



HAL
open science

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

Marion Hulin, Véronique Sirot, Paule Vasseur, Aurelie Mahe, Jean-Charles Leblanc, Julien Jean, Philippe Marchand, Anaïs Venisseau, Bruno Le Bizec, Gilles Rivière

► To cite this version:

Marion Hulin, Véronique Sirot, Paule Vasseur, Aurelie Mahe, Jean-Charles Leblanc, et al.. Health risk assessment to dioxins, furans and PCBs in young children: The first French evaluation. Food and Chemical Toxicology, 2020, 139, pp.111292. 10.1016/j.fct.2020.111292. hal-03185155

HAL Id: hal-03185155

<https://hal.inrae.fr/hal-03185155>

Submitted on 22 Aug 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

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

Marion HULIN^a, Véronique SIROT^a, Paule VASSEUR^b, Aurelie MAHE^a, Jean-Charles LEBLANC^a, Julien JEAN^b, Philippe MARCHAND^c, Anaïs VENISSEAU^c, Bruno LE BIZEC^c, Gilles RIVIERE^{a,*}

^a ANSES, Risk Assessment Department (DER), 14 rue Pierre et Marie Curie, F-94701 Maisons-Alfort, France

^b CNRS UMR 7360, University of Lorraine, F-57070 Metz, France

^c LABERCA, Oniris, INRA, F-44300 Nantes, France

Corresponding author:

Gilles RIVIERE, Risk Assessment Department (DER), French Agency for Food, Environmental and Occupational Health & Safety (ANSES), 14 rue Pierre et Marie Curie, 94701 Maisons-Alfort, France – gilles.riviere@anses.fr

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 90th 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 90th percentile) in the 1-4 months old children to 3.53 ng.kg bw⁻¹.d⁻¹ (5.44 at the 90th 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](#)

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

29 The international agency for research on cancer (IARC) classified PCBs as carcinogenic to humans in
30 2013, so as TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) already classified in 1997. Adverse non-
31 cancer effects associated with oral TCDD exposure include hepatic, neurological, immunological,
32 reproductive, endocrine, and developmental effects. In the offspring of rat, effects on
33 reproduction and development as well as immunological effects were observed after administration
34 of TCDD (Seveso dioxin). The main mechanism of action of TCDD and dioxin-like compounds such as
35 PCDDs, PCDFs, and dl-PCBs, is their binding to the Ah receptor (EFSA 2018). Exposure of infants to
36 PCBs and PCDD/Fs which are neurodevelopmental toxicants is therefore a concern.

37 Due to a number of regulatory measures since the 1980s, the emission of dioxins into the
38 environment and, consequently, human exposure to dioxins, have decreased significantly (Aylward
39 and Hays 2002, EFSA 2018). However, due to their high persistence and bioaccumulation and their
40 toxic potential, dietary dioxins and PCB exposure can be of concern. Different studies and evaluations
41 showed a general decrease in dietary exposure of the European population to dioxins and PCBs since
42 the 2000's. However, exceedance of the reference values was still observed, toddlers and other
43 children being the most exposed groups. In 2012, Sirot et al. concluded that less than 4% of the
44 French population exceeded the health-based guidance value (HBGV) for PCDD/F+dl-PCBs set by
45 JECFA in 2001. For total PCB, it was estimated that 2.6 and 6.5% of, respectively, French adults and
46 French children exceeded the health based guidance value set by Afssa in 2007 (Afssa 2007, Sirot et
47 al. 2012). However this study did not take into account children under 3 years old. This population is
48 known for being more susceptible to contaminants (Landrigan et al. 2003), especially during the
49 prenatal and postnatal period (Makri et al. 2004, Sly and Flack 2008, Diamanti Kandarakis et al.
50 2009). Moreover, they consume more food than adults in proportion to their body weight. As a

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

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

63

64 **2. Material and methods**

65 2.1. Consumption data and sample collection

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

77 The sampling plan has already been described (Hulin et al. 2014). Briefly, on the basis of the
78 consumption survey, the most consumed foods by the children in terms of quantity and/or consumer
79 rates were selected. In addition, some foods known to contribute significantly to the exposure to one
80 of the chemicals of interest were added to the list. Foods were sampled between July 2011 and July
81 2012. For each food item identified, 12 subsamples of equal weight were analysed: every month, one
82 subsample of each food item was bought and prepared “as consumed”, according to the results of a
83 specific on-line survey on food preparation (Hulin et al. 2014). After collection, the 12 subsamples
84 have been grouped, homogenized and frozen (-18°C) prior to analysis. In total, 5 484 food products
85 were purchased to produce 457 composite samples. Selected food items covered more than 97% of
86 the children diet.

87

88 2.2. Sample analyses

89 Among the 457 food samples, PCBs and PCDD/Fs were only analyzed in food items known or
90 supposed to contain PCDD/Fs and PCBs and for which data were not available in our previous study
91 (Sirot et al. 2012). In total, PCBs and PCDD/Fs concentrations were measured in 178 samples: 169
92 infant foods, i.e. products commercialized especially for infant and young children, and 9 common
93 foods. LABERCA, that is the French Reference Laboratory for dioxin and PCB analysis in food,
94 performed the analyses of the
95 samples using method already described elsewhere (Antignac et al. 2006, Costera et al. 2006).

96

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

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

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

110 After removal of fat on a silica gel column loaded with sulfuric acid, PCBs were separated from
111 PCDD/Fs by means of a Florisil® column. The PCDD/F fraction was further cleaned up onto a column
112 consisting of a mixture of Carbopack™ C/Celite® 545. Separation of coplanar (nonortho) PCBs from
113 non-planar PCBs was achieved on an activated mixture of Florisil®/Carbopack™ C/Celite® 545
114 (overnight at 130°C). After addition of external standards for the recovery calculation (¹³C₁₂-1,2,3,4-
115 TCDD for the PCDD/Fs, ¹³C₁₂-PCB111 for the PCBs), the final extract was reconstituted by addition of
116 toluene in the 3 fractions.

117 Chromatographic separation of PCDD/F congeners was carried out on a DB-5MS column
118 (60 m × 0.25 mm i.d., 0.25 µm film thickness; Agilent Technologies, USA), while for PCBs a HT8-PCB
119 column (60 m × 0.25 mm i.d., 0.25 µm film thickness; SGE Analytical Science, UK) was used. PCDD/Fs
120 and PCBs were quantified by gas chromatography (7890A; Agilent Technologies, USA) coupled to
121 high-resolution mass spectrometry (double sector, JMS-700D and 800D; Jeol, Japan).

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

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

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

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

139

140 2.3. Contamination data, exposure calculation and risk assessment

141 In order to evaluate the risk associated with exposure to PCDD/Fs, World Health Organization toxic
142 equivalency factors (WHO TEF) were used to express exposure in the toxic equivalents (TEQs) (Afssa
143 2005)Therefore, for PCDD/Fs, the sum of the 17 congeners (2.3.7.8 - TCDD, 1.2.3.7.8 - PeCDD,
144 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 -
145 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 -
146 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
147 multiplying the analytical concentration of each congener by their individual TEFs (Van den Berg et al.
148 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).

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

$$175 \quad E_{i,j} = \frac{\sum_{k=1}^n C_{i,k} \times L_{k,j}}{BW_i}$$

176

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

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

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

188 The health risk associated with the dietary exposure to each chemical has been assessed by
189 calculating, for each age group, the percentage of children over the health-based guidance value and
190 its 95% confidence interval (CI_{95%}). PCDD/Fs and PCBs have been evaluated separately in this study in
191 order to facilitate the implementation of management measures as sources of each compound's
192 family are different. Additionally, exposure to the sum of PCDDs, PCDFs and dl-PCBs was estimated to
193 make it possible to compare this exposure with the health-based guidance value set by Efsa in 2018
194 (EFSA 2018). For PCDD/Fs, the toxicological reference value of US-EPA (US-EPA 2012) of 0.7 pg
195 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
196 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-](https://www.data.gouv.fr/fr/datasets/donnees-etude-de-lalimentation-totale-infantile/)
222 [lalimentation-totale-infantile/](https://www.data.gouv.fr/fr/datasets/donnees-etude-de-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

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

243 Our results on PCDD/Fs and dl-PCBs were in the same range as those observed in previous studies
244 (Pandelova et al. 2011, EFSA 2012, De Filippis et al. 2014). In an European study (Pandelova et al.
245 2011), the authors estimated that non breast-fed children under 9 months were exposed at levels
246 between 0.14 and $2.79 \text{ pg TEQ}_{\text{WHO05}}.\text{kg bw}^{-1}.\text{d}^{-1}$ depending on the age and the type of infant formula
247 they consumed (milk, soy or hypoallergenic). However, for the 6 ndl-PCBs, concentrations of infant
248 and baby foods with fish or meat were higher than ours ($10\,900 \text{ ng.kg}^{-1}$ on fat basis for the mean and
249 $17\,300 \text{ ng.kg}^{-1}$ for the p99) as well as exposure (between 8.5 and $25.7 \text{ ng.kg bw}^{-1}.\text{d}^{-1}$ under UB and up
250 to $53.5 \text{ ng.kg bw}^{-1}.\text{d}^{-1}$ for the most exposed children) (EFSA 2012). This can be explained either by a
251 difference of contamination of fish and meat or of the quantity of these ingredients in food
252 composition. Concerning infant formulae, our results were in the same order of magnitude as some
253 found in previous studies for both contaminant families (Loran et al. 2009, Pandelova et al. 2011).
254 Due to a decreasing food consumption in proportion to body weight with ages, we expected to have
255 higher exposure levels in young children compared to older ones. However, exposure in 1-4 months
256 children was lower than 13-16 months ones. Moreover, 13-36 months children were exposed in the

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

264 The data used for exposure assessment covered 68% of the total diet and 96% of the diet
265 theoretically contributing to the exposure. That means that 96% of foods consumed by children and
266 known to contribute to PCDD/Fs and PCBs exposure have been taken into account in the exposure
267 estimation. This estimation is therefore a good representation of young children dietary exposure.
268 However, this study did not take into account breastfed children and breastmilk is known to be more
269 contaminated than infant formulae. Data on European countries as analysed in the frame of WHO
270 coordinated studies showed concentration of PCDD/F between 2.40 and 15.9 pg TEQ_{WHO05}.g⁻¹ on fat
271 basis (EFSA 2018) whereas we found concentration of 0.059 and 0.0102 pg TEQ_{WHO05}.g⁻¹ for
272 respectively infant and follow-up formulae. Therefore, it would be important to have a global view on
273 exposure of young children to take into account PCDD/Fs and PCBs burden in breastmilk and to
274 consider the risk/benefit of breastfeeding. However, data on consumption and contamination of
275 human milk is indeed very difficult to obtain. In France, the breastfeeding rate is quite low compared
276 to other OECD countries (OECD 2012): only two out of three newborns are breastfed immediately
277 after birth and only 42% of these infants are still breastfed at the end of the 4th month (Bonet et al.
278 2013). However, it is now recognised that some contaminants, especially persistent organic
279 pollutants, are found in high concentrations in human milk and lead to a potential risk for newborns
280 (EFSA 2011, Ulaszewska et al. 2011). Therefore, collecting data on breast milk contamination in
281 France would be valuable for estimating exposure in this particular population.

282

283 3.2. Risk assessment

284 Based on exposure assessment, the percentages of children exceeding the health-based guidance
285 value (HBGV) were estimated (Table 2). In children over seven months of age, the TDI proposed by
286 the US EPA in 2012 for PCDD/Fs (i.e. $0.7 \text{ pg.kg bw}^{-1}.\text{d}^{-1}$) was observed to be significantly exceeded by
287 4.5% of children from 7 to 12 months, and by 5.1 to 7.4% in the 13-36 months old children,
288 depending on the hypothesis of management of the censored data (LB-UB). In children under six
289 months of age, it was not possible to precisely estimate the percentage of exceedance, as less than 5
290 children exceeded the HBGV, and they were considered as non-representative cases. The cases of
291 exceedance of HBGV were mainly explained by higher consumption of common milk (or cow milk,
292 the single main contributor in children under six months), fish and ultra-fresh dairy products, than in
293 consumers as a whole. When comparing our results on PCDD/F + dl-PCBs with the recent TWI offset
294 by EFSA (EFSA 2018), between 48.9% and 99.6% of children exceed the HBGV according to age
295 groups and the censorship hypothesis.

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

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

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

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

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

335 In terms of health risks, it has also to be reminded that exposures estimated in this study correspond
336 to exposures over a given period of time. On one hand, persistent organic pollutants (POPs), as PCBs
337 and PCDD/Fs can accumulate in the body: thus the dose to which an individual is actually exposed at
338 a given time corresponds not only to the ingested dose but also to the dose present in the body as a
339 result of previous exposure. However, for infants, the body burden due to exposure during the first
340 months of life, in particular through breastfeeding, is limited in time. However, exposure during fetal
341 life, via maternal feeding, can lead to a significant body burden. On the other hand in the case of
342 substances for which infants are not more sensitive than adults and where effects are associated
343 with a long period of exposure, exceedances observed over a limited time period do not necessarily
344 lead to a health risk. In the second French TDS, exceedance was also observed in children and young
345 adults (Sirot et al. 2012). Moreover, based on an integrative risk assessment approach on French
346 contamination data, Béchaux et al. predicted the body burden of the French population in 2030,
347 assuming that the dietary exposure will remain stable at the 2009 level (Bechaux et al. 2014).
348 Therefore, in order to conclude on health risk, it will be of interest to estimate long-life exposure by
349 combining food consumption and data contamination at different life steps as shown in the case of
350 cadmium by Pruvost-Couvreur et al. (Pruvost-Couvreur et al. 2020). This evaluation has been
351 conducted separately for PCB and PCDD/F exposure levels, in view of risk management since sources
352 of pollution for these two groups of substances are different. Even if such approach appears
353 appropriate from a health point of view, the method for risk characterization of cumulated exposure
354 can be discussed: (1) other components having “dioxin-like” mechanism could also be considered
355 such as certain brominated flame retardants and (2) some substances present concomitantly with
356 dioxins and furans can show antagonistic effects that are not taken into account (De Waard et al.
357 2008). To better assess the risk associated to “dioxin-like” effects as a whole, it would be necessary
358 to conduct toxicity studies on mixture effects.

359 **4. Conclusion and recommendations**

360 Dietary exposure to PCDD/Fs and PCBs was identified as a concern for children above 6 months.

361 Exposure, mainly via common food products making a major contribution to exposure of the most
362 exposed children to these compounds should therefore be reduced, i.e. milk, ultra-fresh dairy
363 products and fish. These data allowed to complete the exposure assessment of French population
364 focusing on a sensitive population and strengthen the recommendations on diversification and fish
365 consumption.

366

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

376

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

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-UB¹) 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

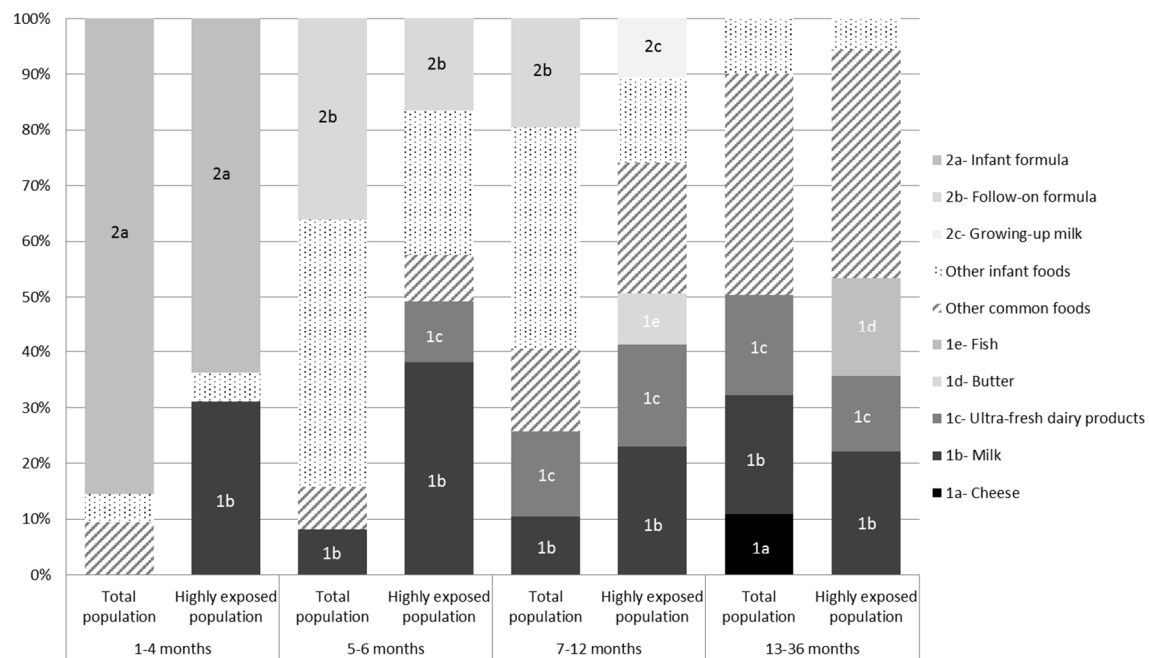
	Mean +/- SD		P90 exposure		% children exceeding the health-based guidance value	
	LB	UB	LB	UB	LB	UB
PCDD/F	(pg TEQ_{WHO05}.kg bw⁻¹.d⁻¹)				Reference dose = 0.7pg TEQ_{WHO05}.kg bw⁻¹.d⁻¹ (USEPA, 2012)	
1-4 months	0.218 +/-0.117	0.318 +/-0.131	0.400	0.488	NC*	NC*
5-6 months	0.239 +/-0.066	0.292 +/-0.071	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 WHO_{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

388 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
 389 (expressed as %)² of the main food groups to the mean exposure (total population) and 90th percentile (highly exposed population) exposure for PCDD/F
 390 (3a), dl-PCB + PCDD/F (3b) and 6 ndl-PCBs (3c)

391 3a. Contribution to PCDD/F exposure

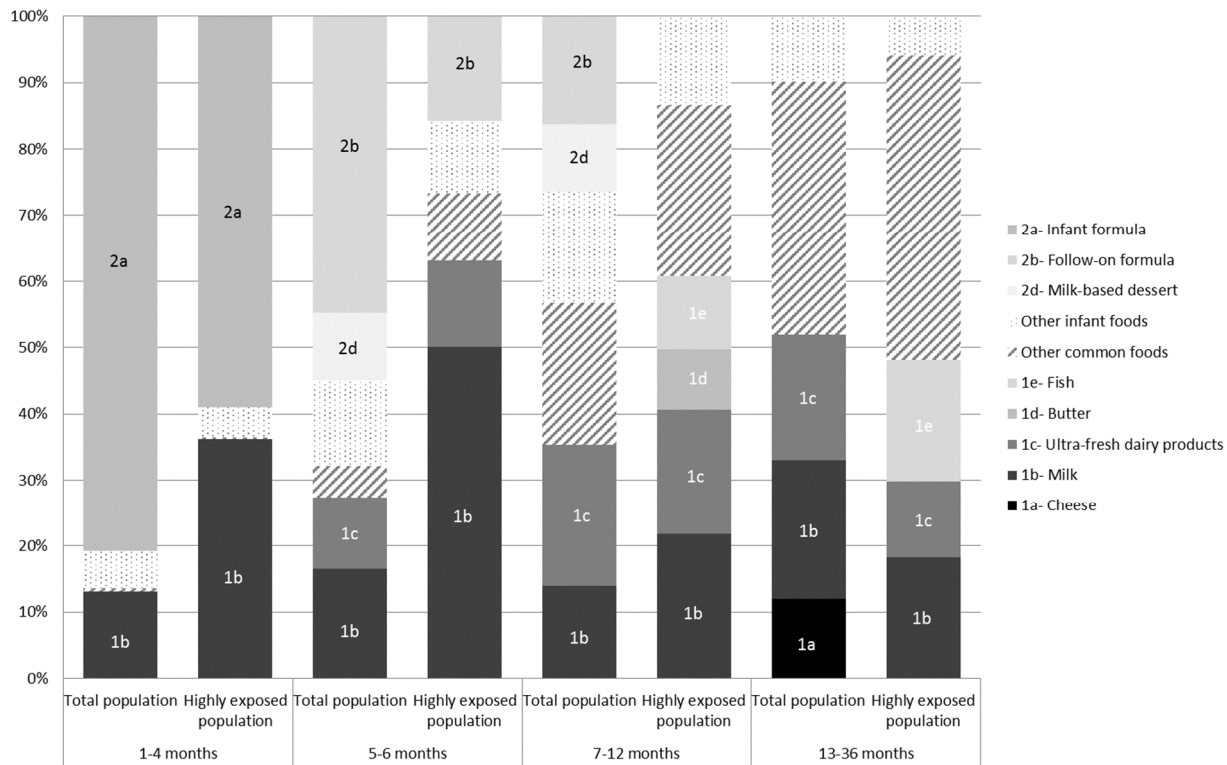


392 .

393

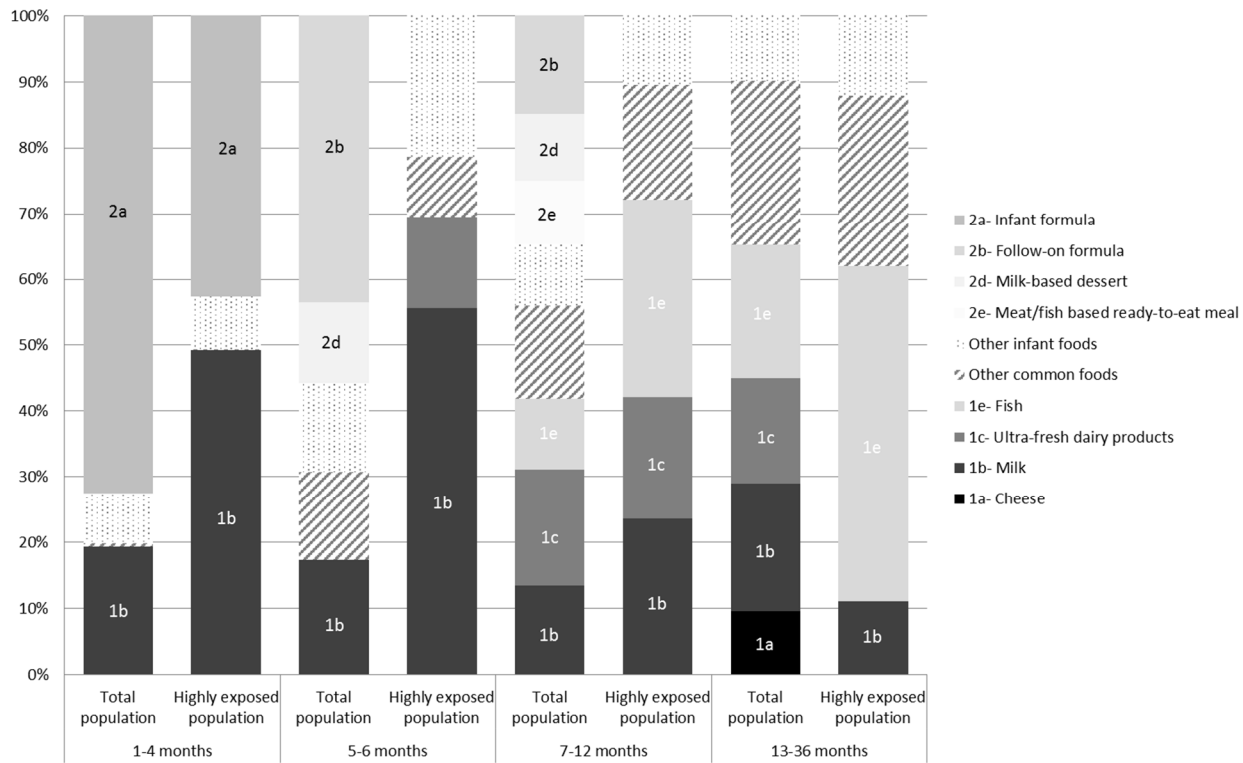
² In this table a “.” signify that the contribution of the food groups for the related age groups has not been considered as any product consumed has been analyzed (low consumption rate and not a major contributors)

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



395

396 3c. Contribution to 6 ndl-PCB exposure



397

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.

405 **Acknowledgments**

406 The authors are grateful to the Anses expert committee panel in charge of assessing the chemical risk
407 in food and the experts from the infant TDS scientific committee and the analytic methods in food,
408 namely: Jean-Pierre Cravédi, Claude Atgié, Pierre-Marie Badot, Jacques Bélégaud, Catherine
409 Bennetau-Pelissero, Emmanuelle Bichon, Valérie Camel, Martine Claw, Christophe Cordella,
410 Guillaume Duflos, Camille Dumat, Cyril Feidt, Jean-Marc Fremy, Jérôme Gay-Queheillard, Philippe
411 Glorennec, Konrad Grob, Thierry Guérin, Laurence Guldner, Nicole Hagen–Picard, Dary Inthavong,
412 Florence Lacoste, Laïla Lakhal, Béatrice Lalère, Claude Lambré, Michel, Laurentie, Raphaëlle Le
413 Garrec, Catherine Leclercq, Eric Marchioni, César Mattéi, André Mazur, Sakina Mhaouty-Kodja,
414 Fabrice Nesslany, Laurent Noel, Alain-Claude Roudot, Patrick Sauvegrain, Rémy Slama, Karine Tack,
415 Eric Verdon and Jean-Paul Vernoux.

416 The infant TDS was supported by the Ministry for food, agriculture and fisheries, the Ministry for
417 health the Ministry for ecology and sustainable development and the French Agency for Food,
418 Environmental and Occupational Health & Safety (ANSES).

419

420

421 **References**

422

423

- 424 Afssa (2005). Rapport de l'Afssa relatif aux dioxines, furanes et PCB de type dioxine : Evaluation de
425 l'exposition de la population française. Maisons-Alfort, France, Afssa: 57 p.
- 426 Afssa (2007). Avis de l'Afssa relatif à l'établissement de teneurs maximales pertinentes en
427 polychlorobiphényles qui ne sont pas de type dioxine (PCB "non dioxin-like", PCB-NDL) dans divers
428 aliments. (saisine n°2006-SA-0305). Maisons-Alfort, Afssa: 28 p.
- 429 Anses (2015). Avis de l'Anses et rapport d'expertise collective relatifs à la consommation de poissons
430 d'eau douce et PCB : aspects réglementaires, méthodologiques et sanitaires. (saisines n°2014-SA-
431 0122 et 2011-SA-0039). Maisons-Alfort, Anses: 107 p.
- 432 Antignac, J. P., P. Marchand, C. Gade, G. Matayron, M. Qannari el, B. Le Bizec and F. Andre (2006).
433 "Studying variations in the PCDD/PCDF profile across various food products using multivariate
434 statistical analysis." *Anal Bioanal Chem* **384**(1): 271-279.
- 435 Aylward, L. L. and S. M. Hays (2002). "Temporal trends in human TCDD body burden: decreases over
436 three decades and implications for exposure levels." *J Expo Anal Environ Epidemiol* **12**(5): 319-328.
- 437 Bechaux, C., M. Zeilmaker, M. Merlo, B. Bokkers and A. Crepet (2014). "An integrative risk
438 assessment approach for persistent chemicals: a case study on dioxins, furans and dioxin-like PCBs in
439 France." *Regul Toxicol Pharmacol* **70**(1): 261-269.
- 440 Berta Vanrullen, I., J. L. Volatier, A. Bertaut, A. Dufour and J. Dallongeville (2014). "Characteristics of
441 energy intake under-reporting in French adults." *Br J Nutr* **111**(7): 1292-1302.
- 442 Bonet, M., L. Marchand, M. Kaminski, A. Fohran, A. Betoko, M. A. Charles and B. Blondel (2013).
443 "Breastfeeding duration, social and occupational characteristics of mothers in the French 'EDEN
444 mother-child' cohort." *Matern Child Health J* **17**(4): 714-722.
- 445 Bramwell, L., D. Mortimer, M. Rose, A. Fernandes, S. Harrad and T. Pless-Mulloli (2017). "UK dietary
446 exposure to PCDD/Fs, PCBs, PBDD/Fs, PBBs and PBDEs: comparison of results from 24-h duplicate
447 diets and total diet studies." *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* **34**(1): 65-
448 77.
- 449 Costera, A., C. Feidt, P. Marchand, B. Le Bizec and G. Rychen (2006). "PCDD/F and PCB transfer to
450 milk in goats exposed to a long-term intake of contaminated hay." *Chemosphere* **64**(4): 650-657.
- 451 De Filippis, S. P., G. Brambilla, E. Dellatte, F. Corrado and M. Esposito (2014). "Exposure to
452 polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), dioxin-like
453 polychlorinated biphenyls (DL-PCBs) and polybrominated diphenyl ethers (PBDEs) through the
454 consumption of prepared meals in Italy." *Food Addit Contam Part A Chem Anal Control Expo Risk
455 Assess* **31**(6): 1114-1126.
- 456 De Waard, W. J., J. Aarts, A. Peijnenburg, T. M. De Kok, F.-J. Van Schooten and L. Hoogenboom
457 (2008). "Ah receptor agonist activity in frequently consumed food items." *Food Additives and
458 Contaminants* **25**(6): 779-787.
- 459 Diamanti Kandarakis, E., J. P. Bourguignon, L. C. Guidice, R. Huauser, G. S. Prins, A. M. Soto, T. Zoeller
460 and A. C. Gore (2009). "Endocrine-disrupting chemicals: an endocrine society scientific statement."
461 *Endocrine reviews* **30**(4): 293-342.
- 462 EFSA (2005). Opinion of the Scientific Panel on Contaminants in the Food Chain on a request from the
463 Commission related to the presence of non dioxin-like polychlorinated bisphenyls (PCB) in feed and
464 food. *The EFSA journal*. Parma, EFSA. **284**.
- 465 EFSA (2010). Results of the monitoring of dioxin levels in food and feed. *EFSA Scientific report*.
466 Parma, EFSA. **8**.

467 EFSA (2011). Scientific Opinion on Polybrominated Diphenyl Ethers (PBDEs) in Food. EFSA Panel on
468 Contaminants in the Food Chain (CONTAM). Parma, Italy, EFSA.

469 EFSA (2012). Scientific Opinion of the EFSA panel on Contaminants in the Food Chain on the presence
470 of dioxins (PCDD/Fs) and dioxin-like PCBs (DL-PCBs) in commercially available foods for infants and
471 young children. The EFSA journal. Parma, EFSA. **10**.

472 EFSA (2014). Guidance on the EU Menu Methodology. . The EFSA journal. Parma, EFSA. **12**: 3944.

473 EFSA (2018). Scientific opinion of the EFSA panel on risk for animal and human health related to the
474 presence of dioxins and dioxin-like PCBs in feed and food. The EFSA journal. Parma, EFSA. **16**.

475 EFSA, FAO and WHO (2011). Joint guidance of EFSA, FAO, WHO. Towards a harmonised Total Diet
476 Study approach: a guidance document. The EFSA journal. Parma, Rome, Geneva, EFSA, FAO, WHO. **9**.

477 Fantino, M. (2005). "[Etude SFAE sur la consommation alimentaire des nourrissons et enfants en bas
478 âge français de 1 mois à 36 mois - Analyse des données nutritionnelles (non publié)]."

479 Fantino, M. and E. Gourmet (2008). "Apports nutritionnels en France en 2005 chez les enfants non
480 allaités âgés de moins de 36 mois." Arch Pediatr **15**(4): 446-455.

481 GEMS/Food-EURO. (2013). ADDENDUM 2013 - Second Workshop on Reliable Evaluation of Low-Level
482 Contamination of Food. Workshop in the frame of GEMS/Food-EURO. Technical report. Kulmbach,
483 Germany, WHO.

484 Hulin, M., N. Bemrah, A. Nougadère, J. L. Volatier, V. Sirot and J. C. Leblanc (2014). "Assessment of
485 infant exposure to food chemicals: the French Total Diet Study design." Food Addit Contam Part A
486 Chem Anal Control Expo Risk Assess **31**(7): 1226-1239.

487 Karjalainen, A. K., T. Hirvonen, H. Kiviranta, H. Sinkko, C. Kronberg-Kippila, S. M. Virtanen, A.
488 Hallikainen, O. Leino, M. Knip, R. Veijola, O. Simell and J. T. Tuomisto (2012). "Long-term daily intake
489 estimates of polychlorinated dibenzo-p-dioxins and furans, polychlorinated biphenyls and
490 polybrominated diphenylethers from food in Finnish children: risk assessment implications." Food
491 Addit Contam Part A Chem Anal Control Expo Risk Assess **29**(9): 1475-1488.

492 Klocke, C. and P. J. Lein (2020). "Evidence Implicating Non-Dioxin-Like Congeners as the Key
493 Mediators of Polychlorinated Biphenyl (PCB) Developmental Neurotoxicity." Int J Mol Sci **21**(3).

494 Landrigan, P. J., C. A. Kimmel, A. Correa and B. Eskenazi (2003). "Children's Health and the
495 Environment: Public Health Issues and Challenges for Risk Assessment." Environ Health Perspect
496 **12**(2): 257-265.

497 Lioret, S., M. Touvier, M. Balin, I. Huybrechts, C. Dubuisson, A. Dufour, M. Bertin, B. Maire and L.
498 Lafay (2011). "Characteristics of energy under-reporting in children and adolescents." Br J Nutr
499 **105**(11): 1671-1680.

500 Loran, S., P. Conchello, S. Bayarri and A. Herrera (2009). "Evaluation of daily intake of PCDD/Fs and
501 indicator PCBs in formula-fed Spanish children." Food Addit Contam Part A Chem Anal Control Expo
502 Risk Assess **26**(10): 1421-1431.

503 Makri, A., M. Goveia, J. Balbus and R. Parkin (2004). "Children's susceptibility to chemicals: a review
504 by developmental stage." J Toxicol Environ Health B Crit Rev **7**(6): 417-435.

505 Malisch, R. and A. Kotz (2014). "Dioxins and PCBs in feed and food--review from European
506 perspective." Sci Total Environ **491-492**: 2-10.

507 Mancini, F. R., V. Sirot, L. Busani, J. L. Volatier and M. Hulin (2015). "Use and impact of usual intake
508 models on dietary exposure estimate and risk assessment of chemical substances: a practical
509 example for cadmium, acrylamide and sulphites." Food Addit Contam Part A Chem Anal Control Expo
510 Risk Assess **32**(7): 1065-1074.

511 Marchand, P., J. P. Antignac, A. Brosseau, C. Gade, A. Venisseau, M.-R. Sabatie, V. Sirot, A. Tard, J. L.
512 Volatier, J. C. Leblanc, F. André and B. Le Bizec (2006). "Factors (trophic levels, fish specie, habitat, fat
513 content...) influencing PCDD/F, PCB and PBDE concentration in fish retailed in France."
514 Organohalogen Compounds **68**: 608-611.

515 Morales-Suarez-Varela, M., N. Lopez Santana, P. Marti Requena, M. I. Beser Santos, I. Peraita-Costa
516 and A. Llopis-Gonzalez (2018). "Estimation of daily intake of polychlorinated biphenyls not similar to
517 dioxins (NDL-PCB) from fish consumption in Spain in different population groups." Public Health Nutr
518 **21**(16): 2959-2968.

519 OECD (2012). OECD Family Database. C01.5 : Breastfeeding rates. OECD. Paris.
520 Pandelova, M., R. Piccinelli, W. L. Lopez, B. Henkelmann, J. M. Molina-Molina, J. P. Arrebola, N. Olea,
521 C. Leclercq and K. W. Schramm (2011). "Assessment of PCDD/F, PCB, OCP and BPA dietary exposure
522 of non-breast-fed European infants." Food Addit Contam Part A Chem Anal Control Expo Risk Assess
523 **28**(8): 1110-1122.
524 Pruvost-Couvreur, M., B. Le Bizec, C. Bechaux and G. Riviere (2020). "A method to assess lifetime
525 dietary risk: Example of cadmium exposure." Food Chem Toxicol **137**: 111130.
526 Sagiv, S. K., S. W. Thurston, D. C. Bellinger, P. E. Tolbert, L. M. Altshul and S. A. Korrick (2010).
527 "Prenatal organochlorine exposure and behaviors associated with attention deficit hyperactivity
528 disorder in school-aged children." Am J Epidemiol **171**(5): 593-601.
529 Sirot, V., A. Tard, A. Venisseau, A. Brosseau, P. Marchand, B. Le Bizec and J. C. Leblanc (2012).
530 "Dietary exposure to polychlorinated dibenzo-p-dioxins, polychlorinated dibenzofurans and
531 polychlorinated biphenyls of the French population: Results of the second French Total Diet Study."
532 Chemosphere **88**(4): 492-500.
533 Sly, P. D. and F. Flack (2008). "Susceptibility of children to environmental pollutants." Ann N Y Acad
534 Sci **1140**: 163-183.
535 Ulaszewska, M. M., E. Zuccato and E. Davoli (2011). "PCDD/Fs and dioxin-like PCBs in human milk and
536 estimation of infants' daily intake: a review." Chemosphere **83**(6): 774-782.
537 US-EPA (2012). EPA's reanalysis of key issues related to dioxin toxicity and response to NAS
538 comments. Rome. Italy. **1. EPA/600/R-10/038F**.
539 Van den Berg, M., L. S. Birnbaum, M. Denison, M. De Vito, W. Farland, M. Feeley, H. Fiedler, H.
540 Hakansson, A. Hanberg, L. Haws, M. Rose, S. Safe, D. Schrenk, C. Tohyama, A. Tritscher, J. Tuomisto,
541 M. Tysklind, N. Walker and R. E. Peterson (2006). "The 2005 World Health Organization reevaluation
542 of human and Mammalian toxic equivalency factors for dioxins and dioxin-like compounds." Toxicol
543 Sci **93**(2): 223-241.
544 Zoeller, R. T., A. L. Dowling and A. A. Vas (2000). "Developmental exposure to polychlorinated
545 biphenyls exerts thyroid hormone-like effects on the expression of RC3/neurogranin and myelin basic
546 protein messenger ribonucleic acids in the developing rat brain." Endocrinology **141**(1): 181-189.

547