An integrative risk assessment approach for persistent chemicals: A case study on dioxins, furans and dioxin-like PCBs in France

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A R T I C L E  I N F O

Article history:
Received 28 October 2013
Available online 16 July 2014

Keywords:
Cumulative risk assessment
Dioxins
PCBs
Biomarker
Pharmacokinetic
Benchmark dose

A B S T R A C T

For persistent chemicals slowly eliminated from the body, the accumulated concentration (body burden), rather than the daily exposure, is considered the proper starting point for the risk assessment. This work introduces an integrative approach for persistent chemical risk assessment by means of a dynamic body burden approach. To reach this goal a Kinetic Dietary Exposure Model (KDEM) was extended with the long term time trend in the exposure (historic exposure) and the comparison of bioaccumulation with body burden references for toxicity. The usefulness of the model was illustrated on the dietary exposure to PolyChlorinatedDibenzo-p-Dioxins (PCDDs), PolyChlorinatedDibenzoFurans (PCDFs) and PolyChlorinated Biphenyls (PCBs) in France. Firstly the dietary exposure to these compounds was determined in 2009 and combined with its long term time trend. In order to take differences between the kinetics of PCDD/F and dl-PCBs into account, three groups of congeners were considered i.e. PCDD/Fs, PCB 126 and remaining dl-PCBs. The body burden was compared with reference body burdens corresponding to reproductive, hepatic and thyroid toxicity. In the case of thyroid toxicity this comparison indicated that in 2009 the probability of the body burden to exceed its reference ranged from 2.8% (95% CI: 1.5–4.9%) up to 3.9% (95% CI: 2.7–7.1%) (18–29 vs. 60–79 year olds). Notwithstanding the decreasing long-term time trend of the dietary dioxin exposure in France, this probability still is expected to be 1.5% (95% CI: 0.3–2.5%) in 2030 in 60–79 olds. In the case of reproductive toxicity the probability of the 2009 body burden to exceed its reference ranged from 3.1% (95% CI: 1.4–5.0%) (18–29 year olds) to 3.5% (95% CI: 2.2–5.2%) (30–44 year olds). In 2030 this probability is negligible in 18–29 year olds, however small though significant in 30–44 year olds (0.7%, 95% CI: 0–1.6%). In the case of hepatic toxicity the probability in 2009 even in 60–79 year olds already was negligible. In conclusion this approach indicates that in France dioxin levels in food form a declining, though still present, future health risk with respect to thyroid and reproductive toxicity.

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1. Introduction

Chemicals like PolyChlorinatedDibenzo-p-Dioxins (PCDDs), PolyChlorinatedDibenzoFurans (PCDFs), PolyChlorinated Biphenyls (PCBs), PolyBrominated Diphenyl Ethers (PBDEs), DichloroDiphenylTrichloroethane (DDT), cadmium and mercury are known to be slowly eliminated from the body. The successive exposures to these chemicals therefore results in bioaccumulation, i.e. increasing levels in the body. For this reason, the accumulated concentration in the body (body burden), rather than the daily exposure, is considered as the proper starting point for the risk assessment of these chemicals (Van Leeuwen and Younes, 2000; US EPA, 2010).

In comparison with a traditional risk assessment a body burden approach requires various methodological adaptations (NRC, 2006; Gies et al., 2007; Sirot et al., 2012). Firstly, the accumulation in the human body results from the net effect of repeated intakes and elimination. The incorporation of such accumulation in the risk assessment procedure needs the explicit incorporation of chemical kinetics. In this context several kinetic models ranging from single compartment toxico-kinetic (TK) models to complex multi-compartment physiologically-based toxicokinetic (PBTK) models may serve the purpose. Secondly, the exposure to bioaccumulating agents may not be limited to one single chemical, but may consist of the exposure to a mixture of related chemicals. Here PCDD/Fs and dl-PCBs are a typical example (Van den Berg et al., 2006).
Thirdly, the accumulation kinetics of persistent chemicals may be impeded by their complex historic exposure pattern. For example, it is well highlighted that the exposure to environmental contaminants such as PCDD/Fs have changed significantly over the last decades due to changes in production, in use and successive regulations (Hays and Aylward, 2003; De Mul et al., 2008). Such changes may be different for closely related chemicals such as PCDFs, PCDDs and dl-PCBs (Consonni et al., 2012). In the case of PCDD/Fs previous studies already have addressed the historic exposure pattern of PCDD/Fs (Van der Molen et al., 1996; Pinsky and Lorber, 1998; Aylward and Hays, 2002). To the best of our knowledge, none of these studies performed a full quantitative risk assessment integrating the historic, long term, exposure of PCDD/Fs and dl-PCBs, the resulting bioaccumulation and the corresponding toxic risk. Therefore, the objective of this study is to develop an integrative risk assessment methodology which takes into account the long-term time trend of the exposure to persistent chemicals, their bioaccumulation in the human body and the corresponding toxicity and to apply this methodology on the long-term exposure of PCDD/Fs and dl-PCBs in France.

As dietary intake represents more than 90% of the human exposure to PCDD/Fs and dl-PCBs (WHO, 2002) only this route of exposure was considered. The current dietary exposure in France was assessed by means of a food questionnaires and contamination data in food and scaled over time in concordance with the method of Van der Molen et al. (1996), Van der Molen (1998). The resulting long-term intake was used as input for the Kinetic Dietary Exposure Model (KDEM) as proposed by Verger et al. (2007) for the exposure to methyl mercury, its accumulation in the body and its corresponding toxic risk. In order to take differences between the kinetics of PCDD/F and dl-PCBs into account (Milbrath et al., 2009) and possible differences in historic evolution of exposure, three groups of congeners were considered separately: PCDD/Fs, PCB 126 and remaining dl-PCBs.

This strategy resulted in long-term simulations of the body burden of PCDD/Fs and dl-PCBs in the French population. The toxic risk, i.e. reproductive, hepatic and thyroid toxicity, associated with these body burdens was obtained by comparison with reference body burdens for these types of toxicity. In concordance with current dioxin risk assessment procedures (Van Leeuwen and Younes, 2000; JECFA, 2001), the latter were obtained by means of interspecies extrapolation of animal toxicity. In this work, animal toxicity was analyzed by means of Bench Mark Dose modeling and associated animal body burdens were extrapolated to man. Body burdens estimated from our model were then compared with reference body burdens through a probabilistic approach using distributions for BMDL and population body burdens.

2. Material and methods

2.1. Dietary exposure and blood concentrations of a fishermen French population

Biomonitoring data such as concentrations in blood provides relevant information for the estimation of kinetic parameters such as half-lives and exposure trends of dioxins (Van der Molen et al., 1996; Van der Molen, 1998; Aylward et al., 2005; Hsu et al., 2010; Fromme et al., 2009). Hence blood concentration of PCDD/Fs and dl-PCBs measured in a population of French fishermen families were used to characterize the long-term exposure of the current French population (Anses/InVS, 2011). The blood data were obtained from the French National study on Dioxin blood levels in French consumers of freshwater fish (ICAR study, Anses/InVS, 2011). In 2009, this study recorded the dioxin concentrations in blood (pg per g fat) of 606 adults between 18 and 75 years of age. All individuals were from fishermen families. The concentrations were converted into total body burdens assuming a balance between all lipid compartments in the body and that the fat content of the human body (BF) varies with age, sex, weight and height according to the equation proposed by Deurenberg et al. (1991) i.e. 

\[ BF\% = 1.20 \times BMI + 0.23 \times age - 10.8 \times sex - 5.4. \]

Consumed quantities of 115 food items covering the main diet of each individual taking part in the study, were collected by means of a food frequency questionnaire and a photograph manual of portions size. Dietary exposure of the 606 individuals was assessed by combining these consumed quantities with concentration data from the ICAR study for freshwater fishes, the CALIPSO study (Leblanc, 2006) for marine fishes and other sea foods and the second French Total Diet Study (Sirot et al., 2012) for other foods known to contribute to the exposure to dioxins. Body burdens and levels of dietary exposure for different age classes of the ICAR population are summarized in Table 1.

2.2. Dietary exposure of the general French population

Exposure data of the French population are provided by the Second French Total Diet Study (Sirot et al., 2012). “Total Diet Studies (TDS)” follow a standardized international methodology and aim at assessing the dietary exposure of individuals for many contaminants taking into account residue levels in foods as consumed at home. In a TDS, exposure is assessed by combining individual food consumption data and residue levels data from food sample analysis. The individual food consumption data used in the Second French Total Diet Study (Sirot et al., 2009) were provided by the second “Individual and National Study on Food Consumption”, INCA2 survey, carried out by the French Food Safety Agency between late 2005 and April 2007 (Dubuisson et al., 2010; Liotet et al., 2010). Two independent population groups were included in the survey: 2624 adults aged 18–79 years and 1455 children aged 3–17 years. Each participant was asked to complete a 7-day food diary as well as other questionnaires on anthropometric and socio-economic factors. Foods declared were subsequently categorized into 1305 “as consumed” food items. The mean of the quantities of the same food consumed by each individual during the week is used in order to assess chronic exposure. The consumption data were combined with contamination data measured for 212 core foods selected to cover about 90% of the whole diet in terms of quantity consumed through a methodology described in Sirot et al. (2009). Levels of dietary exposure for different age classes of the French population are summarized in Table 2.

2.3. The kinetic model

2.3.1. Model definition

Verger et al. (2007) proposed a Kinetic Dietary Exposure Model (KDEM) which describes the dynamic evolution of the dietary exposure over time. Between intakes, the change of human body burden x is described by a simple one-compartment, first order, pharmacokinetic model. For chemicals with long half-lives, absorption time is insignificant compared to the elimination time. In concordance with Emond et al. (2005); US EPA (2010) and EFSA (2011) the absorption of dioxins, furans and DL-PCBs from food was considered to be complete, i.e. 100%. Given one compartmental kinetics, the elimination rate between two eating occasions is given as:

\[ \frac{dx}{dt} = -k \times x(t) \]  

The elimination rate k is described by the apparent elimination half-life HL as \( k = \ln(2)/HL \).
The accumulation in the body is then calculated as follows. At each eating occasion $T_{nl}, n \in N$, the dynamic exposure process jumps with size equal to the intake $U_n$, which is related to this eating occasion. Between intakes the exposure process decreases exponentially according to Eq. (1). The value of the total body burden $X_{n+1}$ at intake time $T_{n+1}$ is thus defined as

$$X_{n+1} = X_n e^{-\Delta T_{n+1}} + U_{n+1}, \quad n \in N$$

(2)

with $\Delta T_{n+1} = T_{n+1} - T_n, n > 1$, the time between two intakes and $X_0$ the initial body burden.

In order to take into account the possible historic variation of the exposure through time, a function of time $f$ is introduced in KDEM to correct the intake estimated from current data (in 2009 in this study):

$$X_{n+1} = X_n e^{-\Delta T_{n+1}} + f(y) U_{n+1}, \quad n \in N$$

$$X_0 = x_0$$

(3)

where $y$ is the year corresponding to the food intake.

### 2.3.2. Model parameters and group of congeners

Milbrath et al. (2009) reviewed the half-lives for individual PCDD/F and dl-PCB and showed that, on average, the half-life of individual PCDD/F congeners approximates that of TCDD. Sequentially Aylward et al. (2013) provided a half-life for the PCDD/F TEQ. In contrast dl-PCB showed a wider variety. Since PCB 126 is the dominant dl-PCB in French food products (Tard et al., 2007), it contributes to around 60% of the dietary exposure of the French population (Table 2) and has a relative high toxic potency (Toxic Equivalency Factor of 0.1, to be compared with the <0.03 for the other dl-PCBs and 1.0 for the most toxic reference, i.e. 2,3,7,8-TCDD), this congener was modeled separately from the PCDD/Fs. The apparent elimination half-lives used for other dl-PCBs and 1.0 for the most toxic reference, i.e. 2,3,7,8-TCDD, this congener was modeled separately from the PCDD/Fs.

<table>
<thead>
<tr>
<th>Classes of age</th>
<th>Dietary exposure per day (pg TEQ2005/kg bw)</th>
<th>Estimated body burden in 2009 (ng TEQ2005/kg bw)</th>
<th>Estimated body burden in 2030 (ng TEQ2005/kg bw)</th>
<th>Half-life considered (years)</th>
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<tr>
<td></td>
<td>2.5th</td>
<td>50th</td>
<td>97.5th</td>
<td>2.5th</td>
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<td>1.5</td>
<td>7.1</td>
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<tr>
<td>60–79</td>
<td>0.5</td>
<td>1.6</td>
<td>5.6</td>
<td>2.1</td>
</tr>
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</table>

PCDD/Fs: half-life for the TEQ (Aylward et al., 2013), PCB126: median value (Milbrath et al., 2009), dl-PCBs: average of median values (Milbrath et al., 2009).
g milk fat; remaining dl-PCBs: 0.13 pg/g milk fat). Given a daily breast milk consumption of 800 ml/day and a fat percentage of 2.7% (Zeilmaker, personal communication; Ffre and Deloraine, 2000), a daily breast milk fat consumption of 21.6 g fat/day could be calculated. Given a body weight 7.6 kg for a 6 months old child (Winter et al., 2003), the initial body burden of breastfed children at 6 months of age was then calculated at 6 × 30 × 21.6/7600 = 4.1 ng TEQ/kg bw. It corresponds to 3.1 ng/kg bw for PCDD/Fs, 0.90 ng/kg bw for PCB-126 and 0.066 ng/kg bw for remaining dl-PCBs.

2.3.3. Simulation of individual body burden

In order to take into account the inter-individual variability, a lifetime exposure trajectory started at the year of birth is simulated for each individual. The consumption is known to be subject to large fluctuations during childhood (Lioret et al., 2010). The age dependency of the intake of the general French population calculated from the INCA2 population is shown in Fig. S1 in the Supplementary Material. Consequently, reference intakes Un at age lower than 18 are simulated by combining the consumption distribution of children observed in the INCA2 study. To be more specific, for each age α between 3 and 17 occurring in the INCA2 database, a reference distribution of the dioxins intake at the age α is estimated by combining the consumption and the contamination data as explained in Section 2.2. Therefore, 2624 individual lifetime exposure trajectories are simulated as follow. Starting with x0, then for each intake time which occurs when the individual is of age α, an intake value Un is sampled according to the distribution of French children of age α. When older than 18 the age dependency of the variability in the intake with age was neglected and Un equal the intake of the individual at his current age.

2.4. Calibration of the function f and validation of the model

2.4.1. PCDD/Fs

Regarding PCDD/Fs Van der Molen et al. (1996), Van der Molen (1998), Pinskyn and Lorber (1998), Aylward and Hays (2002), highlighted a time-trend of the historic exposure that should be taken into account to predict verifiable body burdens. Unfortunately the time-trend in the historic exposure to PCDD/F and dl-PCBs, i.e. consumption pattern and occurrence data, is not available in France. However, cross-sectional biomonitoring data such blood concentrations may be of help. Indeed, when collected at a certain point in time age-dependent PCDD/F and dl-PCB concentrations reveal the accumulation of these compounds resulting from their historic exposure. This allows for defining a function f(y) which scales the age-dependent intake as determined in a certain reference year y (2009 in this work) over time. Fitting a known kinetic model with input the known age-dependent intake coupled to the unknown function f(y) to the known biomonitoring data then results in defining f. In this study Bayesian inferences were carried out to calibrate the function f(y) on French blood data of the ICAR cohort. The chosen function f(y) contains five shape parameters (for details see van der Molen et al., 1996; van der Molen, 1998). These parameters were calibrated on (cross-sectional) blood data in Germany and intake data from the Dutch population. As The Netherlands and France have implemented the same European rules with regard to dioxin emissions to the environment it was decided to hold the parameters which scale the function f(y) across time (parameters B and G) at their default value, i.e. the values 60 and 95 as calibrated on the German/Dutch data which scale and shift f(y) over the time axis. Similarly the parameters which determine the shape of f(y) (parameter C, default value: 3.5) and the background concentration in blood (parameter A, default value: 0.1) were fixed at their default values. Only the parameter H affecting the height of the function was recalibrated on the French data. In this procedure, it was chosen not to give a priori information on the value of the parameter H (i.e. the prior is a gamma distribution with shape parameter k = 0.001 and scale parameter θ = 0.001). The stability of the estimates was checked by estimating the parameter H of f(y) from several samples of 130 individuals. The model was implemented with the software OpenBUGS version 3.1.2 (Lunn et al., 2009).

2.4.2. dl-PCBs

Regarding the dl-PCBs, and in particular PCB 126, Consonni et al. (2012) showed no age-dependency in the blood concentrations of these compounds. Therefore, defining f(y) seems not necessary for dl-PCBs.

2.4.3. Validation

Before using it to predict body burdens of the general French population, the model is implemented on the ICAR population in order to be validated by comparison between observed and estimated body burdens. For each age, a 95% confidence interval is calculated as the interval which contains 95% of the body burdens values predicted for individuals of the corresponding age. Then, it is checked if the observed body burdens are included in this interval.

2.5. Risk assessment

2.5.1. Reference values for body burdens

To interpret the calculated body burdens in terms of toxic risk, reference body burdens were calculated by means of benchmark dose (BMD) analysis. In BMD modeling a dose–response model is fitted to the toxicity data. Subsequently, the dose is derived to correspond to a predetermined percentage change in response (compared to the background) in the case of continuous toxicity data or which results in an effect in the typical, average individual (i.e. ED50) in the case of dichotomous data. The BMD is reported with its lower (5th percentile) and upper (95th percentile) confidence limits: BMDL and BMDU respectively.

Supplementary Material S2 shows the BMD analysis of reproductive, hepatic and thyroid toxicity in experimental animals. This analysis resulted in a BMDL of 171 ng TEQ/kg body fat for reproductive toxicity, corresponding with a 10% decrease in sperm production in offspring of dams which were exposed to TCDD. For thyroid toxicity, the BMDL is 186 ng TEQ/kg body fat, corresponding with a 10% reduction in serum TT4. For hepatic toxicity, the BMDL is 1520 ng TEQ/kg body fat, corresponding with an increase of fatty infiltration in the liver in the average animal.

To extrapolate them to human inter-species and intra-species variability so-called Extrapolation Factor (EF) are used. In the case of dioxins this extrapolation is limited to the extrapolation of inter-human variability of dioxin kinetics (WHO, 2005; SCF, 2001; JECFA, 2001). This variability was quantified by means of a log normally distributed EF with a geometric mean of 1 and a geometric standard-deviation of 2. Then, the Human BMDLs in ng TEQ/kg body fat were converted in ng TEQ/kg body weight considering 20% of fat in human body. Thus, the final BMDL distribution for

- reproductive toxicity was characterized by a mean of 34 ng TEQ/kg body weight, a 2.5th percentile of 8 ng TEQ/kg body weight and a 97.5th percentile of 125 ng TEQ/kg body weight. In pregnant women these body burdens may lead to reduced sperm production in male offspring.
- thyroid toxicity was characterized by a mean of 39 ng TEQ/kg body weight, a 2.5th percentile of 10 ng TEQ/kg body weight and a 97.5th percentile of 146 ng TEQ/kg body weight. During life, these body burdens may lead to reduce thyroid hormone levels.
hepatic toxicity was characterized by a mean of 302 ng TEQ/kg body weight, a 2.5th percentile of 72 ng TEQ/kg body weight and a 97.5th percentile of 1160 ng TEQ/kg body weight. During life these body burdens may lead to fatty infiltration in the liver.

2.5.2. Risk indicators and probabilistic risk assessment

The induction of reproductive toxicity in animals has shown that this effect can be caused by a single exposure of the pregnant dams. Therefore, as a “worst case” approach, it was assumed that a body burden of women of reproductive age (18–44 years) which exceeds the reference BMDL for this effect for at least one day is indicative for reproductive toxicity. Regarding thyroid and hepatic toxicity the same “worst case” approach was applied (see Supplementary Material S3).

Since a distribution was used to take inter-individual variability, a distribution is available for the human BMDL. Since individual simulations were implemented with the model, the body burdens of the 2624 individuals from the INCA2 study were estimated. Consequently, in concordance with Van Der Voet and Slob (2007), a probabilistic risk assessment was conducted. Its implementation can be described as follow:

1. A value of BMDL in ng TEQ/kg bw is randomly sampled from the BMDL distribution and written u.
2. For each of the 2624 individuals, the estimated body burdens for PCDD/F, PCB 126 and remaining dl-PCBs through the life are summed and it is determined whether the estimated individual body burden exceeded the threshold u at least one time i.e. for a time period of at least one day.
3. The number of individuals highlighted in the step 2 provides the probability of exceeding the threshold u.

These steps were repeated 1000 times in order to provide a mean probability (i.e. the mean of the 1000 probabilities provided by the step 3) and its 95% confidence interval (i.e. the 2.5th and the 97.5th percentile).

3. Results

3.1. Model validation and scaling of the dietary intake across time

As shown in Fig. 1A for PCB 126 and Fig. 1B for the remaining dl-PCBs a kinetic model without any specific correction for a historic time-trend for the exposure was able to simulate the accumulation of these compounds in the body of a French subpopulation, i.e. French fishermen. Indeed, regarding PCB126, for 551 individuals (i.e. 91% of the population) the observed body burdens, i.e. blood fat concentrations, fell within the 95% confidence interval of the simulated blood concentrations of the corresponding age. Regarding the remaining dl-PCBs, for 569 individuals (i.e. 94% of the population) the observed body burdens are in this confidence interval. The quality of the model prediction can also be checked from Table 1 which summarizes the simulated and the observed body burdens of individuals of the ICAR study as stratified in 4 age classes.

Regarding PCDD/Fs (Fig. 1C), the kinetic model without historic correction underestimates the body burdens and the addition of the scaling function f(h) was necessary to describe the data. Indeed, without the correction, the kinetic model predicts correctly the body burden for less than 40% of the population. This is low compared to the 91% and 94% for the PCB 126 and other dl-PCBs.

Consequently, a scaling function was calibrated to the data from the approach described in Section 2.4. It results in H = 1.8 with a 95% confidence interval of [1.45; 1.75]. Fig. 2 shows the function f(y) which scales the dietary exposure in France across time for H = 1.8. From Fig. 2, it can be concluded that the biomonitoring data of the ICAR study are compatible with a historic time trend in the exposure which peaks in the 1960s at a level which is 6 times higher than the exposure in France in 2009. Fig. 1C indicates that the model correctly predicts the current age-dependency of the body burdens for families of French fishermen, taking their individual intake history into account. To check the quality of the model, a cross validation was implemented as follow: the data set is randomly divided into 3 subsets respecting the proportion of individuals in each age class. Then the model is fitted from two-thirds of the data set and the number of individual for which the observed body burdens are in the confidence interval of the estimated once is calculated. This procedure is repeated three times and in mean the model predicts well the body burden for 92% of the population. Compared to the 40% of the previous model, it shows that taking into account the historic variation of the exposure in the model improves significantly the prediction quality of the body burden. This finding is also illustrated in Fig. 3 which shows the comparison of the distribution of the simulated sum of the PCDD/F, PCB-126 and remaining dl-PCB TEQ in the blood of the ICAR population with the observed TEQ in blood.

3.2. Simulation of current body burdens of the general French population and risk assessment

From the dietary intakes of the general French population in 2009 and the models proposed in Section 2 current body burdens of the French population were calculated for 3 groups of congeners: (i) PCDD/Fs, (ii) PCB 126 and (iii) the remaining dl-PCBs. The simulated body burdens calculated for four different age groups are presented in Table 2.

Regarding the PCDF/Fs, as expected older individuals have a higher body burden than younger individuals, thereby reflecting the effect of bioaccumulation. Due to their relative high contribution to the dietary exposure and their long half-lives, PCDD/Fs contribution to total body burden is high (around 70%). Regarding PCB 126, Table 2 indicates the high contribution of this congener to the dietary exposure, i.e. higher than 50%, whereas the contribution of PCB 126 to the total body burden is less than 10%. This is caused by the relative low half-life of PCB 126 compared to PCDD/Fs and the other dl-PCB congeners. As expected, regarding other dl-PCBs, due to the mean half-life considered that is around 12 years, the contribution of these congeners to the body burden is higher than the contribution to the dietary exposure.

The distributions of the body burdens presented in Table 2 were compared with the distribution of the reference body burdens indicative for toxicity. As shown in Table 3, the probability that the simulated body burden exceeds the BMDL for reproductive toxicity is below 3.5% regarding the mean value and 5.2% regarding the 97.5th. The probabilities that the body burden in 2009 exceeds the human reference BMDL for thyroid toxicity range from 2.8% in 18–29 years old (mean value, 97.5th percentile: 4.9%) to 3.9% in 60–79 year olds (97.5th percentile: 7.1%). With respect to hepatic toxicity the probability of the current body burden to exceed the reference BMDL for this effect (even in 60–79 year olds) is negligible.

3.3. Simulation of future body burdens of the general French population and corresponding risk

Although Fig. 2 suggests that PCDD/Fs dietary exposure in France would continue to decline after 2009, the unknown uncertainty herein in fact makes such an extrapolation speculative. Consequently, in this work, a “worst case” scenario was chosen i.e. the PCDD/Fs dietary exposure would stay at its current level after 2009. Under this scenario, the body burdens of the French population in 2030 were simulated. Table 2 presents the comparison of the 2030 body burden with the simulated 2009 body
burden. Again, elder individuals have a higher PCDD/F body burden than young ones. So even in 2030 an age-dependency of the body burden is expected. Furthermore, for a given age class (18–29, 30–44, 45–59 and 60–79 years) the body burden decreases between 2009 and 2030, illustrating the effect of the long-term decreasing time trend of the PCDD/F exposure. For example, the mean body burden of individuals of 30 years of age in 2030 would be lower than the mean body burden of individuals of 30 years of age in 2009. Consequently, the cumulative risk related to PCDD/Fs and dl-PCBs is lower in 2030. Indeed, the probabilities that the body burden in 2030 exceeds the human reference BMDL for thyroid toxicity range from 0.3% (mean value, 97.5th percentile: 1.3%) in 18–29 year olds to 1.5% (mean value, 97.5th percentile: 2.5%) in 60–79 year olds. In 18–29 year olds the probability for reproductive toxicity is negligible, whereas for 30–44 olds it is 0.7% (mean value, 97.5th percentile: 1.6%).

4. Discussion

The objective of this work was to develop an integrative approach to assess the toxic risk through a body burden approach for PCDD/Fs and dl-PCBs. The implementation of this approach needed to combine several methods and data. Firstly, the Kinetic dietary exposure model (KDEM) as proposed by Verger et al. (2007) was extended with variable exposure, including inter-individual and intra-individual variability. Furthermore, kinetically, the exposure was divided into PCDD/Fs, PCB-126 and remaining dl-PCBs. In concordance with Aylward et al. (2013) and Milbrath et al. (2009) PCDD/Fs were considered a homogeneous group. PCB 126 was singled out because of its high contribution to the overall TEQ exposure and is relative short half-life. Finally, the remaining dl-PCBs were, as the PCDD/Fs, kinetically considered as a homogeneous group. In order to gain insight in the long-term time trend of the dietary exposure to PCDD/Fs, PCB-126 and remaining dl-PCBs. In concordance with Aylward et al. (2013) and Milbrath et al. (2009) PCDD/Fs were considered a homogeneous group. PCB 126 was singled out because of its high contribution to the overall TEQ exposure and is relative short half-life. Finally, the remaining dl-PCBs were, as the PCDD/Fs, kinetically considered as a homogeneous group. In order to gain insight in the long-term time trend of the dietary exposure to PCDD/Fs, PCB-126 and remaining dl-PCBs in France, a scaling function was calibrated using biomonitoring data of a specific French sub population i.e. fishermen families. This sub-population (i.e. the ICAR population) differs in exposure from the general French population (see Tables 1 and 2). Consequently, the scaling function reflects the historic correction of the background dietary exposure in the ICAR population, which may be assumed similar with that in the general French population, and a correction for the specific historic ICAR intake. However, when
compared with other sources a value of 6 is quite acceptable. Indeed, Van der Molen (1998) mentions 6.7 for PCDD/Fs and dl-PCBs body burdens of the ICAR population (Anses/InVS, 2011) in ng TEQ/kg bw. In our work, the body burden of the French population in 2009 was estimated to an approximate body burden of 3.3 ng TEQ/kg bw. In our work, the body burden of the ICAR population is in concordance with findings by others for the general Dutch and US population. Regarding dl-PCBs, Consonni et al. (2012) found no significant decrease in exposure notably for PCB 126. The KDEM model implemented without scaling function for exposure of PCB 126 and remaining dl-PCBs indeed fitted well with the observed body burdens of the fishermen population. These results, furthermore, are in concordance with the findings of Fernandes et al. (2004) who highlighted that contribution of dl-PCBs to total TEQ has increased between the 1980s and today. The model was validated using the biomonitoring data of the fishermen families. However, to strengthen the validation, the estimated body burdens can be compared with the levels measured in previous French biomonitoring studies. First, Frery and Deloraine (2000) report that breast milk from French women (18–44 years old) in 1998/1999 contains a mean level of 16.5 pg TEQ/g lipid for dioxins and furans only. Considering a default relative fat body of 20%, it corresponds to an approximate body burden of 3.4 ng TEQ/kg bw. Our modeling resulted in an estimated body burden of 1.4–1.8 (18–44 years) in 2009 for PCDD/Fs and a twofold factor between 1998 and 2009. Consequently our results seem consistent with the results of this biomonitoring study. Second, the French dioxin and incinerators study (InVS, 2009) reports a median level in blood of 18.7 pg TEQ/g MG for PCDD/Fs and dl-PCBs for the population of interest (individuals living around municipal solid waste incinerators and individuals living further away) in 2005. This corresponds to an approximate body burden of 3.7 ng TEQ/kg bw. In our work, the body burden of the French population in 2009 was estimated between 2.1 and 4.6, which is thus consistent with the results of this biomonitoring study.

Individual trajectories were simulated in order to take into account the intra- and inter-individual variability in exposure and accumulation kinetics. Some uncertainties remain over the estimation of the body burdens due to the way the KDEM trajectories were simulated and especially regarding childhood. Additional simulations based on different values of the body burden at six months of age show that this body burden can significantly influence the trajectories up to the age of around 20 years. Therefore, before 20 years, the estimations are dependent on the initial body burden. Consequently, the model as proposed in this work cannot be used to assess the risk focusing on the children.

The risk assessment presented here was based on a comparison of body burdens in the general French population with reference values for reproductive, hepatic and thyroid toxicity. Here it should be kept in mind that the assumptions made have added to the “worst case” character of the risk assessment:

- The use of a default relative fat body of 20% in deriving the human BMDLs for reproductive, thyroid and hepatic toxicity may have led to an overestimation of the human risk for these effects. For example, using 30% instead would have led to a 1.5 times lower risk.

### Table 3

<table>
<thead>
<tr>
<th>Effects</th>
<th>BMDL</th>
<th>Classes of age (years)</th>
<th>2009 (%)</th>
<th>2030 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid toxicity</td>
<td>39 [10 ; 146]</td>
<td>18–29</td>
<td>2.8 [1.5 ; 4.9]</td>
<td>0.3 [0 ; 1.3]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30–44</td>
<td>3.1 [1.9 ; 5.2]</td>
<td>0.5 [0 ; 1.1]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45–59</td>
<td>3.5 [2.2 ; 7.3]</td>
<td>0.7 [0 ; 1.4]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60–79</td>
<td>3.9 [2.7 ; 7.1]</td>
<td>1.5 [0.3 ; 2.5]</td>
</tr>
<tr>
<td>Reproductive toxicity</td>
<td>34 [8 ; 125]</td>
<td>18–29</td>
<td>3.1 [1.4 ; 5.0]</td>
<td>0 [0 ; 0]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30–44</td>
<td>3.5 [2.2 ; 5.2]</td>
<td>0.7 [0 ; 1.6]</td>
</tr>
<tr>
<td>Hepatic toxicity</td>
<td>302 [72 ; 1160]</td>
<td>18–29</td>
<td>0 [0 ; 0]</td>
<td>0 [0 ; 0]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30–44</td>
<td>0 [0 ; 0]</td>
<td>0 [0 ; 0]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45–59</td>
<td>0 [0 ; 0]</td>
<td>0 [0 ; 0]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60–79</td>
<td>0 [0 ; 0]</td>
<td>0 [0 ; 0]</td>
</tr>
</tbody>
</table>
In this study a generic kinetic half-life was attributed to PCDD/Fs and dl-PCBs other than PCB 126. It might be argued that congenerspecific half-lives for these compounds might have been used instead. However, doing so would have led to a 1.5 times lower risk (data not shown).

Human toxic risk was defined as the state where a human body burden exceeds set human BMDL reference values for reproductive, thyroid or hepatic toxicity. With regard to reproductive toxicity in animals this effect has a critical window of one single dose at one specific day during pregnancy, i.e. GD 15. Assuming such a narrow window in humans too is “worst case”, considering that the critical human window would comprise a period beyond one day. Furthermore, the risk assessment assumes all women of reproductive age to become pregnant. Similar arguments hold even more for thyroid and hepatic toxicity. Animals experiment suggests the critical time window for these effects to be well beyond one day. However, as even in animals the actual time-span of these windows are unknown one has to fall back on the “worst case” assumption made, i.e. a time-window of one single day.

Furthermore, the used risk indicators (human BMDL values) were obtained by extrapolating animal toxicity to man. Alternatively US EPA has recently identified preliminary reference values for exactly the same endpoints, however based on the interpretation of epidemiological data (US EPA, 2010, see Supplementary Material S4). In the case of thyroid toxicity this study used life-time exposure as the critical time window, the life-time body burden as the dose metric associated with toxicity and a (mean) body burden of 39 ng/kg bw as the reference value for the dose metric. US EPA used the maternal body burden during pregnancy as the dose metric/critical time window and 47 ng/kg bw as the reference value. Using the US EPA’s criteria instead would have led to a lower percentage (0.7%) of the general French population with a body burden exceeding the reference value during reproductive age. For reproductive toxicity the corresponding benchmarks were: maternal body burden during pregnancy and a (mean) of 34 ng/kg bw (this study) vs. the body burden up to ten years of age and <23 ng/kg bw (US EPA). Unfortunately, the uncertainty (for <23 ng/kg bw) in US EPA’s critical body burden for reproductive toxicity does not allow for a comparison with the results of this work. In a follow-up study we are currently studying the appropriateness of the epidemiological data for the methodology applied in this study, i.e. BMD analysis and intra-species extrapolation of toxicity to derive reference values for a human toxicity body burden. It should also be stressed that the effects used in this study are to be considered as subclinical indicators for overt toxicity such as hepatic failure, infertility or long term thyroid dysfunction.

In conclusion, this work combines various data sources (occurrence data, consumption data, biomonitoring data and toxicological data) with several methods (kinetic exposure model, Bayesian inferences, Bench Mark Dose modeling) to arrive at an integrative risk assessment for persistent chemicals. The advantages of the proposed approach are as follows. First, it provides an estimation of the body burden at the population level. Certainly such estimation may be obtained from biomonitoring data as well. However, these studies are costly and require complex protocol management and are usually confined to one point in time. Despite this, some biomonitoring programs could be implemented on long period of time as done in the US by the Centers for Disease Control and Prevention (CDC) and in this case, provide time trend in body burdens. Such programs remain rare and the modeling strategy allows the estimation of an individual’s lifetime dioxin body burden for any year of birth, thereby enabling the development of targeted monitored campaigns. Furthermore, this methodology can generically be applied to any population for which consumption habits are available, even for situations with absent historic dioxin exposure (situations corresponding with the function f(y) set at 1). Moreover, such an approach also allows for the development of specific monitoring scenarios of external exposure and consequences on body burden levels and associated risk. Typical areas of application here are the evaluation of the effectiveness of risk management policy, such as the setting of food standards and its effect on the long term exposure. As an example, we predicted the body burden of the French population in 2030 assuming that the dietary exposure will remain stable at the 2009 level. It results that risk related to PCDD/fs and dl-PCBs would be lower in 2030 but also that congener profiles would continue to change in France. Fernandes et al. (2004) notices for the UK that the relative contribution of the dl-PCBs to the total TEQ exposure increases over time and our results show that this also holds for France. Finally, the proposed modeling approach can be useful to determine the impact of a specific short-term, high level exposure excursing the background exposure on the body burden. Typical examples here are the consumption of accidental contaminated food items such as eggs or fish or specific consumption patterns such as the eating of contaminated freshwater fish.

**Conflict of interest**

RIVM-WHO Collaborating Centre Pathogens in Food and Water This sponsor had no involvement in the study design; collection, analysis and interpretation of data; the writing of the manuscript; or the decision to submit the manuscript for publication.

**Acknowledgments**

This work was supported by the WHO programme for the estimation the burden of foodborne diseases (FERG), ANSES and RIVM.

**Appendix A. Supplementary data**

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.yrtph.2014.07.004.

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