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Manon Pruvost-Couvreur, Camille Béchaux, Gilles Rivière, Bruno Le Bizec

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1 Impact of sociodemographic profile,
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6 Manon Pruvost-Couvreur^{a,b}, Camille Béchaux^b, Gilles Rivière^b, Bruno Le Bizec^a
7

8 ^aLaboratoire d'Etude des Résidus et Contaminants dans les Aliments (LABERCA), INRAE, Oniris, Nantes
9 F-44307, France

10 ^bRisk Assessment Department - French Agency for Food, Environmental and Occupational Health and
11 Safety, 14 Rue Pierre et Marie Curie, 94700 Maisons-Alfort, France
12

13 Corresponding author: Gilles RIVIERE

14 Risk Assessment Department

15 French Agency for Food, Environmental and Occupational Health and Safety

16 14 Rue Pierre et Marie Curie

17 94700 Maisons-Alfort

18 France

19 gilles.riviere@anses.fr
20

21 Abstract

22 Polychlorinated biphenyls (PCBs) are persistent organic pollutants triggering numerous adverse
23 effects. Because they are present in various food, dietary exposure of the population to these
24 contaminants must be estimated to assess the related health risk. However, the classical risk
25 assessment approach allows only short-term estimates of exposure and does not account for dietary
26 changes, evolution of food contaminations and bioaccumulation of PCBs through life. The approach
27 presented here assesses lifetime PCB exposure trajectories according to birth year and individual
28 sociodemographic profiles. Moreover, a physiologically based toxicokinetic model was developed to
29 simulate lifetime PCB plasma concentrations, while considering physiological changes with age. A focus
30 on the long-term impact of breastfeeding is also presented in order to consider the risk related to PCBs
31 and due to the mother-to-child transfer. For example, the exposure of an individual born in 1972
32 exceeds the critical value of 20 ng PCB/kg bw/day half as often as an individual born in 1932 throughout
33 their lifetime but 13 times more often than an individual born in 2012, according to our simulations.
34 In addition, even if breastfeeding clearly leads to much higher dietary exposures than formula feeding,
35 the long-term impact on PCB body burden remains negligible. Risk assessment related to PCB lifetime
36 trajectories is described and discussed.

37

38 Keywords

39 Lifetime exposure, risk assessment, polychlorinated biphenyls, physiologically based toxicokinetic
40 modelling

41 1. Introduction

42 While food provides essential nutrients, it also carries non-intentionally added contaminants which
43 may trigger adverse effects. Consequently, it is necessary to assess the quantity of chemical ingested
44 and to determine the dose of contaminant that may induce a risk for health. To this aim, dietary
45 exposures are usually evaluated at population level using consumption surveys during which
46 individuals report their dietary consumption over a short period of time (up to a maximum of seven
47 days). These studies, in combination with food contamination data, allow estimating the dietary
48 exposure of a population. Exposures are then compared with a health-based guidance value (HBGV)
49 that represents the dose below which a risk for health can be excluded (for a review see Pruvost-
50 Couvreur et al. (2020a)). This approach assumes a constant lifetime exposure scenario. However, food
51 consumption habits vary with age and living conditions. Additionally, food contamination evolves with
52 time due to new or evolving regulations and new food processing.

53 Polychlorinated biphenyls (PCBs) is a group of 209 congeners which are persistent organic pollutants
54 (UNEP 2001). Because of their ability to bind to the aryl hydrocarbon receptor, twelve PCB congeners
55 are considered “dioxin-like” (dl-PCB). Other congeners bearing a different biological activity are
56 categorised “non-dioxin-like” (ndl-PCB). PCBs can trigger neurotoxic, reprotoxic, immunotoxic,
57 endocrine and dermal effects, and are carcinogenic to humans (ATSDR 2014; Lauby-Secretan et al.
58 2013). More than 90% of PCB exposure comes from food, mainly from seafood and dairy products
59 (EFSA 2005; JECFA 2016). In France, the infant total diet study (iTDS) conducted between 2010 and
60 2016, and the second total diet study (TDS2) conducted between 2006 and 2011, identified PCBs as
61 being chemicals of concern since a part of the French population has a PCB dietary exposure exceeding
62 the reference value (ANSES 2011, 2016). Moreover, environmental PCB concentrations hugely varied
63 over time (Breivik et al. 2016; Jung et al. 2008). This evolution induced changes in food contamination
64 and therefore in human exposure.

65 Complex mechanistic models are now able to predict human exposure to persistent organic pollutants
66 based on historical emissions data (McLachlan et al. 2018; Nøst et al. 2019; Quinn et al. 2001 ;Wania
67 et al. 2017; Wood et al. 2016). However, the use of these models has also highlighted the difficulty of
68 predicting, on an individual basis, lifetime exposure trajectories. In fact, since dietary exposure
69 depends on many individual characteristics such as consumption habits, generation or socio-
70 demographic profile, it is complex to gather all relevant data throughout an individual's life in relatively
71 short surveys.

72 We propose here an approach that can be easily generalized to different substances and could be used
73 in a routine assessment, with the aim of simulating trajectories of lifetime exposure to food
74 contaminants for different profiles of individuals representing the general French population. This
75 approach also makes it possible to estimate and consider the evolution of dietary exposures as a
76 function of generation and to assess the impact of certain consumption practices, such as a
77 breastfeeding period of at least 6 months, as recommended by the WHO, on dietary exposures. In fact,
78 the high lipophilicity of PCBs predisposes them to high excretion in breast milk and therefore
79 breastfeeding appears as an important source of PCB exposure in infants (DeKoning and Karmaus
80 2000).

81 We present here the application of the developed approach on the example of the French population's
82 dietary exposure to PCBs. The model predictions, obtained among others from physiologically based
83 toxicokinetics (PBTK) modelling, are compared with biomonitoring data in order to validate their
84 robustness. The example of PCBs, very documented substances for which many works have shown the
85 relevance of the life-time and historical study, allowed us to show the feasibility of a lifetime study in
86 the evaluation of the risks for the consumer, with a generalized approach.

87

88

89 2. Materials and methods

90 2.1. Lifetime trajectories simulation

91 The method developed to simulate lifetime exposure trajectories from sociodemographic individual
92 profiles was presented elsewhere (Pruvost-Couvreur et al. 2020b). Briefly, relationships between
93 short-term dietary exposures through total diet and individual sociodemographic characteristics were
94 studied by multivariate regressions, by age group. For individual characteristics significantly correlated
95 with exposure (called “stratification parameters”), a lifetime trajectory was simulated, using national
96 surveys data. Then, exposure was predicted at each life stage from stratification parameters, using
97 previously performed regressions.

98 In this study, simulations were performed from dietary exposures estimated in the French iTDS
99 focusing on infants from 1 month to 3 years old (n=705) (ANSES 2016) and the French TDS2 focusing
100 on children from 3 to 17 years old and adults from 18 to 79 years old (n=3 362) (ANSES 2011). In the
101 TDS2, since only 52% of fish consumption was represented in food sampling, an additional scenario
102 was computed, allowing the consideration of all fishes and seafood consumed in the French population
103 (Sirot et al. 2012). In TDSs, dietary exposures to total PCBs were assumed equal to the sum of exposures
104 to the six ndl-PCBs (*i.e.* PCB-28, PCB-52, PCB-101, PCB-138, PCB-153 and PCB-180) multiplied by 2 (EFSA
105 2012).

106 Correlations between sociodemographic parameters and PCB exposures were determined
107 considering, for each age group, the statistical relationship with the exposure to the sum of the six ndl-
108 PCBs. Consequently, stratification parameters were the same regardless of the congener, but could
109 vary with age group.

110 After the identification of stratification parameters and the simulation of individual lifetime
111 sociodemographic profiles, exposure trajectories were predicted for each of the six ndl-PCBs. Then,
112 the six trajectories were summed and multiplied by 2 for each virtual individual, to obtain lifetime

113 trajectories of exposure to total PCBs. Because exposures to the six congeners are correlated in TDSs,
114 trajectories were simulated considering this correlation. In fact, for French adults, Pearson correlations
115 scores varied between 0.37 for exposures to PCB-28 and PCB-180 and 1.00 for exposures to PCB-138
116 and PCB-153. PCB-153 was considered as reference congener because it is the main contributor to the
117 total PCB exposure in TDSs and is highly correlated with each of the remaining ndl-PCBs
118 (supplementary materials, Figures S1-S4).

119 This method was applied iteratively to simulate lifetime exposure trajectories for a population of
120 10 000 individuals.

121 All calculations and simulations were carried out in R version 3.6.1.

122

123 2.2. Evolution of PCB exposures over time

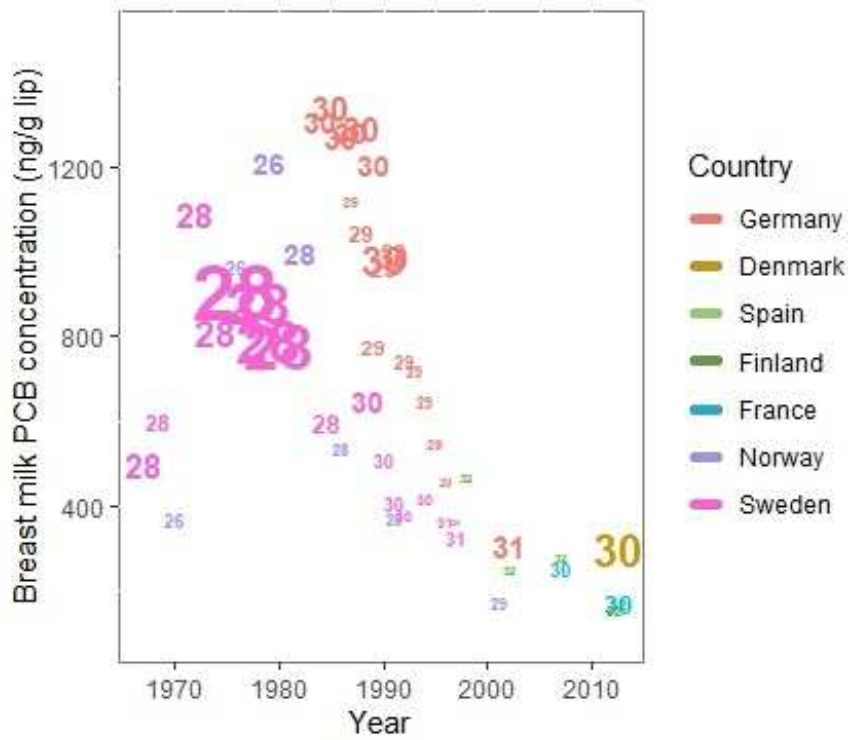
124 Using dietary exposures estimated in the context of TDSs to simulate exposure trajectories, implies
125 assuming that PCB food contamination has remained constant over time. However, it is known that
126 this contamination hugely varied in the last 80 years (Breivik et al. 2016). Indeed, global production of
127 PCBs started at the beginning of the 1930s and reached its peak in the 1970s. Production of PCBs has
128 been banned from many countries in the late 1970s, including France (INERIS 2012). Consequently,
129 food is now less contaminated than in the 1970s, at the peak of PCBs production.

130 Evolution of PCB food contamination is documented in the literature but measurements are too
131 heterogeneous to allow the assessment of an accurate temporal trend; oldest records measured
132 industrial mixtures and do not allow the identification of congeners, whereas the most recent records
133 provide independent measurements of each congener (Butcher et al. 1997).

134 However, several publications recorded PCB concentrations in breast milk over time in Europe
135 (Antignac et al. 2016; Focant et al. 2013; Furst et al. 1994; Noren and Meironyte 2000; Polder et al.
136 2008; Schade and Heinzow 1998; Schuhmacher et al. 2013; Wittsiepe et al. 2007) (Figure 1). When

137 levels of total PCBs in breast milk were not reported in articles, they were considered equal to the sum
 138 of PCB-138, PCB-153 and PCB-180 concentrations multiplied by 1.7 (AFSSA 2010).

139



151 where $F(t)$ is the body burden at age t , $k(t)$ is the elimination parameter of the considered substance
152 at age t , $G(t)$ is the dietary intake measured nowadays at age t and $g(year_t)$ is the correction factor
153 of dietary exposure, depending on birth year and age.

154 The elimination parameter $k(t) = \ln(2)/T_{1/2}(t)$ varied according to age and congener, where $T_{1/2}(t)$
155 is the elimination half-life at age t , from Grandjean et al. (2008) and Ritter et al. (2011). The function
156 g is approximated by a quadratic spline and is equal to 1 in years covered by the French TDSs. This
157 definition allows a large variety of shapes for g , while depending only on three parameters to be
158 estimated.

159 Because 52 values of breast milk concentrations were known, as well as mean age of mothers,
160 recording years and dietary intakes measured nowadays, it was possible to determine 52 g correction
161 functions by solving equation (2) for each of these 52 measured breast milk PCB concentrations. The
162 selected g correction function was this minimising the system composed by the 52 equations (2).

$$F(t) - \sum_{i=1}^{t-1} \left(g(year_i) \times G(i) \times \exp \left(- \sum_{j=i+1}^t k(j) \right) \right) - g(t) \times G(t) = 0 \quad (2)$$

163

164 To account for uncertainty on parameters of the kinetic model and variability of physiological
165 parameters, the system of equations was solved 1 000 times, varying physiological parameters each
166 time. Body weight was allowed to vary by 10%, the lipid fraction in the body by 40% and half-lives of
167 PCBs by 50% around the mean value.

168 The estimated g correction function was supposed to be applied to women and men. To study the
169 impact of generation on lifetime exposures to PCB, trajectories were simulated for a population born
170 in 2012 with food contaminations measured in TDSs, as well as for populations born in 1992, 1972,
171 1952 and 1932 by applying the mean of the 1 000 correction functions to each exposure trajectory in
172 the virtual population.

173

174 2.3. PBTK model

175 Because PCBs accumulate in the organism and because their accumulation may induce adverse effects
176 (EFSA 2005; JECFA 2016), lifetime body burden is of interest in the context of health risk assessment.

177 A PBTK model was developed to convert dietary exposure trajectories into body burden trajectories.
178 This model allowed the assessment of quantities of PCBs in different compartments of the body, from
179 differential equations and information on kinetic data of PCBs. The model was composed by five
180 compartments: brain, liver, adipose tissues, richly perfused tissues (*i.e.* lungs, pancreas, heart, gastro-
181 intestinal tract, kidneys, spleen and stomach) and poorly perfused tissues (*i.e.* muscles, bones and
182 skin). These compartments were selected because PCBs accumulate in adipose tissues and can trigger
183 adverse effects on brain and liver. Poorly and richly perfused tissues were studied separately
184 considering that blood flow has an important impact on the distribution of PCBs in the body.

185 Body weight under the age of 3 was determined according to age and gender (WHO Multicentre
186 Growth Reference Study Group 2006). After 3 years old, body mass index (BMI) trajectories were
187 available. Body weight was determined according to BMI, age and gender, according to an equation
188 assessed on a population simulated with the software PopGen (McNally et al. 2015). The equation was
189 validated on the population of the TDS2 (Pruvost-Couvreur et al. 2020b).

190 Volume of compartments and cardiac output evolved with age and gender. During children's growth
191 and development, volumes of compartments were determined from equations of Haddad et al. (2001)
192 or from data of ICRP (1979) and Valentin (2002). In adulthood, volumes of all compartments except
193 adipose tissues were assumed to be constant and equal to values given by ICRP (1979) and Valentin
194 (2002) for adults. It was assumed that the volume of the adipose compartment was equal to the
195 difference between 90% of the body volume and the sum of the volumes of remaining compartments.
196 The residual 10% corresponded to non-considered organs or tissues (blood volume for example).

197 Blood flows in the different compartments were defined as fractions of the cardiac output according
198 to values given by Luecke et al. (2007).

199 Fractions of lipids at different ages were given by ICRP (1979) and Valentin (2002) and evolutions
200 between given fractions were assumed linear. Partition coefficients were equal to the ratio between
201 the fraction of lipids in the considered compartment and the fraction of lipids in blood.

202 Elimination half-lives were considered by congener and evolved with the volume of lipids in the body
203 and the volume of liver, according to the equation given by Alcock et al. (2000). Elimination half-lives
204 of reference for PCB-138, PCB-153 and PCB-180 were those reported by Ritter et al. (2011). This
205 approach allows considering the individual volumes of lipids and liver in the elimination process,
206 contrary to what could be done in the model presented previously for the evolution of dietary
207 exposure to PCBs, where these details were not known.

208 PCB-138, PCB-153 and PCB-180 plasma concentrations were calculated independently before being
209 summed up and multiplied by 1.7 to assess the total concentration of PCBs in plasma that is considered
210 as a surrogate to the body burden of total PCBs (AFSSA 2010). This model assumed that the body
211 burden at birth was negligible with respect to the body burden accumulated over the entire life.

212 To consider inter-individual physiological variability, random factors (called “variation factors” in this
213 work) were applied to parameters of the model (supplementary materials, Table S1). Variation factors
214 in the volumes of compartments were determined on the basis of data from the PopGen software
215 (McNally et al. 2015). They were drawn in such a way that the quantile of the variation factor of the
216 body weight was equal to the quantile of the variation factor of each of the compartments. Variation
217 factors in lipid fractions were from ICRP (1979) and Valentin (2002). Given the high variability of PCB
218 half-lives in the literature (Ritter et al. 2011), half-lives variation factors were allowed to range from
219 0.5 to 1.5.

220 The model was validated by comparing simulated body burden trajectories with PCB plasma
221 concentrations measured in the French population (supplementary material, Part 4). Moreover, a

222 global sensitivity analysis was realised to identify input parameters contributing the most to the
223 variability of PCB body burden (supplementary materials, Part 5).

224

225

226 2.4. Breastfeeding in childhood

227 Due to their high lipophilicity, PCBs are present in breast milk in higher concentrations than in infant
228 formula (Lackmann et al. 2004).

229 To estimate the exposure of the population in a "worst case" scenario, breastfeeding must be taken
230 into account. The SFAE study recorded consumption data used the iTDS to assess the exposure of non-
231 breast-fed children under the age of 3 (Fantino and Gourmet 2008). Concentrations of PCBs in infant
232 formulae recorded in the iTDS for infants under 6 months of age were replaced by those in breast milk.
233 PCB concentrations in breast milk were those from the data used to assess the evolution of PCB
234 exposure between the 1960s and nowadays (see Section 2.2). A curve of the evolution of breast milk
235 PCB concentrations over time was fitted with the function *smooth.spline* in R version 3.6.1.

236 Then, PCB exposure trajectories were computed for infants born between the 1970s and nowadays,
237 and breast-fed during their first six months of life.

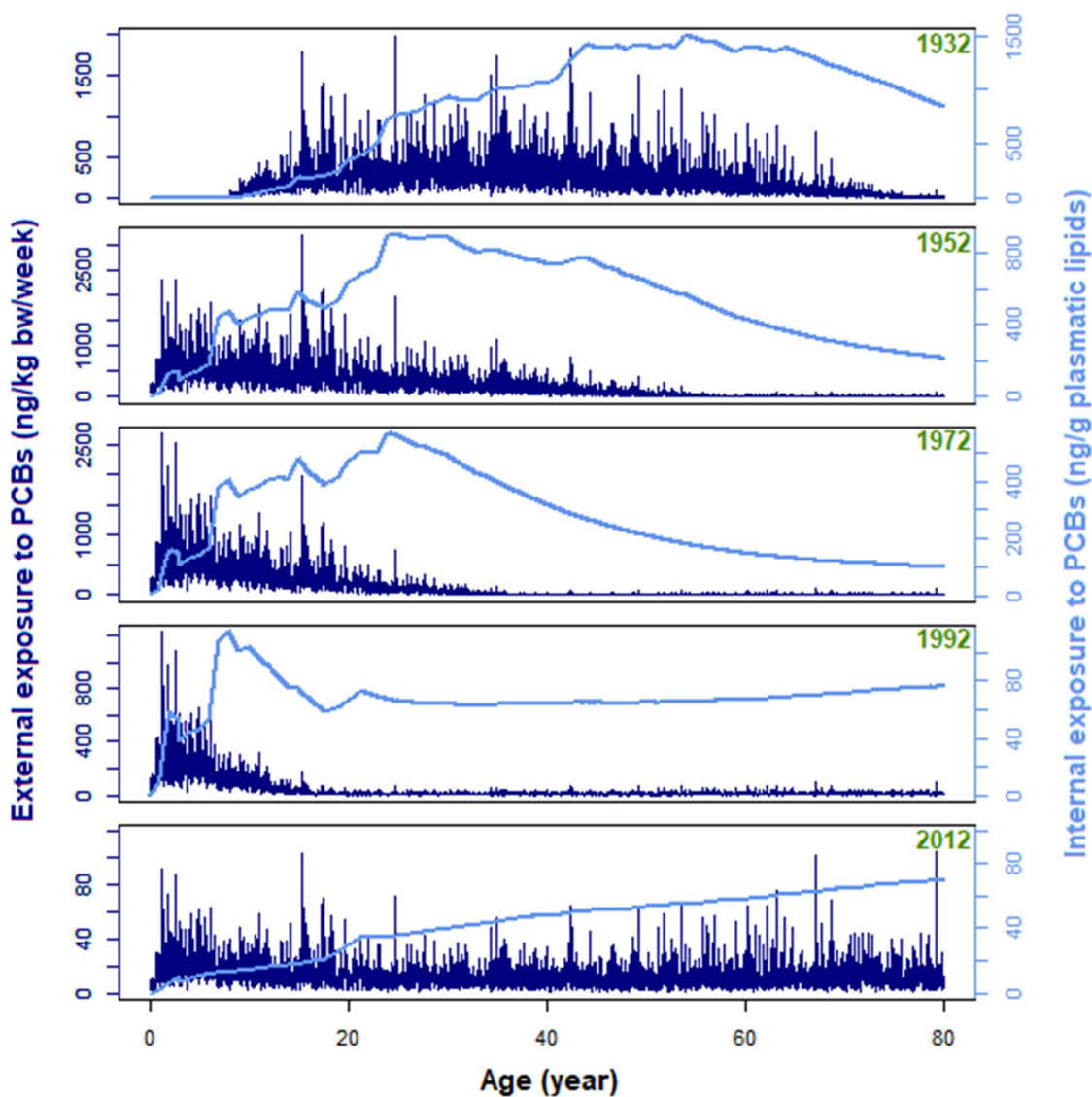
238

239 3. Results

240 3.1. Impact of sociodemographic characteristics and generation on lifetime 241 trajectories

242 PCB exposures were related to gender, BMI, region of residence, household income, frequency of
243 canteen meals in childhood and marital status and educational level in adulthood. In fact, at least one
244 modality of each of these variables was related to statistically different PCB exposures (p-value <0.1)
245 that other modalities for at least one age group (supplementary materials, Table S3).

246 Generation also had a significant impact on PCB dietary exposures. According to our simulations, PCB
 247 dietary exposures at the end of the 1960s were on average 25 times higher than those estimated when
 248 considering concentrations measured nowadays (95% PI [15; 38]). Considering the average of
 249 predicted evolutions of PCB dietary exposures, the body burden at the age of 40 was 1 183 ng/g lipids
 250 (95% PI [657; 1 908]) for an individual born in 1932, whereas it was 289 ng/g lipids (95% PI [152; 474])
 251 for an individual of the same age born in 1972. Assuming that PCB exposures will remain constant in
 252 the future, the body burden of an individual born in 2012 at the age of 40 would be 53 ng/g lipids (95%
 253 PI [31; 85]). An example of lifetime exposure and body burden trajectories is provided for a man,
 254 according to his birth year in Figure 2.



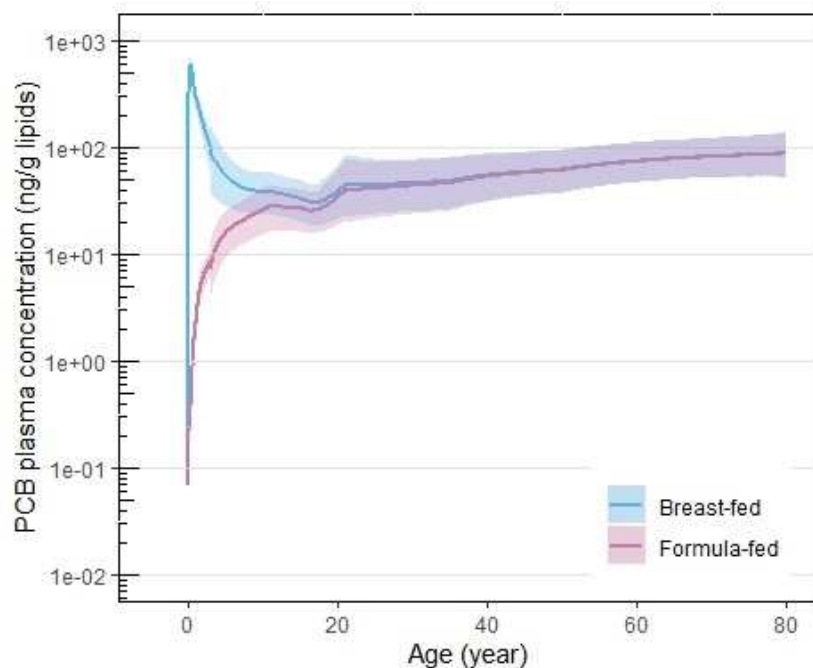
255
 256 *Figure 2: Example of lifetime exposure (dark blue) and body burden (light blue) trajectories according to birth year (green)*

257

258 3.2. Impact of breastfeeding on lifetime trajectories

259 PCB concentrations in breast milk varied over the last decades. It was on average 1 030 ng/g lipids in
260 the 1980s (95% CI [560; 1330]) and around 200 ng/g lipids in the 2010s (see Section 2.2).
261 Concentrations of PCBs measured in the 2010s in infant formulae in the French infant TDS were
262 between 0.4 and 4.3 ng/g lipids, depending on the food (ANSES 2016). Therefore, breastfed children
263 are much more exposed to PCBs than other children.

264 According our simulations, body burden is much higher for breast-fed infants than for formula-fed
265 infants during the first six months of life. However, this difference disappears with time (Figure 3). At
266 the sixth month of life of a child born in 2012, the estimated PCB plasma concentration was on average
267 614 ng/g lipids for a breast-fed child and 0.6 ng/g lipids for a formula-fed child. At 3 years old, the ratio
268 between body burdens of breast-fed and formula-fed children decreased to 12.4, and it was on
269 average 1.5 at 10 years old. At the age of 20, body burdens were similar, regardless of dietary scenarios
270 considered in childhood. In the same way, the ratio between areas under the curves is about 64
271 between birth and the age of 3, but it is about 1.3 when considering the entire life. Thus, the long-term
272 impact of breastfeeding on PCB body burden and associated health risks is negligible.



273

274 *Figure 3: PCB body burden trajectories according to food scenario in childhood. Solid lines are mean trajectories and*
 275 *coloured areas are 95% prediction intervals.*

276

277 **3.3. Risk assessment**

278 Numerous HBGVs were derived for PCBs by different health agencies for food safety (Table 1).

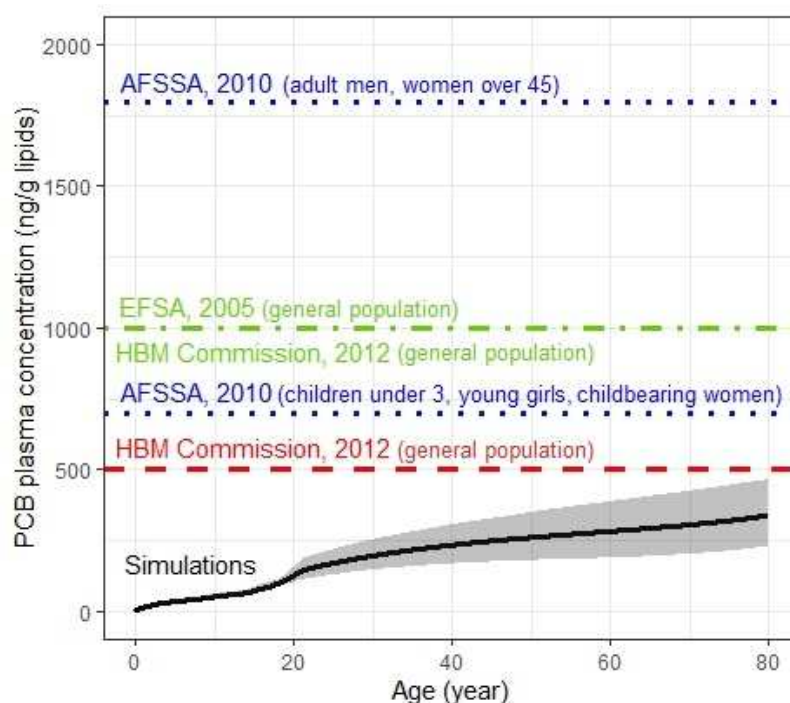
279 *Table 1: Threshold values derived for external and internal exposures to PCBs*

Value	Adverse effect	Reference
External health based guidance values		
30 ng/kg bw/day (subchronic)	Neurological effects in young monkey after exposure from birth to 20 weeks	(ATSDR 2000)
20 ng/kg bw/day (chronic)	Immunological effects in adult monkey after 23 months of exposure	(AFSSA 2007; ATSDR 2000; RIVM 2001; US EPA 1994)
Internal critical concentrations		
1 000 ng/g lipids	Neurological and immunological effects after perinatal exposure	(EFSA 2005)
700 ng/g lipids (children under 3, girls and women of childbearing age)	Effects on mental and motor development in children after <i>in utero</i> exposure	(AFSSA 2010)
1 800 ng/g lipids (boys over 3, adult men and women over 45)	Concentration triggering no neurological effect in adults over 50 years of age	(AFSSA 2010)

500 ng/g lipids	Concentration triggering no adverse effect	(HBM Commission 2012)
1 000 ng/g lipids	Neurological, immunological, auditory, metabolic and thyroid effects in the most sensitive individuals	(HBM Commission 2012)

280

281 The chronic external HBGV of 20 ng PCB/kg bw/day is widely used by risk assessors. It has been
 282 established based on a no observed adverse effect level in animals, to which uncertainty factors were
 283 applied. This approach appears conservative since the body burden simulated from a constant lifetime
 284 exposure of 20 ng PCB/kg bw/day was lower than critical concentrations proposed by the different
 285 agencies from human data (Figure 4). However, it does not allow the consideration of lifetime
 286 bioaccumulation of PCBs, on the first hand because animal experiments were realised during only two
 287 years. This duration represents the lifetime of the animals however it does not allow to represent the
 288 amount of substance that can be accumulated over 80 years. Additionally, it does not allow studying
 289 plasma PCB concentrations induced by fluctuating dietary exposures.



290

291 *Figure 4: Body burden trajectory (black solid line) and its 95% prediction interval (grey area) resulting from a lifetime*
 292 *exposure to the chronic HBGV of 20 ng/kg bw/day. Comparison with different critical concentrations (coloured dashed lines).*

293

294 Individuals born in 2012 and formula-fed in childhood are expected to have exposure trajectories
295 exceeding the chronic external HBGV of 20 ng/kg bw/day during on average 2.2 years whereas
296 individuals born in 1972 exceeded the HBGV during 27 years through life and individuals born in 1932
297 during 56 years (Table 2). Breast-fed infants systematically had a dietary exposure above the chronic
298 HBGV during the breastfeeding period, regardless of birth year.

299 ATSDR recommends the use of the subchronic external HBGV of 30 ng/kg bw/day for exposures
300 occurring during 15 to 364 days. Because this value was derived from experiments in newborn
301 monkeys, in this work, comparisons between the subchronic HBGV and simulated exposure
302 trajectories were only computed for the first year of life. During the first year, 2.8% of formula-fed
303 children born in 2012 had exposures above the subchronic HBGV, maximum during three non-
304 consecutive weeks. Breast-fed children had exposures exceeding the subchronic HBGV during the
305 entire breastfeeding period.

306 Breastfeeding induced PCB plasma concentrations higher than 500 ng/g lipids for almost all children,
307 even those born recently. For formula-fed populations, exceedances of critical plasma concentrations
308 were highly correlated with birth year; more than 99% of the population born in 1932 or in 1952 had
309 body burdens exceeding 500 ng/g lipids at least once whereas no one born in 1992 reached this PCB
310 plasma concentration during their lifetime. The value of 1 800 ng/g lipids was never reached by
311 individuals born in 1972, but was exceeded by more than 4% of individuals born in 1952 and by more
312 than 14% of individuals born in 1932 (Table 2).

313 *Table 2: Duration of exceedance of the chronic HBGV of 20 ng/kg bw/day over life and percentages of the simulated population*
314 *having a body burden trajectory exceeding a critical concentration over life, according to birth year and diet in childhood*

Diet in childhood	Birth year	Arithmetic mean of the duration of exceedance of	95% prediction interval of the duration of exceedance of	Percentage of the population exceeding the body burden of 500 ng/g lipids	Percentage of the population exceeding the body burden of 1 800 ng/g lipids
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		the chronic HBGV (year)	the chronic HBGV (year)		
Infant formulae	2012	2.2	0.8 – 4.0	0.0%	0.0%
	1992	11.4	8.9 – 13.8	0.0%	0.0%
	1972	27.3	23.0 – 31.1	78.9%	0.0%
	1952	47.2	43.7 – 50.1	99.8%	4.1%
	1932	56.5	51.7 – 60.6	100.0%	14.6%
Breast milk	2012	2.7	1.3 – 4.5	99.8%	0.0%

315

316 4. Discussion

317 4.1. Limits of simulations

318 Limits of the method developed to simulate lifetime exposure trajectories were discussed elsewhere
319 (Pruvost-Couvreur et al. 2020b). Briefly, several hypotheses on changes of sociodemographic
320 characteristics throughout life were made, that can impact exposure trajectories, like the probability
321 to move from a region to another, according to age.

322 Moreover, the assessment of dietary exposure to total PCBs from the six non dioxin-like congeners and
323 of PCB plasma concentration from three congeners is a source of uncertainty. In fact, even if these
324 hypotheses were verified in other studies (ANSES and InVs 2011; IARC 2016), variability in the
325 distribution of congeners exists and was not taken into account here.

326 We must also emphasize that only dietary exposure was considered here, because nowadays the total
327 exposure to PCBs is overwhelmingly triggered by the diet. In contrast, hypothetically, other sources of
328 exposure, such as air pollution, may have had a higher contribution to total exposure in earlier
329 generations. Future work, incorporating the exposome concept, is therefore required to integrate
330 these different sources of exposure and to best assess the health risk for older generations.
331 Furthermore, the correction function applied to exposure trajectories to consider the generational
332 effect was assessed from limited and averaged data, especially before 1960. Before this date,
333 confidence level in the correction function is weak. Moreover, the correction function considered in
334 the proposed risk assessment was a mean function. More extreme lifetime trajectories may therefore

335 exist, that may explain the fact that the tail of the distribution of simulated concentrations is more
336 truncated than the tail of the distribution of measured concentrations. Yet, because mean PCB plasma
337 concentrations modelled from simulated exposure trajectories were within the same order of
338 magnitude as those measured in the French population, PCB exposure trajectories and evolution of
339 food contamination were adequately assessed. In fact, geometric means of simulated PCB plasma
340 concentrations were similar to those measured in another French study, even if the highest percentiles
341 are lower in the simulations (supplementary material, Part 4). It should also be mentioned that the
342 correction function, as proposed in this work, makes it possible to estimate the overall evolution of
343 dietary exposures, but does not allow the consideration of the evolution of consumption and
344 contamination of specific foodstuffs.

345

346 4.2. Body burden at birth and maternal depuration

347 PCBs were assumed to be rapidly eliminated in childhood due to their short elimination half-lives
348 (Alcock et al. 2000). For this reason, PCB plasma concentrations at birth were considered negligible in
349 comparison with lifetime accumulation. This assumption was supported by the comparison between
350 plasma concentrations of breast-fed and those of formula-fed infants; body burdens were extremely
351 different during breastfeeding period but were not after several years (Figure 3). This observation
352 indicates that PCB body burdens in the first months of life have a little impact on the body burden after
353 few years.

354 Pregnancy and breastfeeding act as elimination pathways for persistent organic pollutants (Alcala and
355 Phillips 2017; Caspersen et al. 2016; Quinn et al. 2011). However, potential maternal depurations due
356 to pregnancies and periods of breastfeeding were not considered in the model, due to the lack of
357 consensual data regarding fetal-maternal exchanges. Ratios between PCB concentrations in fetal and
358 maternal matrices reported in the literature were too variable to establish a robust transfer rate; ratios
359 between PCB concentrations in umbilical cord and maternal bloods were from 0.18 to 9.29, according

360 to congeners and studies, when adjusted to lipid weight (Bergonzi et al. 2009; DeKoning and Karmaus
361 2000; Jeong et al. 2018; Lancz et al. 2015; Mori et al. 2014; Needham et al. 2011; Patayova et al. 2013;
362 Soechitram Shalini et al. 2004; Vizcaino et al. 2014). Similarly, ratios between non lipid adjusted PCB
363 concentrations in umbilical cord and maternal bloods were also variable (from 0.087 to 0.59) (Covaci
364 et al. 2002; Mori et al. 2014; Patayova et al. 2013; Porpora et al. 2013; Vizcaino et al. 2014). Finally,
365 reported concentrations in placental to maternal blood lipids ratios ranged from 0.13 to 1.80 (Bergonzi
366 et al. 2009; DeKoning and Karmaus 2000; Jeong et al. 2018; Vizcaino et al. 2014). Furthermore, not
367 considering the potential mother depuration is conservative since it overestimates the maternal PCB
368 plasma concentration and since PCB concentrations in breast milk were estimated from the literature
369 and not from maternal contamination.

370

371 4.3. Breastfeeding

372 In breastfeeding scenario, daily consumption of breast milk was considered to be equal to that of infant
373 formula consumption recorded in the SFAE study. Under this assumption, 807 g and 835 g of breast
374 milk was consumed daily by 1-3 months and 4-6 months age groups, respectively. Recommendations
375 of breast milk consumption are 690 mL/day from 1 to 3 months and 770 mL/day from 4 to 6 months
376 of age (US EPA 2011). Our selected assumption on breast milk consumption was thus protective.

377 Considering risk assessment, exceedances of external and internal HBGVs observed regardless of birth
378 year for breast-fed infants must be discussed. In fact, body burdens of breast-fed infants, even much
379 higher than those of formula-fed children, exceeded critical thresholds only for few months (i.e. during
380 the breastfeeding period). At the end of the breastfeeding period, PCB plasma concentrations
381 decreased rapidly because of short elimination half-lives of PCBs in childhood. On the contrary, body
382 burdens in adulthood were more stable because of longer elimination half-lives. Exceedances of critical
383 concentration values in adulthood could therefore appear more of concern because they were likely
384 to last longer. However, childhood is a sensitive period for development and infants may be more

385 susceptible to adverse effects than adults (ATSDR 2000; EFSA 2017). Therefore, a health risk induced
386 by exposures leading to exceedances of critical internal concentrations during the breastfeeding period
387 cannot be excluded.

388

389 4.4. Risk assessment approach

390 Even if the external chronic HBGV of 20 ng/kg bw/day is selected by several safety agencies to assess
391 PCB health risk, it is not unanimously accepted. According to EFSA (2005) and JECFA (2016),
392 toxicokinetic data on PCBs are too limited to set a HBGV. Additionally, adverse effects triggered by
393 PCBs are less correlated with dietary external exposures than with internal concentrations which
394 reflect accumulation of PCBs in the body.

395 Furthermore, comparisons between body burden trajectories and critical concentrations were easier
396 than comparisons between exposure trajectories and external HBGVs. In fact, external HBGVs were
397 derived from experiments exposing monkeys during a given period to a mix of PCBs. This duration must
398 be scaled from animal to human and uncertainty factors were applied to account for differences of
399 toxicokinetics between species. Moreover, because exposure trajectories were fluctuating,
400 exceedances of the external HBGV were intermittent making it difficult to assess health risk over long
401 periods of time. On the contrary, body burden trajectories were less variable due to the
402 bioaccumulative nature of PCBs (Figure 2). Since an internal critical value is a concentration of a
403 substance in a human matrix below which there is no risk of health impairment anticipated, it could
404 be considered that exceeding a critical concentration over life is an alert in terms of risk.

405 However, since the establishment of the different HBGVs, new studies observed adverse effects in
406 women during pregnancy or in children after pre- or post-natal exposures at PCB levels lower than
407 500 ng/g lipids (Alvarez-Pedrerol et al. 2009; Baba et al. 2018; Chevrier et al. 2008; Neugebauer et al.
408 2015; Takser et al. 2005). Unfortunately, the large diversity of observed effects coupled with PCB

409 internal concentrations does not allow the assessment of a new accurate internal critical
410 concentration.

411 In conclusion, external and internal approaches appear to be complementary, as well as short-term
412 and lifetime risk assessment. Lifetime body burden trajectories seem more appropriate to assess
413 health risk over the life course because they account for lifetime PCB bioaccumulation. However, the
414 external approach was shown to be more protective. Estimating lifetime trajectories allows identifying
415 individual characteristics and behaviours impacting the dietary exposure as well as assessing the long-
416 term results of such behaviours, accounting for past and future exposures. Complementarily, the more
417 classical risk assessment approach based on short-term measurements allows identifying immediate
418 health risk and potentially acting on the food regulation.

419

420 5. Conclusions

421 Lifetime health risk related to the presence of PCBs in food was assessed. Simulations highlight the
422 important impact of generation on PCB exposures; PCB levels in the environment have been steadily
423 decreasing since the 1970s, depending on the country and the regulations in place. Residual PCB
424 concentrations in food are following the same trend with a time delay due to the accumulation of PCBs
425 along the food chain (Breivik et al. 2016).

426 Lifetime exposure trajectories and simulations of body burdens allow a refinement of classical risk
427 assessment; although French TDSs observed exceedances of the chronic external HBGV of
428 20 ng/kg bw/day for babies (2.7%) (ANSES 2016), children (6.5%) and adults (2.6%) (ANSES 2011), our
429 simulations show that current exposures induce lifetime body burdens lower than critical plasma
430 concentrations. It has to be highlighted that, for breast-fed children, PCB dietary exposures are high
431 because of the lifetime accumulation of PCBs in their mother's body. However, even for breast-fed
432 children, estimated PCB plasma concentrations are shown to decrease rapidly after the end of the
433 breastfeeding period and no differences are observed after 20 years. The ratio between the lifetime

434 area under the mean body burden trajectory for breast-fed individuals and the area under the mean
435 body burden trajectory for formula-fed individuals was close to 1.

436

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440

441 Declaration of competing interest

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444

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621

622 Figure and table captions

623 Figure 1: Evolution of PCB concentrations in breast milk in last decades, according to median mothers'
624 age (indicated value), number of samples in the study (size of text) and country (colour of text)

625 Figure 2: Example of lifetime exposure (dark blue) and body burden (light blue) trajectories according
626 to birth year (green)

627 Figure 3: PCB body burden trajectories according to food scenario in childhood. Solid lines are mean
628 trajectories and coloured areas are 95% prediction intervals.

629 Figure 4: Body burden trajectory (black solid line) and its 95% prediction interval (grey area) resulting
630 from a lifetime exposure to the chronic HBGV of 20 ng/kg bw/day. Comparison with different critical
631 concentrations (coloured dashed lines).

632

633 Table 1: Threshold values derived for external and internal exposures to PCBs

634 Table 2: Duration of exceedance of the chronic HBGV of 20 ng/kg bw/day over life and percentages of
635 the simulated population having a body burden trajectory exceeding a critical concentration over life,
636 according to birth year and diet in childhood

