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Running Title: Health risk of indoor SVOCs in France

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KEY WORDS

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

ABSTRACT

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

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

INTRODUCTION

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

Many of these SVOCs are suspected of having adverse health effects. Some exhibit an endocrine disruption mechanism, leading to potential effects on male reproduction. This is the case for phthalates, which have been studied extensively in human and other mammals. 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 adresses 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

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

METHODS

Chemical-by-chemical risk assessment

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

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

With

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

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

f_{oral}: Oral bioavailability

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

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

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

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

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

With

CSF: Cancer slope factor $(\text{mg/kg-bw/d})^{-1}$

ED: Exposure duration (30 years)

LD: Life duration (70 years)

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

Cumulative risk assessment

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

Hereafter we present:

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

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

Tier 1:

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

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

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

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

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

Tier 2:

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

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

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

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

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

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

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

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

Where CSF_i is the CSF of the index compound.

Special case of PCBs:

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

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

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

RESULTS

Chemical-by-chemical risk assessment

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

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

[Figure 1]

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

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

[Figure 2]

Cumulative risk assessment

Tier 1 assessment for the neurotoxic SVOCs:

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

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

[Figure 3]

[Figure 4]

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

Tier 1 assessment for the reprotoxic SVOCs:

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

to the windows of exposure considered in the toxicological testing available for the derivation of the RfD. Eleven RfDs were retrieved from literature and 5 were constructed (see Table S7).

Reprotoxic effects may occur for some mixtures. HIs were above 1 for 95% of children (5^{th} percentiles, data not shown), and close to 9 for 5% of them, for the mixture of 11 reprotoxic SVOCs. For the pregnant women's exposure, HIs were above 1 for 5% of them, for the mixture of 9 reprotoxic SVOCs (Figure 5). For adults, HIs were lower than 1 for the mixture of 7 SVOCs (see Table S8 for detailed results).

[Figure 5]

[Figure 6]

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

<u>Tier 2 assessment:</u>

[Table 1]

19 SVOCs are included in tier 2 according to the availability of RPF, relative potencies, or TEF in the literature. However, considering that TEF or RPF were derived from different 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 5^{th} 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 50^{th} and the 95^{th} 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 50^{th} and the 95^{th} percentiles of CumER (Figure 8).
328 For pregnant women's exposure, DBP and DiBP contributed most to the 50^{th} and the 95^{th}
329 percentiles of CumHQs (Figure 9).

330 <u>Special case of PCBs:</u>

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]

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

[Figure 11]

DISCUSSION

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

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

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

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

Relevance of toxicological and epidemiological data for risk assessment

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

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

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

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

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

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

Similarly,

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

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

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

Selected compounds and missing data

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

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

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

Exposure data

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

Toxicity indicators

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

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

CONCLUSIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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