Multiple exposures to indoor contaminants: Derivation of benchmark doses and relative potency factors based on male reprotoxic effects

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Abstract

Semi-Volatile Organic Compounds (SVOCs) are commonly present in dwellings and several are suspected of having effects on male reproductive function mediated by an endocrine disruption mode of action. To improve knowledge of the health impact of these compounds, cumulative toxicity indicators are needed. This work derives Benchmark Doses (BMD) and Relative Potency Factors (RPF) for SVOCs acting on the male reproductive system through the same mode of action.

We included SVOCs fulfilling the following conditions: detection frequency (>10%) in French dwellings, availability of data on the mechanism / mode of action for male reproductive toxicity, and availability of comparable dose-response relationships.

Of 58 SVOCs selected, 18 induce a decrease in serum testosterone levels. Six have sufficient and comparable data to derive BMDs based on 10 or 50% of the response. The SVOCs inducing the largest decrease in serum testosterone concentration are: for 10%, bisphenol A (BMD_{10}= 7.72E-07 mg/kg bw/d; RPF_{10}= 7033679); for 50%, benzo[a]pyrene (BMD_{50}= 0.030 mg/kg bw/d; RPF_{50}= 1630), and the one inducing the smallest one is benzyl butyl phthalate (RPF_{10} and RPF_{50}= 0.095).

This approach encompasses contaminants from diverse chemical families acting through similar modes of action, and makes possible a cumulative risk assessment in indoor environments. The main limitation remains the lack of comparable toxicological data.

Keywords: semi-volatile organic compounds; benchmark doses; cumulative risk assessment; reproduction; mixture; toxicity

1. Introduction

Semi-volatile organic compounds (SVOCs) include numerous molecules belonging to different chemical families such as phthalates, polycyclic aromatic hydrocarbons (PAHs), musks, polybromodiphenyl ethers (PBDEs), polychlorobiphenyls (PCBs) or pyrethroid insecticides (Weschler and Nazaroff, 2008). They can be defined as "organic compounds with vapour pressures between 10^{-14} and 10^{-4}atm (10^{-9} to 10Pa)" and whose boiling point is between (240 to 260°C) and (380 to 400°C) (NF ISO 16000-6, 2006) (Weschler and Nazaroff, 2008). They are used for their technical properties in a large variety of building materials and consumer products (plastics, paints, cleaning agents, biocides, furniture, etc.), and are also emitted by combustion processes. Due to their widespread usage and chemical properties, their presence is ubiquitous in indoor environments, in both settled dust and air (gaseous phase and particulate matter) (Mercier et al., 2011, Blanchard et al., 2014). Many SVOCs are suspected of having endocrine disruption mechanisms, leading to potential effects on male reproduction. Among them, phthalates are considered anti-androgenic compounds, responsible for an inhibition of steroidogenesis (Svechnikov et al., 2008), leading to a decrease in anogenital distance and nipple retention, as well as an increase in the incidence of hypospadias and cryptorchidism in rats exposed during the prenatal period (Gray et al., 2000). A significant decrease in serum testosterone levels was observed in rodents following oral exposure to BDE-99 (Alonso et al., 2010), benzo[a]pyrene (B(a)P) (Liang et al., 2012) or cypermethrin (Jin et al., 2011). In addition, in rats, cypermethrin decreases expression of the androgen receptor after 2 weeks of oral exposure (Liu et al., 2010). The effects of bisphenol A (BPA) on testosterone synthesis may be controversial, yet further studies have shown BPA to have negative effects on this hormone. For example, Salian et al. observed a significant decrease in testosterone concentration in rats pre and postnatally exposed

(Salian et al., 2009). Della Seta et al. observed the same phenomenon following exposure from postnatal day 23 to postnatal day 30 (Della Seta et al., 2006).

In humans, authors have demonstrated in vitro endocrine disruption properties for a mixture including phthalates and BPA (Christen et al., 2012) and also for DEHP and MEHP alone (Desdoits-Lethimonier et al., 2012).

SVOC endocrine properties have also been suggested through epidemiological studies. Hauser et al. observed a dose-dependent negative association between monobutyl phthalate (MBP) and sperm concentration and motility in a population of 463 male partners of subfertile couples (Hauser et al., 2006). Others groups found similar results between MBP and MEP exposure, and sperm mobility / concentration (Duty et al., 2003); metabolites of long-chained phthalates (MEHP and MiNP) and testosterone production (Meeker et al., 2009); MBP and MEHP and serum-free testosterone (Pan et al., 2006); flame retardant (PBDEs) and serum testosterone concentration (Johnson et al., 2013), and sperm quality (Abdelouahab et al., 2011); BPA and male sexual function (Li et al., 2010) or semen quality (Meeker et al., 2010). Alteration of protein expression can represent important key events in a modes of action (MOAs), or molecular initiating event in an adverse outcome pathways (AOPs), leading to an adverse outcome (Chepelev et al., 2014). Sonich-Mullin defined MOA as a “biologically plausible series of key events leading to an effect” (Sonich-Mullin et al., 2001). An AOP is conceptually similar to a MOA but includes an initial point of interaction of a chemical with biological systems (Meek et al., 2014). It is difficult to know and understand the entire MOA/AOP leading to reprotoxic effects but with a view of the preview information, we can consider the alteration of protein synthesis (e.g. testosterone) as a potential early key event leading to reprotoxic effects.

As underline by Chepelev, protein expression analysis could contributed in health risk assessment (Chepelev et al., 2014). Thus, Cumulative Risk Assessment (CRA) could be used to address this

concern, with a view to assessing whether environmental exposure levels to SVOCs pose a risk, and to help set maximum exposure levels not to be exceeded in indoor environments. A variety of CRA methodologies have already been suggested and recently reviewed (Fournier et al., 2014a). Some of them, including toxic equivalency factors (TEF) and relative potency factors (RPF) approaches have been used to identify relative toxic potencies on various chemical mixtures. This is the case of dioxins and PCBs (Ahlborg et al., 1994); polychlorinated dibenzo-p-dioxins (PCDD) (OME, 1985); pesticides (Jensen et al., 2013) and PAHs (Nisbet and LaGoy, 1992). These approaches are based on the dose additivity assumption (Loewe and Muischnek, 1926) as suggested by the US EPA (US EPA, 2002) and consider a common mode of action (US EPA, 2000). This assumption does not take into account the possibility of toxicological interactions that are not, or are rarely expected with exposure to low doses of contaminants(ATSDR, 2004). These approaches were extended to other SVOCs including phthalates, fungicides or pyrethroids (Christiansen et al., 2012; Hannas et al., 2011; Kortenkamp and Faust, 2010; Wolansky et al., 2005), but none of them is based on real exposure, where a variety of chemical families are encountered.

The aim of this work is to estimate RPFs based on comparable benchmark doses (BMDs) for multiple reprotoxic contaminants present in indoor environments. The choice of the BMD rather than the NOAEL/LOAEL as an indicator of the toxicity was decided to reduce uncertainty due to data heterogeneity (EFSA, 2006).

2. Material and Method

2.1. Selection and grouping of indoor SVOCs

The selection of chemicals was made on the basis of different measurement campaigns in French dwellings (Mandin et al., 2014a, 2014b ; Blanchard et al., 2014), where 66 compounds selected from a previous ranking (Bonvallot et al., 2010) were simultaneously analysed in a range of environmental media (air, gas phase or particle matter, settled dust) using a multi-residue method (Mercier et al., 2012, 2014). SVOCs were selected where they were detected in more than 10% of the investigated houses (from 30 to 285 according to the campaign).

SVOC grouping was based on our previously described approach (Fournier et al., 2014b). Briefly, hazard identification, for each chemical, was performed by means of a literature review on its reprotoxic effects. To be eligible, the toxicological studies (in vivo or in vitro) should describe the target organs or cells, or the mechanisms of action on the male reproductive system or organs. SVOCs were then grouped by common effect, mode and/or mechanism of action. According to the data, and in order to estimate RPFs, we chose to select the group including the largest number of SVOCs, and for which a biological pathway is known.

2.2. Benchmark doses derivation

The BMD is defined as a dose (or concentration) producing a predetermined change in the response rate of an effect (known as the benchmark response or BMR) compared with the background response rate of this effect (US EPA, glossary: http://www.epa.gov/risk_assessment/glossary.htm). It provides a quantitative indicator of the toxicity of a compound based on the modelling of the entire dose-response relationship. BMDs were derived by means of the following steps: i) selection of suitable dose-response datasets, ii) choice of BMR, iii) fitting models using experimental data, and iv) selection of the best fitting model.

For each compound, we based our BMD calculation on one selected study, describing the most robust dose-response dataset. This kind of approach was also applied recently by Chepelev in

136 order to derive BMDs for the protein expression involved in testicular toxicity (Chepelev et al.,
137 2014).
138
139 **2.3. Selecting dose-response datasets**
140 For each SVOC, available dose-response datasets were collected and selected on the basis of a
141 compromise between the amount of data available and comparability of the data between
142 compounds. The following criteria were used: i) availability of data for at least 3 dose levels and
143 1 control group; ii) same species (though not necessarily the same strain); iii) same window of
144 susceptibility (but not necessarily the same exposure duration); iv) same exposure route; v)
145 availability of raw data or means and standard errors of the means (SEM) or standard deviations
146 (SD) for each selected response. Where SDs were not provided in the publication and could not
147 be collected from the authors, a graphical estimation was made as described by the US EPA (US
148 EPA, 2005). If only SEMs were given, these were converted to SDs using the following equation:
149 $SD = SEM \times \sqrt{n}$, where n is the sample size.
150
151 **2.4. Choice of BMR for a common effect**
152 The response chosen should be linked to a reproductive effect and related to a maximum number
153 of SVOCs in order to consider a CRA. The Benchmark Response (BMR) is associated with the
154 BMD as a change in response relative to background (Crump, 1984). According to the data, this
155 response could be continuous (e.g., relative change from the control) or dichotomous (e.g.,
156 presence or absence of an effect) (US EPA, 2012). In case of RPF derivation, the response should
157 either be linked to a specific mechanism of action or a consequence of a common mode of action
158 (a biological pathway leading to an adverse effect on the reproductive system). Because this

response occurs at organism or cellular scale, it is a continuous response. Response rates in each dataset were expressed as a proportion of the background response rate (i.e. background=1). Where the adverse effect threshold is unknown, the BMRs used in this study will be default values recommended by the US EPA (e.g., a decrease of 1 control SD for continuous datasets and 10% for dichotomous dataset) or a response level that would be qualified as adverse.

2.5. Selection of the best fitting model

BMDs were computed using the PROAST software (www.rivm.nl/proast v32.2). The data was continuous summary data (raw data was rarely available) and the Hill family of models was selected for modelling the dose-response relationships, as follow in equations 1 to 4 (2 to 4 parameters):

$$y = a\left(1 - \frac{x}{b + x}\right) \quad (1)$$

$$y = a\left(1 - \frac{x^d}{b^d + x^d}\right) \quad (2)$$

$$y = a\left(1 + \frac{(c-1)x}{b + x}\right) \quad (3)$$

$$y = a\left(1 + \frac{(c-1)x^d}{b^d + x^d}\right) \quad (4)$$

Where x is toxic compound concentration, a is the background response, b is the concentration of the compound inducing 50% of the effect, d is the slope, and $a*c$ is the response to an infinite dose. The best fitting model from the Hill family was selected according to the procedure described by Slob (Slob, 2002) with the likelihood ratio test. This tests whether increasing the number of parameters in a model results in a statistically significant improvement to fit.

2.6. RPF estimation

RPFs were estimated using the previously-derived BMDs, according to the equation below:

$$RPF_i = \frac{BMD_{ref}}{BMD_i}$$

Where RPF_i is the RPF of the compound "i"; BMD_i is the BMD of the compound "i"; BMD_{ref} is the BMD of the reference compound.

RPFs express the potency of a compound "i" according to the reference compound. This reference compound can be the most toxic compound within a group of compounds, or the most documented for the selected effect.

3. Results

Fifty-eight SVOCs were selected based on the criteria described in the previous section, and are presented in table 1. Of these, 23 were documented as having male reprotoxic properties regardless of the mode or mechanism of action. A more precise description lead to the identification of 3 groups having different modes of action and potentially acting via different biological pathways. These pathways are summarized in figure 1 (adapted from Fournier et al. 2014a).

The group including the largest number of SVOCs - and for which the biological pathway is known - is the group whose effect is described as decreasing the concentration of steroidogenesis enzymes, resulting in a lower testosterone level; 18 SVOCs were concerned.

3.1. Benchmark Doses Derivation

3.1.1. Selection of Dose-Response Datasets

Dose-response datasets meeting our selection criteria were available for just 6 of the 18 compounds acting on steroidogenesis enzymes. The response measured in the toxicological studies was the serum concentration of testosterone after oral-route exposure of adult male rodents.

Lindane, dieldrin, alpha-endosulfan, chlorpyrifos-ethyl, deltamethrin, triclosan, 4-*tert*-octylphenol and BDE-99 were excluded because there was no available dose-response relationship for this effect (only one- and two- tested doses, respectively). Four other SVOCs were excluded (permethrin, DBP, DiBP, DiNP) due to lack of comparable data (exposure of rodents during different windows of susceptibility, i.e. pre- or post- natal).

The central estimation (BMD) was used as the basis for calculation of RPFs rather than the BMDL (Benchmark Dose Lower Bound = lower limit of a one-sided confidence interval on the BMD) which integrates uncertainty to experimental data, as suggested by the US EPA in 2010 (US EPA, 2010).

Table 2 briefly summarizes the selected study protocols and the decrease in serum testosterone relative to control results. In each case, dose-response data was obtained in adult rats orally exposed through sub-chronic to chronic exposure (15 to 150 days). There are 9 orders of magnitude between the highest dose tested (for DEHP) and the lowest one (for BPA).

3.1.2. Choice of Response and BMR

Serum testosterone concentration was measured in all studies. A decrease in this response was observed according to dose. It is reasonable to consider that this decrease may be linked to adverse effects such as cryptorchidism, hypospadias or male fertility impairment, depending on the window of susceptibility, as suggested by a group of experts of the United Nations Environment Programme (UNEP) and WHO (WHO/UNEP, 2013). Two different BMRs were chosen: a 10% and a 50% decrease in response compared to control serum testosterone. We

consider a decrease of 50% of the serum testosterone to be significant (equivalent to the highest documented standard deviation in our selected SVOCs). The use of a BMR equivalent to 1 control standard deviation from the control mean is recommended by the US EPA (US EPA, 2012). The use of 10% as a BMR is intended to compare contaminants' toxicity at lower doses, though authors consider this effect size not meaningful. Eisenberg and colleagues observed a 10% difference in testosterone concentration between fertile and infertile men (Eisenberg et al., 2011). Furthermore, a 10% decrease in serum testosterone corresponds to the lowest documented standard deviation in our selected SVOCs.

3.1.3. BMD Estimations

The corresponding BMD_{10} and BMD_{50} are shown in table 3 (associated graphs are shown in supplementary data). Equation 2, with 3 estimated parameters and a null response at infinite doses, was selected for BPA. Equation 3, with 3 estimated parameters, slope equal to 1 and a non-null response at infinite doses, was selected for DEHP. Equation 1, with 2 free parameters, slope equal to 1 and a null response at infinite doses, was selected for the other four SVOCs. Since the response at infinite doses is equal to 0, BMD_{50} is the dose resulting in a 50% decrease relative to the background response. Resulting RPFs for a 10% (RPF_{10}) and 50% (RPF_{50}) decrease are shown in table 4. The control values were included in the BMD calculations.

4. Discussion and Conclusion

In this study, we derived BMDs for 6 SVOCs pertaining to different chemical families to which people are exposed in indoor environments, leading to RPF for BBP, BPA, B[a]P, DEP, DEHP

247 and cypermethrin. We have adapted the traditional risk assessment approach (NRC, 1983) by
248 adding a grouping step, depending on SVOCs' effects, as suggested in our previous work
249 (Fournier et al, 2014b). This was done on the basis of their mode of action. In a second step, we
250 calculated BMDs for the 6 SVOCs for which we were able to obtain sufficient information,
251 which in turn allowed RPFs to be derived.

252 The RPFs calculation is based on the dose additivity assumption because it seems to best describe
253 the reality of mixture toxicity. In fact, the toxic equivalency and dose additivity models have
254 already proved their potency in the mixture effects prediction. For example, Rider et al., in 2008,
255 tested different hypotheses for predicting mixture reproductive effects in male offspring rats
256 exposed during the period of sexual differentiation (Rider et al., 2008). They compared the
257 observed responses from a mixture of 4 pesticides and 3 phthalates with predicted responses
258 generated using a toxic equivalency approach and dose addition, response addition or integrated
259 addition models. They validated the dose additivity assumption and showed that toxic
260 equivalency and dose addition models provide the best fit to their observed responses even for
261 chemicals from different families which do not necessarily act via the same cellular mechanism
262 of action. There were several reasons for basing our RPF calculation on a 10% and 50% decrease
263 in testosterone synthesis (BMD_{10} and BMD_{50}), defined respectively as RPF_{10} and RPF_{50}. First of
264 all, as mentioned above, we do not know which level of inhibition of testosterone is harmful to
265 human health. In this case, the US EPA recommends the use of an endpoint that is equivalent to a
266 decrease of 1 control SD (US EPA, 2012). In our case, we have chosen to apply respectively the
267 smallest and the largest of the documented control SDs (near 50% for BBP and 10% for BPA) for
268 the choice of BMR.

We chose cypermethin as the index compound because its range of tested doses is intermediate among those tested for the other SVOCs. The difference in ranges of tested doses and toxicity between contaminants yields a large range of RPF values (a factor of 10^9 between BPA and BBP for RPF_{10}, a factor of 10^6 between B[a]P and BBP). The choice of the reference compound, however, modifies neither the toxicity of each contaminant nor the order of their potency for the effect of interest.

According to the RPF_{10}, BPA shows the most toxic among the considered SVOCs (7,033,679 times more potent than cypermethrin for this effect) and BBP the least toxic (10.5 times less potent than cypermethrin). According to the RPF_{50}, B(a)P seems to be the most toxic (1,630 times more potent than cypermethrin for this effect) and BBP the least one (10.5 times less potent than cypermethrin).

For a 50% reduction in testosterone levels, we can observe that B(a)P is more toxic than BPA, while this latter is most potent at 10% of the effect. According to our data, BPA is the most potent of of the study SVOCs at low doses. This is due to the difference between BPA and the other SVOCs in terms of the slope of the curves (inclusion of the "d" parameter, see equation 2).

Our data does not allow to derive a BMD_{50} (and RPF_{50}) for DEHP because, according to the Hill equation used by PROAST, when the DEHP concentration is infinite, the response (decrease in serum testosterone concentration) only approaches 0.43 (=BMD_{43}). The derivation of a BMD_{50} for the DEHP could be performed with other data which investigated the same response, but specifically in pubertal rats (Noriega et al., 2009). According to this data, the BMD_{10} would be 102.45 mg/kg bw/day and the BMD_{50} 922.07 mg/kg bw/day.

We see here that the BMD_{10} based on adult data from Tonk et al. is 20 times lower than the BMD_{10} based on pubertal rat from Noriega et al. This comparison shows that the toxic potency of DEHP compared to other compounds could be modified regarding to the window of exposure, leading difficult the extrapolation of the "pubertal" BMD_{50} to an "adult" BMD_{50}.

In our case, three SVOCs (B[a]P, DEP and BBP) had parallel dose-response curves compared to the reference compound's curve (cypermethrin) with a slope equal to 1 and a response at infinite concentrations equal to 0. On the other hand, for DEHP, at infinite concentrations, the response only approaches 0.43 rather than 0 and for BPA, the slope was different from 1. In these cases, the dose-response curves were not parallel compared to the reference. Thus, from a statistical point of view, the RPFs for B[a]P, DEP and BBP are more reliable than those for DEHP and BPA.

The main limitation of this work in a perspective of CRA for chemicals humans are exposed to, is the lack of available and comparable data in the scientific literature. Among the 58 SVOCs that were considered, others than the one we could include might be reprotoxic, but no study has been published to date. Only 23 have been documented as having reprotoxic properties. Of these, 18 are able to decrease testosterone synthesis. At the final step, the literature provided sufficient comparable information for BMD calculation only for 6.

This limitation of the available information was recently underlined by Wignall et al. in their standardization of BMD calculations (Wignall et al., 2014). Another impediment is the lack of comparability of the data in terms of the range of tested doses, windows of exposure, animal strain, time of exposure, etc. The most striking example is the tested doses range, from 0.000005 mg/kg bw/day for BPA, to 1000 mg/kg bw/day for DEHP, suggesting that BPA is the most

312 potent toxic SVOC of our group for the study effect (abatement of serum testosterone
313 concentration); however, its action remains a subject of controversy in the literature. Our
314 requirements in term of data comparability (same species, same window of exposure, etc.) and
315 obviously the lack of data availability limit the datasets for our RPF computations. The more
316 precise and comparable we require our data to be, the less such data is available.

317 There is no data to compare with in the literature regarding RPFs derived from a variety of
318 chemical families. Among phthalates, RPFs were derived for DEHP and BBP acting on
319 testosterone synthesis (Benson, 2009; Hannas et al., 2011). In his CRA, Benson derived RPF for
320 6 phthalates including DEHP and BBP. For DEHP, the endpoint was smallness - or absence of -
321 male reproductive organs. For BBP (and the 4 other phthalates), the endpoint was decrease in
322 foetal testosterone production. The resulting RPFs were 1 and 0.21, based on the IC95 lower
323 bound of the BMD_{10} or the IC95 lower bound of the BMD corresponding to one standard
324 deviation for DEHP and BBP respectively. According to this method, DEHP appears to be 5
325 times more potent than BBP, which is in line with our findings (10 times more potent according
326 to BMD_{10}). This difference in potency might be explained by the use of different toxicity
327 indicators (BMDL versus BMD), the use of two different endpoints (small or absent male
328 reproductive organs for DEHP and a decrease in testosterone production for BBP), and a different
329 window of exposure (prenatal period for Benson, adult age for our work).

330 More recently, Hannas et al. have calculated RPFs for 5 phthalates. In contrast to Benson, they
331 undertook the *in vivo* tests on the same endpoint (decrease of foetal testosterone production) in
332 their own laboratory, making their data more comparable. They measured foetal testosterone
333 production and the expression of steroidogenesis enzymes after 5 days of *in utero* exposure for
334 each phthalate. The potency estimations were based on the derived effective doses 50 (ED_{50}),

corresponding to the dose responsible for 50% decrease of the foetal testosterone, equivalent to a BMD_{50}. In this case, DEHP appears to be one of the least potent phthalates for this effect, in contrast to our data. This could be explained by the level of response associated with the chosen indicators (10% versus 50%) or by the difference of window of exposure. In this case, only DEHP is similar to the compounds included in our study so no potency comparison can be made.

While Benson concludes that DEHP is one of the most toxic phthalates within its chemical group (2.5 and 4 times more potent than DiNP and DiBP respectively) using different endpoints, Hannas finds that DEHP is approximately equipotent with DiBP and DiNP (RPFs of 0.06, 0.11 and 0.15 for DiNP, DEHP and DiBP respectively) for the same endpoint.

For RPF calculations, it is very important to use comparable data and the same endpoint in order to conduct a robust CRA. Also, future experiments should strive to standardise protocols (animals tested, time of exposure, etc.) as well as the ranges and number of doses tested, which should be as close as possible to human real exposures, allowing us to establish a dose-response curve.

Our approach takes into account actual population exposures, compounds from different chemical families, and common effects and modes of action of SVOCs. For these reasons, we think it is realistic and useful for future CRA studies. Research must continue in this direction to improve the consideration of actual exposures in CRA.

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Figure 1: Adverse outcome pathway of 23 indoor semi volatile organic compounds (SVOCs) on the reproductive, adapted from (Fournier et al., 2014b).

[1](Gray et al., 2000); [2](Pan et al., 2006); [3](Borch et al., 2006); [4](Pereira et al., 2008); [5](Abdelouahab et al., 2011); [6](Alonso et al., 2010); [7](D'Cruz et al., 2012); [8](Chung et al., 2011); [9](Kuriyama and Chahoud, 2004); [10](Saradha et al., 2009); [11](Ronco et al., 2001); [12](Zhang et al., 2007); [13](Hu et al., 2011); [14](Singh and Pandey, 1990); [15](Schein and Thomas, 1975); [16](Fiorini et al., 2004); [17](Farag et al., 2010); [18](Ismail and Mohamed, 2012); [19](Kumar et al., 2009); [20](Sainath et al., 2011); [21](Wilson et al., 2004); [22](Hannas et al., 2012); [23](Mograbi et al., 2003); [24](Posnack et al., 2015); [25](Liu et al., 2005); [26](Tonk et al., 2012); [27](Nagao et al., 2000); [28](Pereira et al., 2008); [29](Jiang et al., 2007); [30](Borch et al., 2004); [31](Shi et al., 2010); [32](Jayachandra and D'Souza, 2014)

Table 1: Selected Semi Volatile Organic Compounds as candidates for grouping (detected in more than 10% of the French dwellings investigated)

Chemical families	Name
Phthalates	DEHP, DEP, DBP, BBP, DiBP, DiNP, DMP
Polybromodiphenyl ethers (PBDEs)	BDE-28, BDE-47, BDE-85, BDE-99, BDE-100, BDE-153, BDE-154, BDE-209
Polychlorobiphenyls (PCBs)	PCB-28, PCB-31, PCB-52, PCB-77, PCB-101, PCB-105, PCB-118, PCB-138, PCB-153, PCB-180
Polycyclic aromatic hydrocarbons (HAPs)	acenaphtene, anthracene, benzo(a)pyrene, fluorene, phenanthrene, fluoranthene, pyrene, benzo(a)anthracene, chrysene, benzo(k)fluoranthene, benzo(b)fluoranthene, indeno(1,2,3-cd)pyrene, benzo(g,h,i)perylene, dibenzo(a,h)anthracene
Pesticides	4',4-DDE, 4',4-DDT, dieldrine, alpha-endosulfan, lindane, chlorpyrifos-ethyl, diazinon, cyfluthrine, cypermethrine, deltamethrine, permethrine, oxadiazon, tributylphosphate
Others	4-tert-butylphenol, 4-tert-octylphenol, bisphenol A, galaxolide, tonalide, triclosan

Based on (Mandin et al., 2014a) ; (Mandin et al., 2014b); (Blanchard et al., 2014)

Table 2: Available information in the literature on reproductive effects for the 6 Semi Volatile Organic Compounds retained for BenchMark Dose calculation

SVOC	Tested animals	Number of animals	Time of exposure	Route of exposure	Tested doses (mg/kg bw/day)	Response (standard deviation) (relative to control)	Reference
BBP	Adult SD rats	25	105 days	Oral	0 20 100 500	1 (0.46) 1.03 (0.54) 0.77 (0.37) 0.54 (0.31)	Nagao et al., 2000
BPA	Adult Wistar rats	6	45 days	Oral	0 0.000005 0.00005 0.05 0.5	1 (0.1) 0.84 (0.05) 0.74 (0.05) 0.62 (0.04) 0.44 (0.06)	D'Cruz et al., 2012
B[a]P	Adult SD rats	9	90 days	Oral	0 0.001 0.01 0.1	1 (0.31) 1 (0.29) 0.64 (0.17) 0.25 (0.12)	Chung et al., 2011
DEP	Adult Wistar rats	6	150 days	Oral	0 0.57 1.425 2.85	1 (0.13) 0.69 (0.11) 0.63 (0.056) 0.41 (0.025)	Pereira et al., 2008
DEHP	Adult Wistar rats	5	40 days	Oral	0 1 3 10 30 100 300 1000	1 (0.42) 0.79 (0.17) 0.70 (0.27) 1.15 (0.50) 0.52 (0.30) 0.62 (0.32) 0.47 (0.16) 0.48 (0.18)	Tonk et al., 2012
Cyper-methrin	Adult SD rats	12	15 days	Oral	0 6.25 12.5 25 50	1 (0.35) 0.84 (0.35) 0.79 (0.19) 0.65 (0.33) 0.49 (0.16)	Hu et al., 2011

SVOCs: Semi Volatile Organic Compounds; SD: Sprague Dawley

Table 3: Benchmark dose 10 and benchmark dose 50 for the 6 selected SVOCs

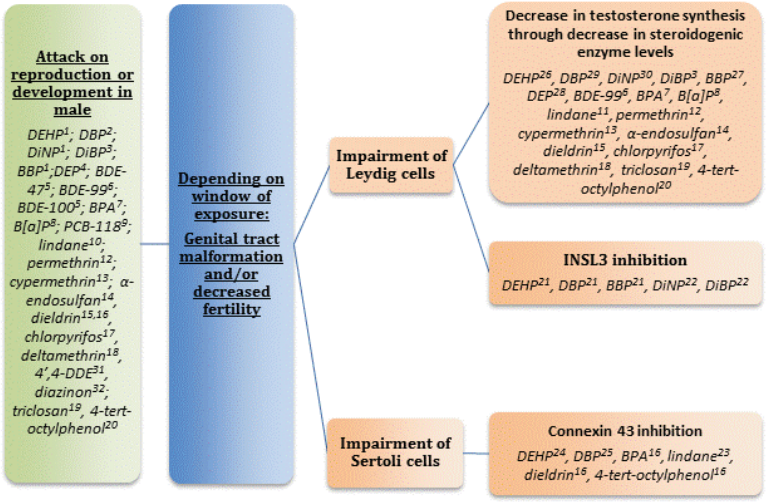
SVOC	Number of Hill parameters	BMD10 (mg/kg bw/day)	BMD50 (mg/kg bw/day)
B[a]P	2	0.0034	0.030
BPA	3	7.72E-07	0.27
DEP	2	0.24	2.18
DEHP	3	5.04	/
Cypermethrin	2	5.43	48.90
BBP	2	57.34	520

SVOCs: Semi Volatile Organic Compounds; BMD_{10}: Benchmark Doses responsible of 10% of the selected effect

Table 4: Relative Potency Factor 10 and Relative Potency Factor 50 calculations from BenchMark Doses for 6 Semi Volatile Organic Compounds detected in more than 10% of French dwellings and acting on testosterone synthesis in adult male rats

SVOC	RPF_{10}	RPF_{50}
B[a]P	1597	1630
BPA	7033679	181
DEP	22.63	22
DEHP	1.08	/
Cypermethrin	1	1
BBP	0.095	0.095

SVOCs: Semi Volatile Organic Compounds; RPF_{10}: Relative Potency Factors for 10% of the selected effect



Highlights

- Semi-volatile organic compounds (SVOCs) detected in more than 10% of French dwelling were selected
- SVOCs were grouped according to their reprotoxic mode of action
- Benchmark Doses and Relative Potency Factors based on a decrease in testosterone level in male rodent were derived
- The main limitation is the lack of comparable toxicological data.