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1 **Chemical by chemical and cumulative risk assessment of residential indoor exposure to**
2 **semivolatile organic compounds in France**

3

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17 **Running Title: Health risk of indoor SVOCs in France**

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22 **KEY WORDS**

23 Mixture, health risk, public health, environmental health, contaminant.

24 **ABSTRACT**

25 Background: The toxic effects of environmental exposure to chemicals are increasingly being
26 studied and confirmed, notably for semivolatile organic compounds (SVOCs). These are
27 found in many products and housing materials, from which they are emitted to indoor air,
28 settled dust and other surfaces. Objectives: The objective of this work is to assess the human
29 health risk posed by residential indoor exposure to 32 SVOCs, assessed in previous
30 nationwide studies. Methods: A chemical-by-chemical risk assessment, using a hazard
31 quotient (HQ) or excess risk (ER) method, was supplemented by a cumulative risk assessment
32 (CRA). For CRA, a hazard index (HI) method, as well as higher tier approaches using relative
33 potency factors (RPFs) or toxic equivalency factors (TEFs) were used for the following
34 endpoints: neurotoxicity, reproductive toxicity, genotoxicity and immunotoxicity. Results:
35 HQs were above 1 for 50% of French children from birth to 2 years for BDE 47, and for 5%
36 of children for lindane and dibutyl phthalate (DBP). Corresponding hazards are reprotoxic for
37 BDE 47 and DBP, and immunotoxic for lindane. The CRA approach provided additional
38 information of reprotoxic risks ($HI > 1$) that may occur for 95% of children and for 5% of the
39 offspring for pregnant women's exposure. The SVOCs contributing most to these risks were:
40 PCB 101 and 118, BDE 47, and DBP. The higher tier CRA approaches showed that exposure
41 to dwellings' SVOC mixtures were of concern for 95% of children for neurotoxic compounds
42 having effects linked with neuronal death. To a lesser extent, effects mediated by the aryl
43 hydrocarbon receptor (AhR) or by a decrease in testosterone levels may concern 5% of
44 children and adults. Lastly, unacceptable immunotoxic risk related to exposure to 8 indoor
45 PCBs was also observed for 5% of children. Conclusions: In view of uncertainties related to

46 compounds' toxicity for humans, these results justify the implementation of preventive
47 measures, as well as the production of more standardized and comprehensive toxicological
48 data for some compounds.

49 **INTRODUCTION**

50 People are exposed to an increasing number of chemicals, present in all media such as food,
51 water, air, soil, clothes, etc. Exposure in residential indoor environments is of particular
52 concern, due to their ubiquitous contamination and to the large amount of time people spent
53 inside. Among chemicals found in dwellings, semivolatile organic compounds (SVOCs)
54 represent a large class of organic compounds belonging to different chemical families and
55 having a vapor pressure of between 10^{-14} and 10^{-4} atm (Weschler and Nazaroff 2008).
56 Because of their diverse properties - plasticizer, flame retardant, biocide, etc. (Mercier et al.,
57 2011), they are used in a wide range of materials and products (wall materials, furniture,
58 household cleaning products, etc.). Their particular physical-chemical properties render them
59 capable of migrating from their sources and partitioning between indoor air, settled dust and
60 other surfaces (Weschler and Nazaroff 2010); people are thus exposed via inhalation,
61 ingestion and dermal contact. A recent study has estimated aggregate exposure from
62 measurement data for 32 SVOCs from different chemical families, frequently detected in
63 French dwellings (Pelletier et al., 2017a): 6 phthalates, 4 polycyclic aromatic hydrocarbons
64 (PAHs), 2 organophosphorus (OPs), 3 organochlorines (OCs), 2 polycyclic musks, 8
65 polychlorinated biphenyls (PCBs), and 7 polybromodiphenylethers (PBDEs).

66 Many of these SVOCs are suspected of having adverse health effects. Some exhibit an
67 endocrine disruption mechanism, leading to potential effects on male reproduction. This is the
68 case for phthalates, which have been studied extensively in human and other mammals.
69 Specific effects on testosterone synthesis have also been shown following rodent exposure to

70 PBDEs (BDE 99) and PAHs (benzo[a]pyrene) (Fournier et al., 2016). They are also known to
71 be neurotoxic in experimental mammals, and numerous epidemiological studies suggest an
72 association between early-life exposure to SVOCs (OCs, OPs, PCBs, PBDEs, PAHs, and
73 phthalates) and behavioral impairment later in life (Fournier et al., 2017). PAHs (especially
74 benzo[a]pyrene) and some OCs or OPs pesticides are also known to be carcinogenic
75 compounds (IARC 2010; Inserm 2013). Many SVOCs thus have common toxic effects,
76 especially in early life, justifying cumulative risk assessment (CRA). For CRA we chose to
77 focus i) on neurotoxicity, reproductive toxicity, and genotoxic carcinogenicity because these
78 endpoints are related to systems which are particularly sensitive to chemical exposure during
79 early life ii) on SVOCs with mixture based toxicological data when available.

80 CRA addresses exposure from multiple compounds, based on defined criteria such as chemical
81 structure, mechanism of action, target organ or toxic effect (EFSA 2008; Boobis et al. 2008).
82 These methods are usually based on the fundamental concept of additivity, and are described
83 extensively elsewhere (Sarigiannis and Hansen 2012; Fournier et al., 2014a). The CRA issue
84 is a challenging one, and a consensus has been reached that hierarchical approaches should be
85 adopted, with each tier being more refined - more certain and less cautious - than the previous
86 one (Meek et al., 2011).

87 The objective of this study, conducted within the framework of the ECOS project (Glorennec
88 et al., 2011), was to assess the public health risk posed by 32 SVOCs. Briefly the ECOS
89 project aimed to develop multi-residue analytical methods appropriate to indoor
90 contamination (Mercier et al., 2012, 2014), as well as to measure indoor contamination in
91 France (Mandin et al., 2016; Blanchard et al., 2014), group compounds on the basis of
92 common toxicity (Fournier et al., 2014b), and develop mixture toxicity indicators (Fournier et
93 al., 2016, 2017). Using nationwide measurements, we assessed exposure (by inhalation,
94 contact and ingestion) to 32 indoor SVOCs on a population basis, that is, the distributions of

95 exposure are representative of those of the population living in France (Pelletier et al., 2017b).
96 A chemical-by-chemical risk assessment was completed using lower to higher tier CRA, as
97 recommended by Meek et al. (2011), based on reference doses from risk assessment databases
98 and mixture toxicity indicators from the literature.

99 **METHODS**

100 **Chemical-by-chemical risk assessment**

101 For non-carcinogenic SVOCs, hazard quotients (HQ, unitless) were calculated as follows:

$$HQ = \frac{ADD}{RfD \times f_{oral}} \quad (1)$$

102 With

103 ADD: Aggregate Daily Dose (mg/kg-bw/d)

104 RfD: Reference dose (mg/kg-bw/d)

105 f_{oral} : Oral bioavailability

106 ADDs were retrieved from a previous exposure study encompassing air inhalation, dust
107 ingestion, and dermal contact and are expressed as internal doses; 32 SVOCs were selected on
108 the basis of their health interest and because they were detected in both the air and the settled
109 dust of French dwellings (Pelletier et al. 2017b). Briefly, in this previous study, ADDs were
110 simulated on the basis on nationwide representative measurements (Mandin et al., 2014,
111 2016) in airborne particulate matter and dust for most compounds, which were combined with
112 a static partitioning model and human exposure factors. This two-dimensional Monte Carlo
113 simulation revealed that the exposure variance was mainly driven by the contamination
114 variability rather than by the uncertainty in modeling parameters.

115 RfD is an estimate of a daily oral exposure that is likely to be without an appreciable risk of
116 deleterious effects during a lifetime (US EPA 2002). For this risk assessment, RfDs based on
117 oral exposure were preferred because they were available for most SVOCs. We retrieved
118 RfDs, or their equivalents (minimal risk levels or acceptable daily intakes), from the
119 following online databases: the Integrated Risk Information System (IRIS) from US EPA
120 (<https://www.epa.gov/iris>), the toxicological profiles from Agency for Toxic Substances and
121 Disease Registry (ATSDR) (<https://www.atsdr.cdc.gov/>), the Joint Meeting on Pesticide
122 Residues (JMPR) from the WHO ([http://apps.who.int/pesticide-residues-jmpr-](http://apps.who.int/pesticide-residues-jmpr-database/Home/Range/A-C)
123 [database/Home/Range/A-C](http://apps.who.int/pesticide-residues-jmpr-database/Home/Range/A-C)), the Joint FAO/WHO Expert Committee on Food Additives
124 (JECFA) (<http://apps.who.int/food-additives-contaminants-jecfa-database/search.aspx>), the
125 Office of Environmental Health Hazard Assessment (OEHHA)
126 (<http://oehha.ca.gov/chemicals>), Health Canada ([https://www.canada.ca/en/health-](https://www.canada.ca/en/health-canada.html)
127 [canada.html](https://www.canada.ca/en/health-canada.html)), the French agency for food, environment and occupational safety (ANSES)
128 (<https://www.anses.fr/fr>), and the EU pesticide database from European Commission
129 (<http://www.efsa.europa.eu/>). RfDs were selected according to the following criteria: i) status
130 = final (non-provisional), ii) methods = derived from classical dose-response data, and iii)
131 update = not the oldest value. Finally, where previous criteria were met for several RfDs, the
132 most conservative was chosen (see Table S1). Where no RfDs were available for individual
133 PCBs or PBDEs compounds, we made the assumption of similar toxic potency between
134 congeners having the same molecular formula (same number of halogenated atoms) and used
135 the RfD of the known congener. Because ADDs are internal doses, RfDs were converted into
136 internal doses using oral bioavailability coefficients (f_{oral}). These are the fraction of a
137 contaminant reaching the digestive system and absorbed into the systemic circulation
138 (Rostami and Juhasz 2011). See Table S2 for corresponding f_{oral} coefficient for each
139 compound. Where RfDs were based on studies using adult mammals, the risk was assessed

140 for the exposure of both an adult (aged 21 to 30 years, as an example) and a child (from birth
141 to the age of 2 years, as an example) because the uncertainty factors applied for intra-species
142 variability are supposed to take into account differences in the sensitivity of responses within
143 a species (US EPA, 2008). Given that early-life (pre- and postnatal periods) is considered as a
144 very vulnerable period, where RfDs were based on prenatal studies, the risk was assessed only
145 for the exposure of a pregnant woman (aged 21-30 years, as an example). And where RfDs
146 were based on postnatal studies, the risk was assessed only for the exposure of a child (from
147 birth to the age of 2 years, as an example). Lastly, HQs were calculated for median and high
148 uptake estimates (ADD 50th and 95th percentiles, respectively).

149 For genotoxic carcinogen SVOCs, excess risks (ER, unitless) were calculated as follows for
150 an adult continuously exposed from birth to the age of 30 years:

$$ER = ADD \times (CSF \times f_{oral}) \times \frac{ED}{LD} \quad (2)$$

151

152 With

153 CSF: Cancer slope factor (mg/kg-bw/d)⁻¹

154 ED: Exposure duration (30 years)

155 LD: Life duration (70 years)

156 CSF is an estimate of the increased cancer risk from oral exposure to a dose of 1 mg/kg/d over
157 a lifetime (US EPA 2005). CSFs were retrieved from literature using the same method as for
158 RfDs (see Table S1). Finally, ERs were calculated for median and high uptake estimates
159 (ADD 50th and 95th percentiles, respectively).

160 **Cumulative risk assessment**

161 CRA methods are based on the assumption that additivity is plausible at low doses such as
162 environmental exposures. In this assessment we did not consider potential interaction other
163 than additivity. Among current literature referring to CRAs applied to SVOCs, most focus on
164 methods using a hazard index (HI) or relative potency factors (RPF) (Pelletier et al., 2017b).
165 The HI entails the addition of each chemical's risk indicator for SVOCs affecting common
166 endpoints; it is considered a Tier 1 approach for CRA. RPFs rely on both the existence of a
167 common biological endpoint (e.g. neuronal cell death) and high quality dose-response data for
168 individual chemical on that endpoint, and so may be considered a higher tier method than HI.
169 Similarly, the toxic equivalency factor (TEF) approach, specifically developed for dioxins and
170 related compounds, relies on the existence of a clearly identified principal mechanism of
171 action common to all chemicals included in the mixture and on having relative potency of
172 each chemical relative to an index chemical for that mechanism (e.g. AhR activation). The
173 RPF approach is considered a more general method and is used for other compounds such as
174 PAHs, endocrine disruptors, and pesticides. Both the RPF and TEF approaches convert the
175 dose of each compound into an index chemical-equivalent dose by scaling its toxicity relative
176 to the index chemical.

177 Hereafter we present:

- 178 • Tier 1: estimation of HIs or ER for selected endpoints: neurotoxicity, reproductive
179 toxicity, and genotoxicity.
- 180 • Tier 2: estimation of cumulative hazard quotients (CumHQ) or cumulative excess risks
181 (CumER) using RPFs and TEFs published in the literature (it includes PAHs and
182 gastro-intestinal cancer, PCB-DLs and activation of AhR, phthalates and anti-
183 androgenic properties, different SVOCs and decreased testosterone levels or neuronal
184 death) ;

- 185 • Specific case for SVOCs with mixture based toxicological data (it includes only PCBs
186 and immunotoxicity).

187 Tier 1:

188 HI (unitless) is the sum of n HQs for n SVOCs, using equation (3):

$$HI = \sum_{x=1}^n \frac{ADD_x}{RfD_x \times f_{oral_x}} \quad (3)$$

189

190 In this risk assessment, we retrieved oral RfDs for neurotoxic and reprotoxic effects from the
191 same databases as for the chemical-by-chemical assessment (see Tables S5 and S7). Where no
192 RfD based on reprotoxic or neurotoxic endpoint was available, a literature survey was
193 conducted in order to retrieve neurotoxic or reprotoxic points of departure (POD). Using the
194 Web Of Knowledge™ website (Thomson Reuters, www.webofknowledge.com) publications
195 were selected primarily by searching in the ‘topic’ field (title, abstract, and key words):
196 (“SVOC name” AND (neurotoxicity OR (reproductive OR reprotoxic OR endocrine
197 disruptor)). Secondly, abstract reading was used as a means of filtering out irrelevant
198 publications. Next, study selection criteria included: i) *in vivo* oral exposure of mammals (by
199 diet or gavage) and where possible ii) testing several (or at least one) dose(s) in comparison
200 with a control group. Lastly, if previous criteria were met, PODs were chosen preferentially if
201 benchmark doses (BMD) > no observed adverse effect level (NOAEL) > low observed
202 adverse effect level (LOAEL). We found neurotoxic PODs for 17 SVOCs out of 32 and
203 reprotoxic PODs for 15 SVOCs out of 32. RfDs were calculated by dividing the available
204 POD by uncertainty factors (UF). UF were applied for intraspecies variability (UF_H),
205 interspecies variability (UF_A), extrapolation from a LOAEL to a NOAEL (UF_L), database
206 deficiency (UF_D), and extrapolation from acute/subchronic (< 28 days/28 to 90 days) to

207 chronic exposure (> 90 days) (UF_s) (US EPA 2008). f_{oral} coefficients were used to convert
208 RfDs into internal doses (see Table S2). Finally, HIs were calculated for median and high
209 uptake estimates (ADD 50th and 95th percentiles, respectively).

210 Benzo[a]pyrene and lindane are genotoxic compounds (cf. chemical-by-chemical risk
211 assessment) but were not combined because they induce different types of tumors (i.e.,
212 gastrointestinal and liver respectively).

213 Tier 2:

214 We search the literature for available RPFs and TEFs or relative potencies for the 32 SVOCs
215 included in this study. We found adequate data for: 2 PCBs for toxic effects mediated by the
216 aryl hydrocarbon receptor (AhR) (Van den Berg 1998, 2006), 4 PAHs for carcinogenic effects
217 (Ineris 2003), 3 and 5 phthalates (Benson et al., 2009; Hannas et al., 2011) for reprotoxic
218 effects driven by anti-androgenic properties, and 4 SVOCs belonging to different chemical
219 classes — PAHs and phthalates — for reprotoxic effects driven by a decrease in testosterone
220 levels (Fournier et al., 2016). We also estimated RPFs from neuronal death relative potencies
221 (i.e. comparable BMDs) published by Fournier et al. (2017) for 9 SVOCs: benzo[a]pyrene,
222 diethylhexyl phthalate (DEHP), PCB 52, PCB 153, dieldrin, chlorpyrifos, lindane, BDE 47,
223 and BDE 99 (see Table S9). In this last case, chlorpyrifos was chosen as the index compound
224 based on the following criteria: i) well-known neurotoxic effect and ii) available RfDs from
225 databases of good quality and covering as many age groups as possible.

226 RPFs (unitless) express the potency of a compound “x” according to the index compound “i”
227 and were estimated as follows:

$$RPF_x = \frac{BMD_i}{BMD_x} \quad (4)$$

228 For non-carcinogenic SVOCs, CumHQs (unitless) were then calculated as follows for n
229 compounds:

$$CumHQ = \frac{\sum_{x=1}^n (ADD_x \times RPF_x)}{RfD_i \times f_{oral_i}} \quad (5)$$

230 Where RfD_i is the RfD of the index compound. The same equation is used for the TEF
231 approach, replacing the RPFs with TEFs.

232 For genotoxic carcinogen SVOCs, CumERs (unitless) were then calculated as follows for n
233 compounds:

$$CumER = \sum_{x=1}^n (ADD_x \times RPF_x) \times (CSF_i \times f_{oral_i}) \times \frac{ED}{LD} \quad (6)$$

234 Where CSF_i is the CSF of the index compound.

235 Special case of PCBs:

236 In addition for PCBs, we considered the mixture, because RfDs were directly available for
237 industrial mixtures of PCBs (Aroclor). The RfD of 20 ng/kg-bw/d for immunotoxic effect of
238 Aroclor 1254 was chosen, because this mixture contains our 8 PCBs. This RfD was proposed
239 by the US EPA in 1996 (US EPA 1996), and extended to the 209 PCBs congeners by the
240 ATSDR (ATSDR 2000), RIVM (Baars et al. 2001) and Afssa (Afssa 2003). Because the 8
241 congeners included in this study (PCB 28, 31, 52, 101, 105, 118, 138, and 153) represent 34%
242 of the total composition of Aroclor 1254 (ATSDR 2000), we consider an RfD of 7 ng/kg-
243 bw/d ($20 \times 34 / 100$) (see Table S10).

244 In this case HI (unitless) is estimated using equation (7):

$$HI = \frac{\sum (ADD_x \times \frac{1}{f_{oral_x}})}{RfD_{Aroclor\ 1254} \times 0,34} \quad (7)$$

245

246 **RESULTS**

247 **Chemical-by-chemical risk assessment**

248 Risk assessment could be carried out for 21 SVOCs of the 32 initially considered: 19, 16, and
249 9 for the exposures of children, adults, and pregnant women respectively. Indeed, no RfDs
250 were available in the databases for PCBs (28, 31, 52, 101, 105, 118, 138, and 153) and BDEs
251 (28, 153, and 154) or for their congeners having the same molecular formula.

252 ADD compared to oral $RfD \cdot f_{oral}$ are presented in Figure 1 for the population having the
253 highest HQ for each compound. HQs are >1 for part of the population if ADD box plot
254 intersects the RfD. For di-isononyl phthalate (DiNP) and di-isobutyl phthalate (DiBP), RfDs
255 were available only following in utero exposure (see Table S1), which enable risk
256 assessments only for pregnant women exposure. Detailed HQs are presented in Table S3.

257 [Figure 1]

258 Health effects may occur for 3 SVOCs considered separately. HQs were above 1 for 50% of
259 children for BDE 47 for reprotoxic effect, and for 5% of children for lindane for immunotoxic
260 effect and dibutyl phthalate (DBP) for reprotoxic effect. For the other compounds, the risk
261 associated with residential SVOC exposure may be considered as acceptable, according to
262 common criteria, with HQs much lower than 1.

263 ERs of the genotoxic carcinogens: benzo[a]pyrene and lindane are shown in Figure 2. They
264 are lower than 10^{-5} (Y axis) and may therefore be considered as acceptable (WHO 2008).

265 [Figure 2]

266 **Cumulative risk assessment**

267 Tier 1 assessment for the neurotoxic SVOCs:

268 17 SVOCs are included because there is evidence of neurotoxicity: 15, 6, and 6 were
269 considered for the exposures of children, adults, and pregnant women, respectively, according
270 to the windows of exposure considered in the toxicological testing available for the derivation
271 of the RfD. Seven RfDs were retrieved from literature and 10 were constructed (see Table
272 S5).

273 HIs were always below 1 (Figure 3 and Table S6 for detailed results). Neurotoxic risks for
274 each age group may therefore be considered acceptable.

275 [Figure 3]

276 [Figure 4]

277 Figure 4 shows the relative contribution of each chemical to neurotoxic HIs for the exposures
278 of children, adults and pregnant women. For the children's exposure, DEHP and DBP each
279 contributed 22% and 42% to the 95th percentile of HI respectively, followed by dieldrin
280 (12%). Other SVOCs contributed less than 10% each. For the adults' exposure, DBP
281 contributed 59% to the 95th percentile of HI, followed by dieldrin (17%), DiBP (13%) and
282 DEHP (12%). Other SVOCs contributed less than 10% each. For the pregnant women's
283 exposure, lindane contributed to 47% of the neurotoxic risk for offspring, followed by PCB
284 52 (39%) for the highest exposure. Other SVOCs contributed less than 5% each. Similar
285 results were found for the median exposure for all populations.

286 Tier 1 assessment for the reprotoxic SVOCs:

287 15 SVOCs are included because there is evidence of reproductive toxicity: 11, 7, and 9 were
288 considered for the exposures of children, adults, and pregnant women, respectively, according

289 to the windows of exposure considered in the toxicological testing available for the derivation
290 of the RfD. Eleven RfDs were retrieved from literature and 5 were constructed (see Table S7).
291 Reprotoxic effects may occur for some mixtures. HIs were above 1 for 95% of children (5th
292 percentiles, data not shown), and close to 9 for 5% of them, for the mixture of 11 reprotoxic
293 SVOCs. For the pregnant women's exposure, HIs were above 1 for 5% of them, for the
294 mixture of 9 reprotoxic SVOCs (Figure 5). For adults, HIs were lower than 1 for the mixture
295 of 7 SVOCs (see Table S8 for detailed results).

296 [Figure 5]

297 [Figure 6]

298 Figure 6 shows the relative contribution of each chemical to reprotoxic HIs for the exposures
299 of children, adults and pregnant women. For the children's exposure, PCBs 101/118
300 contributed 45% to the 95th percentile of HI, followed by BDE 47 (25%) and DBP (20%).
301 Other SVOCs contributed less than 10% each. For the adults' exposure, dieldrin contributed
302 45% to the 95th percentile of HI, followed by DEHP (31%), benzo[a]pyrene (12%) and DBP
303 (10%). Other SVOCs contributed less than 10% each. For the pregnant women's exposure,
304 the sum of PCBs 101/118 contributed to 52% of the reprotoxic risk for offspring, followed by
305 DBP (47%) for the highest exposure. Other SVOCs contributed less than 1% each. Similar
306 results were found for the median exposure for all populations (Figure 6).

307 Tier 2 assessment:

308 [Table 1]

309 19 SVOCs are included in tier 2 according to the availability of RPF, relative potencies, or
310 TEF in the literature. However, considering that TEF or RPF were derived from different
311 biological endpoints, relatively simple mixtures, containing 2 to 9 compounds, were

312 considered for each endpoint, as reported in Table 1. For children, neurotoxic effects via
313 neuronal death due to a mixture of 9 SVOCs from different chemical classes were likely to
314 occur for 95% of them (HI=1 at 5th percentiles of exposure, data not shown). Toxic effects
315 mediated by the AhR due to a mixture of 2 PCBs were likely to occur for 5% of children.
316 Reprotoxic effects via a decrease in testosterone level due to a mixture of benzo[a]pyrene and
317 3 phthalates were likely to occur for 25% of children and 5% of adults. For pregnant women's
318 exposure, CumHQs were below 1 for exposure to mixtures of 5 and 3 phthalates with anti-
319 androgenic effects.

320 [Figure 7]

321 [Figure 8]

322 [Figure 9]

323 Figures 7, 8 and 9 show the relative contribution of each chemical to CumERs and CumHQs
324 for each age group. PCB 105, diethyl phthalate (DEP), and DEHP contributed largely to the
325 50th and the 95th percentiles of CumHQs for both children's and adults' exposure (Figures 7
326 and 8). For the gastrointestinal cancer risk associated with PAH exposure of adults,
327 benzo[a]pyrene contributed largely to the 50th and the 95th percentiles of CumER (Figure 8).
328 For pregnant women's exposure, DBP and DiBP contributed most to the 50th and the 95th
329 percentiles of CumHQs (Figure 9).

330 Special case of PCBs:

331 Immunotoxic risks may occur for 5% of children because of exposure to the 8 PCBs. For
332 adults and pregnant women's exposure, HIs were lower than 1 (Figure 10).

333 [Figure 10]

334 A summary of the main findings for both chemical-by-chemical and cumulative risk
335 assessments is presented in Figure 11.

336 [Figure 11]

337 **DISCUSSION**

338 Health risks posed by residential indoor exposure to 32 SVOCs in France were assessed. The
339 chemical-by-chemical assessment revealed unacceptable risk for children because of their
340 exposures to BDE 47 (reprotoxic effect), DBP (reprotoxic effect), and lindane (immunotoxic
341 effect) (Figure 1). No unacceptable risks were identified for other chemicals and for adults or
342 pregnant women.

343 The CRA approach identified additional risks: Tier 1 CRA revealed unacceptable reprotoxic
344 risks ($HI > 1$) for children and for pregnant women's exposure. The following SVOCs
345 contributed most to the risk: PCB 101 and 118, BDE 47, and DBP (Figure 6). Tier 2 CRA
346 showed that neurotoxic effects via neuronal death, due to a mixture of chlorpyrifos,
347 benzo[a]pyrene, DEHP, PCB 52, PCB 153, dieldrin, lindane, BDE 47, and BDE 99 (Table 1),
348 could be hazardous for children. Tier 2 also showed that reprotoxic effects were associated
349 with a decrease in testosterone levels and might be hazardous for highly exposed children and
350 adults, due to a mixture of benzo[a]pyrene, DEHP, DEP, and benzyl butyl phthalate (BBP)
351 (Table 1). For toxic effects mediated by the AhR, exposure to PCB 105 and PCB 118 might
352 be hazardous for highly exposed children (Table 1). Equal TEFs were estimated by the WHO
353 (Van den Berg et al., 1998, 2006) for both compounds and we found PCB 105 to be the most
354 contributive pollutant (Figures 7 and 8) only because its exposure was higher than PCB 118 (3
355 ng/kg-bw/d, p95 values for a children's exposure estimated from Pelletier et al. (2017b), data
356 not shown). Lastly, the special case of PCBs CRA revealed unacceptable immunotoxic risk
357 for children's exposure to 8 indoor PCBs (Figure 10).

358 Study strengths include: i) CRA of numerous SVOCs from different chemical families for
359 different populations, ii) use of nationwide representative exposure estimates, and iii) use of
360 refined, tiered CRA approaches with HI, RPF and TEF being used successively.

361 Study limitations include the existence of uncertainties, mainly due to: i) the relevance of
362 toxicological and epidemiological data for risk assessment, ii) the number of compounds
363 included in the mixtures, iii) exposure data, and iv) RfD and RPF/TEF construction.

364 **Relevance of toxicological and epidemiological data for risk assessment**

365 The assessment requires a certain level of caution for accurate interpretation, due mainly to
366 the transposition of effects from animal to human and the weight of evidence of the effect in
367 humans.

368 For the first tier of the CRA approach, in terms of reprotoxic effects, no RfD for reprotoxic
369 endpoint were available in literature for PCBs. The RfD_{rep} value we constructed for PCB 101
370 and 118 was based on decreased relative testes and ovary weight in offspring (F1 and F2)
371 after subchronic exposure of pregnant mice from GD 0 to PND 21 (see Table S7). Human
372 studies supported the endocrine-disrupting capacity of PCBs (Dallinga et al., 2002; Den Hond
373 et al., 2002). Dallinga et al. (2002) observed a significantly decreased sperm count in relation
374 to an elevated PCBs (included PCB 118) metabolites level in the blood of men with normal
375 semen quality and Den Hond et al. (2002) showed a significant delay in puberty in boys
376 (reduction in the genitals and lower testicular volume). These results confirmed the relevance
377 of this endpoint for humans. For BDE 47 the RfD was based on a specific female endpoint:
378 decreased uterus weight in 2 month-old female rats after a single exposure on postnatal day
379 (PND) 10 (see Table S1). This endpoint appears relevant to humans. For phthalates, in
380 particular DBP and DEHP, toxicity indicators were based on their anti-androgenic properties,
381 which have been extensively studied (Gray et al., 2006; Kay et al., 2014). Furthermore,

382 epidemiological and experimental studies have also confirmed their effects as endocrine
383 disruptors as well as their reprotoxic effects on human health (Swan et al., 2005; Habert et al.,
384 2009). This endpoint therefore appears relevant to humans.

385 In terms of immunotoxic effects, the RfD for lindane was based on biphasic changes in cell-
386 and humoral-mediated immunity to red blood cells in adult female mice after chronic
387 exposure (24 weeks) (see Table S1). Although the immunotoxic effects of lindane have been
388 confirmed by other oral studies (Dorsey 2005), it is difficult to relate human health effects to
389 specific immunotoxic parameters in laboratory animals due to the complexities of the immune
390 system (Abadin et al., 2007) and this endpoint has not been studied in humans.

391 In the tier-2 CRA approach, the results concerning neurotoxic risk are surprising since the
392 most contributive pollutant was DEHP (Figures 7 and 8). A first explanation is that exposure
393 to this compound was much higher than for the others (2 to 4 orders of magnitude higher than
394 PCBs, PBDEs, or organo-chlorinated pesticides, i.e., 2 µg/kg-bw/d, p95 values for children's
395 exposure estimated from Pelletier et al. (2017b), data not shown). In addition, the toxicity data
396 used to derive its RPF indicate that DEHP is as potent as some insecticides (i.e., dieldrin or
397 chlorpyrifos) in inducing neuronal cell death. These data were retrieved from the study of Lin
398 et al. (2011), which found a 10% decrease in neuronal viability in neuroblastoma cells of
399 mice, starting at 10 µM. DEHP is best known for its reproductive toxicity as an
400 antiandrogenic compound. However, recent animal studies have shown that it may induce
401 toxic effects in the rat brain (Guida et al., 2014). Associations between human phthalate
402 exposure, including DEHP, and impairment of cognitive development, school-age
403 intelligence, and autism spectrum disorders have also been suggested (Cho et al. 2010,
404 Kobrosly et al. 2014, Yolton et al. 2011). While these observations are based only on limited
405 studies, they are of concern and lead us to recommend further studies to better understand the
406 neurotoxicity of phthalates, as suggested by Miodovnick et al. (2014).

407 The results concerning the tier-2 reprotoxic risk associated with a decrease in testosterone
408 level may also be considered surprising in the particular case of DEP, which is highlighted as
409 the most contributive pollutant (Figures 7 and 8). Our use of data from the study of Pereira et
410 al. (2008) could explain this result. The authors found a 10% decrease in testosterone levels in
411 rats starting from 0.24 mg/kg-bw/d. DEP is usually not considered to be as toxic as other
412 long-chain phthalate esters (i.e., DEHP or DBP), based on toxicity studies that have produced
413 inconsistent results. Some studies showed negative results in rodents exposed at high doses
414 (Api 2001) but others showed lower reproductive performance in mice and decreased serum
415 testosterone levels in rats (NTP 1984, Fujii et al. 2005). A mechanistic hypothesis explaining
416 this potential reproductive effect may not be related to Sertoli cell impairment, as for other
417 phthalates. Rather, it might be explained by indirect action on Leydig cells, with lipid
418 peroxidation and decreased antioxidant defense at the testicular level (Pereira et al., 2008).
419 Epidemiological studies in humans have also suggested associations between DEP exposure
420 (metabolite measurement) and sperm modifications (Duty et al., 2003; Duty et al., 2004;
421 Hauser et al., 2006), but again, results have been inconsistent (Lottrup et al., 2006;
422 Matsumoto et al., 2008). DEP exposure in these studies may be a surrogate for other risk
423 factors associated with reproductive disorders, as suggested by some authors (Hauser et al.,
424 2006). Moreover DEP did not appear among the SVOCs contributing to health risks to
425 pregnant women (Table 1, Figure 9) because no relative potencies have been published for
426 this specific window of exposure. DEP does not appear to induce a reduction in fetal
427 testosterone and insulin-like growth factor-3, as other phthalates do (Gray et al., 2000).

428 Similarly,

429 For PCBs (sum of 8 congeners), the RfD of the Tier 2 assessment was based on
430 immunological effects in adult monkeys (see Table S10). Monkeys appeared more sensitive
431 than other species (rats, mice, guinea pigs and rabbits) for effects on antibody responses after

432 oral exposure and provided a better animal model due to phylogenetic and biological
433 similarities to humans (Tryphonas 1994, 1995). However, the exposure-response relationship
434 between PCB exposure and altered immune functions in humans has not yet been fully
435 documented, and only suggestive evidence is shown (Levin et al, 2005).

436 To summarize, given the present state of knowledge, critical reprotoxic effects appear
437 relevant to humans for indoor exposure to PCB 101 and PCB 118, DEP, DBP, and to a lesser
438 extent, BDE 47. Similar conclusions could be drawn about the immunotoxicity of PCBs,
439 based primarily on consistent results from animal data. The specific case of DEP should,
440 however, be interpreted with caution due to inconsistent results for the toxicological data. It is
441 possible that DEP may act through an alternative mechanism involving oxidative stress
442 (Pereira et al., 2008). This should be investigated in further studies. For phthalates (DEHP and
443 DBP), extrapolation of neurotoxicity data from animal models to humans has led to a lower
444 level of confidence, but some recent epidemiological data suggest neurobehavioral
445 impairment and lead us to recommend further studies. The same conclusion could be reached
446 for lindane, although its immunotoxicity in humans has not been studied.

447 **Selected compounds and missing data**

448 The refinement of this risk assessment by using a tier-2 approach strongly depends on the
449 availability of data on the mode or mechanism of action, which influences the number of
450 compounds included in the mixtures. For example, the RPF and TEF approaches were
451 conducted for mixtures of only 2 PCBs for toxic effects mediated by the AhR, without
452 including other compounds known to be capable of binding to the AhR (such as
453 organochlorine, brominated compounds or PAHs), because no RPFs or TEFs are available in
454 the literature. It is also the reason why only 4 SVOCs and 5 or 3 phthalates were included for
455 reprotoxic effects and only 9 SVOCs for neurotoxic effects (Table 1). We also made a

456 distinction between pre- and postnatal periods and adulthood, and this resulted in studying
457 different mixtures containing different SVOCs for each age group, e.g. neurotoxic CRA was
458 conducted for 15 compounds for the children's exposure, for 9 compounds for the adults'
459 exposure, and for 6 compounds for the pregnant women's exposure (Figure 3). In terms of
460 effects, age-related differences in susceptibility to contaminants are due to the fact that critical
461 periods of structural and functional development are happening during pre- and postnatal life.
462 The nervous, immune, respiratory, reproductive and endocrine systems are in a particularly
463 sensitive stage of development at these early periods of life (Selevan et al., 2000). Increasing
464 evidence of sensitive populations, in terms of exposure and toxic effects, demands clearer
465 distinctions between the different windows of exposure (US EPA 2002), in particular to avoid
466 either overestimation of the risk for adults in cases where data are available only for juveniles
467 or gestating mammals or underestimation of the risk for pregnant women when data are
468 available only for adults. Thorough studies may allow the inclusion of new compounds in the
469 different mixtures, which could raise the risk – for example, HI for children's exposure to 15
470 neurotoxic SVOCs was found to be 0.6, but could reach (or even exceed) 1 were other
471 SVOCs to be included.

472 Regarding exposure, the main limitation is that, despite the relatively high number of SVOCs
473 considered compared to other works, many could not be included in this study because they
474 were not assessed by our previous exposure research (Pelletier et al., 2017b), e.g., pyrethroids,
475 bisphenols, etc. The most obvious example is the absence of most PAHs (only 3 of them were
476 considered) and other carcinogenic compounds in the carcinogenic risk estimation. Our
477 conclusions are therefore limited to the SVOCs studied, and health risks are necessarily
478 underestimated, as the question actually addressed is narrower than that of the risk posed by
479 SVOCs in general. This limitation also affects the contribution of particular compounds to the
480 risk for a given endpoint.

481 **Exposure data**

482 Uncertainty in results may also be due to the exposure data. However, ADDs were estimated
483 using a probabilistic approach and two-dimensional Monte Carlo simulations. Compared to a
484 more traditional deterministic approach, this has the main advantage of taking into account
485 both uncertainty (lack of knowledge about a parameter) and variability (heterogeneity of a
486 parameter in a population) of input parameters. The sensitivity analysis conducted by Pelletier
487 et al. (2017b) revealed that exposure estimate variance was mainly driven by indoor
488 contamination variability (C_{gas} , C_{part} and C_{dust}), and only secondarily by uncertainty in
489 physical and chemical parameters. Furthermore, because ADDs decrease with age (due to the
490 increased body weight), where risks related to a single effect could be estimated for several
491 age groups, they were always higher for those children exposed from birth to the age of 2
492 years. These exposure estimates were found to be consistent with those from studies similar in
493 terms of levels of exposures and predominant pathways. Because risks were assessed for the
494 95th percentile of exposure, risks may be underestimated for the most exposed, given that
495 exposure concentrations above the 95th percentile are skewed and often can be much higher at
496 the 99th percentile.

497 **Toxicity indicators**

498 The uncertainty linked to RfD construction may also strongly influence the results. For
499 several compounds that are at risk, the RfDs had a UF as high as 1,000 (i.e. BDE 47, DBP,
500 and lindane) or even 3,000 (i.e. PCB 101 and PCB 118) – this could be considered as low
501 confidence, reflecting major uncertainties in the databases and in particular because of using
502 LOAELs instead of NOAELs and BMDs. Furthermore, internal RfDs were estimated using
503 oral bioavailability coefficients. Averaged values for f_{oral} were used (see Table S2). For
504 chemical-by-chemical risk assessment, internal RfDs were also estimated using the minimum

505 and maximum values (data not shown) of f_{oral} distributions from Pelletier et al. (2017b). HQ
506 results could be up to 10 times higher when using minimum f_{oral} values and up to 2 times
507 lower when using maximum f_{oral} values for some SVOCs having broad distribution for this
508 parameter (e.g. lindane and dieldrin). The most contrasted example is lindane, with an HQ of
509 22 when using the minimum value and of 1 when using the maximum value (for the p95 of
510 children's exposure). However, although results may vary depending on the f_{oral} value,
511 identification of the compounds that are at risk remains unchanged. Uncertainties could also
512 be related to the read-across extrapolations, required where some of the congeners lacked
513 toxicological data, i.e. RfDs for BDE and PCB congeners. Finally, for RPF and TEF
514 construction, the uncertainties mainly depend on data comparability: for example concerning
515 different exposure routes (intratracheal, breast implants, and cutaneous contact) (Ineris 2003),
516 endpoints (decrease in fetal testosterone level for all phthalates versus smallness - or absence
517 of - male reproductive organs for DEHP) (Benson 2009), windows of exposure (prenatal,
518 postnatal, and adult), and types of experimental systems (cell lines versus primary cultures),
519 strains (mice, rats, and humans) and types of cells (e.g. pheochromocytoma versus
520 neuroblastoma cells) (Fournier et al., 2017).

521 **CONCLUSIONS**

522 This risk assessment, notably its cumulative aspect, allowed the identification of residential
523 aggregated indoor exposures that lead to unacceptable risk for a certain portion of the French
524 population. Furthermore, it allowed the identification of the most contributive compounds for
525 different health effects namely DBP, DEP, DEHP, BDE 47, lindane, and PCBs. Based on
526 evidence for effects in humans, it is thus possible to prioritize chemicals for prevention (DBP,
527 DEP, and some PCBs), while simultaneously taking indoor contribution to total exposure and
528 the effectiveness of prevention measures into account. This work also makes it possible to
529 prioritize supplemental scientific studies to clarify their impact in terms of risk to human

530 health, especially neurologic effects of phthalates and, to a lesser extent, reproductive effects
531 of BDE 47, and immunotoxic effects of lindane and PCBs. More generally, to enable a
532 broader cumulative risk assessment, it seems important to ensure that contamination data
533 encompass new chemicals and that toxicological studies are comparable and publicly
534 available. Finally, it is interesting to note that in certain cases, i.e. exposure to neurotoxic
535 compounds, Tier 1 assessments were less conservative than Tier 2 assessments. This finding
536 reveals that for cumulative risks, a lower-tier assessment may not be sufficient in every case.

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750 **Table 1:** Cumulative hazard quotient (CumHQ) and cumulative excess risk (CumER) using
751 toxic equivalency factors (TEF) and relative potency factors (RPF).

752 **Figure 1:** Comparison between residential indoor aggregate daily doses (5th, 25th, 75th, and
753 95th percentiles) with internal reference doses ($RfD \cdot f_{oral}$) represented by dots. Unit is mg/kg-
754 bw/d. France 2003-2011.

755 **Figure 2:** Excess risk for residential indoor exposure to benzo[a]pyrene and lindane (50th and
756 95th percentiles) for an adult continuously exposed from birth to the age of 30 years. France
757 2003-2011.

758 **Figure 3:** Hazard index for neurotoxic effects due to residential exposure to indoor SVOCs
759 (50th and 95th percentiles). France 2003-2011.

760 **Figure 4:** Relative contribution of chemicals to the neurotoxic hazard index.

761 **Figure 5:** Hazard index for reprotoxic effects due to residential exposure to indoor SVOCs
762 (50th and 95th percentiles). France 2003-2011.

763 **Figure 6:** Relative contribution of chemicals to the reprotoxic hazard index.

764 **Figure 7:** Relative contribution of chemicals to cumulative hazard quotients for children's
765 exposure.

766 **Figure 8:** Relative contribution of chemicals to cumulative hazard quotients and cumulative
767 excess risks for adults' exposure.

768 **Figure 9:** Relative contribution of chemicals to cumulative hazard quotients for pregnant
769 women's exposure.

770 **Figure 10:** Hazard index for immunotoxic effects due to residential exposure to indoor PCBs
771 (50th and 95th percentiles). France 2003-2011.

772 **Figure 11:** Summary of the main results of the chemical-by-chemical and cumulative risk
773 assessment.