concentrations would remain constant until the exposure would change.

In summary, for the analysis and interpretation of temporal trends observed in biomonitoring data, a consistent quantitative framework is needed. This thesis has provided an improved understanding of publicly available PK models. In light of the increased collection and availability of human biomonitoring data of persistent chemicals, the methods and insights developed in this thesis have contributed to this field of research.
5.2 Outlook

In this work the population pharmacokinetic model was employed hydrophobic POPs which are already regulated under the Stockholm Convention. However, soon after the regulation of PBDEs and HBCDD, alternatives brominated flame retardants were discovered in the indoor environment (Stapleton et al. 2008) as well as in breast milk (Zhou et al. 2014). Although these alternative flame retardants are not (yet) as abundant as PBDEs and HBCDD, with improved analytical methods these chemicals might be detected more frequently and any increase in concentration in environmental media and in humans will be observed (Covaci et al. 2011). Any measurement of these chemicals that are currently performed fall into the preban period. Consistent data sets such as concurrent repeated analysis of exposure media (dust, food, indoor air) as well as human blood or breast milk samples (CSD or CSTD) will enable to estimate the intrinsic elimination half-lives of these alternative chemicals already in the preban period using the population PK model.

The time-variant population pharmacokinetic model was developed and used for hydrophobic POPs. Since such contaminants mainly distribute into lipid tissues within the human body, the parametrization of the changing lipid volume with age is a very important aspect of the model. However, this PK model can be adapted for other POPs, such as per- and polyfluoroalkyl substances (PFASs), as it was done by Wong et al. (2014). In this case, the storage volume has to be modified to represent the volume of distribution. In a next step, the PK model can be adapted to also include precursors. An example would be perfluorooctane sulfonic acid (PFOS) and its various precursors (also known as PreFOS). The relevance of PreFOS exposure to the body burden of PFOS is under investigation (Martin et al. 2010; Gebbink et al. 2015). However, biotransformation rates of PreFOS to PFOS determined in rats are currently used for humans. Once the PK model is properly adjusted for the investigation of PFASs, intrinsic elimination half-lives of PreFOS can be fitted using the large amount of human biomonitoring data and intake estimates of PFOS and PreFOS.
6

References


Bu Q, MacLeod M, Wong F, et al. 2015. Historical intake and elimination of polychlorinated biphenyls and organochlorine pesticides by the Australian population reconstructed from biomonitoring data. Environ Int 74: 82-88.


Chapter 6


References


Appendices

Supporting information for Chapters 2, 3, and 4
Supporting information for Chapter 2
A1.1 Input parameters

Body weight and body lipid for South African women

In Figure A1.1 the temporal development of a South African woman’s body weight and body lipid weight is shown. The corresponding lipid fraction is listed in Table A1.1. The growth-related increase of body weight of South African females was modeled by using mean body weight data of female children (Cameron 2003), teenagers (Department of Health 2007), and adults (Puoane et al. 2002). For the pharmacokinetic (PK) model, we linearly interpolated the data to obtain a growth curve for an average South African female. We used the age-dependent lipid fractions for girls from Veldhuis et al. (2005) for the age of 0–17 years; the final lipid fraction was assumed to be 30% for the age of 20 and above (Levitt et al. 2005) for a nulliparous female. With every birth, the mother loses more water than fat (ICRP 1975). Consequently, her lipid fraction increases accordingly and was set constant for the rest of her life. Two studies report lipid fraction in South African children (Monyeki et al. 2005; Amusa et al. 2011). Amusa et al. (2011) reported fairly constant body lipid fraction of 25% for girls from grade 1 to 7, and Monyeki et al. (2005) reported 15.6–18.6% for girls aged 7–14 years.

Figure A1.1. Development of the body (black) and lipid weight (grey) of a nulliparous (solid line) and a primiparous South African woman (dotted).

Because of this high range found in these two studies, we used the values presented by Veldhuis et al. (2005), which are between the extremes. Pregnancy weight gain was assumed to be 0.3 kg/week (IOM 1996). After childbirth, the woman reaches the pre-pregnancy weight after almost four months. Pregnancy duration was assumed to be 270 days (~39 weeks) (Kruger 2005). For subsequent children, the same weight gain and weight loss pattern was assumed.
Table A1.1. Body weight and lipid fraction at different ages of a nulliparous South African woman.

<table>
<thead>
<tr>
<th>age</th>
<th>body weight (kg)</th>
<th>lipid fraction (–)</th>
</tr>
</thead>
<tbody>
<tr>
<td>birth</td>
<td>3.0</td>
<td>0.15</td>
</tr>
<tr>
<td>1 month</td>
<td>3.5</td>
<td>0.16</td>
</tr>
<tr>
<td>2 months</td>
<td>4.0</td>
<td>0.20</td>
</tr>
<tr>
<td>3 months</td>
<td>4.5</td>
<td>0.24</td>
</tr>
<tr>
<td>4 months</td>
<td>5.0</td>
<td>0.25</td>
</tr>
<tr>
<td>5 months</td>
<td>5.5</td>
<td>0.26</td>
</tr>
<tr>
<td>6 months</td>
<td>6.0</td>
<td>0.26</td>
</tr>
<tr>
<td>7 months</td>
<td>6.5</td>
<td>0.26</td>
</tr>
<tr>
<td>8 months</td>
<td>7.0</td>
<td>0.26</td>
</tr>
<tr>
<td>9 months</td>
<td>7.5</td>
<td>0.25</td>
</tr>
<tr>
<td>10 months</td>
<td>8.1</td>
<td>0.25</td>
</tr>
<tr>
<td>11 months</td>
<td>8.6</td>
<td>0.24</td>
</tr>
<tr>
<td>1 year</td>
<td>9.1</td>
<td>0.24</td>
</tr>
<tr>
<td>2 years</td>
<td>11.3</td>
<td>0.21</td>
</tr>
<tr>
<td>5 years</td>
<td>18.0</td>
<td>0.17</td>
</tr>
<tr>
<td>10 years</td>
<td>31.6</td>
<td>0.20</td>
</tr>
<tr>
<td>15 years</td>
<td>51.7</td>
<td>0.24</td>
</tr>
<tr>
<td>20 years</td>
<td>60.1</td>
<td>0.30</td>
</tr>
<tr>
<td>40 years</td>
<td>73.0</td>
<td>0.30</td>
</tr>
<tr>
<td>60 years</td>
<td>73.5</td>
<td>0.30</td>
</tr>
<tr>
<td>70 years</td>
<td>69.8</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Uptake via inhalation

Uptake via inhalation of ΣDDT (=p,p'-DDT and o,p'-DDT) and ΣDDE (=p,p'-DDE and o,p'-DDE) was estimated according to Equation A1.1:

\[
U_i,\text{inh}(t_{\text{age}}) = E_{\text{inh}} \times f_{\text{indoor}} \times r_{\text{inh}}(t_{\text{age}}) \times c_{i,\text{air}}
\]

Eq. A1.1

where \( U_{i,\text{inh}}(t_{\text{age}}) \) is the age-dependent uptake of substance \( i \) \((i = \Sigma\text{DDT} \text{ or } \Sigma\text{DDE}) \) (ng/d) via inhalation, \( E_{\text{inh}} \) is the uptake efficiency (dimensionless), \( f_{\text{indoor}} \) is the time spent indoors (h/d), \( r_{\text{inh}}(t_{\text{age}}) \) are the default values for an age-dependent inhalation rate for women (m\(^3\)/d), \( c_{i,\text{air}} \) is the ΣDDT or ΣDDE concentrations in indoor air (ng/m\(^3\)) used for our base case scenario. The corresponding values are shown in Table A1.2 and Table A1.3.
Table A1.2. Inhalation rates ($r_{inh}$) for women (U.S. EPA 1997)

<table>
<thead>
<tr>
<th>age group (years)</th>
<th>inhalation rate ($r_{inh}$) (m$^3$/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>4.5</td>
</tr>
<tr>
<td>1–2</td>
<td>6.8</td>
</tr>
<tr>
<td>2–5</td>
<td>8.3</td>
</tr>
<tr>
<td>5–8</td>
<td>10</td>
</tr>
<tr>
<td>8–11</td>
<td>13</td>
</tr>
<tr>
<td>11–19</td>
<td>12</td>
</tr>
<tr>
<td>&gt;19</td>
<td>11.3</td>
</tr>
</tbody>
</table>

Table A1.3. Values for ΣDDT and ΣDDE concentrations in indoor air (Singh et al. 1992; Bouwman et al. 2009; Van Dyk et al. 2010; Ritter et al. 2011), uptake efficiency ($E_{inh}$) and time spent indoors ($f_{indoor}$) (Bouwman et al. 2009)

<table>
<thead>
<tr>
<th>parameter</th>
<th>symbol</th>
<th>unit</th>
<th>value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΣDDT concentration</td>
<td>$c_{\Sigma\text{DDT,air}}$</td>
<td>ng/m$^3$</td>
<td>5 000</td>
</tr>
<tr>
<td>ΣDDE concentration</td>
<td>$c_{\Sigma\text{DDE,air}}$</td>
<td>ng/m$^3$</td>
<td>185</td>
</tr>
<tr>
<td>uptake efficiency via inhalation</td>
<td>$E_{inh}$</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>time fraction spent indoors</td>
<td>$f_{indoor}$</td>
<td>h/d</td>
<td>8</td>
</tr>
</tbody>
</table>

Uptake via diet

The daily uptake of ΣDDT and ΣDDE was calculated for each food item individually, namely chicken muscle, chicken fat, chicken egg, leafy vegetables, and fish according to Equations A1.2 and A1.3:

$$U_{i,\text{diet}}(t_{age}) = E_{\text{diet}} \times \sum_j (r_{i,j}(t_{age}) \times c_{i,j})$$  Eq. A1.2

$$U_{i,\text{fish}}(t_{age}) = E_{\text{diet}} \times (r_{i,fish}(t_{age}) \times f_{lip,fish} \times c_{i,fish})$$  Eq. A1.3

where $U_{i,\text{diet}}(t_{age})$ is the overall daily uptake of substance $i$ ($i = \Sigma\text{DDT}$ or $\Sigma\text{DDE}$) (ng/d) from food items $j$ ($j =$ chicken muscle, chicken fat, chicken egg, leafy vegetables), $E_{\text{diet}}$ is the dietary uptake efficiency (dimensionless; here assumed to be equal to 1) for all food items, $r_{i,j}(t_{age})$ 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 (van Dyk et al. 2010). Because Barnhoorn et al. (2009) reported lipid-normalized concentrations for the fish $O. mosambicus$, we used Equation A1.3 for the uptake of chemical with this particular fish; in Equation A1.3, $U_{i,\text{fish}}(t_{age})$ is the daily
uptake of $i$ from fish (ng/d), $r_{i,fish}$ ($t_{age}$) is the consumption rate of fish (g/d), $f_{lip,fish}$ is the lipid fraction of $O. mossambicus$ (dimensionless), and $c_{i,fish}$ is the lipid-normalized concentration (ng/g lipid).

The daily consumption rates for chicken meat, fish, chicken eggs, and leafy vegetables were derived from Nel and Steyn (2002), see Table A1.4. Nel and Steyn (2002) reported daily consumption rates per capita for the age categories 1–5 years, 6–9 years, and >10 years. Because we used differently defined age categories in our model calculations (0.5–3 years, 3–6 years, 6–10 years, 10–50 years, and >50 years), we attributed the values from Nel and Steyn (2002) to the age categories 3–6 years, 6–10 years, and 10–50 years. In order to obtain consumption rates for the additional age categories of 0.5–3 years and >50 years, we applied proportionality factors according to the recommended calorific intake for an adult female by Rose et al. (2002), see Table A1.5. The amount of chicken meat presented by Nel and Steyn (2002) was assumed to consist of roughly 90% muscle and 10% fat. The overall fat content of native South African chicken was calculated to be about 10% based on chicken carcass composition reported by van Marle-Köster and Webb (2000) and on the lipid content in chicken skin, white meat, and dark meat (50% white and 50% dark meat, rough assumption) presented by van Heerden et al. (2002) for South African chicken.

Table A1.4. Food item consumption rates from Table 26 in Nel and Steyn (2002).

<table>
<thead>
<tr>
<th>age group (years)</th>
<th>chicken meat (g/d)</th>
<th>chicken eggs (g/d)</th>
<th>fish (g/d)</th>
<th>leafy vegetables (g/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5–3</td>
<td>6.3</td>
<td>4.8</td>
<td>3.6</td>
<td>18.1</td>
</tr>
<tr>
<td>3–6</td>
<td>8.7</td>
<td>6.7</td>
<td>5.0</td>
<td>25.2</td>
</tr>
<tr>
<td>6–10</td>
<td>10.3</td>
<td>5.2</td>
<td>3.9</td>
<td>21.9</td>
</tr>
<tr>
<td>10–50</td>
<td>16.9</td>
<td>13.9</td>
<td>5.4</td>
<td>41.6</td>
</tr>
<tr>
<td>&gt;50</td>
<td>14.5</td>
<td>12.0</td>
<td>4.6</td>
<td>35.8</td>
</tr>
</tbody>
</table>

Table A1.5. Proportionality factors used to obtain age-adjusted food consumption rates for 0.5–3 years and >50 years (Rose et al. 2002).

<table>
<thead>
<tr>
<th>age group (years)</th>
<th>proportionality factor (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5–3</td>
<td>0.59</td>
</tr>
<tr>
<td>10–50</td>
<td>1</td>
</tr>
<tr>
<td>&gt;50</td>
<td>0.86</td>
</tr>
</tbody>
</table>

For the concentration of $\Sigma$DDT or $\Sigma$DDE in chicken fat, we combined the data reported by van Dyk et al. (2010) and by Barnhoorn et al. (2009). Both studies investigated the contaminant concentrations in chicken fat. However, based on the arithmetic mean,
the values reported by both studies differ by a factor of 6 for DDT and by 24 for DDE. Because both studies cover chickens which lived in villages where IRS is performed regularly and seem to be equally valid, we gave the same weight to the data from these two studies. In doing so, we (i) used the median values (as presented by van Dyk et al. (2010), and re-calculated from the data reported by Barnhoorn et al. (2009)) instead of mean values since the median is more robust and outliers have less weight; (ii) accounted for the high variability by choosing the median values of van Dyk et al. (2010) as the upper bound and the median values of Barnhoorn et al. (2009) as the lower bound; and (iii) used the median of the medians of both studies as the intermediate concentrations and set them as our default concentrations for ΣDDT and ΣDDE, see Table A1.6. Barnhoorn et al. (2009) measured the ΣDDT and ΣDDE concentrations in fish fat of Mozambique tilapia (*Oreochromis mossambicus*). The fat content of this fish was assumed to be 3.6% (Abou et al. 2011; Naeem et al. 2011). The median ΣDDT and ΣDDE concentrations on wet-weight basis in chicken eggs were provided by Riana Bornman (unpublished data).

**Table A1.6.** Median ΣDDT and ΣDDE concentrations in different food items (Barnhoorn et al. 2009; van Dyk et al. 2010). Concentration in chicken eggs was provided by Riana Bornman (unpublished).

<table>
<thead>
<tr>
<th>food item</th>
<th>unit</th>
<th>ΣDDT</th>
<th>ΣDDE</th>
</tr>
</thead>
<tbody>
<tr>
<td>chicken muscle</td>
<td>ng/g</td>
<td>134</td>
<td>263</td>
</tr>
<tr>
<td>chicken fat (default&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>ng/g</td>
<td>24 440</td>
<td>47 086</td>
</tr>
<tr>
<td>chicken fat (upper bound&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>ng/g</td>
<td>45 380</td>
<td>87 072</td>
</tr>
<tr>
<td>chicken fat (lower bound&lt;sup&gt;c&lt;/sup&gt;)</td>
<td>ng/g</td>
<td>3 500</td>
<td>7 100</td>
</tr>
<tr>
<td>chicken eggs</td>
<td>ng/g</td>
<td>4 037</td>
<td>6 879</td>
</tr>
<tr>
<td>leafy vegetables</td>
<td>ng/g</td>
<td>70</td>
<td>10</td>
</tr>
<tr>
<td>fish</td>
<td>ng/g lipid</td>
<td>3 721</td>
<td>3 697</td>
</tr>
</tbody>
</table>

<sup>a</sup> median of median concentrations presented by van Dyk (2010) and Barnhoorn et al. (2009)

<sup>b</sup> sum of median concentrations of p,p′- and o,p′-isomer of DDT and DDE (van Dyk et al. 2010)

<sup>c</sup> median concentrations of p,p′-isomers of DDT and DDE (Barnhoorn et al. 2009)

**Uptake via breast milk**

We assumed that ΣDDT and ΣDDE lost by the mother via breastfeeding is directly ingested by the infant. The ΣDDT and ΣDDE uptake via breast milk, \( U_{i,milk}(t_{age}^{\text{infant}}) \), in ng/d, was calculated as

\[
U_{i,milk}(t_{age}^{\text{infant}}) = E_{milk} \times k_{bf}(t_{age}^{\text{mother}}, t_{bf}) \times m_{i}(t_{age}^{\text{mother}}) \tag{A1.4}
\]

where \( k_{bf}(t_{age}^{\text{mother}}, t_{bf}) \) is the rate constant (1/d) for breastfeeding from Equation 2.5 in Chapter 2, \( E_{milk} \) is the uptake efficiency from breast milk (dimensionless), and \( m_{i}(t_{age}^{\text{mother}}) \) is the mass (ng) of substance \( i \) in lipids as a function of the mother’s age. Table A1.7 shows the values used for the calculation of the uptake via breast milk. The
Appendix

Infants were always exclusively breastfed and therefore, $U_{i,diet}$ was replaced by $U_{i,milk}$ for the whole duration of breastfeeding. The corresponding mass balance (Equation A1.5) for the infant is described as

$$\frac{dm_i(t_{age}^{\text{infant}})}{dt} = U_{i,milk}(t_{age}^{\text{infant}}) + U_{i,inh}(t_{age}^{\text{infant}}) - (k_{i,met}(t_{age}^{\text{infant}}) + k_{ex}(t_{age}^{\text{infant}})) \times m_i(t_{age}^{\text{infant}})$$

Eq. A1.5

Table A1.7. Values used for breast milk uptake.

<table>
<thead>
<tr>
<th>parameter</th>
<th>symbol</th>
<th>unit</th>
<th>value</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>lipid content in breast milk</td>
<td>$f_{lip,milk}$</td>
<td>%</td>
<td>3.27</td>
<td>Bouwman (1990)</td>
</tr>
<tr>
<td>0–4 months</td>
<td></td>
<td>%</td>
<td>3.82</td>
<td>Bouwman (1990)</td>
</tr>
<tr>
<td>9–12 months</td>
<td></td>
<td>%</td>
<td>4.24</td>
<td>Bouwman (1990)</td>
</tr>
<tr>
<td>13–24 months</td>
<td></td>
<td>%</td>
<td>4.99</td>
<td>Bouwman (1990)</td>
</tr>
<tr>
<td>breast milk consumption rate during 1. year</td>
<td>$r_{milk}$</td>
<td>g/d</td>
<td>800</td>
<td>Bouwman et al. (2006)</td>
</tr>
<tr>
<td>breast milk consumption rate during 2. year</td>
<td>$r_{milk}$</td>
<td>g/d</td>
<td>600</td>
<td>Da Costa et al. (2010)</td>
</tr>
<tr>
<td>uptake efficiency via breast milk</td>
<td>$E_{milk}$</td>
<td>–</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Intrinsic elimination

The overall intrinsic elimination of $\Sigma DDT$ and $\Sigma DDE$ is the sum of metabolic degradation and non-metabolic excretion (Kreuzer et al. 1997). Because excretion is represented directly in the mass-balance equation of the model, the uptake efficiency of the chemical is implicitly calculated by the model itself. Therefore, we assumed an initial uptake efficiency of 100% from all exposure routes ($E_{diet}, E_{inh}, E_{milk}$). The daily lipid excretion via feces was linearly interpolated between birth and the age of 18 (= adult) (ICRP, 1975). For female adults over 18 years, we assumed constant fecal lipid excretion. All parameter values are shown in Table A1.8.
Table A1.8. Parameter values for elimination processes.

<table>
<thead>
<tr>
<th>parameter</th>
<th>symbol</th>
<th>unit</th>
<th>value</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>liver weight as fraction of body weight</td>
<td>( f_{\text{liv}} )</td>
<td>%</td>
<td>2.4</td>
<td>ICRP (1975)</td>
</tr>
<tr>
<td>reference liver weight</td>
<td>( m_{\text{liv,ref}} )</td>
<td>kg</td>
<td>1.8</td>
<td>this work</td>
</tr>
<tr>
<td>reference lipid weight</td>
<td>( m_{\text{lip,ref}} )</td>
<td>kg</td>
<td>21.9</td>
<td>this work</td>
</tr>
<tr>
<td>density of liver</td>
<td>( p_{\text{liv}} )</td>
<td>kg/L</td>
<td>1.0</td>
<td>Brown et al. (1997)</td>
</tr>
<tr>
<td>density of lipids</td>
<td>( p_{\text{lip}} )</td>
<td>kg/L</td>
<td>0.9</td>
<td>Brown et al. (1997)</td>
</tr>
<tr>
<td>reference metabolic rate constant for ( \Sigma ) DDT</td>
<td>( k_{\text{\Sigma DDT,met}}^{\text{ref}} )</td>
<td>1/d</td>
<td>6.6E-4</td>
<td>this work</td>
</tr>
<tr>
<td>reference metabolic rate constant for ( \Sigma ) DDE</td>
<td>( k_{\text{\Sigma DDE,met}}^{\text{ref}} )</td>
<td>1/d</td>
<td>1.0E-4</td>
<td>this work</td>
</tr>
<tr>
<td>female fecal lipid excretion</td>
<td>( r_{\text{lip,feces}} )</td>
<td>g lipid/d</td>
<td></td>
<td>ICRP (1975)</td>
</tr>
<tr>
<td>birth</td>
<td></td>
<td></td>
<td>3.0</td>
<td>ICRP (1975)</td>
</tr>
<tr>
<td>18 years</td>
<td></td>
<td></td>
<td>4.5</td>
<td>ICRP (1975)</td>
</tr>
<tr>
<td>&gt;18 years</td>
<td></td>
<td></td>
<td>4.5</td>
<td>ICRP (1975)</td>
</tr>
</tbody>
</table>

### A1.2 Sensitivity analysis

We performed a sensitivity analysis by increasing and decreasing 15 different model parameters by factors of 1.5 and 0.67, respectively, to identify which parameters most strongly influence the modeled concentration curve shown in Figure 2.1 in Chapter 2. We recorded the change in concentration levels by adjusting one parameter at a time; Table A1.9 presents the 15 parameters considered plus the lipid fraction in breast milk for which we test a constant and a time-variant value. For the last five parameters listed in Table A1.9, the model sensitivity is very low and, therefore, their effects are not displayed graphically.

Figure A1.2 shows the effects of changes in body weight and body lipid fraction on the value of the predicted concentration. These two parameters have the strongest influence on the model results, because they determine the conversion of mass into concentration (Equation 2.2 in Chapter 2) and also affect all the rate constants (metabolic elimination, non-metabolic elimination, and the \( \Sigma \) DDT and \( \Sigma \) DDE elimination during breastfeeding), see Equations 2.3–2.5 in Chapter 2. The effects of these two variables are identical because they occur in the model always in the product of \( \text{bw} \times f_{\text{lip}} \).
Table A1.9. Model parameters for which the sensitivity of the modeled concentration of total DDT (=ΣDDT and ΣDDE) is determined.

<table>
<thead>
<tr>
<th>parameter</th>
<th>symbol</th>
<th>unit</th>
<th>shown in</th>
</tr>
</thead>
<tbody>
<tr>
<td>female body weight</td>
<td>$bw$</td>
<td>kg</td>
<td>Fig. A.1.2</td>
</tr>
<tr>
<td>female body lipid fraction</td>
<td>$f_{lip}$</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>reference liver weight</td>
<td>$m_{liv,ref}$</td>
<td>kg</td>
<td>Fig. A.1.3</td>
</tr>
<tr>
<td>reference lipid weight</td>
<td>$m_{lip,ref}$</td>
<td>kg</td>
<td>Fig. A.1.3</td>
</tr>
<tr>
<td>mass of chicken consumed daily</td>
<td>$m_{chicken}$</td>
<td>g/d</td>
<td>Fig. A.1.4</td>
</tr>
<tr>
<td>concentration in chicken fat</td>
<td>$c_{chicken, fat}$</td>
<td>ng/g</td>
<td>Fig. A.1.4</td>
</tr>
<tr>
<td>concentration in chicken egg</td>
<td>$c_{egg}$</td>
<td>ng/g</td>
<td>Fig. A.1.4</td>
</tr>
<tr>
<td>fraction of chicken fat to overall mass of chicken</td>
<td>$f_{chicken, fat}$</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>mass of chicken egg consumed</td>
<td>$m_{egg}$</td>
<td>g/d</td>
<td>Fig. A.1.4</td>
</tr>
<tr>
<td>lipid fraction of breast milk (constant or variable)</td>
<td>$f_{lip, milk}$</td>
<td>–</td>
<td>Fig. A.1.5</td>
</tr>
<tr>
<td>mass of breast milk consumed</td>
<td>$m_{milk}$</td>
<td>g/d</td>
<td>Fig. A.1.5</td>
</tr>
<tr>
<td>fraction of time spent indoors</td>
<td>$f_{indoor}$</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>concentration in indoor air of ΣDDT and ΣDDE</td>
<td>$c_{air}$</td>
<td>ng/m$^3$</td>
<td>not shown</td>
</tr>
<tr>
<td>inhalation rate</td>
<td>$r_{inh}$</td>
<td>m$^3$/d</td>
<td>not shown</td>
</tr>
<tr>
<td>mass of fish</td>
<td>$m_{fish}$</td>
<td>g/d</td>
<td>not shown</td>
</tr>
<tr>
<td>mass of leafy vegetables</td>
<td>$m_{veg}$</td>
<td>g/d</td>
<td>not shown</td>
</tr>
</tbody>
</table>

Varying the reference values of liver and lipid volume of a 40-year-old South African woman has a similar effect on the predicted concentration as shown in Figure A1.2, see Figure A1.3. These two parameters influence the first-order rate constant for metabolic elimination ($k_{i, met}, k_{i, met}^{ref}$). The reference liver volume and lipid volume are calculated by dividing the reference masses of liver ($m_{liv,ref}$) and lipid ($m_{lip,ref}$) by their densities ($p_{liv}, p_{lip}$). Therefore, we varied the reference mass of liver and lipid by a factor of 1.5 and 0.67. The predicted concentrations differ by a factor of approximately 1.5 from the base case scenario of a nulliparous woman when either of these parameters is changed a by a factor of 1.5 or 0.67.

Figure A1.4 shows the effects of five parameters related to the consumption of chicken on the value of the predicted concentration. The five parameters have similar influences on the model results; the concentrations calculated with the model increase by a factor of approximately 1.2 when any of these parameters is increased by a factor of 1.5. The parameter for which there is considerable model sensitivity as well as a wide range of actual variability is the concentration of total DDT in chicken fat. This is why the ranges shown in Figure 2.1 in Chapter 2 are based on the variability of this parameter.
Figure A1.5 shows the effect of a constant vs. time-variant lipid fraction of the breast milk over the course of breastfeeding as well as the effect of variation of the consumed amount of breast milk by factors of 1.5 and 0.67. The change in predicted concentrations is less than a factor of 1.3 for both parameters.

Figure A1.6 shows the age-dependent intrinsic elimination half-lives of ΣDDT and ΣDDE. As described in Kreuzer et al. (1997), infants and children have a much faster elimination rates, which finally level off at the values reported in Ritter et al. (2009).
Figure A1.4. Effect of the five model parameters related to consumption of chicken on the calculated concentrations (changes of the base case values by factors of 1.5 and 0.67). For abbreviations used in the legend, see Table A1.9.

Figure A1.5. Effect of the daily consumption rate of breast milk ($m_{\text{milk}}$) on the calculated concentrations (changes of the base case values by factors of 1.5 and 0.67). Further, the effect of constant and time-variant lipid fraction of breast milk is shown ($f_{\text{lip,milk}}$).
**Figure A1.6.** Age-dependent intrinsic elimination half-lives of ΣDDT and ΣDDE calculated by the model.

### A1.3 References


Appendix


Supporting information for Chapter 3
A2.1 Parameterization of the time-variant population pharmacokinetic (PK) model

Equation A2.1 defines the time course of the chemical concentration in a representative individual born at time $t_{\text{birth}}$:

$$\frac{dC(t_{\text{age}})}{dt} = \frac{U_{\text{ref}}(t) \times M_{\text{bw}}(t_{\text{age}}) \times P(t_{\text{age}}) \times F}{M_{\text{lip}}(t_{\text{age}})} - \left( k_{\text{elim}} + \frac{1}{M_{\text{lip}}(t_{\text{age}})} \times \frac{dM_{\text{lip}}(t_{\text{age}})}{dt} \right) \times C(t_{\text{age}}) \quad \text{Eq. A2.1}$$

where $t_{\text{age}}$ (years) is the age of the individual; $C(t_{\text{age}})$ (ng/g lipid) is the lipid-normalized concentration of chemical in the body; $U_{\text{ref}}(t)$ (ng/kg/d) is the reference daily uptake of the chemical for an adult and depends on the year of sampling, $t$; $M_{\text{bw}}(t_{\text{age}})$ (kg) and $M_{\text{lip}}(t_{\text{age}})$ (kg lipid) are the body weight and the body lipid weight as a function of age, respectively; $P(t_{\text{age}})$ (dimensionless) is a proportionality factor adapting $U_{\text{ref}}(t)$ to younger ages; $F$ (g lipid/kg lipid) is a unit conversion factor; $k_{\text{elim}}$ (1/d) is the first-order rate constant describing intrinsic elimination. Importantly, $U_{\text{ref}}$ represents the absorbed amount of chemicals (= uptake) from all sources and pathways (excluding breast milk) that contribute to the PBDE concentration in the body. The model was programmed in Matlab R2013a and solved with a 3-day resolution.

Transfer of chemical via breast milk

The daily human milk consumption rate, $r_{\text{bm}}(t_{\text{age}})$ (g/d) and the lipid fraction of the human milk, $f_{\text{lip,bm}}(t_{\text{age}})$ (dimensionless) are described dependent on the age of the infant ($t_{\text{age}}$) (years) and his/her body weight ($M_{\text{bw}}$) (kg) according to Verner et al. (2013) (Equations A2.2 and A2.3):

$$r_{\text{bm}}(t_{\text{age}}) = (-0.0024 \times t_{\text{age}} + 0.0063) \times M_{\text{bw}}(t_{\text{age}}) \times 24 \times 1000 \quad \text{Eq. A2.2}$$

$$f_{\text{lip,bm}}(t_{\text{age}}) = 0.0034 \times \ln(t_{\text{age}}) + 0.0414 \quad \text{Eq. A2.3}$$

Proportionality factor

We derived the proportionality factor, $P(t_{\text{age}})$ in Equation A2.1, by dividing the uptake rates of younger age groups by the uptake rate of adults (Table A2.1). The empirical proportionality factors show steps, because they represent whole age groups, i.e. 1–6, 6–12, 12–20, and >20 years (Figure A2.1, black and blue diamonds). Since no exposure estimate is given for infants < 1 years in Lorber (2008), we assumed it to be 50% of that of the group of 1–6 years. We used a Weibull function to interpolate the proportionality
Appendix

factors for uptakes of the different age groups (black and blue lines). We used data from Lorber (2008) as base case (panel A in Figure A2.1). As an alternative, we used the median uptake rates for the U.S. population from Trudel et al. (2011) (panel B in Figure A2.1).

Table A2.1. Derivation of proportionality factors.

<table>
<thead>
<tr>
<th>age group</th>
<th>Lorber (2008)</th>
<th>factor (unitless)</th>
<th>Trudel et al. (2011)*</th>
<th>factor (unitless)</th>
</tr>
</thead>
<tbody>
<tr>
<td>infants</td>
<td>49.3/2 = 24.7</td>
<td>3.2</td>
<td>5.5*0.7 = 3.85</td>
<td>3.5</td>
</tr>
<tr>
<td>toddlers</td>
<td>49.3</td>
<td>6.4</td>
<td>4.4</td>
<td>4</td>
</tr>
<tr>
<td>children</td>
<td>14.4</td>
<td>1.87</td>
<td>2.2</td>
<td>2</td>
</tr>
<tr>
<td>teenager</td>
<td>9.1</td>
<td>1.18</td>
<td>1.25</td>
<td>1.14</td>
</tr>
<tr>
<td>adult</td>
<td>7.7</td>
<td>1</td>
<td>1.1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Table S7 of Trudel et al. (2011).

Figure A2.1. Interpolated proportionality factors $P(t_{\text{age}})$ (lines) fitted to empirical proportionality factors (diamonds). A: Lorber (2008); B: Trudel et al. (2011).

Least-squares optimization

For each optimization, we used 29 empirical data points (see section 3.3.2 of Chapter 3). By minimizing the sum of squared residuals weighted (SSRW), we maximized $R^2$ (Equation A2.4):

$$R^2 = 1 - SSRW = 1 - \frac{\sum_{i=1}^{n}(y_i - f_i)^2}{\sum_{i=1}^{n}(y_i - y)^2}$$  
Eq. A2.4

where $n$ is the number of empirical data points, here $n = 29$, $y_i$ is the empirical data point $i$, $f_i$ is the equivalent modeled value, and $y$ is the empirical sample mean.
A2.2 Modeled and measured cross-sectional age-concentration profile for the male population

![Graph showing modeled and measured concentration profiles for different years and chemicals]

Figure A2.2. Modeled age-concentration profiles (blue: scenario A; green: scenario B; red: scenario C) fitted to the biomonitoring data (dots) from the male population.

A2.3 Input data for the PBDE bottom-up approach
The lipid fraction of breast milk was set to 3.3% (Toms et al. 2012). The transfer fraction from dust to skin was set to 13% (Trudel et al. 2011); the dermal absorption fraction was set to 3% (Roper et al. 2006).
<table>
<thead>
<tr>
<th>Congener-specific parameters</th>
<th>Unit</th>
<th>BDE-47</th>
<th>BDE-99</th>
<th>BDE-100</th>
<th>BDE-153</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption fraction from dust diet, inhalation</td>
<td>(%)</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>Absorption fraction from breast milk</td>
<td>(%)</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>Concentration in air at home (mean)</td>
<td>ng/m³</td>
<td>3</td>
<td>0.0285</td>
<td>0.0094</td>
<td>0.0024</td>
</tr>
<tr>
<td>Concentration in air in the office (mean)</td>
<td>ng/m³</td>
<td>3</td>
<td>0.1298</td>
<td>0.0100</td>
<td>0.0025</td>
</tr>
</tbody>
</table>

Note: Concentrations in dust at home (Toms et al. (2009a), (2009b)) were sampled in 2003/04. Assumption: if concentration < LOD, LOD/2 was used.

Table A2.2. Congener-specific parameters.
### Table A2.3. Age-dependent parameters.

<table>
<thead>
<tr>
<th>sex congener</th>
<th>infants 0–3 mths</th>
<th>infants 3–12 mths</th>
<th>toddlers 1–6 yrs</th>
<th>children 6–12 yrs</th>
<th>teenagers 12–20 yrs</th>
<th>adults &gt;20 yrs</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>body weight, [kg]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>females</td>
<td>5</td>
<td>8</td>
<td>17</td>
<td>32</td>
<td>58</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td><strong>fraction of time spent home, [-]</strong></td>
<td>0.77</td>
<td>0.77</td>
<td>0.68</td>
<td>0.62</td>
<td>0.60</td>
<td>0.66</td>
<td>U.S. EPA (2011)</td>
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<td><strong>fraction of time spent in the office, [-]</strong></td>
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<td><strong>daily intake of breast milk, [g/d]</strong></td>
<td>727</td>
<td>0</td>
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<td>0</td>
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<td><strong>dust ingestion rate, [g/cm²]</strong></td>
<td>3.40E-05</td>
<td>0.03</td>
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<td>0.06</td>
<td>0.06</td>
<td>0.03</td>
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<tr>
<td><strong>dust adhered to skin, [g/cm²]</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>males</td>
<td>3233</td>
<td>4367</td>
<td>6800</td>
<td>11500</td>
<td>17550</td>
<td>20700</td>
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<tr>
<td>females</td>
<td>3000</td>
<td>4200</td>
<td>6660</td>
<td>11250</td>
<td>16200</td>
<td>18123</td>
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<td>0.22</td>
<td>0.25</td>
<td>0.27</td>
<td>0.27</td>
<td>0.29</td>
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<tr>
<td><strong>inhalation rate, [m³/d]</strong></td>
<td>3.38</td>
<td>3.94</td>
<td>7.10</td>
<td>10.59</td>
<td>17.23</td>
<td>15.27</td>
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</tr>
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<td><strong>daily intake via diet, [ng/d]</strong></td>
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<td>males</td>
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<td>43.6</td>
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<td>11.6</td>
<td>18.5</td>
<td>26.2</td>
<td>25.1</td>
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<td>1.7</td>
<td>2.7</td>
<td>3.9</td>
<td>3.7</td>
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<tr>
<td>females</td>
<td>BDE-47 0</td>
<td>21.5</td>
<td>19.3</td>
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<td>30.8</td>
<td>28.9</td>
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<td>11.1</td>
<td>16.1</td>
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<td>2.9</td>
<td>3.2</td>
<td>3.0</td>
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<td>1.6</td>
<td>2.4</td>
<td>2.6</td>
<td>2.5</td>
<td></td>
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</table>

*assumption; value of <3 months equivalent to 50% of value of 3–12 months. *assumption; free surface area = 50% of arms plus 50% of legs plus hands.
A2.4 Congener-specific uptake rates from the model simulations

Table A2.4. Congener-specific uptake rates (ng/kg/d).

<table>
<thead>
<tr>
<th>age groups</th>
<th>BDE-47</th>
<th>BDE-99</th>
<th>BDE-100</th>
<th>BDE-153</th>
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<td>scenario A</td>
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<td></td>
<td></td>
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<tr>
<td>infants (0–3 mo)</td>
<td>25</td>
<td>9.4</td>
<td>6.9</td>
<td>11</td>
</tr>
<tr>
<td>infants (3–12 mo)</td>
<td>5.7</td>
<td>3.5</td>
<td>1.2</td>
<td>0.76</td>
</tr>
<tr>
<td>toddlers</td>
<td>9.6</td>
<td>5.9</td>
<td>2.1</td>
<td>1.3</td>
</tr>
<tr>
<td>children</td>
<td>2.8</td>
<td>1.8</td>
<td>0.61</td>
<td>0.38</td>
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<tr>
<td>teens</td>
<td>1.5</td>
<td>0.95</td>
<td>0.33</td>
<td>0.21</td>
</tr>
<tr>
<td>adults</td>
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<td>0.93</td>
<td>0.33</td>
<td>0.20</td>
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<td>scenario B</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>infants (0–3 mo)</td>
<td>25</td>
<td>8.8</td>
<td>6.9</td>
<td>11</td>
</tr>
<tr>
<td>infants (3–12 mo)</td>
<td>4.4</td>
<td>0.96</td>
<td>1.4</td>
<td>0.82</td>
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<td>7.4</td>
<td>1.6</td>
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<td>children</td>
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<td>0.26</td>
<td>0.38</td>
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<tr>
<td>adults</td>
<td>1.2</td>
<td>0.25</td>
<td>0.37</td>
<td>0.22</td>
</tr>
<tr>
<td>scenario C</td>
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<td></td>
<td></td>
<td></td>
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<td>infants (0–3 mo)</td>
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<td>infants (3–12 mo)</td>
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<td>0.78</td>
<td>0.60</td>
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<td>toddlers</td>
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<td>1.0</td>
</tr>
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<td>children</td>
<td>1.4</td>
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<tr>
<td>teens</td>
<td>0.74</td>
<td>0.16</td>
<td>0.21</td>
<td>0.16</td>
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<tr>
<td>adults</td>
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<td>0.15</td>
<td>0.21</td>
<td>0.16</td>
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<tr>
<td>bottom-up</td>
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<td>infants (0–3 mo)</td>
<td>44</td>
<td>13</td>
<td>6.7</td>
<td>21</td>
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<tr>
<td>infants (3–12 mo)</td>
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<td>1.7</td>
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<td>children</td>
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<td>0.12</td>
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<td>teens</td>
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<td>0.39</td>
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<td>0.058</td>
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<tr>
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<td>0.50</td>
<td>0.30</td>
<td>0.055</td>
<td>0.044</td>
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</tbody>
</table>

A2.5 References


FSANZ (Food Standards Australia New Zealand). 2007. Polybrominated diphenyl ethers (PBDE) in food in Australia. Canberra:FSANZ.


A3

Supporting information for Chapter 4
Table A3.1. Input data for and model output of the CSTD half-life tool for BDE-47 (tool available on http://www.sust-chem.ethz.ch/downloads).

<table>
<thead>
<tr>
<th>input data</th>
<th>year</th>
<th>concentration (ng/g lipid)</th>
<th>reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2004</td>
<td>1.7&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
<td>2006</td>
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<td>Glynn et al. (2012)</td>
</tr>
<tr>
<td></td>
<td>2008</td>
<td>1.2</td>
<td>Lignell et al. (2012)</td>
</tr>
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<td>2010</td>
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<td>Lignell et al. (2012)</td>
</tr>
<tr>
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<td>0.82</td>
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</table>

<table>
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<th>input data</th>
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<th>reference</th>
</tr>
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<tr>
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<td>Törnkvist et al. (2011)</td>
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**model output**

<table>
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<td></td>
</tr>
<tr>
<td>intrinsic elimination half-life</td>
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<td>2.2 years</td>
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<sup>a</sup>weighted average
### Table A3.2. Input data for and model output of CSTD half-life tool for DDT (tool available on http://www.sust-chem.ethz.ch/downloads).

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<th>Reference</th>
</tr>
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<td>Norén and Meironyté (2000)</td>
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<td></td>
<td>1996</td>
<td>12.5(^a)</td>
<td>Glynn et al. (2012)/Norén and Meironyté (2000)</td>
</tr>
<tr>
<td></td>
<td>1997</td>
<td>14(^a)</td>
<td>Glynn et al. (2012)/Norén and Meironyté (2000)</td>
</tr>
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<td></td>
<td>1998</td>
<td>7.9</td>
<td>Glynn et al. (2012)</td>
</tr>
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<td>Glynn et al. (2012)</td>
</tr>
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<td>Glynn et al. (2012)</td>
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</tr>
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<td>2.2</td>
<td>Lignell et al. (2014)</td>
</tr>
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<th>Intake (ng/d)</th>
<th>Reference</th>
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#### Model output

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<th>( t_{1/2}^{elim} )</th>
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</thead>
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<tr>
<td>Intrinsic elimination half-life</td>
<td>1.9 years</td>
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</table>

\(^a\) weighted average  
\(^b\) same approach as in Ritter et al. (2009)
Table A3.3. Input data for and model output of CSTD half-life tool for PCB-153 (tool available on http://www.sust-chem.ethz.ch/downloads).

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<th>reference</th>
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**model output**

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<sup>a</sup>weighted average
### Table A3.4.


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<td>Glynn et al. (2012)</td>
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<td>2008</td>
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<td>Glynn et al. (2012)</td>
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<td>2012</td>
<td>7.2</td>
<td>Lignell et al. (2014)</td>
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</tbody>
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<th>reference</th>
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</table>

### Model output

- CSTD-based half-life: \( t_{1/2}^{\text{CSTD}} \) = 14.9 years
- Intrinsic elimination half-life: \( t_{1/2}^{\text{elim}} \) = 2.4 years

\(^a\) Vaz et al. (1995) expressed intakes as ng/kg/d assuming a body weight of 60 kg.
A3.1 References


