Environment International 113 (2018) 202–213

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Review article

Bioaccessibility and bioavailability of environmental semi-volatile organic compounds *via* inhalation: A review of methods and models

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ARTICLE INFO

Handling Editor: R.J. Latcher

Keywords:
SVOCs
Respiratory tract
Absorption
Deposition
Inhalation exposure
Internal dose

ABSTRACT

Semi-volatile organic compounds (SVOCs) present in indoor environments are known to cause adverse health effects through multiple routes of exposure. To assess the aggregate exposure, the bioaccessibility and bioavailability of SVOCs need to be determined.

In this review, we discussed measurements of the bioaccessibility and bioavailability of SVOCs after inhalation. Published literature related to this issue is available for 2,3,7,8-tetrachlorodibenzo-p-dioxin and a few polycyclic aromatic hydrocarbons, such as benzo[*a*]pyrene and phenanthrene. Then, we reviewed common modeling approaches for the characterization of the gas- and particle-phase partitioning of SVOCs during inhalation. The models are based on mass transfer mechanisms as well as the structure of the respiratory system, using common computational techniques, such as computational fluid dynamics. However, the existing models are restricted to special conditions and cannot predict SVOC bioaccessibility and bioavailability in the whole respiratory system.

The present review notes two main challenges for the estimation of SVOC bioaccessibility and bioavailability *via* inhalation in humans. First, *in vitro* and *in vivo* methods need to be developed and validated for a wide range of SVOCs. The *in vitro* methods should be validated with *in vivo* tests to evaluate human exposures to SVOCs in airborne particles. Second, modeling approaches for SVOCs need to consider the whole respiratory system. Alterations of the respiratory cycle period and human biological variability may be considered in future studies.

1. Introduction

Semi-volatile organic compounds (SVOCs) are defined as molecules with vapor pressures between 10^{-9} and 10 Pa at 25 °C (Weschler and Nazaroff, 2008). SVOCs originate from indoor and outdoor sources and are widely present in people's everyday lives (Blanchard et al., 2014). Common indoor environmental SVOCs include phthalate esters used as plasticizers; polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) used as flame retardants; organochlorine and organophosphorus pesticides; synthetic musks; polycyclic aromatic hydrocarbons (PAHs); and alkylphenols used as additives in detergents, fuels, lubricants, polymers, and other products. These compounds are present in the gas phase and absorbed on airborne particles, settled dust, and indoor surfaces (Bi et al., 2015; Blanchard et al., 2014; Mandin et al., 2016).

Most SVOCs cause adverse health effects, including neurotoxic and reprotoxic effects (Fournier et al., 2014). Chemicals such as organochlorines (*e.g.*, dichlorodiphenyltrichloroethane and PCBs), brominated compounds (*e.g.*, PBDEs), bisphenol A, PAHs, alkylphenols, pesticides, and a variety of phthalate esters have endocrine-disrupting properties (De Coster and Van Larebeke, 2012). In addition, some phthalate esters have been shown to play a role in atopic diseases such as asthma, eczema and rhinitis (Bekö et al., 2015; Bornehag et al., 2004; Hsu et al., 2012; Jaakkola and Knight, 2008; Kolarik et al., 2008). PAHs,

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https://doi.org/10.1016/j.envint.2018.01.024
Received 30 August 2017; Received in revised form 22 January 2018; Accepted 23 January 2018

especially benzo[*a*]pyrene (BaP), and some organochlorine and organophosphate pesticides are also known to be carcinogenic compounds according to the International Agency for Research on Cancer. Inhalation exposure may play an important role in the exposure to SVOC, such as some PAHs and phthalate esters (Jaakkola and Knight, 2008; Kim et al., 2013; Pelletier et al., 2017). If it is less obvious for other SVOCs, the contribution of the inhalation route to indoor SVOC exposure has been estimated as being important for PBDEs, PCBs, pesticides, musks, and phthalate esters with high volatility (Pelletier et al., 2017).

Human exposure to environmental SVOCs can occur *via* the ingestion of settled dust, dermal absorption, and inhalation (Weschler and Nazaroff, 2008), as the compounds partition between different phases in the air, on indoor surfaces, and in settled dust. The SVOC concentrations in the gas phase, particle phase, and settled dust are commonly used for the estimation of human exposure to environmental SVOCs (Pelletier et al., 2017). However, the use of rough concentrations may overestimate the uptake of SVOCs because a fraction of the SVOCs may not be bioaccessible or bioavailable. To improve the health risk assessment associated with the multiple routes of SVOC exposure, the bioaccessible or bioavailable concentrations should be determined (Semple et al., 2004). The definitions of bioaccessibility and bioavailability from the perspectives of toxicologists and environmental scientists are diverse (Reichenberg and Mayer, 2006; Semple et al., 2004). In the present study, the bioaccessible fraction of a compound is defined as the amount that is released into the body fluid and available for absorption (Caboche et al., 2011; Collins et al., 2015; Rostami and Juhasz, 2011), whereas the bioavailable fraction is defined as the amount that can cross a biological membrane and reach systemic circulation (Collins et al., 2015; Rostami and Juhasz, 2011; Yu et al., 2012). Using the bioavailability increases the accuracy of the exposure assessment. Due to difficulties in the measurement of the bioavailability, as it requires measurements in human biological endpoints, SVOC bioaccessible concentrations from environmental media can be used as a substitute. The fraction of a compound released into the fluid of an organism (the bioaccessible fraction) is higher than that subsequently transferred into the bloodstream (the bioavailable fraction) (Kastury et al., 2017).

The bioaccessibility and bioavailability of a number of SVOCs *via* ingestion and dermal contact have been studied through *in vitro* and *in vivo* tests, respectively. In the *in vitro* bioaccessibility studies, the absorption of SVOCs was studied employing real or simulated human gastrointestinal (He et al., 2016; Juhasz et al., 2014; Kang et al., 2012; Wang et al., 2013; Yu et al., 2012) or skin receptor (Beriro et al., 2016) fluids. In the *in vivo* bioavailability studies, human or animal subjects were exposed to SVOCs by ingestion (Wu et al., 2007) or dermal contact (Abdallah et al., 2015; Morrison et al., 2016; Wester et al., 1990), and the SVOC concentration in the blood, urine, or organism was measured (Beriro et al., 2016; Koch et al., 2005).

The bioaccessibility and bioavailability of inhaled metals in ambient particles have been critically reviewed (Boisa et al., 2014; Kastury et al., 2017; Wiseman, 2015). Significant methodological differences were observed among the studies within the compositions of leaching agents used during the extraction and the use of static *versus* dynamic methods. The bioaccessibility and bioavailability of inhaled SVOCs have rarely been studied. Inhaled SVOCs may exist in both the gas and particle phases, which can deposit in respiratory tracts by four mechanisms and become bioaccessible (Fig. 1) (Pankow, 2001): the deposition of gas-phase compounds (GD: gas deposition), deposition of gas-phase compounds evaporated from the inhaled particles (EGD: evaporated gas deposition), deposition of inhaled particles followed by the deposition of the gas-phase compounds evaporated from the deposited particles (PDEGD: particle deposition and evaporated gas deposition), and deposition of inhaled particles followed by the diffusion of compounds from the deposited particles to the fluid of the respiratory tracts (PDD: particle deposition and diffusion). These four general mechanisms can be applied to a number of compounds including SVOCs.

Thus, in this paper we aim to (1) review the existing measurement methods addressing the bioaccessibility and bioavailability of SVOCs *via* inhalation, (2) review the existing mathematical models addressing the bioaccessibility and bioavailability of SVOCs and other chemical compounds relevant for SVOCs *via* inhalation, and (3) discuss the key challenges to determining the SVOC bioaccessibility and bioavailability *via* inhalation.

To carry out the review, peer-reviewed papers were retrieved using "bioaccessibility" OR "bioavailability" AND "inhalation" as key words in the Google Scholar, Science Direct, and PubMed search engines, regardless of the date of publication.

2. Measurements of SVOC bioaccessibility and bioavailability following inhalation

2.1. SVOC bioaccessibility (in vitro tests)

Five articles have been found on the bioaccessible fraction that is soluble in the fluid environment of a target organism that address the desorption of SVOCs due to the PDEGD and PDD mechanisms. Three of them were published after the year 2000. The bioaccessibility of certain particle-phase PAHs was measured *in vitro* using synthetic lung fluids, and the desorbed PAHs were extracted with solvents (Gerde and Scholander, 1989).

The *in vitro* method frequently differs from one study to another. Woodstove particles containing BaP were added into phospholipid vesicles to simulate the transport of particle-phase BaP into biomembranes (Bevan and Yonda, 1985). After 18 h of incubation in phospholipid vesicles at 37 °C, the BaP was extracted with ethyl acetate at 50 °C. Meanwhile, the total extractable amount of BaP in the woodstove particles was assessed by adding 2 g of BaP into 9 ml of toluene and placing the mixture at 70–80 °C for 48–72 h. The results showed that 98–100% of the particle-phase BaP was extractable with toluene, of which 25% entered the phospholipid vesicles. This value has not been compared to data from *in vivo* studies.

Gerde et al. measured the bioaccessibility of 120 μg of inhaled particle-phase BaP by extraction in 17 ml of 1-octanol as a synthetic lung fluid at 37 °C in a cylindrical glass reactor with a two-bladed impeller (Gerde et al., 2001). The inhaled particles were BaP-coated diesel soot containing 14.5 ng BaP per μg soot (25% of a monomolecular layer). The soot-adsorbed BaP decreased from 25% to 16% within 48 h. This value is similar to that of the *in vivo* study obtained 5.6 months after the inhalation exposure of dogs to the same particles. Therefore, the authors concluded that 36% of the total soot-adsorbed BaP, *i.e.*, 9% of the monomolecular layer, was bioaccessible, and that the remaining BaP was retained on the particles in the lung. However, when the carrier particles were composed of silica in powder form with a 3.5 μm diameter and pores of 80 Å in diameter, the bioaccessible fraction of 100 mg of BaP/silica powder extracted with 17 ml of 1-octanol in a stirred reactor under the same temperature was > 85% within 5 min after inhalation (Ewing et al., 2006). This value has not been compared to data from *in vivo* studies.

Borm et al. measured the bioaccessibility of five different inhaled particle-phase PAHs in saline containing dipalmitoylphosphatidylcholine (DPPC) in different concentrations (100–10,000 μg/ml) in the dark in a shaking water bath for 24 h at 37 °C (Borm et al., 2005). The studied particles were reference diesel and four types of carbon black with different properties, *i.e.*, with the surface area ranging from 20 to 300 m^2/g. The carbon black particles contained 0.001–191 ng PAHs per mg particle. The leachable PAHs were extracted for 60 s using tertiary butyl methyl ether. The fraction of PAHs desorbed from the particles into the DPPC solutions was < 1.2% for phenanthrene, < 0.4% for pyrene, < 1.0% for anthracene, < 1.3% for chrysene, and < 1.3% for fluoranthene. These results were compared with the data of the PAH–DNA adducts obtained 13 weeks after the inhalation exposure of rats to the same particles. The results of the *in vivo* study showed that a small fraction of these particle-phase PAHs could become bioavailable