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Blood levels of persistent organic pollutants among women in France in the 90's: main profiles and individual determinants.

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1 **Abstract**

2 *Context and objectives:* Persistent organic pollutants (POPs) are a group of organic chemical
3 compounds potentially toxic to human health. The objectives of this study were 1) to describe the
4 levels of POPs biomarkers in blood samples from French women collected during the 1990s and to
5 compare them with levels measured in two more recent French studies, 2) to identify POPs exposure
6 profiles, and 3) to explore their main determinants.

7 *Methods:* 73 POPs biomarkers were measured in the blood of 468 women from the French E3N
8 cohort (aged 45 to 73 years), collected between 1994-1999: 28 per- and polyfluoroalkyl substances, 27
9 organochlorine pesticides, 14 polychlorinated biphenyls and 4 polybrominated diphenyl ethers. POPs
10 biomarker levels were described and compared with levels measured in two more recent French
11 studies conducted by the French National Public Health Agency, the ENNS and Esteban studies.
12 Principal component analysis was performed on POPs quantified in at least 75% of samples to identify
13 the main exposure profiles. Linear regression models were used to estimate the associations between
14 anthropometric, socio-demographic and lifestyle characteristics and exposure to these profiles.

15 *Results:* Among the 73 biomarkers measured, 41 were quantified in more than 75% of samples. Levels
16 of most pollutants that were also measured in the Esteban of ENNS studies have decreased over time.
17 Six POPs exposure profiles were revealed, explaining 62.1% of the total variance. Most of the
18 characteristics studied were associated with adherence to at least one of these profiles.

19 *Conclusion:* This study highlighted that most of the pollutants for which a comparison was possible
20 decreased over the 10 or 20 years following the E3N blood collection, and identified those which, on
21 the contrary, tended to increase. The health effects of the profiles identified could be assessed in future
22 studies. The determinants identified should be confirmed in larger populations.

23 **Keywords:** persistent organic pollutants; biomarkers; profiles

24 **Introduction**

25 Persistent organic pollutants (POPs) are a heterogeneous group of organic chemicals that share several
26 common properties. They degrade slowly and are mobile over long distances, making them
27 widespread and persistent for long periods in the environment. They can bioaccumulate in the fatty
28 tissues of living organisms, thus biomagnifying along the food chain. They are potentially toxic to
29 human health and the environment. Consequently, an international treaty to reduce their production,
30 use and release, the Stockholm Convention, was signed in 2001 and came into force in 2004 (United
31 Nation Environment Program 2019).

32 Different chemical families have been listed as POPs. Organochlorine pesticides (OCPs) are a group
33 of synthetic pesticides introduced in the 1940s, and used for agriculture and vector-borne diseases
34 control. They have been progressively banned for most uses between the 1970s and the 2000s in
35 France (Tagne-Fotso et al. 2021), and registered in the Stockholm convention between 2001 and 2011
36 (United Nation Environment Program 2019). Polychlorinated biphenyls (PCBs) are a class of
37 chemicals widely used between the 1930s and the 1970s for a variety of industrial and commercial
38 purposes (in electric condensers and transformers, heat and hydraulic exchangers, plastics, paints,
39 lacquers, varnishes, glues, inks, cables, synthetic textiles...). Their production and use have been
40 banned since 1987 in France (Balestier et al. 2021), and they have been registered on the Stockholm
41 convention in 2001 (United Nation Environment Program 2019). Polybrominated diphenyl ethers
42 (PBDEs) are a class of compounds used as flame-retardants since the 1970s in a wide array of
43 products (textiles, plastics, polyurethane foams, electronic circuits...) (Fillol et al. 2019). The
44 commercialization and use of the three PBDE commercial mixtures have been progressively regulated
45 since the 2000s in Europe (penta-BDE and octa-BDE in 2003, deca-BDE in 2008), and the production
46 of new electronic devices containing PBDEs has been forbidden since 2006 (Parlement européen et
47 conseil de l'union européenne 2003; 2023). PBDEs have been added to the Stockholm convention in
48 2009 (United Nation Environment Program 2019). Per- and polyfluoroalkyl substances (PFASs) are a
49 family of chemicals used since the 1950s for various industrial applications and in everyday consumer
50 products (clothing, carpets, leather, footwear, food packaging, cosmetics, etc) (Oleko et al. 2019). The
51 use of the two main substances, perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid
52 (PFOA), has been restricted in France since 2009 under the Registration, Evaluation, Authorization
53 and Restriction of Chemicals (REACH) regulation (European Commission 2007). They have been
54 registered on the Stockholm convention in 2009 and 2019 respectively, and the
55 perfluorohexanesulfonic acid (PFHxS) has been added in 2022 (United Nation Environment Program
56 2019). In France, a ministerial action plan on PFASs has been published by the Ministry for
57 Ecological Transition and Territorial Cohesion in January 2023, to strengthen the protection of people
58 and the environment against the risks associated with the exposure to PFASs (Ministère de la
59 Transition écologique et de la Cohésion des territoires 2023).

60 Via a variety of mechanisms such as endocrine disruption (Bonefeld Jørgensen, Autrup, and Hansen
61 1997; Bonefeld-Jørgensen et al. 2001; Sonthithai et al. 2016; Kanaya et al. 2019; Maras et al. 2006),
62 oxidative stress (Karami-Mohajeri and Abdollahi 2010) and inflammation (Hennig et al. 2002),
63 exposure to these pollutants may cause various health problems such as cancer, reproductive
64 problems, cardiovascular and metabolic diseases (Guo et al. 2019; Ashraf 2017). To monitor the levels
65 of exposure, the French National Public Health Agency has set up a national biomonitoring system,
66 which made it possible to collect the first national data on levels of internal exposure to these
67 substances. Two cross-sectional studies have been carried out in the general population of mainland
68 France: the National Nutritional and Health Study (ENNS), conducted in 2006 and 2007, and the
69 Health Study on Environment, Biomonitoring, Physical Activity and Nutrition (Esteban) conducted
70 between 2014 and 2016 (Tagne-Fotso et al. 2021; Balestier et al. 2021; Oleko et al. 2019; Fillol et al.
71 2019; Frery et al. 2013; Masson, n.d.). These studies have shown that, despite the regulations, the
72 French population is still widely exposed to POPs due to their persistence in the environment and the
73 trophic chains. Food represents the main source of exposure for the general population (Anses 2011a;
74 2011b), but water, air, and certain consumer products also contribute to exposure. These substances
75 have long half-lives in human bodies (Milbrath et al. 2009; Li et al. 2022; Sjödin et al. 2020) and tend
76 to accumulate in adipose tissue, but more information is needed to better understand the trajectory of
77 exposure over a lifetime. It has been shown that some individual and lifestyle characteristics (such as
78 age, diet, BMI, breastfeeding, etc.) could have an impact on POPs blood levels (Li et al. 2022; Curren
79 et al. 2015; Henríquez-Hernández et al. 2017; McAdam and Bell 2023; Llop et al. 2010).

80 The objectives of the present study were: 1) to describe the levels of biomarkers of POPs between
81 1994 and 1999, in the blood samples of women of the French E3N cohort study (*“Etude*
82 *Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale”*) and to
83 compare them with levels measured in two more recent French studies, 2) to identify POPs exposure
84 profiles, and 3) to explore the individual characteristics (including anthropometric, socio-demographic
85 and lifestyle characteristics) associated with these profiles.

86 **Materials and methods**

87 *Study population*

88 The E3N study is an ongoing prospective cohort including only women, that started in France in 1990.
89 The detailed protocol has been described previously (Françoise Clavel-Chapelon and E3N Study
90 Group 2015; F. Clavel-Chapelon et al. 1997). The study included 98,995 women born between 1925
91 and 1950 and covered by the French national health insurance plan for people working for the national
92 education system, the Mutuelle Générale de l'Education Nationale (MGEN). These women have been
93 followed-up by self-administered questionnaires sent every two or three years. A good participation
94 rate has been maintained over time (approximately 83%). The study received approval from the

95 French National Commission for Data Protection and Privacy, and all participants provided written
96 informed consent.

97 Participants in the E3N study were invited to donate blood between 1994 and 1999, making it possible
98 to collect blood samples from approximately 25,000 women. Each sample was separated into 28
99 aliquots (i.e. plasma, serum, buffy coat, leukocytes and erythrocytes) which were stored in plastic
100 straws in liquid nitrogen containers (-196°C) in a biobank. A random sample of 468 women was
101 selected among participants for whom there was still enough biological material available in the
102 biobank to perform the measures (i.e., 5 plasma straws and 2 serum straws), who had answered the
103 dietary questionnaire sent in 1993, and who were not included in any other ongoing case cohort study
104 involving the use of plasma or serum.

105 *Measurement of biomarkers of POPs*

106 The levels of 73 biomarkers of POPs were measured in serum (for PFAS) or plasma (for other POPs).
107 by the LABERCA's Human Biomonitoring (HBM) platform, using fully validated (2002/657/CE
108 decision) and accredited methods (ISO 17025 standard) as described elsewhere (Benoit et al. 2022).
109 Briefly, 28 PFAS were determined in serum conducting a preliminary alkaline digestion followed by a
110 two-stage Solid Phase Extraction purification using polymeric Oasis HLB and graphitized carbon
111 (ENVI-Carb) cartridges, before liquid chromatography coupled to tandem mass spectrometry (6410,
112 Agilent Technologies, USA) measurement. For the rest of POPs, plasma samples were submitted to
113 precipitation of proteins with acid formic followed by C18 solid phase extraction eluted with hexane.
114 The levels of 14 PCBs and 4 PBDEs were measured using gas chromatography (7890A; Agilent
115 Technologies, USA) coupled to a high-resolution mass spectrometer, double sector (JMS-700D and
116 800D; JEOL, Japan) operating at a resolution of 10,000 (10% valley). The levels of 27 OCPs were
117 measured with GC coupled to tandem mass spectrometry with a triple quadrupole analyzer (7010,
118 Agilent Technologies, USA). The quantification was achieved according to the isotopic dilution
119 method (i.e., using ¹³C labeled analogous as internal standards). The lipid content was determined in
120 plasma with enzymatic kits (Biolabo, Maizy, France) independently for phospholipids (PL),
121 triglycerides (TG), total cholesterol (TC) and free cholesterol (FC). Total serum lipids (TSL) were
122 estimated using the Akins formula: $TSL = 1.677*(TC - FC) + FC + TG + PL$ (Akins, Waldrep, and
123 Bernert 1989).

124 For each biomarker, the lower limit of quantification varied depending on the sample. The number and
125 proportion of non-quantified values, as well as the minimum and maximum lower limits of
126 quantification for each substance, are shown in Supplementary Table 1.

127 The following biomarkers of POPs were measured:

- 128 – 28 per- and polyfluoroalkyl substances (PFASs) in the serum: perfluorotetradecanoic acid
 129 (PFTeDA), perfluorotridecanoic acid (PFTrDA), perfluorododecanoic acid (PFDoDA),
 130 perfluoroundecanoic acid (PFUnDA), perfluorodecanoic acid (PFDA), perfluorononanoic acid
 131 (PFNA), perfluorooctanoic acid (PFOA), perfluoroheptanoic acid (PFHpA),
 132 perfluorohexanoic acid (PFHxA), perfluoropentanoic acid (PFPeA), perfluorobutanoic acid
 133 (PFBA), perfluorotridecanesulfonic acid (PFTrDS), perfluorododecanesulfonic acid
 134 (PFDoDS), perfluoroundecanesulfonic acid (PFUnDS), perfluorodecanesulfonic acid (PFDS),
 135 perfluorononanesulfonic acid (PFNS), perfluorooctanesulfonic acid (PFOS) and its linear
 136 isomer (n-PFOS), perfluoroheptanesulfonic acid (PFHpS), perfluorohexanesulfonic acid
 137 (PFHxS), perfluoropentanesulfonic acid (PFPeS), perfluorobutanesulfonic acid (PFBS),
 138 perfluorooctanesulfonamide (PFOSA), N-methylperfluorooctanesulfonamidoacetic acid (N-
 139 MeFOSAA), N-ethylperfluorooctane sulfonamidoacetic acid (N-EtFOSAA), 2,3,3,3-
 140 tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)propanoic acid (GenX), dodecafluoro-3H-4,8-
 141 dioxanonanoate (DONA), 9-chlorohexadecafluoro-3-oxanonane-1-sulfonate (F53B major),
 142 11-chlororeicosafuoro-3-oxaundecane-1-sulfonate (F53B minor);
- 143 – 27 organochlorine pesticides (OCPs) in the plasma: p,p'- dichlorodiphenyltrichloroethane
 144 (p,p'-DDT), o,p'-dichlorodiphenyltrichloroethane (o,p'-DDT), p,p'-
 145 dichlorodiphenyldichloroethylene (p,p'-DDE), o,p'-dichlorodiphenyldichloroethylene (o,p'-
 146 DDE), p,p'-dichlorodiphenyldichloroethane (p,p'-DDD), o,p'-dichlorodiphenyldichloroethane
 147 (o,p'-DDD), γ -hexachlorocyclohexane (γ -HCH), α -hexachlorocyclohexane (α -HCH), Δ -
 148 hexachlorocyclohexane (Δ -HCH), β -hexachlorocyclohexane (β -HCH), α -chlordan, γ -
 149 chlordan, oxychlordan, trans-nonachlor, cis-nonachlor, heptachlor, trans-heptachlor
 150 epoxide, cis-heptachlor epoxide, α -endosulfan, β -endosulfan, endosulfan sulfate, dieldrin,
 151 aldrin, endrin, mirex, hexachlorobenzene (HCB), pentachlorobenzene (PeCBz);
- 152 – 14 polychlorinated biphenyls (PCBs) in the plasma:
- 153 ○ 8 'dioxin-like' congeners (DL-PCBs), corresponding to congeners having a spatial
 154 structure similar to polychlorinated dibenzo-para-dioxins and polychlorinated
 155 dibenzofurans and capable of activating the aryl hydrocarbon receptor (Kafafi et al.
 156 1993; Van den Berg et al. 2006): 2,3,3',4,4'-pentachlorobiphenyl (PCB-105),
 157 2,3,4,4',5-pentachlorobiphenyl (PCB-114), 2,3',4,4',5-pentachlorobiphenyl (PCB-118),
 158 2,3',4,4',5'-pentachlorobiphenyl (PCB-123), 2,3,3',4,4',5-hexachlorobiphenyl (PCB-
 159 156), 2,3,3',4,4',5'-hexachlorobiphenyl (PCB-157), 2,3',4,4',5,5'-hexachlorobiphenyl
 160 (PCB-167), 2,3,3',4,4',5,5'-heptachlorobiphenyl (PCB-189);
 - 161 ○ 6 'non-dioxin-like' congeners (NDL-PCBs), corresponding to the other congeners,
 162 which induce toxicity mainly by other mechanisms: 2,4,4'-trichlorobiphenyl (PCB-
 163 28), 2,2',5,5'-tetrachlorobiphenyl (PCB-52), 2,2',4,5,5'-pentachlorobiphenyl (PCB-

164 101), 2,2',3,4,4',5'-hexachlorobiphenyl (PCB-138), 2,2',4,4',5,5'-hexachlorobiphenyl
165 (PCB-153) and 2,2',3,4,4',5,5'-heptachlorobiphenyl (PCB-180);

166 – 4 polybrominated diphenyl ethers (PBDEs) in the plasma: 2,2',4,4'-tetrabromodiphenyl ether
167 (PBDE-47), 2,2',4,4',5-pentabromodiphenyl ether (PBDE-99), 2,2',4,4',6-pentabromodiphenyl
168 ether (PBDE-100), 2,2',4,4',5,5'-hexabromodiphenyl ether (PBDE-153).

169 *Exposure determinants*

170 Information on school educational level (<12 years; 12 to 14 years; >14 years of studies) and place of
171 residence (urban, i.e. living in a commune or a group of communes with more than 2,000 inhabitants;
172 rural) (Binachon et al. 2014) were collected through the baseline questionnaire sent in 1990.
173 Information on parity, i.e. the number of children live born, stillborn or of unknown vital status at birth
174 (nulliparous; one or two children; ≥ 3 children), and on the cumulated duration of previous
175 breastfeeding (none; <6 months; ≥ 6 months), were collected through the second questionnaire sent in
176 1992. A validated semi-quantitative food questionnaire sent in 1993 assessed the participants' typical
177 diet over the previous year (Van Liere et al. 1997). Daily dietary intakes of 208 foods were collected
178 (in g/day), making it possible to estimate the usual daily consumption of 8 main food groups which
179 were used in the present analyses: red meat, white meat, *charcuterie* (sausage, *andouille*, *pâté*,
180 *rillettes*, blood sausage, andouillette...), offal (liver, tongue, brains, heart, kidneys, tripe...), fish,
181 vegetables, fruits, and dairy foods. Adherence to French dietary guidelines was estimated using the
182 simplified “Programme National Nutrition Santé - guidelines score 2” (sPNNS-GS2) (Chaltiel et al.
183 2019; 2021). For women reporting extreme energy intake values (i.e., below the 1st or above the 99th
184 percentiles of the ratio between energy intake and energy requirement, n=9), we considered the
185 reported values as missing for the dietary variables described above (i.e., food groups consumptions
186 and adherence to the sPNNS-GS2) . Body mass index (BMI) was obtained from height and weight
187 collected at each follow-up questionnaire, allowing to estimate the variation of BMI between the
188 baseline questionnaire and blood collection (in kg/m² per year). Information related to menopause
189 (menopausal status, hormone treatments, date of last period, side effects of menopause, gynecological
190 operations, etc.) was collected at each follow-up questionnaire, allowing to estimate age at menopause.
191 This latter was used to estimate time since menopause at blood collection (set to null if the woman was
192 premenopausal at blood collection).

193 *Statistical analyses*

194 Characteristics of the study population were described in the overall study sample: mean and standard
195 deviation were presented for continuous variables, and numbers and proportions for categorical
196 variables. Median and 95th percentiles of POPs biomarkers levels measured in this study were
197 described and compared with levels measured in two more recent French biomonitoring studies, the

198 ENNS and Esteban studies (Castetbon et al. 2009; Fillol et al. 2021). These two cross-sectional studies
199 used a three-stage cluster sampling (1st level: municipalities or group of municipalities; 2nd stage:
200 household; 3rd stage: individual) stratified by geographical areas (8 French regions) and degree of
201 urbanization (5 degrees). Nationally representative samples of the general population living in
202 mainland France during the 2006-2007 (ENNS) and 2014–2016 (Esteban) periods were selected.
203 Fasting blood samples were collected, and chemical biomarker levels were measured in the serum. We
204 restricted our comparisons to adult women, aged 18 to 74 years, for which the biomarkers of interest
205 were measured (N=254 for ENNS and N=428 maximum for Esteban).

206 For the rest of the analyses, the biomarkers having more than 25% undetected values were not
207 included in further statistical analyses, and one woman for whom the PFAS could not be measured due
208 to insufficient serum amount was excluded, resulting in 41 POPs and 467 women. The remaining non-
209 quantified values for POPs were imputed by the lower limit of quantification divided by $\sqrt{2}$
210 (Supplementary table 1), as recommended when exposure distributions are not highly skewed
211 (Hornung and Reed 1990).

212 A heat-map representing Spearman rank correlation coefficients between levels of POPs was
213 constructed. A principal component analysis (PCA) was performed on standardized POPs (i.e., divided
214 by their standard deviation) to identify the main POPs exposure profiles. The number of principal
215 components, representing the main POPs exposure profiles, to be retained was chosen using the scree-
216 plot of variance explained and the interpretability of the principal components obtained. A varimax
217 rotation was performed on the final number of components retained to increase their interpretability.
218 This is an oblique rotation which generally results in each original variable being correlated with one
219 component, and each component representing only a small number of variables (Kaiser 1958;
220 Bountziouka and Panagiotakos 2021).

221 To explore the associations between anthropometric, socio-demographic and lifestyle characteristics
222 with these profiles, linear regression models were performed, estimating associations between
223 covariates of interest and the POPs exposure profiles identified by PCA. The set of exposures of
224 interest was selected based on prior knowledge: age at blood collection, school educational level, place
225 of residence at inclusion, duration of previous breastfeeding, parity, BMI variation per year between
226 baseline and blood collection, time since menopause at blood collection, and daily average
227 consumption of the main food groups. A directed acyclic graph (DAG) was constructed to identify, for
228 each exposure of interest, the potential confounders for which the analyses should be adjusted to
229 estimate their direct effect on adherence to the POPs exposure profiles, and to highlight the variables
230 for which the analyses should not be adjusted for (e.g., colliders) (Supplementary figure 1). According
231 to this DAG, all exposures can be adjusted on all of the other covariates to estimate their direct effects,

232 so all the exposures were included in the same model. Fractional polynomials were used to account for
233 potential non-linear relationships, and multiple imputation was performed to deal with missing data.
234 Thus, the analyses were performed according to the following steps:

- 235 1) The best fractional polynomials to model the relation between each continuous exposure of
236 interest and each POPs exposure profile were chosen (Royston and Altman 1994; Axell 2005)
237 using fully adjusted models, excluding the missing data for the given exposure and
238 temporarily imputing the missing data for the other covariates with mode or median.
- 239 2) Multiple imputation by chained equation was performed on missing data, generating 10
240 imputed datasets for each outcome (i.e., adherence to each of the six POPs exposure profiles)
241 (Buuren and Groothuis-Oudshoorn 2011). All covariates of the fully adjusted models,
242 including polynomial terms identified in the first step, were included in the corresponding
243 imputation models.
- 244 3) For each outcome (i.e., adherence to each POPs exposure profiles), the final models were
245 fitted on the 10 corresponding datasets, and the estimations on each dataset were pooled using
246 Rubin's rules to obtain estimates of the measures of association of interest (Rubin 2018).

247 All statistical tests were two-sided, and the threshold for statistical significance was set at 5%.
248 Statistical analyses were performed using the Statistical Analysis Systems software, version 9.4 (SAS
249 Institute, Cary, NC) and the R software, version 4.0.3.

250 *Sensitivity analyses*

251 An analysis that kept, for the dietary variables, the value originally reported in the questionnaires was
252 performed to assess the potential effect of imputing dietary variables for women who declared energy
253 intake values considered extreme (N=9). Additionally, to explore the associations between adherence
254 to French dietary guidelines and the six exposure profiles of POPs, adherence to sPNNS-GS2 was
255 included in the fully adjusted models instead of the daily average consumption of the main food
256 groups.

257 **Results**

258 *Characteristics of the study population*

259 The study population was composed of 468 women aged between 45 and 73 years at blood collection.
260 The characteristics of these women are presented in Table 1. A comparison between the characteristics
261 of the women included in the sample and those of the women included in the E3N cohort is presented
262 in the Supplementary table 2.

263 *Description of levels of biomarkers of POPs and comparison with other French studies*

264 A description of levels of biomarkers of POPs per volume of serum or plasma in the present study is
265 presented in the first three columns of Table 2. Supplementary table 1 provides a description of OCPs,
266 PCBs and PBDEs per gram of fat (obtained by dividing the pollutant concentration expressed per
267 gram of plasma by the fat content in the plasma classically determined by enzymatic measurement) as
268 well as additional information about non-quantified values and lower limits of detections for all POPs.
269 Among the PFASs and OCPs measured, just over half had at least 25% unquantified values, while
270 PBDEs were almost all quantified and PCBs all quantified.

271 A comparison with levels reported in the ENNS and Esteban studies are presented in the rightmost six
272 columns of Table 2. Among the 28 PFASs measured in the E3N cohort (1995-1999), 17 were also
273 measured in the Esteban study (2014-2016). A decrease in median levels between these two studies
274 was observed for N-EtFOSAA (0.57 ng/mL in E3N to <0.05 ng/mL in Esteban, i.e. at least 91%
275 reduction), PFOS (33.66 to 3.85 ng/mL, i.e. 89% reduction), N-MeFOSAA (0.38 to <0.05 ng/mL, i.e.
276 at least 87% reduction), PFOSA (0.59 to <0.20 ng/mL, i.e. at least 66% reduction), PFOA (5.16 to
277 1.89 ng/mL, i.e. 63% reduction), PFHpS (at least 49% reduction) and PFHxS (26% reduction).
278 Increases in median levels of PFDA (0.21 to 0.33 ng/mL, i.e. 57% increase), PFNA (37% increase)
279 and PFUnDA (27% increase) were observed. For other biomarkers (PFBA, PFDoDA, PFHpA, PFHxA
280 PFPeA, PFDS and PFBS), median levels were globally stable or non-detected in both studies. Among
281 the 27 OCPs measured in the E3N cohort (1995-1999), 6 were measured in the ENNS study (2006-
282 2007) and 18 in the Esteban study (2014-2026). Between the E3N and Esteban studies, median levels
283 of β -HCH (952.76 pg/mL in E3N to 76.57 pg/mL in Esteban, i.e. 92% reduction), p,p'-DDE (1708.20
284 to 390.46 pg/mL, i.e. 77% reduction), p,p'-DDT (32.41 to <10 pg/mL, i.e. at least 69% reduction), cis-
285 heptachlor epoxide (46.75 to 14.68 pg/mL, i.e. 69% reduction), oxychlordane (64.88 to 21.45 pg/mL,
286 i.e. 67% reduction), dieldrin (57.78 to 19.47 pg/mL, i.e. 66% reduction), and trans-nonachlor (45.42 to
287 16.82 pg/mL, i.e. 63% reduction) have decreased. Median level of HCB has slightly decreased (of
288 28%) between the E3N and ENNS studies. For other biomarkers (o,p'-DDT, o,p'-DDE, γ -HCH, α -
289 HCH, α -chlordane, γ -chlordane, cis-nonachlor, trans-heptachlor epoxide, aldrin, endrin and

290 Table 1: Characteristics of the study population: 468 women of the French E3N cohort study.

	Mean (Standard deviation) or Number (Percent)
Sociodemographic characteristics	
Age at blood collection (years), Mean (Standard deviation)	56.89 (6.48)
School educational level (years), Number (Percent)	
Missing value	14 (2.99)
<12	43 (9.19)
[12-14]	236 (50.43)
>14	175 (37.39)
Place of residence , Number (Percent)	
Missing value	35 (7.48)
Urban areas	392 (83.76)
Rural areas	41 (8.76)
Body mass index at inclusion in the cohort (kg/m ²), Mean (Standard deviation)	22.57 (2.95)
Missing value, Number (Percent)	7 (1.50)
Body mass index at blood collection (kg/m ²), Mean (Standard deviation)	23.92 (3.57)
Variation of body mass index between inclusion in the cohort and blood collection (kg/m ² per year), Mean (Standard deviation)	0.19 (0.23)
Missing value, Number (Percent)	7 (1.50)
Hormonal and reproductive information	
Menopausal status at blood collection , Number (Percent)	
Premenopausal	110 (23.50)
Postmenopausal	358 (76.50)
Time since menopause at blood collection (years), Mean (Standard deviation)	6.98 (7.03)
History of breastfeeding , Number (Percent)	
Missing value	24 (5.13)
No breastfeeding	146 (31.20)
Cumulative duration of breastfeeding <6 months	191 (40.81)
Cumulative duration of breastfeeding ≥6 months	107 (22.86)
Parity , Number (Percent)	
Nulliparous	54 (11.53)
One or two children	260 (55.56)
More than two children	154 (32.91)
Dietary habits	
Red meat consumption (g/day), Mean (Standard deviation)	60.69 (36.54)
White meat consumption (g/day), Mean (Standard deviation)	67.29 (30.52)
Charcuterie consumption (g/day), Mean (Standard deviation)	13.83 (14.35)
Offal consumption (g/day), Mean (Standard deviation)	7.78 (10.78)
Fish consumption (g/day), Mean (Standard deviation)	40.42 (27.57)
Vegetables consumption (g/day), Mean (Standard deviation)	402.43 (166.13)
Fruits consumption (g/day), Mean (Standard deviation)	349.46 (188.53)
Dairy food consumption (g/day), Mean (Standard deviation)	367.74 (202.70)
Adherence to the sPNNS-GS2 , Mean (Standard deviation)	3.98 (2.94)

291 Number (percentage) of missing data are indicated in an additional line, if any. For dietary consumption variables, the means and
292 standard deviations are given after excluding women who declared aberrant energy intakes (N=9, i.e.1.92%).
293 sPNNS-GS2: simplified “Programme National Nutrition Santé - guidelines score 2”

294 Table 2: Description and comparison of levels of biomarkers of persistent organic pollutants between three French studies at different periods: the French E3N
 295 cohort study, the National Nutritional and Health Study (ENNS) and the Health Study on Environment, Biomonitoring, Physical Activity and Nutrition
 296 (Esteban).

	E3N			ENNS			Esteban		
	1995-1999			2006-2007			2014-2016		
	Women, 45-73 years			Women, 18-74 years			Women, 18-74 years		
	Serum (PFAS)/Plasma (other POPs)			Serum			Serum		
	N	Median	95 ^e percentile	N	Median	95 ^e percentile	N	Median	95 ^e percentile
Per-and polyfluoroalkyl substances (PFASs) in ng/mL									
perfluorotetradecanoic acid (PFTeDA)	467	<LOQ	0.11						
perfluorotridecanoic acid (PFTrDA)	467	<LOQ	0.08						
perfluorododecanoic acid (PFDoDA)	467	<LOQ	0.06				428	<LOQ (0.05)	0.09
perfluoroundecanoic acid (PFUnDA)	467	0.15	0.33				428	0.19	0.43
perfluorodecanoic acid (PFDA)	467	0.21	0.47				428	0.33	0.79
perfluorononanoic acid (PFNA)	467	0.57	1.15				428	0.78	1.91
perfluorooctanoic acid (PFOA)	467	5.16	11.94				428	1.89	4.96
perfluoroheptanoic acid (PFHpA)	467	0.13	0.61				428	<LOQ (0.20)	<LOQ (0.20)
perfluorohexanoic acid (PFHxA)	467	<LOQ	<LOQ				428	<LOQ (0.20)	<LOQ (0.20)
perfluoropentanoic acid (PFPeA)	467	<LOQ	<LOQ				428	<LOQ (0.05)	<LOQ (0.05)
perfluorobutanoic acid (PFBA)	467	<LOQ	0.20				428	<LOQ (0.50)	<LOQ (0.50)
perfluorotridecanesulfonic acid (PFTrDS)	467	<LOQ	<LOQ						
perfluorododecanesulfonic acid (PFDoDS)	467	<LOQ	<LOQ						
perfluoroundecanesulfonic acid (PFUnDS)	467	<LOQ	<LOQ						
perfluorodecanesulfonic acid (PFDS)	467	<LOQ	<LOQ				428	<LOQ (0.19)	<LOQ (0.19)
perfluorononanesulfonic acid (PFNS)	467	<LOQ	<LOQ						
perfluorooctanesulfonic acid (PFOS)	467	33.66	63.40				428	3.85	12.93
perfluoroheptanesulfonic acid (PFHpS)	467	0.37	0.68				428	<LOQ (0.19)	0.42
perfluorohexanesulfonic acid (PFHxS)	467	1.47	3.91				428	1.09	3.08
perfluoropentanesulfonic acid (PFPeS)	467	0.03	0.07						

perfluorobutanesulfonic acid (PFBS)	467	<LOQ	<LOQ				428	<LOQ (0.19)	<LOQ (0.19)
perfluorooctanesulfonamide (PFOSA)	467	0.59	1.51				428	<LOQ (0.20)	<LOQ (0.20)
N-ethylperfluorooctane sulfonamidoacetic acid (N-EtFOSAA)	467	0.57	1.93				428	<LOQ (0.05)	<LOQ (0.05)
N-methylperfluorooctanesulfonamidoacetic acid (N-MeFOSAA)	467	0.38	1.17				428	<LOQ (0.05)	0.12
2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)propanoic acid (GenX)	467	<LOQ	<LOQ						
dodecafluoro-3H-4,8-dioxananoate (DONA)	467	<LOQ	<LOQ						
9-chlorohexadecafluoro-3-oxanonane-1-sulfonate (F53B major)	467	<LOQ	<LOQ						
11-chlororeicosafuoro-3-oxaundecane-1-sulfonate (F53B minor)	467	<LOQ	<LOQ						

Organochlorine pesticides (OCPs) in pg/mL

p,p'-dichlorodiphenyltrichloroethane (p,p'-DDT)	468	32.41	207.19	254	30.0	166.2	421	<LOQ (10.0)	49.92
o,p'-dichlorodiphenyltrichloroethane (o,p'-DDT)	468	<LOQ	20.00				421	<LOQ (10.0)	<LOQ (10.0)
p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE)	468	1708.20	6785.62	254	899	5564	421	390.46	3041.90
o,p'-dichlorodiphenyldichloroethylene (o,p'-DDE)	468	1.03	3.35				421	<LOQ (10.0)	<LOQ (10.0)
p,p'-dichlorodiphenyldichloroethane (p,p'-DDD)	468	2.96	14.88						
o,p'-dichlorodiphenyldichloroethane (o,p'-DDD)	468	<LOQ	1.58						
γ -hexachlorocyclohexane (γ -HCH)	468	<LOQ	46.80	254	<LOD (10.0)	<LOQ (30.0)	421	<LOQ (10.0)	20.32
α -hexachlorocyclohexane (α -HCH)	468	<LOQ	10.34	254	<LOQ (6.0)	9.9	421	<LOQ (10.0)	<LOQ (10.0)
Δ -hexachlorocyclohexane (Δ -HCH)	468	<LOQ	<LOQ						
β -hexachlorocyclohexane (β -HCH)	468	952.76	2465.57	254	196	1595	421	76.57	687.97
α -chlordane	468	<LOQ	<LOQ				421	<LOQ (10.0)	<LOQ (10.0)
γ -chlordane	468	<LOQ	<LOQ				421	<LOQ (10.0)	<LOQ (10.0)
oxychlordane	468	64.88	127.78				421	21.45	70.14
trans-nonachlor	468	45.42	89.85				421	16.82	57.37
cis-nonachlor	468	7.19	16.85				421	<LOQ (10.0)	11.31
heptachlor	468	<LOQ	<LOQ						
trans-heptachlor epoxide	468	<LOQ	<LOQ				421	<LOQ (10.0)	<LOQ (10.0)
cis-heptachlor epoxide	468	46.75	138.92				421	14.68	51.50
α -endosulfan	468	<LOQ	<LOQ						
β -endosulfan	468	<LOQ	<LOQ						
endosulfan sulfate	468	<LOQ	<LOQ						
dieldrin	468	57.78	153.99				421	19.47	60.06

aldrin	468	<LOQ	3.65				421	<LOQ (10.0)	<LOQ (10.0)
endrin	468	<LOQ	15.86				421	<LOQ (10.0)	<LOQ (10.0)
mirex	468	<LOQ	12.71				421	<LOQ (10.0)	12.19
hexachlorobenzene (HCB)	468	246.95	613.20	254	178	652			
pentachlorobenzene (PeCBz)	468	5.71	12.51						

Non-dioxin-like polychlorinated biphenyls (NDL-PCBs) in pg/mL

2,4,4'-trichlorobiphenyl (PCB-28)	468	12.69	44.89	254	17.5	44.3			
2,2',5,5'-tetrachlorobiphenyl (PCB-52)	468	4.44	13.96	254	<LOD (2.0)	11.59			
2,2',4,5,5'-pentachlorobiphenyl (PCB-101)	468	6.27	19.49	254	8.6	24.9			
2,2',3,4,4',5'-hexachlorobiphenyl (PCB-138)	468	604.14	1237.94	254	561.5	1416.6			
2,2',4,4',5,5'-hexachlorobiphenyl (PCB-153)	468	1276.72	2465.26	254	864.1	2020.0			
2,2',3,4,4',5,5'-heptachlorobiphenyl (PCB-180)	468	991.36	1895.11	254	721.7	1484.5			

Dioxin-like polychlorinated biphenyls (DL-PCBs) in pg/mL

2,3,3',4,4'-pentachlorobiphenyl (PCB-105)	468	37.77	110.00						
2,3,4,4',5-pentachlorobiphenyl (PCB-114)	468	11.81	25.75						
2,3',4,4',5-pentachlorobiphenyl (PCB-118)	468	243.60	602.65						
2,3',4,4',5'-pentachlorobiphenyl (PCB-123)	468	2.11	6.78						
2,3,3',4,4',5-hexachlorobiphenyl (PCB-156)	468	125.95	233.03						
2,3,3',4,4',5'-hexachlorobiphenyl (PCB-157)	468	27.58	53.43						
2,3',4,4',5,5'-hexachlorobiphenyl (PCB-167)	468	42.88	88.97						
2,3,3',4,4',5,5'-heptachlorobiphenyl (PCB-189)	468	11.72	23.87						

Polybrominated diphenyl ethers (PBDEs) in pg/mL

2,2',4,4'-tetrabromodiphenyl ether (PBDE-47)	468	2.50	9.82				425	1.18	4.92
2,2',4,4',5-pentabromodiphenyl ether (PBDE-99)	468	0.69	2.72				425	0.26	1.13
2,2',4,4',6-pentabromodiphenyl ether (PBDE-100)	468	0.85	2.93				425	0.36	1.50
2,2',4,4',5,5'-hexabromodiphenyl ether (PBDE-153)	468	2.52	4.96				425	3.68	9.35

297 ENNS: National Nutritional and Health Study. Esteban: Health Study on Environment, Biomonitoring, Physical Activity and Nutrition. LOD: Lower limit of detection; LOQ: Lower limit of quantification. Where the
298 median or 95th percentile value was not quantified, the detection limit of the corresponding sample is shown in parentheses, except for the E3N study in which the LOQ of a given substance varies depending on the
299 samples. We considered any non-quantified values to be lower than any quantified value.

301 mirex), median levels were globally stable or non-detected in the two or three available studies. The 6
302 NDL-PCBs measured in the E3N cohort (1995-1999) were also measured in the ENNS study (2006-2007):
303 between these two periods, a decrease in median levels of PCB-52 (4.44 to <2 pg/mL; i.e. at least 55%
304 reduction), 153 (32% reduction), 180 (27% reduction) and 138 (7% reduction) was observed, while PCB-28
305 and 101 median level have slightly increased (of respectively 38% and 37%). No DL-PCB has been
306 measured in the ENNS and Esteban studies. The 4 PBDEs measured in the E3N cohort (1995-1999) were
307 also measured in the Esteban study (2014-2016): median levels of PBDE-99 (0.69 to 0.26 pg/mL, i.e. 62%
308 reduction), PBDE-100 (0.85 to 0.36 pg/mL, i.e. 57% reduction) and PBDE-47 (2.50 to 1.18 pg/mL, i.e.
309 53% reduction) have decreased, while PBDE-153 median level has increased (of 46%).

310 *POPs exposure profiles and associated factors*

311 Correlations between levels of biomarkers of POPs are presented in the Supplementary figure 2. Spearman
312 correlation coefficients ranged between -0.14 and 0.96 and were globally higher for POPs belonging to the
313 same family of chemicals.

314 A total of 6 exposure profiles (i.e., principal components) were retained, explaining 62.1% of the variance.
315 The scree-plot is presented in the Supplementary figure 3. Loading factors of the final exposure profiles are
316 presented in Table 3. The first exposure profile explained 16.0% of the initial exposure matrix variance, and
317 was characterized by high loading factors for DL-PCBs, NDL-PCBs and nonachlors. The second exposure
318 profile explained 13.9% of the variance and was characterized by high loading factors for OCPs and DL-
319 PCBs. The third exposure profile explained 11.0% of the variance and was characterized by high loading
320 factors for PFAS. The fourth exposure profile explained 8.7% of the variance and was characterized by
321 high loading factors for both DL- PCBs and NDL-PCBs. The fifth exposure profile explained 8.0% of the
322 variance and was characterized by high loading factors for PBDEs. The sixth exposure profile explained
323 4.6% of the variance and was characterized by high loading factors for DDT metabolites.

324 Regression coefficients and p-values for the associations between the covariates of interest and adherence
325 to each exposure profile are presented in Table 4, and the shapes of the associations are presented in
326 Supplementary figures 4A and 4B.

327 For the “DL-PCBs, NDL-PCBs and nonachlors” profile, positive associations were highlighted for
328 vegetables consumption, this association being linear, and fish and seafood consumption, with a non-linear
329 but monotonic association: the higher the consumption of vegetables and fish and seafood, the greater the
330 adherence to the profile. Conversely, a higher annual increase in BMI and a higher consumption of white
331 meat were linearly and negatively associated with adherence to this profile. Finally, fruits consumption
332 showed a non-linear and non-monotonic association: the adherence to this profile increased and then
333 decreased as fruits consumption increased.

334

335 Table 3: Loading factors for POPs in the 6 retained principal components ordered by decreasing variance, after performing a principal component analysis with
 336 varimax rotation on biomarkers of 41 POPs in the blood samples of women of the French E3N cohort study (N=467).

Principal component 1 (16.0%) DL-PCBs, NDL-PCBs & nonachlors		Principal component 2 (13.9%) OCPs & DL-PCBs		Principal component 3 (11.0%) PFASs		Principal component 4 (8.7%) DL-PCBs & NDL-PCBs		Principal component 5 (8.0%) PBDEs		Principal component 6 (4.6%) DDT metabolites	
PCB-180	0.93	heptachlor-epoxyde-cis	0.85	PFOS	0.83	PCB-52	0.80	PBDE-100	0.97	p,p'-DDD	0.70
PCB-189	0.92	oxychlordane	0.72	PFNA	0.83	PCB-101	0.80	PBDE-99	0.95	o,p'-DDE	0.68
PCB-157	0.91	HCB	0.70	PFHpS	0.82	PCB-105	0.64	PBDE-47	0.94	p,p'-DDE	0.55
PCB-156	0.89	β-HCH	0.70	PFOA	0.72	PCB-118	0.63	PBDE-153	0.65	dieldrin	0.30
PCB-153	0.86	trans-nonachlor	0.65	PFDA	0.68	PCB-123	0.63	N-MeFOSAA	0.14	PFUnDA	0.24
PCB-167	0.70	PCB-105	0.61	PFUnDA	0.59	PCB-28	0.56	PCB-138	0.13	PCB-28	0.21
PCB-138	0.70	PCB-118	0.61	PFPeS	0.55	PCB-114	0.48	p,p'-DDE	0.12	PCB-138	0.20
PCB-114	0.58	PCB-123	0.60	PFHpA	0.43	PCB-167	0.30	PCB-153	0.12	cis-nonachlor	0.19
trans-nonachlor	0.44	cis-nonachlor	0.58	PFHxS	0.41	PFOSA	0.24	PCB-167	0.09	PeCBz	0.17
cis-nonachlor	0.41	dieldrin	0.57	PFOSA	0.35	p,p'-DDE	0.23	cis-nonachlor	0.07	trans-nonachlor	0.17
oxychlordane	0.32	PCB-167	0.50	cis-nonachlor	0.28	PCB-138	0.23	PCB-157	0.07	PCB-153	0.15
PFUnDA	0.31	PCB-114	0.49	N-MeFOSAA	0.24	PeCBz	0.20	PFUnDA	0.06	PCB-101	0.13
PCB-118	0.31	PCB-138	0.44	N-EtFOSAA	0.24	PCB-153	0.19	trans-nonachlor	0.06	PFHxS	0.12
PFDA	0.28	p,p'-DDE	0.41	trans-nonachlor	0.18	p,p'-DDD	0.18	PCB-105	0.06	PFDA	0.12
PCB-105	0.25	PCB-153	0.32	PCB-167	0.12	PCB-156	0.17	PCB-118	0.06	PCB-105	0.12
PCB-123	0.23	PCB-28	0.29	PCB-189	0.12	β-HCH	0.16	PCB-180	0.06	heptachlor-epoxyde-cis	0.11
PCB-101	0.23	PCB-156	0.27	PCB-153	0.12	PFHpA	0.15	PFNA	0.04	PCB-118	0.09
PBDE-153	0.22	o,p'-DDE	0.18	PCB-180	0.12	o,p'-DDE	0.13	PFOSA	0.04	PCB-180	0.07
p,p'-DDE	0.20	PCB-157	0.18	dieldrin	0.10	N-EtFOSAA	0.12	oxychlordane	0.04	PBDE-100	0.07
β-HCH	0.19	PFHpS	0.16	PCB-156	0.10	PCB-157	0.12	PCB-156	0.04	PFPeS	0.06
PFOS	0.16	PFNA	0.15	PCB-157	0.09	PFOA	0.11	PCB-101	0.04	PFNA	0.05
PFOSA	0.16	PFOS	0.12	PCB-101	0.09	dieldrin	0.08	o,p'-DDE	0.03	PCB-189	0.04
PeCBz	0.14	PCB-180	0.08	PCB-138	0.09	PFPeS	0.06	PFHpS	0.02	PBDE-153	0.04
PFNA	0.12	PFHpA	0.07	oxychlordane	0.08	heptachlor-epoxyde-cis	0.05	PFOA	0.02	PCB-167	0.03
o,p'-DDE	0.12	PFOA	0.06	PCB-105	0.08	HCB	0.04	p,p'-DDD	0.02	β-HCH	0.02
HCB	0.10	N-EtFOSAA	0.06	heptachlor-epoxyde-cis	0.07	PCB-180	0.04	PCB-123	0.02	PCB-123	0.02
PFHpS	0.07	p,p'-DDD	0.06	PCB-123	0.07	PBDE-100	0.03	PCB-189	0.02	PCB-52	0.01
dieldrin	0.07	PBDE-100	0.05	PCB-118	0.06	PFNA	0.02	PFHxS	0.01	oxychlordane	0.00
N-MeFOSAA	0.06	PBDE-47	0.04	PCB-52	0.06	PBDE-47	0.02	PCB-114	0.01	PBDE-99	0.00
PBDE-100	0.05	PeCBz	0.03	PBDE-153	0.06	PBDE-99	0.02	PCB-28	0.01	PCB-156	-0.01
PCB-52	0.04	PCB-189	0.03	p,p'-DDD	0.04	oxychlordane	0.01	PFDA	0.00	PBDE-47	-0.01

p,p'-DDD	0.03	PBDE-99	0.03	PCB-114	0.04	PFHpS	0.00	PCB-52	0.00	PCB-114	-0.02
PFHpA	0.01	PFOSA	0.01	PBDE-100	0.04	PFOS	0.00	PFOS	-0.01	PCB-157	-0.02
N-EtFOSAA	0.01	PCB-101	0.01	PCB-28	0.03	PCB-189	0.00	PFHpA	-0.01	PFHpA	-0.05
PBDE-47	0.00	PFHxS	-0.01	o,p'-DDE	0.01	PBDE-153	0.00	heptachlor-epoxyde-cis	-0.02	HCB	-0.08
PBDE-99	0.00	PFPeS	-0.02	PBDE-47	0.01	PFDA	-0.03	PFPeS	-0.03	PFOA	-0.09
PFOA	-0.01	PFDA	-0.04	PeCBz	0.00	N-MeFOSAA	-0.03	N-EtFOSAA	-0.03	PFOS	-0.10
PFPeS	-0.03	PFUnDA	-0.04	PBDE-99	-0.02	PFUnDA	-0.05	HCB	-0.03	PFHpS	-0.11
PFHxS	-0.05	PBDE-153	-0.06	β -HCH	-0.03	trans-nonachlor	-0.05	dieldrin	-0.03	N-MeFOSAA	-0.12
heptachlor-epoxyde-cis	-0.05	PCB-52	-0.10	HCB	-0.07	cis-nonachlor	-0.06	PeCBz	-0.04	N-EtFOSAA	-0.22
PCB-28	-0.05	N-MeFOSAA	-0.11	p,p'-DDE	-0.07	PFHxS	-0.08	β -HCH	-0.05	PFOSA	-0.26

337 The horizontal line delimits the biomarkers with loadings greater than 0.40 in absolute value, used to name the principal components.

338

339 Table 4: Estimation of regression coefficients (β) and their 95% Confidence Intervals (95% CI) for the associations between anthropometric, socio-demographic and
 340 lifestyle characteristics and six exposure profiles of POPs in the blood samples of women of the French E3N cohort study (N=467).

	Principal component 1 DL-PCBs, NDL-PCBs & nonachlors		Principal component 2 OCPs & DL-PCBs		Principal component 3 PFASs		Principal component 4 DL-PCBs & NDL-PCBs		Principal component 5 PBDEs		Principal component 6 DDT metabolites	
	β [95% CI]	p	β [95% CI]	p	β [95% CI]	p	β [95% CI]	p	β [95% CI]	p	β [95% CI]	p
Age at blood collection , for a one-year increase	0.01 [-0.01,0.04]	0.322	0.03 [0.01,0.05]	0.009	0 [-0.03,0.02]	0.765	0.03 [0.0,0.06]	0.047	-0.01 [-0.04,0.02]	0.569	-0.01 [-0.04,0.02]	0.452
School educational level		0.650		0.895		0.532		0.040		0.223		0.846
<12 years	Ref		Ref		Ref		Ref		Ref		Ref	
[12-14] years	0.03 [-0.27,0.33]		-0.07 [-0.36,0.22]		-0.09 [-0.4,0.22]		0.25 [-0.06,0.57]		0.02 [-0.3,0.35]		-0.03 [-0.35,0.3]	
>14 years	0.11 [-0.21,0.42]		-0.07 [-0.37,0.24]		0.01 [-0.31,0.34]		0.41 [0.08,0.74]		0.19 [-0.15,0.53]		0.03 [-0.31,0.37]	
Place of residence		0.495		0.004		0.468		0.196		0.75		0.937
Urban	Ref		Ref		Ref		Ref		Ref		Ref	
Rural	0.1 [-0.19,0.39]		0.42 [0.13,0.7]		-0.11 [-0.42,0.19]		-0.2 [-0.51,0.1]		0.07 [-0.35,0.49]		-0.01 [-0.33,0.31]	
History of breastfeeding		0.109		0.768		0.486		0.641		0.564		0.008
No breastfeeding	Ref		Ref		Ref		Ref		Ref		Ref	
Cumulative duration of breastfeeding <6 months	0.22 [-0.01,0.45]		-0.08 [-0.3,0.14]		-0.11 [-0.35,0.12]		0.11 [-0.14,0.35]		0 [-0.25,0.25]		0.09 [-0.15,0.34]	
Cumulative duration of breastfeeding \geq 6 months	0.05 [-0.22,0.31]		-0.06 [-0.31,0.2]		-0.16 [-0.43,0.11]		0.11 [-0.16,0.39]		0.13 [-0.16,0.41]		0.41 [0.13,0.69]	
Parity		0.142		0.522		0.495		0.157		0.34		0.026
Nulliparous	Ref		Ref		Ref		Ref		Ref		Ref	
One or two children	-0.02 [-0.34,0.3]		0.05 [-0.26,0.36]		0 [-0.32,0.32]		-0.2 [-0.53,0.14]		0.22 [-0.12,0.57]		-0.08 [-0.41,0.26]	
More than two children	-0.21 [-0.56,0.13]		0.15 [-0.18,0.48]		-0.12 [-0.47,0.23]		-0.34 [-0.7,0.03]		0.28 [-0.09,0.66]		-0.35 [-0.72,0.02]	
Variation of BMI between inclusion and blood collection , for an increase of one kg/m ² per year	-1.17 [-1.54,-0.79]	<0.001	NL	<0.001	0.1 [-0.28,0.49]	0.601	0.14 [-0.25,0.53]	0.488	-0.02 [-0.43,0.39]	0.923	0.34 [-0.06,0.74]	0.095
Time since menopause at blood collection , for a one-year increase	0 [-0.03,0.02]	0.851	NL	0.010	NL	<0.001	0.01 [-0.01,0.04]	0.338	0.01 [-0.02,0.03]	0.613	0 [-0.03,0.02]	0.856
Red meat consumption , for a one-SD increase	0.07 [-0.06,0.2]	0.300	0.05 [-0.07,0.17]	0.429	0.09 [-0.04,0.22]	0.193	-0.02 [-0.15,0.12]	0.785	0.07 [-0.07,0.2]	0.339	0.12 [-0.02,0.26]	0.082
White meat consumption , for a one-SD increase	-0.16 [-0.28,-0.03]	0.016	0.06 [-0.07,0.18]	0.373	-0.06 [-0.19,0.07]	0.389	-0.04 [-0.18,0.09]	0.537	-0.05 [-0.19,0.08]	0.441	-0.1 [-0.24,0.03]	0.142
Charcuterie consumption , for a one-SD increase	-0.04 [-0.13,0.04]	0.329	0.09 [0.01,0.18]	0.030	0.03 [-0.06,0.12]	0.501	-0.01 [-0.1,0.08]	0.864	-0.05 [-0.14,0.05]	0.335	0 [-0.09,0.09]	0.978
Offal consumption , for a one-SD increase	0.05 [-0.03,0.14]	0.236	0 [-0.09,0.08]	0.965	-0.02 [-0.11,0.07]	0.710	-0.01 [-0.1,0.09]	0.915	-0.04 [-0.14,0.05]	0.380	NL	0.001
Fish and seafood consumption , for a one-SD increase	NL	<0.001	0.04 [-0.04,0.12]	0.351	0.22 [0.13,0.31]	<0.001	-0.08 [-0.17,0.01]	0.092	0.15 [0.05,0.24]	0.002	0.04 [-0.05,0.13]	0.418
Vegetables consumption , for a one SD-increase	0.1 [0.01,0.19]	0.033	0.11 [0.02,0.19]	0.018	NL	0.022	0.11 [0.01,0.2]	0.031	-0.01 [-0.11,0.08]	0.779	0.09 [-0.01,0.19]	0.067
Fruits consumption , for a one-SD increase	NL	0.003	NL	0.001	NL	0.010	-0.09 [-0.18,0.01]	0.068	-0.09 [-0.19,0]	0.056	0 [-0.09,0.1]	0.930
Dairy food consumption , for a one-SD increase	-0.01 [-0.09,0.08]	0.877	-0.03 [-0.12,0.05]	0.417	-0.06 [-0.15,0.03]	0.208	-0.05 [-0.14,0.04]	0.290	-0.04 [-0.14,0.05]	0.366	-0.01 [-0.1,0.09]	0.906

341 SD: Standard deviation; NL: Non-linear relationship; β are given for one standard deviation increase of the principal components.

342 A higher age at blood collection, a longer time elapsed since menopause, being resident in a rural area
343 at baseline, having higher consumption of charcuterie and vegetables were positively associated with
344 adherence to the “OCPs and DL-PCBs” profile. The association was non-linear for time since
345 menopause. Conversely, negative and non-linear associations were highlighted for annual increase in
346 BMI and fruit consumption.

347 A longer time elapsed since menopause, a higher vegetable consumption and a higher fish and seafood
348 consumption were positively associated with adherence to the “PFASs” profile. This association was
349 linear only for fish and seafood consumption. A negative, non-linear association was highlighted
350 between fruit consumption and adherence to this profile.

351 A higher age at blood collection, a higher school educational level and higher vegetables consumption
352 were positively (and linearly for continuous variables) associated with the “DL-PCBs & NDL-PCBs”
353 profile.

354 A higher fish and seafood consumption was positively and linearly associated with adherence to the
355 “PBDEs” profile.

356 Parity and duration of previous breastfeeding were associated with adherence to the “DDT
357 metabolites” profile: nulliparous women and those who had breastfed had a higher adherence to this
358 profile. A higher offal consumption was positively and non-linearly associated with adherence to this
359 profile.

360 *Sensitivity analyses*

361 The results of the analyses that kept, for dietary variables, the values originally reported in the
362 questionnaires (instead of imputing values for women reporting extreme energy intake values) were
363 globally unchanged compared to the main analyses, with few exceptions. For the “PFASs” profile, the
364 association with vegetable consumption became non-significant, and the association with fruit
365 consumption became positive and linear. For the “DL-PCBs & NDL-PCBs” profile, the association
366 with vegetable consumption became non-linear, decreasing then increasing (data not shown).

367 The analyses including adherence to French dietary guidelines showed a negative association with the
368 “PFASs” profile, and a non-linear negative association with the “DDT metabolites” profile
369 (Supplementary figure 5).

370 **Discussion**

371 This study describes for the first time the blood chemical exposure levels for multiple POPs in a
372 sample of adult women living in France in the 90's and compares them with the levels in adult women
373 at two more recent periods in France (2006-2007, and 2014-2016), showing a general decreasing trend
374 of exposure levels to most POPs over time in France. Since there are no data on blood exposure levels
375 in France before the 2000s, this study is important for determining whether the restriction strategies
376 have been effective. Actually, few biomonitoring studies reporting contamination levels of PCBs and
377 OCP in French breast milk collected are available before that date (Bordet et al. 1993), however we
378 did not integrate in the time trend study due to high fat variations and the imperfect blood/milk
379 partition ratios preventing the direct comparison (Mannetje et al. 2012). In any case, the levels of
380 PCBs and OCP in fat breast-milk in the early 1990s were in average in the range 6-287 ng/g, with the
381 exception of DDE that peaked at up to 2.2 mg/g (Bordet et al. 1993) consistent with our findings.

382 Concerning the OCPs, the decrease of levels of most substances is consistent with the regulations set
383 up since the 1970s. Concerning the NDL-PCBs, lower levels were observed in the Esteban study for
384 all PCBs except PCB-28 and PCB-101. Level reductions of most PCBs are compatible with the ban of
385 their production in 1987. However, it should be noted that measures to eliminate PCB-containing
386 equipment are more recent (2001 and 2013) (Ineris 2017), which could explain the lack of decrease
387 observed for some congeners. Concerning PBDEs, the regulations are more recent (between 2003 and
388 2009), which could explain why relatively slight decreases were observed between the E3N and
389 Esteban studies for most PBDEs. The lack of decrease of PBDE-153 between these two studies could
390 be partly related to its longer half-life than that of the other congeners (Sjödin et al. 2020), which can
391 lead to a slower decline in exposure levels. Finally, among the PFASs measured in both E3N and
392 Esteban studies, levels of the most important substances have decreased, including those registered in
393 the Stockholm convention (PFOA, PFOS and PFHxS), while others have increased (PFUnDA, PFDA
394 and PFNA) or remained globally stable. Other PFASs, like those used as PFOA / PFOS replacement
395 substances (GenX, DONA, F53B-major, F53B-minor) have not been measured in Esteban or ENNS
396 studies, not allowing to make a comparison.

397 Based on the blood levels of 41 POPs measured in 467 women of the E3N prospective cohort, this
398 study identified six main profiles of exposure to POPs: the "PCBs and nonachlors" profile, the "OCPs
399 and DL-PCBs" profile, the "PFASs" profile, the "DL-PCBs & NDL-PCBs" profile, the "PBDEs"
400 profile and the "DDT metabolites" profile. Some anthropometric, socio-demographic and lifestyle
401 factors were shown to be associated with the profiles of exposure to POPs. First, the age at blood
402 collection was positively associated with adherence to the "OCPs & DL-PCBs" and "DL-PCBs &
403 NDL-PCBs" profiles, which is consistent with the fact that POPs bioaccumulate in the body
404 throughout life. The positive association between the rural place of residence and the "OCPs & DL-
405 PCBs" profile is consistent with a plausible higher exposition to pesticides in rural areas. Parity was
406 negatively associated with the "DDT metabolites" profile which is consistent with the hypothesis that

407 parity reduces the level of exposure to POPs by transmitting part of the woman's body burden to the
408 child (Berg et al. 2014; Brantsæter et al. 2013). The negative associations between the variation of
409 BMI and the adherence to the "PCBs & nonachlors" and "OCPs and DL-PCBs" profiles are consistent
410 with the hypothesis that loss of weight may contribute to increasing serum levels of lipophilic POPs,
411 which are stored in fat and partly released during weight loss (Jansen et al. 2017). A longer time
412 elapsed since menopause was associated with an increased adherence to the "OCPs and DL-PCBs"
413 and "PFASs" profiles. This may be explained by the fact that POPs are eliminated in part by
414 menstruation, so menopausal women may eliminate these substances less quickly (Colles et al. 2020).
415 Unexpectedly, a higher school educational level was positively associated with the "DL-PCBs &
416 NDL-PCBs" profile, and history of breastfeeding was positively associated with the "DDT
417 metabolites" profile. Finally, some dietary variables were associated with adherence to some profiles.
418 While some associations were consistent with the presence of POPs in some food groups (fish and
419 seafood consumption positively associated with the "PCBs & nonachlors", "PFASs" and "PBDEs"
420 profiles; charcuterie positively associated with the "OCPs and DL-PCBs" profile; offal positively
421 associated with the "DDT metabolites" profile; vegetables consumption positively associated with the
422 "PCBs & nonachlors", "OCPs and DL-PCBs", "PFASs" and "DL-PCBs & NDL-PCBs" profiles),
423 other results were unexpected (non-monotonic and negative associations between fruits consumption
424 and the "PCBs & nonachlors", "OCPs & DL-PCBs" and "DL-PCBs & NDL-PCBs" profiles; negative
425 association between white meat consumption and the "PCBs and nonachlors" profile). Overall,
426 previous studies investigating the links between dietary factors and internal pollutant levels tended to
427 show positive associations with the consumption of animal products such as fish, meat and dairy
428 products, and more rarely with the consumption of vegetables, fruit and cereals (Gasull et al. 2011;
429 Zahira, Lestari, and Aris 2021).

430 This study presents some limitations. Firstly, unlike the ENNS and Esteban studies which selected
431 samples representative of the French population, the sample used in this study was made up of women
432 from the E3N cohort affiliated to the French national education health insurance scheme. Their
433 average level of education is higher than that of the general French adult population, and their overall
434 lifestyle is healthier. The links between socio-economic position and levels of exposure to POPs may
435 vary depending on the substance of interest, so that levels measured in the women E3N cohort could
436 be higher or lower compared to those of the general French population in the 90's. In addition, the
437 small sample size limits also the extrapolation of the results to the general population. Consequently,
438 the variations observed between the exposure levels reported in the E3N study and those in the ENNS
439 or Esteban studies may have been over- or underestimated. However, given the widespread
440 distribution of POPs in the environment, we can assume that their levels are globally homogeneous in
441 the general population and consequently we can suppose that the level of E3N women is not very
442 different from that of women in the general French population. It should also be noted that the ENNS

443 and Esteban studies include women aged 18 to 74 years, whereas our study includes older women (45
444 to 73 years). Given that POPs accumulate in the body throughout life, and that, overall, their presence
445 in the environment decreases over time, older women probably have higher levels of most POPs than
446 younger women. Thus, if the comparison had only included women of the same age as those in the
447 E3N cohort, the levels observed in the ENNS and Esteban studies would probably have been higher,
448 and therefore the decreases observed over time less marked. Finally, concerning the exploration of the
449 determinants of adherence to the different profiles of POPs, it should be noted that a high number of
450 statistical tests were performed to test the association between each factor and each POPs exposure
451 profile, increasing the risk of false positive discoveries.

452 The present study has also several strengths. It made it possible to measure the presence of numerous
453 pollutants in blood samples at an early stage in France. These measurements thus allowed to observe
454 the evolution of blood pollutant levels over time, and to link them with the regulations put in place
455 and, as such, can help to evaluate their effectiveness. Additionally, the availability of a large amount
456 of information collected in the E3N cohort has enabled us to study a variety of determinants and to
457 adjust the estimates of their effects on each other.

458 In conclusion, this study showed that most of the POPs for which a comparison was possible
459 decreased over the 10 or 20 years following the E3N blood collection, and identified those which, on
460 the contrary, tended to increase or remain stable. However, it should be noted that many pollutants
461 were not measured in the ENNS and Esteban studies, in particular PFOA / PFOS replacement
462 substances (GenX, DONA, F53B-major, F53B-minor), which currently have little or no regulation.
463 Additionally, this study made it possible to identify POPs exposure profiles whose effects on health
464 could be assessed in future toxicological or epidemiological studies. The characteristics identified as
465 being associated with adherence to these profiles should be confirmed in larger populations and could
466 enable specific prevention strategies to be put in place.

Declarations

Ethics approval

The E3N study was approved by the French National Commission for Data Protection and Privacy (ClinicalTrials.gov identifier: NCT03285230). The E3N blood collection study was approved by the Bicêtre ethics committee (CPP-IDF-VII, IRB # IORG0001140).

Informed consent

All participants included in the E3N study gave written informed consent, and informed consent was obtained for novel biomarkers testing.

Availability of data and materials

The data used in this study are not publicly available.

Author contributions

Pauline Frenoy: Conceptualization, Methodology, Formal analysis, Writing - Original Draft, Visualization. **German Cano-Sancho:** Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing. **Jean-Philippe Antignac:** Conceptualization, Methodology, Investigation, Resources, Writing - Review & Editing. **Philippe Marchand:** Investigation, Resources, Writing - Review & Editing. **Chloé Marques:** Writing - Review & Editing. **Xuan Ren:** Writing - Review & Editing. **Gianluca Severi:** Writing - Review & Editing. **Vittorio Perduca:** Conceptualization, Methodology, Writing - Review & Editing. **Francesca-Romana Mancini:** Conceptualization, Methodology, Writing - Review & Editing, Supervision, Project administration, Funding acquisition.

Competing interests

The authors declare that they have no competing interests that could have appeared to influence the work reported in this paper.

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