Health risk assessment to dioxins, furans and PCBs in young children: The first French evaluation

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Highlights

- A total diet study focusing on non-breastfed children under 3 years of age was conducted in France for the very first time
- This study aimed at evaluating the risk associated with exposure to chemical substances through food diet
- PCDD/Fs and PCBs were detected in a large portion of the target food samples (between 49 to 100 % of the 180 samples analyzed)
- Situation has been identified as a concern for PCDD/Fs and PCBs after 6 months of age
- Efforts should continue to reduce the exposure of the population

Abstract

A total diet study (TDS) was conducted between 2010 and 2016 to characterize the health risk related to chemical residues in food of French not breastfed children under three years of age (infant TDS). Among the targeted substances, polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and polychlorinated biphenyls (PCBs) have been characterized as they accumulate through the food chain, especially in lipid-rich food items, and because they have been associated with a number of adverse effects in humans.

Food samples (n=180) were collected to be representative of the dioxins and PCB exposure through the whole diet of non-breastfed children from 1 to 36 months old and prepared as consumed (including cooking) prior to analysis.

Dietary exposure was then assessed for 705 representative children under 3 years of age based on their food consumptions recorded through a 3-consecutive-days record. Levels of PCDD/Fs and PCBs in infant food were lower than those observed in common food, leading to significant differences in exposure according to age groups. Mean exposures to PCDD/Fs ranged from 0.22 to 0.44 pg TEQ_{WHO05}.kg $bw^{-1}.d^{-1}$ (0.40 to 0.65 at the 90^{th} percentile), depending on the age group and the hypothesis considered to manage left-censored data. Mean exposure to non-dioxin-like PCBs ranged from 0.87 ng.kg $bw^{-1}.d^{-1}$ (1.55 at the 90^{th} percentile) in the 1-4 months old children to 3.53 ng.kg $bw^{-1}.d^{-1}$ (5.44 at the 90^{th} percentile) in the 13-36 months old children. For dioxins and NDL-PCBs, the tolerable daily intake (TDI) was exceeded for some age groups, in particular for older ones.

Therefore, appropriate management measures must continue for reducing exposure; it concerns mainly common milk in youngest children, ultra-fresh dairy products and fish. For PCBs, recommendations on fish consumption should be reminded. Moreover, toxicity studies focusing on mixtures of dioxin-like compounds should be encouraged in order to take into account effect of mixtures.

Keywords

Total Diet Study, PCDD/F and PCBs, exposure assessment, population exposure, contaminants, risk characterization

1. Introduction

Polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) are generated during thermal (fires, incinerations, etc.) or chemical processes, whereas polychlorobiphenyls (PCBs) have been produced and used until 1987 for their excellent electric insulators explaining their extensive use as coolant fluids in power transformers and capacitors. PCDDs, PCDFs and PCBs regroup 75, 135 and 209 congeners respectively and are classified as persistent organic pollutants. They accumulate along the food chain and are mainly stored in fatty tissues. Food appears to be the main route of exposure of these substances for the general population with food representing more than 90% of the total exposure (EFSA 2005, EFSA 2010, EFSA 2018). Certain congeners of the dioxin, furan, and polychlorinated biphenyl family are known as -dioxin-like- as a result of chemical structures, physico-chemical properties, and toxic responses similar to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), the index chemical for dioxin-like compounds (also known as Seveso dioxin).

The toxicity of PCBs varies significantly depending on the species and on the different congeners within the same species, the number and position of the chlorine atoms on the phenyl nuclei determining their toxicity. Based on structural and toxicological properties, PCBs are grouped into 2 categories, the “dioxin-like PCBs” (dl-PCBs) and the “non dioxin-like PCBs” (ndl-PCBs). The sum of 6 “non-dioxin-like” PCBs (28, 52, 101, 138, 153, 180) is generally considered as representing 50% of the total concentration of PCBs (AFSSA, 2007).

Besides the activation of the Ah (aryl hydrocarbon) receptor by dl-PCBs, several other receptors are involved in the PCB response for both categories: receptors of sexual steroids (estrogens, androgens), thyroid hormones, neurotransmitters or calcic receptors (RyR). The number of targets affected by a same congener and the multiplicity of congeners in each PCB mixtures resulting in pollution explain the diversity of adverse effects observed in contaminated individuals: cutaneous, hepatic, metabolic, immunologic, neurologic, endocrine disruption. Both human and animal studies

identified the developing brain as a vulnerable target of PCBs (Zoeller et al. 2000, Sagiv et al. 2010). Recent studies suggested that the non-dioxin-like PCBs are primarily responsible for the developmental neurotoxicity associated with PCBs (Klocke and Lein 2020).

The international agency for research on cancer (IARC) classified PCBs as carcinogenic to humans in 2013, so as TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) already classified in 1997. Adverse non-cancer effects associated with oral TCDD exposure include hepatic, neurological, immunological, reproductive, endocrine, and developmental effects. In the offspring of rat, effects on reproduction and development as well as immunological effects were observed after administration of TCDD (Seveso dioxin). The main mechanism of action of TCDD and dioxin-like compounds such as PCDDs, PCDFs, and dl-PCBs, is their binding to the Ah receptor (EFSA 2018). Exposure of infants to PCBs and PCDD/Fs which are neurodevelopmental toxicants is therefore a concern.

Due to a number of regulatory measures since the 1980s, the emission of dioxins into the environment and, consequently, human exposure to dioxins, have decreased significantly (Aylward and Hays 2002, EFSA 2018). However, due to their high persistence and bioaccumulation and their toxic potential, dietary dioxins and PCB exposure can be of concern. Different studies and evaluations showed a general decrease in dietary exposure of the European population to dioxins and PCBs since the 2000's However, exceedance of the reference values was still observed, toddlers and other children being the most exposed groups. In 2012, Sirot et al. concluded that less than 4% of the French population exceeded the health-based guidance value (HBGV) for PCDD/F+dl-PCBs set by JECFA in 2001. For total PCB, it was estimated that 2.6 and 6.5% of, respectively, French adults and French children exceeded the health based guidance value set by Afssa in 2007 (Afssa 2007, Sirot et al. 2012). However this study did not take into account children under 3 years old. This population is known for being more susceptible to contaminants (Landrigan et al. 2003), especially during the prenatal and postnatal period (Makri et al. 2004, Sly and Flack 2008, Diamanti Kandarakis et al. 2009). Moreover, they consume more food than adults in proportion to their body weight. As a

result, this population is considered more vulnerable than other groups to chemicals' exposure. There are few studies in Europe that have investigated non breasted infant and toddler exposure to PCDD/Fs and PCBs (Pandelova et al. 2011, EFSA 2012, De Filippis et al. 2014). More recently, in 2018, EFSA concluded that the exposure to PCDD/Fs and dl-PCBs was of concern for all age groups including infants and toddlers (EFSA 2018).

In our study, we aimed at evaluating the exposure of the French infants to PCBs and PCDD/Fs present in food as contaminants using the Total Diet Study (TDS) approach. TDSs aim at providing contamination data for food prepared as consumed by the population, and exposure data, in order to help risk managers in their decisions (EFSA et al. 2011). In 2010, the French Agency for Food, Environmental and Occupational Health & Safety (Anses) launched the first French infant TDS focusing on children under 3 years old. This paper aims at presenting the contamination and the exposure data generated during the course of this study for PCBs and PCDD/Fs.

2. Material and methods

2.1. Consumption data and sample collection

Consumption data are those from the cross-sectional survey on individual dietary consumption in children under 3 years conducted by the Syndicat Français des Aliments de l'Enfance et de la Nutrition Clinique, © « Etude SOFRES 2005 / Université de Bourgogne – Pr M. Fantino pour le Syndicat Français des Aliments de l'Enfance » (Fantino 2005, Fantino and Gourmet 2008). In this survey, dietary consumption data of 705 French children aged from 1 month to 3 years were recorded between January and March 2005. Children were selected through proportionate quota sampling based on the age, the occupation of the mother and the family socioeconomic category. People who took care of the children have completed 3-consecutive-days records to describe all food consumptions including brands, quantities and portion sizes. Breast-fed children, even partially, were excluded from this survey. Information on the body weight was also recorded on the child's health record.

The sampling plan has already been described (Hulin et al. 2014). Briefly, on the basis of the consumption survey, the most consumed foods by the children in terms of quantity and/or consumer rates were selected. In addition, some foods known to contribute significantly to the exposure to one of the chemicals of interest were added to the list. Foods were sampled between July 2011 and July 2012. For each food item identified, 12 subsamples of equal weight were analysed: every month, one subsample of each food item was bought and prepared "as consumed", according to the results of a specific on-line survey on food preparation (Hulin et al. 2014). After collection, the 12 subsamples have been grouped, homogenized and frozen (-18°C) prior to analysis. In total, 5 484 food products were purchased to produce 457 composite samples. Selected food items covered more than 97% of the children diet.

2.2. Sample analyses

Among the 457 food samples, PCBs and PCDD/Fs were only analyzed in food items known or supposed to contain PCDD/Fs and PCBs and for which data were not available in our previous study (Sirot et al. 2012). In total, PCBs and PCDD/Fs concentrations were measured in 178 samples: 169 infant foods, i.e. products commercialized especially for infant and young children, and 9 common foods. LABERCA, that is the French Reference Laboratory for dioxin and PCB analysis in food, performed the analyses of the

samples using method already described elsewhere (Antignac et al. 2006, Costera et al. 2006).

Picograde® quality solvents were purchased from LGC Promochem (Wesel, Germany), and dichloromethane was from Biosolve (Dieuze, France). Sulfuric acid was purchased from Panreac Quimica (Barcelona, Spain). Silica gel and sodium sulfate were from Merck (Darmstadt, Germany), Florisil® and Carbopack™ C from LGC Promochem (Wesel, Germany). ^{13}C-PCDD/Fs, ^{13}C-dl-PCB-77/81/105/114/118/123/126/156/157/167/169/189, ^{13}C-ndl-PCB-28/52/101/138/153/180, were

purchased from Wellington Laboratories (Guelph, Ontario, Canada). All calibration standards and spiking solutions were prepared by serial dilutions in toluene.

Food samples were first freeze-dried before grinding. The ^{13}C-labeled internal standards were added to the samples before the extraction step. Lipids were extracted from lyophilised samples by Pressurised Liquid Extraction (Büchi, Rungis, France) using a toluene/acetone mixture (70:30, v/v), pressure set at 100 bar and temperature at 120 °C. The solvent was then evaporated and the lipid content of the sample was determined gravimetrically. Finally, before purification, the dried fat extract was redissolved in n-hexane.

After removal of fat on a silica gel column loaded with sulfuric acid, PCBs were separated from PCDD/Fs by means of a Florisil® column. The PCDD/F fraction was further cleaned up onto a column consisting of a mixture of Carbopack™ C/Celite® 545. Separation of coplanar (nonortho) PCBs from non-planar PCBs was achieved on an activated mixture of Florisil®/Carbopack™ C/Celite® 545 (overnight at 130°C). After addition of external standards for the recovery calculation ($^{13}C_{12}$-1,2,3,4-TCDD for the PCDD/Fs, $^{13}C_{12}$-PCB111 for the PCBs), the final extract was reconstituted by addition of toluene in the 3 fractions.

Chromatographic separation of PCDD/F congeners was carried out on a DB-5MS column (60 m × 0.25 mm i.d., 0.25 µm film thickness; Agilent Technologies, USA), while for PCBs a HT8-PCB column (60 m × 0.25 mm i.d., 0.25 µm film thickness; SGE Analytical Science, UK) was used. PCDD/Fs and PCBs were quantified by gas chromatography (7890A; Agilent Technologies, USA) coupled to high-resolution mass spectrometry (double sector, JMS-700D and 800D; Jeol, Japan).

All the procedures integrated the necessary quality assurance parameters to fulfil the requirements of the European Commission Regulation (EU) N° 252/2012 of March 2012 laying down methods of sampling and analysis for the official control of levels of dioxins, dioxin-like PCBs and non-dioxin-like PCBs in certain foodstuffs. Analysis were performed

upon an accredited system ISO-17025. The method used have been validated and is accredited ISO-17025.

To ensure the quality of the analysis, besides the use of appropriate internal standards in each sample, labelled standards were added at the end of each process in order to calculate recoveries. Moreover, cleaned laboratory glassware was rinsed with dichloromethane prior to use and the analyses were carried out in an over-pressurized room to minimise environmental contamination.

Further, a continuous monitoring of the analytical procedure was implemented through procedural blanks. As the analytical contamination is fully under control, blank control was not deducted. Reproducibility was assessed using quality control samples (QC) regularly characterised over years. The accuracy of the analytical method is further ensured by regular participation of the laboratory to proficiency tests organized by the European Reference Laboratory (EURL) for POPs.

2.3. Contamination data, exposure calculation and risk assessment

In order to evaluate the risk associated with exposure to PCDD/Fs, World Health Organization toxic equivalency factors (WHO TEF) were used to express exposure in the toxic equivalents (TEQs) (Afssa 2005)Therefore, for PCDD/Fs, the sum of the 17 congeners (2.3.7.8 - TCDD, 1.2.3.7.8 - PeCDD, 1.2.3.4.7.8 - HxCDD, 1.2.3.6.7.8 - HxCDD, 1.2.3.7.8.9 - HxCDD, 1.2.3.4.6.7.8- HpCDD, OCDD, 2.3.7.8 - TCDF, 1.2.3.7.8 - PeCDF, 2.3.4.7.8 - PeCDF, 1.2.3.4.7.8 - HxCDF, 1.2.3.6.7.8 - HxCDF, 1.2.3.7.8.9 - HxCDF, 2.3.4.6.7.8 - HxCDF, 1.2.3.4.6.7.8 -HpCDF, 1.2.3.4.7.8.9 -HpCDF, OCDF) was calculated by multiplying the analytical concentration of each congener by their individual TEFs (Van den Berg et al. 2006, EFSA 2012) named TEFWHO05. Exposure to PCBs was measured by the mean of 6 ndl-PCBs

149 (28, 52, 101, 138, 153, 180), as their sum represents 50% of the total concentration of PCBs (AFSSA,
150 2007)

151 Censored data (results below the limits of detection (LOD) and quantification (LOQ)) were processed
152 according to a substitution method based on the WHO recommendations (GEMS/Food-EURO. 2013).
153 It involved framing the actual level using the lowest (lower-bound (LB)) and highest (upper-bound
154 (UB)) values possible. The LB was calculated by assuming that all values below the LOD were equal to
155 zero and those between the LOD and the LOQ were equal to the LOD. The UB was calculated by
156 assuming that all values below the LOD were equal to the LOD and those between the LOD and the
157 LOQ were equal to the LOQ. Exposure data were then estimated according to both the LB and UB
158 hypotheses. For the 6 ndl-PCB, as all samples were detected, concentration was the same for LB and
159 UB hypothesis. Therefore only one result was presented.

160 In order to complete the diet coverage, some additional regional and national data from French TDS2
161 have been used for contamination of common food as the present study focused on infant foods
162 (Sirot et al. 2012). These data were based on a sampling of 1 319 food samples collected in the whole
163 metropolitan French territory divided into eight regions between 2007 and 2009. For each food
164 samples, 15 subsamples representative of the population food consumption have been bought and
165 prepared as consumed by the population prior to analyses, according to the general TDS
166 methodology and as it was done in the present study.

167 For each food items, the analytic result obtained on the pooled sample was associated with the
168 individual consumption values, based on a deterministic approach as suggested by EFSA, FAO and
169 WHO for TDS approach (EFSA et al. 2011). When available, the allocation of those concentrations to a
170 food consumed by an individual took into account its home region. If no regional data was available,
171 national data were used. For infant formulae that are diluted prior to use, the type and brand of
172 water used to reconstitute the products were also considered (Hulin et al. 2014).

Exposure was therefore assessed individually, for each child of the consumption survey, according to the following formula:

$$\mathbf{E_{i,j}} = \frac{\sum_{k=1}^{n} C_{i,k} \times L_{k,j}}{BW_i}$$

where $E_{i,j}$ is the mean daily exposure to contaminant j of individual i, n is the number of foods in the diet, $C_{i,k}$ is the daily consumption of food k by individual i, $L_{k,j}$ is the concentration of contaminant j in food k, and BW_i is the body weight of individual i.

Mean, standard deviation, and 90th percentile (P90) of exposure were then calculated for the population divided into four age groups: 1-4 months (N=124), 5-6 months (N=127), 7-12 months (N=195) and 13-36 months (N=259). Total exposure levels (LB-UB) to PCDD/Fs, dl-PCBs + PCDD/Fs and to the 6 ndl-PCBs of children under 1 year according to the type of milk consumed have also been calculated. In order to study the impact of milk consumption on exposure, student tests have been performed between the type of consumers.

The food contribution to the mean exposure has been assessed as the percentage of the total exposure due to the consumption of each food group.

The health risk associated with the dietary exposure to each chemical has been assessed by calculating, for each age group, the percentage of children over the health-based guidance value and its 95% confidence interval ($CI_{95\%}$). PCDD/Fs and PCBs have been evaluated separately in this study in order to facilitate the implementation of management measures as sources of each compound's family are different. Additionally, exposure to the sum of PCDDs, PCDFs and dl-PCBs was estimated to make it possible to compare this exposure with the health-based guidance value set by Efsa in 2018 (EFSA 2018). For PCDD/Fs, the toxicological reference value of US-EPA (US-EPA 2012) of 0.7 pg TEQ.kg $bw^{-1}.d^{-1}$ has been considered; for PCB a tolerable daily intake (TDI) of 10 ng.kg $bw^{-1}.d^{-1}$ has been considered to evaluate the risk associated with the 6 NDL-PCB, mostly found in foodstuffs and

197 which represent 50% of all PCB congeners in food (Afssa 2007). For the sum of PCDD/Fs and dl-PCBs,
198 the health-based guidance value set at 2 pg TEQ.kg bw^{-1}.$week^{-1}$ by Efsa (EFSA 2018) on the basis of a
199 decrease of the sperm quality in 9 years old infants exposed during childhood was considered to
200 evaluate the risk.

201 ## 2.4. Collective appraisal

202 The collective assessment of the risk linked to PCDD/F and PCB exposures has been conducted with
203 the expert panel dealing with chemical contaminants in food.

204

205 ## 3. Results and discussion

206 ### 3.1. Food contamination and exposure

207 Most analyses were performed on infant foods, as data on common foods were available elsewhere
208 (Sirot et al. 2012). The percentages of detection and concentration data are shown in table 1. The
209 highest mean concentrations of PCDD/Fs were measured in the food category “infant milk-based
210 desserts” (0.4 pg $TEQ_{WHO05}g^{-1}$ fresh weight under LB-UB). However, the most contaminated infant
211 food item was a pool of jars of salmon cooked with sorrel with a concentration of 0.025 pg
212 $TEQ_{WHO05}.g^{-1}$ fresh weight, followed by two samples of infant biscuits (0.062-0.010 and 0.041-0.010 pg
213 $TEQ_{WHO05}.g^{-1}$ fresh weight according to LB-UB hypothesis, Table 1). For both dl and ndl-PCBs, the
214 highest levels in infant foods were found in the food category “meat or fish based ready-to-eat
215 meals” and “milk-based desserts”. For ndl-PCB concentrations of 41.5 and 40.3 $ng.kg^{-1}$ fresh weight,
216 respectively, (corresponding to 2150 $ng.kg^{-1}$ and 1679 $ng.kg^{-1}$ on fat basis, Table 1) were measured.
217 For dl-PCB, concentrations were respectively of 0.004-0.005 pg $TEQ_{WHO05}.g^{-1}$ fresh weight according
218 to LB-UB hypothesis for “meat and fish based ready-to-eat meals” and 0.008 pg $TEQ_{WHO05}.g^{-1}$ fresh
219 weight for “milk-based dessert”. For these substances, concentrations in infant foods were generally
220 low compared with common foods. Details on concentrations by congeners for each food items
221 analyzed in this study are available online (https://www.data.gouv.fr/fr/datasets/donnees-etude-de-
222 lalimentation-totale-infantile/).

223 Based on these data and the ones measured in the previous French TDS (Sirot et al. 2012), exposure
224 of children was estimated for different age groups according to food diversification (Table 2). For
225 PCDD/Fs as well as PCBs, exposure levels were higher for 13-36 months than for 1-4 months. Mean
226 PCDD/F exposures ranged between 0.22 pg $TEQ_{WHO05}.kg\ bw^{-1}.d^{-1}$in 1-4 months and 0.38 pg
227 $TEQ_{WHO05}.kg\ bw^{-1}.d^{-1}$ in 13-36 months under LB hypothesis. Under UB, mean exposure ranged from
228 0.29 and 0.44 pg $TEQ_{WHO05}.kg\ bw^{-1}.d^{-1}$. When considering PCDD/Fs and dl-PCBs, mean exposure of 13-
229 36 months reached 1.07 pg $TEQ_{WHO05}.kg\ bw^{-1}.d^{-1}$ in UB hypothesis and 1.61 pg $TEQ_{WHO05}.kg\ bw^{-1}.d^{-1}$ for
230 P90. Mean exposure to ndl-PCBs (UB=LB) ranged from 0.87 $ng.kg\ bw^{-1}.d^{-1}$ in the 1-4 months old

children to 3.53 ng.kg $bw^{-1}.d^{-1}$ in the 13-36 months old children. P90 ranged from 1.55 ng.kg $bw^{-1}.d^{-1}$ to 3.53 ng.kg $bw^{-1}.d^{-1}$. Starting at the age of 7 months, milk, ultra-fresh dairy products and cheese contributed to the exposure of PCCD/Fs and PCBs between 30 to 60 % (Figure 1). High differences were indeed observed in exposure according to the type of milk consumed by children. Among our study population, three children (2 among the 1-4 months and 1 among the 13-36 months) appeared to be highly exposed to the PCDD/Fs (between 1.03 and 1.40 pg TEQ_{WHO05}.kg $bw^{-1}.d^{-1}$ under the UB hypothesis). These children have consumed during the three days of the dietary survey a high quantity of common milk (cow milk, 700 to 1 068 $g.d^{-1}$) as well as cream for the oldest child. Children consuming exclusively common cow milk were indeed exposed at least 2 fold more than the ones consuming infant formulae ($p<0.03$ to $p<0.001$, Table 4). For older children, fish appeared to be a main contributor of PCB in highest exposed children between 13 and 36 months. Details on food groups' contribution for each age groups are available in supplementary materials (Table S1).

Our results on PCDD/Fs and dl-PCBs were in the same range as those observed in previous studies (Pandelova et al. 2011, EFSA 2012, De Filippis et al. 2014). In an European study (Pandelova et al. 2011), the authors estimated that non breast-fed children under 9 months were exposed at levels between 0.14 and 2.79 pg TEQ_{WHO05}.kg $bw^{-1}.d^{-1}$ depending on the age and the type of infant formula they consumed (milk, soy or hypoallergenic). However, for the 6 ndl-PCBs, concentrations of infant and baby foods with fish or meat were higher than ours (10 900 $ng.kg^{-1}$on fat basis for the mean and 17 300 $ng.kg^{-1}$for the p99) as well as exposure (between 8.5 and 25.7 ng.kg $bw^{-1}.d^{-1}$ under UB and up to 53.5 ng.kg $bw^{-1}.d^{-1}$for the most exposed children) (EFSA 2012). This can be explained either by a difference of contamination of fish and meat or of the quantity of these ingredients in food composition. Concerning infant formulae, our results were in the same order of magnitude as some found in previous studies for both contaminant families (Loran et al. 2009, Pandelova et al. 2011). Due to a decreasing food consumption in proportion to body weight with ages, we expected to have higher exposure levels in young children compared to older ones. However, exposure in 1-4 months children was lower than 13-16 months ones. Moreover, 13-36 months children were exposed in the

same range of magnitude than 3-6 years old children from the second French TDS for PCDD/Fs, but lower for the 6 ndl-PCBs (Sirot et al. 2012). This can be explained by the gradual introduction of foods, in conjunction with diversification, that are more contaminated than infant formulae. Cow milk consumption instead of infant formulae lead also to higher exposure in young children. These observations reinforce the importance of following recommendations on food diversification and not consuming common cow milk before the age of one year as already recommended based on nutritional needs. .

The data used for exposure assessment covered 68% of the total diet and 96% of the diet theoretically contributing to the exposure. That means that 96% of foods consumed by children and known to contribute to PCDD/Fs and PCBs exposure have been taken into account in the exposure estimation. This estimation is therefore a good representation of young children dietary exposure. However, this study did not take into account breastfed children and breastmilk is known to be more contaminated that infant formulae. Data on European countries as analysed in the frame of WHO coordinated studies showed concentration of PCDD/F between 2.40 and 15.9 pg $TEQ_{WHO05}.g^{-1}$ on fat basis (EFSA 2018) whereas we found concentration of 0.059 and 0.0102 pg $TEQ_{WHO05}.g^{-1}$ for respectively infant and follow-up formulaeTherefore, it would be important to have a global view on exposure of young children to take into account PCDD/Fs and PCBs burden in breastmilk and to consider the risk/benefit of breastfeeding. However, data on consumption and contamination of human milk is indeed very difficult to obtain. In France, the breastfeeding rate is quite low compared to other OECD countries (OECD 2012): only two out of three newborns are breastfed immediately after birth and only 42% of these infants are still breastfed at the end of the 4^{th} month (Bonet et al. 2013). However, it is now recognised that some contaminants, especially persistent organic pollutants, are found in high concentrations in human milk and lead to a potential risk for newborns (EFSA 2011, Ulaszewska et al. 2011). Therefore, collecting data on breast milk contamination in France would be valuable for estimating exposure in this particular population.

3.2. Risk assessment

Based on exposure assessment, the percentages of children exceeding the health-based guidance value (HBGV) were estimated (Table 2). In children over seven months of age, the TDI proposed by the US EPA in 2012 for PCDD/Fs (i.e. 0.7 pg.kg $bw^{-1}.d^{-1}$) was observed to be significantly exceeded by 4.5% of children from 7 to 12 months, and by 5.1 to 7.4% in the 13-36 months old children, depending on the hypothesis of management of the censored data (LB-UB). In children under six months of age, it was not possible to precisely estimate the percentage of exceedance, as less than 5 children exceeded the HBGV, and they were considered as non-representative cases. The cases of exceedance of HBGV were mainly explained by higher consumption of common milk (or cow milk, the single main contributor in children under six months), fish and ultra-fresh dairy products, than in consumers as a whole. When comparing our results on PCDD/F + dl-PCBs with the recent TWI offset by EFSA (EFSA 2018), between 48.9% and 99.6% of children exceed the HBGV according to age groups and the censorship hypothesis.

For the 6 ndl-PCBs, the cases in which the TDI selected (10 ng.kg $bw^{-1}.d^{-1}$) was exceeded were significant from the age of one year (2.7% CI95% [1.2 ; 4.1]). The limits were not exceeded for children under six months of age. Between seven months and one year, once again it was not possible to estimate precisely the extent to which the limits were exceeded, given the limited number of children concerned (n<5). In children exceeding the heath-based guidance value, 82% of the exposure was from fish consumption. They had all consumed high quantity of salmon in the 3 day of the consumption survey: 21 $g.d^{-1}$ for those children vs. 12 $g.d^{-1}$ for all children.

Results on risk assessment for PCDD/Fs or PCBs in young children differ according to studies (Loran et al. 2009, Pandelova et al. 2011, Karjalainen et al. 2012, De Filippis et al. 2014, Morales-Suarez-Varela et al. 2018). The differences can be explained by methodological choices. In our study for example, we were not able to cover all specific consumptions or populations. There may therefore be various

uncertainties regarding the representativeness of the subjects and their consumption regarding the population under consideration, i.e. infants and young children living in metropolitan France. Moreover, the use of a food diary has already been associated with reporting biases that may lead to (Lioret et al. 2011, Berta Vanrullen et al. 2014). Thus, certain food intakes are likely to be unrecorded, particularly food ingested between the main meals within a day. This uncertainty may lead to an underestimation of the risk. Finally, the consumption study used to estimate chronic intakes and exposures is based on a collection of intakes over 3 days. This short period leads to a high variability compared to a longer collection period and may lead to uncertainty in the estimates in relation to the exposure period considered (from a few months to 2 years depending on the age groups considered). Nevertheless, EFSA recommends 2 non-consecutive 24^{th}-recalls for food consumption data collection (EFSA 2014). Even if it was consecutive day, in our study we had recalls on 3 days. It has to be known that there are statistical methods to reduce this uncertainty, known as intra-individual variance reduction methods, but these have not been used in the present work. This choice is protective because it will tend to overestimate high exposures (the mean will be correctly estimated), and thus overestimate the possible risk (Mancini et al. 2015).

As already explained, the TDS approach in the present study ensured to have a good representation of the whole diet. Nonetheless, milk and milk products as well as fish were the main contributors in all studies. Concerning fish, the contamination data in our study only focused on a limited number of species, but the literature showed that other species can contain PCB concentrations equal to or higher than salmon (Marchand et al. 2006). In their study, Morales-Suarez-Varela and al. showed that even if fish is under the regulatory levels in most samples, daily intake in consumers of large quantities of fish were exceeding toxicological reference values for ndl-PCBs (Morales-Suarez-Varela et al. 2018). Therefore, even though PCB levels in fish have been falling over the past few years (Anses 2015), recommendations on fish consumption have to be reminded. Moreover, according to our results and previous ones, a debate should be conducted on the maximum values laid down by the regulations and the choice of matrices to be regulated for both substance families. Special

attention should be given to the youngest age groups due to their special vulnerability and higher exposure.

In terms of health risks, it has also to be reminded that exposures estimated in this study correspond to exposures over a given period of time. On one hand, persistent organic pollutants (POPs), as PCBs and PCDD/Fs can accumulate in the body: thus the dose to which an individual is actually exposed at a given time corresponds not only to the ingested dose but also to the dose present in the body as a result of previous exposure. However, for infants, the body burden due to exposure during the first months of life, in particular through breastfeeding, is limited in time. However, exposure during fetal life, via maternal feeding, can lead to a significant body burden. On the other hand in the case of substances for which infants are not more sensitive than adults and where effects are associated with a long period of exposure, exceedances observed over a limited time period do not necessarily lead to a health risk. In the second French TDS, exceedance was also observed in children and young adults (Sirot et al. 2012). Moreover, based on an integrative risk assessment approach on French contamination data, Béchaux et al. predicted the body burden of the French population in 2030, assuming that the dietary exposure will remain stable at the 2009 level (Bechaux et al. 2014). Therefore, in order to conclude on health risk, it will be of interest to estimate long-life exposure by combining food consumption and data contamination at different life steps as shown in the case of cadmium by Pruvost-Couvreur et al. (Pruvost-Couvreur et al. 2020). This evaluation has been conducted separately for PCB and PCDD/F exposure levels, in view of risk management since sources of pollution for these two groups of substances are different. Even if such approach appears appropriate from a health point of view, the method for risk characterization of cumulated exposure can be discussed: (1) other components having “dioxin-like” mechanism could also be considered such as certain brominated flame retardants and (2) some substances present concomitantly with dioxins and furans can show antagonistic effects that are not taken into account (De Waard et al. 2008). To better assess the risk associated to “dioxin-like” effects as a whole, it would be necessary to conduct toxicity studies on mixture effects.

4. Conclusion and recommendations

Dietary exposure to PCDD/Fs and PCBs was identified as a concern for children above 6 months. Exposure, mainly via common food products making a major contribution to exposure of the most exposed children to these compounds should therefore be reduced, i.e. milk, ultra-fresh dairy products and fish. These data allowed to complete the exposure assessment of French population focusing on a sensitive population and strengthen the recommendations on diversification and fish consumption.

Through their diet, individuals are exposed to a multitude of contaminants from diverse chemical classes. Phenomena of competition, additivity or synergy can occur between several substances, which may lead to the organism responding in an unexpected way with regard to the known toxicological effects for each substance. This question of mixtures cannot be limited solely to a mixture of compounds belonging to the same chemical class. It is therefore necessary to identify mixtures (or "cocktails") of substances that are relevant in health terms and realistic from the point of view of population exposure. Data collected in this study are a real opportunity for identifying the cocktails to which children are actually exposed, and could therefore provide input for studies of the potential associations between these cocktails of substances and the health effects.

377

378 Table 1. Levels PCDD/F, dl-PCB (a) and 6 ndl-PCB (b) in food consumed by French infants and toddlers

379 a.

	N	% detection	Fresh weight								Fat basis							
			LB				UB				LB				UB			
			Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max
	PCDD/F (pg $TEQ_{WHO05}.g^{-1}$)																	
Milk-based beverage	8	77.9	0.001	0.000	0.001	0.002	0.002	0.000	0.002	0.003	0.062	0.013	0.041	0.080	0.102	0.018	0.065	0.119
Cereals-based food	5	64.7	0.002	0.003	0.000	0.006	0.005	0.005	0.001	0.010	0.068	0.059	0.021	0.162	0.219	0.207	0.059	0.480
Milk-based dessert	6	83.3	0.004	0.001	0.002	0.005	0.004	0.001	0.003	0.005	0.146	0.042	0.076	0.199	0.174	0.021	0.150	0.206
Growing-up milk	9	65.4	0.003	0.002	0.001	0.006	0.004	0.002	0.002	0.007	0.150	0.121	0.036	0.358	0.213	0.110	0.095	0.405
Soup, puree	11	88.2	0.002	0.001	0.001	0.003	0.002	0.001	0.001	0.004	0.105	0.031	0.066	0.164	0.139	0.041	0.083	0.204
Fruit purée	4	55.9	0.001	0.000	0.000	0.001	0.002	0.001	0.002	0.003	0.166	0.090	0.062	0.278	0.441	0.200	0.252	0.723
Vegetable-based ready-to-eat meal	20	63.5	0.001	0.001	0.000	0.002	0.002	0.001	0.001	0.004	0.093	0.068	0.034	0.347	0.205	0.096	0.109	0.528
Meat/fish based ready-to-eat meal	45	82.5	0.002	0.004	0.001	0.025	0.003	0.004	0.001	0.025	0.145	0.181	0.041	1.127	0.197	0.195	0.068	1.127
Infant formula	28	82.1	0.001	0.001	0.000	0.004	0.002	0.001	0.001	0.004	0.059	0.046	0.017	0.239	0.088	0.050	0.044	0.239
Follow-on formula	33	89.3	0.002	0.001	0.001	0.005	0.002	0.001	0.001	0.005	0.102	0.058	0.044	0.327	0.122	0.057	0.067	0.328
	dl-PCB (pg $TEQ_{WHO05}.g^{-1}$)																	
Milk-based beverage	8	59.4	0.001	0.000	0.000	0.001	0.001	0.000	0.001	0.001	0.028	0.015	0.002	0.049	0.046	0.010	0.037	0.063
Cereals-based food	5	28.3	0.000	0.000	0.000	0.000	0.002	0.002	0.000	0.005	0.007	0.014	0.000	0.033	0.080	0.059	0.029	0.151
Milk-based dessert	6	87.5	0.008	0.004	0.004	0.013	0.008	0.003	0.005	0.013	0.316	0.109	0.247	0.531	0.321	0.106	0.249	0.531
Growing-up milk	9	92.6	0.004	0.003	0.000	0.008	0.004	0.003	0.001	0.008	0.217	0.207	0.022	0.564	0.219	0.206	0.025	0.564
Soup, puree	11	62.1	0.001	0.001	0.000	0.005	0.002	0.001	0.000	0.005	0.089	0.060	0.029	0.235	0.100	0.058	0.040	0.236
Fruit purée	4	64.6	0.001	0.001	0.001	0.002	0.001	0.001	0.001	0.002	0.181	0.068	0.126	0.274	0.203	0.051	0.156	0.275
Vegetable-based ready-to-eat meal	20	87.5	0.002	0.001	0.000	0.005	0.002	0.001	0.001	0.005	0.149	0.080	0.046	0.413	0.162	0.076	0.077	0.413
Meat/fish based ready-to-eat meal	45	80.4	0.004	0.012	0.000	0.081	0.005	0.012	0.000	0.081	0.235	0.553	0.002	3.641	0.243	0.551	0.020	3.641
Infant formula	28	76.8	0.001	0.001	0.000	0.005	0.001	0.001	0.000	0.005	0.033	0.061	0.001	0.307	0.039	0.061	0.010	0.307
Follow-on formula	33	79.0	0.001	0.002	0.000	0.008	0.001	0.002	0.000	0.008	0.070	0.120	0.012	0.625	0.075	0.118	0.016	0.625

380

381 b.

	N	% detection	Fresh weight				Fat basis			
			Mean	SD	Min	Max	Mean	SD	Min	Max
	6 ndl-PCBs (ng.kg^{-1})									
Milk-based beverage	8	100	5.4	1.8	3.6	8.1	260.7	97.6	160.7	437.6
Cereals-based food	5	100	6.6	8.3	0.8	19.8	277.8	214.0	117.5	602.9
Milk-based dessert	6	100	40.3	25.7	23.1	91.2	1679.3	1001.0	968.1	3687.1
Growing-up milk	9	100	15.2	10.9	3.5	30.1	929.3	827.4	213.9	2450.7
Soup, puree	11	100	12.9	16.8	2.5	60.9	701.8	599.4	309.4	2363.6
Fruit purée	4	100	7.6	3.2	4.6	10.8	1230.2	132.2	1060.9	1384.0
Vegetable-based ready-to-eat meal	20	100	11.6	4.6	3.4	21.4	885.6	409.6	578.2	2373.1
Meat/fish based ready-to-eat meal	45	100	41.5	128.4	2.1	852.7	2149.6	5821.5	197.8	38383.3
Infant formula	28	100	4.5	3.8	1.8	16.6	200.7	193.8	68.5	951.7
Follow-on formula	33	100	8.9	6.8	2.6	31.7	464.1	443.5	104.5	2578.9

382 *N: number of composite samples analysed*

383 *LB: Lower bound hypothesis; UB: Upper bound hypothesis. For the 6 ndl-PCBs, concentrations were equal under the LB and UB hypothesis.*

384

385 Table 2. Exposure levels (LB-UB[1]) to PCDD/Fs, dl-PCBs + PCDD/Fs and 6 ndl-PCBs of children under 3 years of age and percentage of exceedance of the

386 health-based guidance value

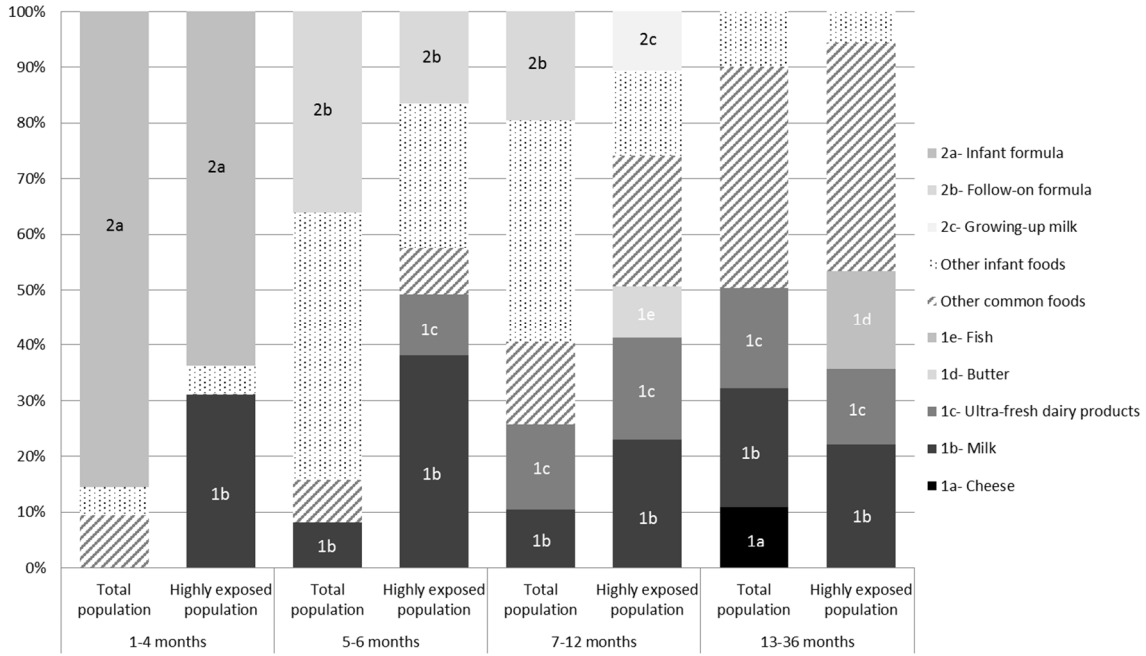
	Mean +/- SD		P90 exposure		% children exceeding the health-based guidance value	
	LB	**UB**	**LB**	**UB**	**LB**	**UB**
PCDD/F	**(pg TEQ_{who05}.kg $bw^{-1}.d^{-1}$)**				**Reference dose = 0.7pg TEQ_{WHO05}.kg $bw^{-1}.d^{-1}$ (USEPA, 2012)**	
1-4 months	0.218 +/-0.117	0.318 +/-0.131	0.400	0.488	NC*	NC*
5-6 months	0.239 +/-0.066	0.292 +/-0.071	0.410	0.454	0	NC*
7-12 months	0.288 +/-0.121	0.347 +/-0.136	0.491	0.574	4.5 [0.7 ; 8.2]	4.5 [0.7 ; 8.2]
13-36 months	0.383 +/-0.239	0.444 +/-0.254	0.579	0.651	5.1 [3.1 ; 7.0]	7.4 [5.0 ; 9.7]
dl-PCB + PCDD/F	**(pg TEQ WHO_{who05}.kg $bw^{-1}.d^{-1}$)**				**Reference dose = 0.3 pg $_{WHO05}$.kg $bw^{-1}.d^{-1}$ (EFSA, 2018)**	
1-4 months	0.366 +/-0.356	0.484 +/-0.378	0.600	0.69	48.9 [37.9 ; 60.0]	82.9 [74.6 ; 91.3]
5-6 months	0.458 +/-0.325	0.524 +/-0.336	1.00	1.04	64.9 [50.0 ; 79.7]	82.7 [70.9 ; 94.4]
7-12 months	0.675 +/-0.477	0.747 +/-0.499	1.18	1.32	84.0 [77.3 ; 90.6]	92.6 [87.8 ; 97.3]
13-36 months	0.989 +/-0.529	1.067 +/-0.540	1.52	1.61	99.2 [98.4 ; 100.0]	99.6 [99.1 ; 100.0]
6 ndl-PCB	**(ng.kg $bw^{-1}.d^{-1}$)**				**TDI = 10 ng.kg $bw^{-1}.d^{-1}$ (AFSSA, 2007)**	
1-4 months	0.874 +/-0.861		1.55		-	
5-6 months	1.40 +/-0.550		2.77		-	
7-12 months	2.28 +/-1.99		3.74		NC*	
13-36 months	3.53 +/-4.13		5.45		2.7 [1.2 ; 4.2]	

387 *Mean +/- SD correspond to the mean of exposure and associated standard deviation. [] correspond to the 95% confidence interval.*

[1] LB= Lower bound – UB = Upper bound

LB: Lower bound hypothesis; UB: Upper bound hypothesis * NC: not calculated as less than 5 children exceeded the HBGV Table 3. Contributions under LB hypothesis (expressed as %)[2] of the main food groups to the mean exposure (total population) and 90th percentile (highly exposed population) exposure for PCDD/F (3a), dl-PCB + PCDD/F (3b) and 6 ndl-PCBs (3c)

3a. *Contribution to PCDD/F exposure*



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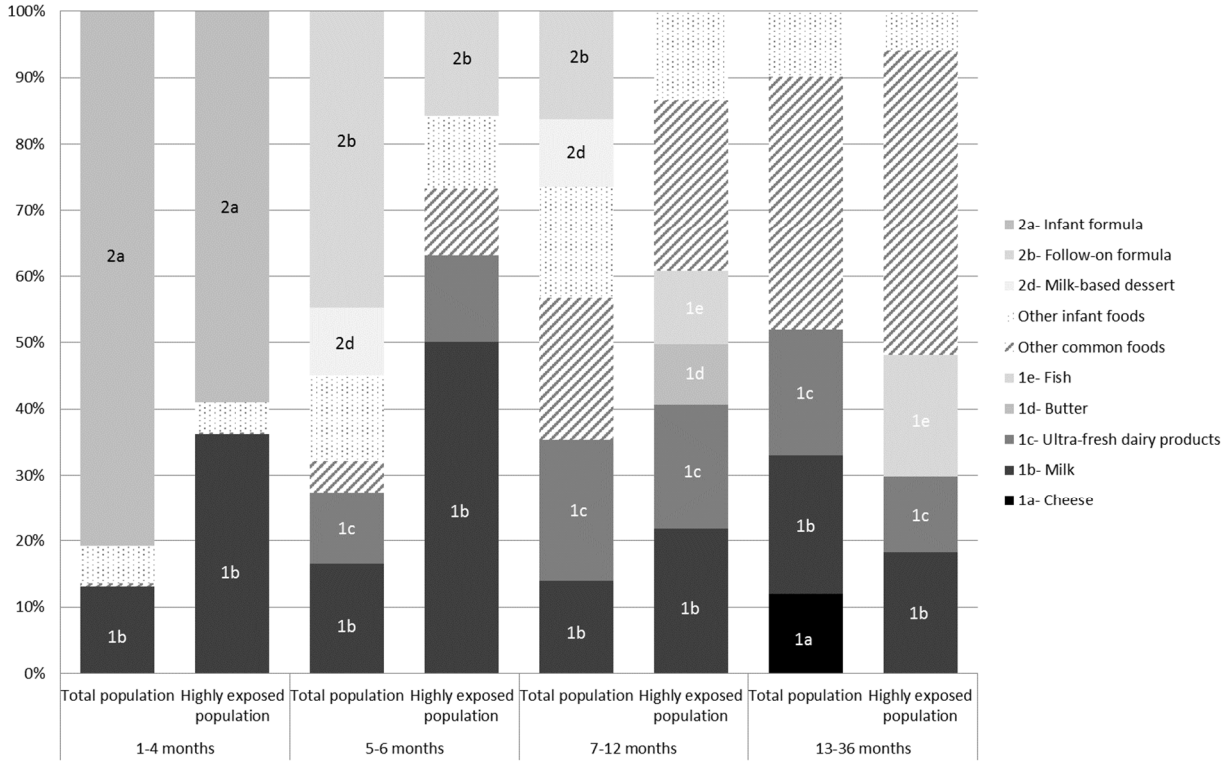
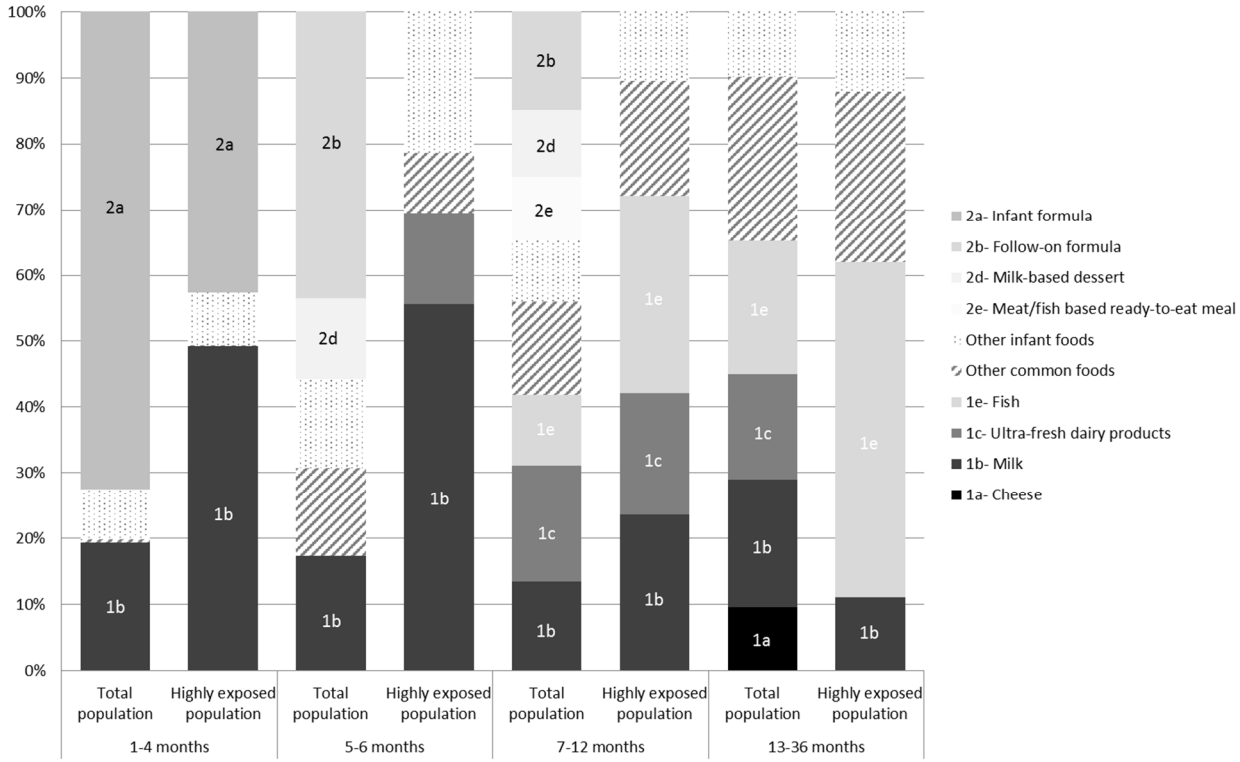
[2] In this table a "." signify that the contribution of the food groups for the related age groups has not been considered as any product consumed has been analyzed (low consumption rate and not a major contributors)

394 3b. *Contribution to dl-PCB + PCDD/F exposure*



395

396 3c. *Contribution to 6 ndl-PCB exposure*



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398

399 *Only food groups contributing to more than 10% are represented individually*

400 Table 4. Total exposure levels (LB) to PCDD/Fs and 6 ndl-PCBs of children under 1 year according to the type of milk consumed, common cow milk (C), infant

401 formulae (IA) and the regimen

402

	1-4 months		5-6 months			7-12 months		
Type of milk consumed	C	IA	C	C+IA	IA	C	C+IA	IA
N (%)	3 (2.4%)	121 (97.6%)	11 (8.7%)	9 (7.1%)	107 (84.2%)	107 (84.2%)	17 (8.7%)	156 (80%)
Exposure to PCDD/Fs (pgTEQ $_{WHO05}$.kg bw^{-1}.d^{-1})	0.74	0.20	0.43^{a}	0.29^{b}	0.21^{c}	0.46^{a}	0.31^{b}	0.25^{c}
Exposure to PCDD/Fs+dl-PCBs (pgTEQ $_{WHO05}$.kg bw^{-1}.d^{-1})	1.76	0.33	1.09^{a}	0.62^{b}	0.37^{c}	1.19^{a}	0.73^{a}	0.57^{a}
Exposure to PCBs ? 6 ndl-PCBs? (ng.kg bw^{-1}.d^{-1})	6.16	0.72	3.45^{a}	1.77^{b}	1.14^{c,}	3.87^{a}	2.37^{a}	1.98^{b}

403 a,b,c: on a same line between the different types of consumers, and separately for the age groups, the values with a different index letter are significantly

404 different $p<0.05$ (Student test). Due to small sample size, statistical comparison has not been performed for 1-4 months.

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