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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} = 7,033,679); 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.

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}–10 Pa)" and whose boiling point is between (240–260 °C) and (380–400 °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

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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 order to derive BMDs for the protein expression involved in testicular toxicity (Chepelev et al., 2014).

2.3. Selecting dose-response datasets

For each SVOC, available dose-response datasets were collected and selected on the basis of a compromise between the amount of data available and comparability of the data between compounds. The following criteria were used: i) availability of data for at least 3 dose levels and 1 control group; ii) same species (though not necessarily the same strain); iii) same window of susceptibility (but not necessarily the same exposure duration); iv) same exposure route; v) availability of raw data or means and standard errors of the means (SEM) or standard deviations (SD) for each selected response. Where SDs were not provided in the publication and could not be collected from the authors, a graphical estimation was made as described by the US EPA (US EPA, 2005). If only SEMs were given, these were converted to SDs using the following equation: $SD = SEM \times \sqrt{n}$, where n is the sample size.