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Review article

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

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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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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

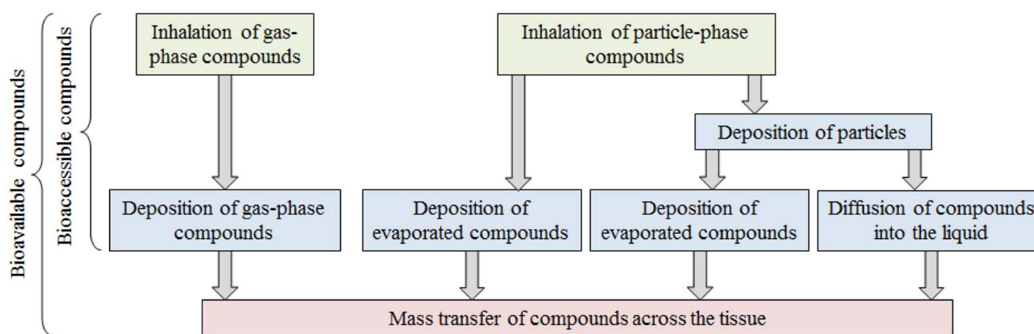

Fig. 1. Model schematics for the evaluation of the bioaccessibility and bioavailability *via* inhalation.

when the particles have a high PAH content.

A summary of the results from these studies on SVOC bioaccessibility is presented in Table 1. Together, the literature describes the bioaccessibility of 7 PAHs (BaP, benzo[*k*]fluoranthene, phenanthrene, pyrene, anthracene, chrysene, and fluoranthene) following an inhalation scenario. The bioaccessibilities of BaP and benzo[*k*]fluoranthene vary between 25% and > 85%, while the bioaccessibilities of the other 5 PAHs are < 1.3%. The methods for measuring the bioaccessibility of SVOCs in lung lining fluids differed between studies. There are many factors that may affect the bioaccessibility, depending on the method. For example, different SVOC-carrier particles were used, including woodstove particles, diesel soot, carbon black, and silica, and their different physical and chemical properties may affect the bioaccessibility of the SVOCs. Additionally, different fluids were used to simulate the lung lining fluid following a scenario of particle deposition within the airways: water, phospholipid vesicles, 1-octanol, and DPPC. The extraction mediums include ethyl acetate, 1-octanol, tertiary butyl methyl ether, and toluene, which also have different properties that may affect the bioaccessibility of the SVOCs. Moreover, the time of incubation and the temperature varied among these studies, and both are factors that can affect the results. More studies are needed to explain the differences across the compounds and studies.

In summary, the determined bioaccessible fraction may depend on many different parameters such as the composition and volume of the simulated lung fluid, the nature of the particles, the extraction time, the temperature, and the agitation. Various methods have been reported, resulting in difficulties in comparing the results among the studies. Therefore, it is important to validate the *in vitro* results using data from *in vivo* studies. Moreover, the proper quality control/quality assurance of the analysis of the extraction fluid is essential for bioaccessibility measurements (Rodríguez-Navas et al., 2017). Guney et al. suggested developing more rigor measurement methods for future studies of inhalation exposure (Guney et al., 2016).

2.2. SVOC bioavailability (in vivo and ex vivo tests)

Ten articles have been found on the bioavailable fraction that reaches the systemic circulation of a subject, and four of them were published after the year 2000. The bioavailability of 2,3,7,8-tetrachlorodibenzo-p-dioxin and some PAHs *via* particle-phase inhalation was measured in human and animal subjects. Measurements of the SVOC bioavailability in humans were performed *in vivo* by Gardiner et al., where the bioavailability of pyrene was analyzed in five non-smokers who worked in plants manufacturing carbon black (Gardiner et al., 1992). In this study, the pyrene in the air of the working environment was assumed to be the only source of exposure, and the concentration of 1-hydroxypyrene was measured in their urine at the end of the working shift as an indicator of the bioavailability of pyrene. The results varied largely from one individual to another. The average concentration of 1-hydroxypyrene was 0.3 μmol 1-hydroxy-pyrene per mol creatinine, while the average pyrene concentration in airborne particles was 8 mg/m^3. Although there were no control groups in the study, the urine values of the workers on the Monday, after a weekend without working in the plant, were lower than the rest of the week's values (*p*-value = 0.000137). The authors noted that due to the diversity of SVOC sources in everyday human life, this method can be applied to only special cases.

Investigations of bioavailability have more frequently been carried out in animals, *e.g.*, rats and dogs. Gerde et al. measured the *in vivo* bioavailability of inhaled particle-phase BaP in 3 dogs (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 particles were pushed once into the dog lungs over a 4–5 s period, and the dogs were apneic for the next 2 min. Blood samples were taken continuously for 1 h directly after the exposure. Eighteen percent of the soot-adsorbed BaP was bioavailable within 4.3 min after inhalation. Other *in vivo* bioavailability tests in animals using similar methods are summarized in Table 2 (Gøtze et al., 1994; Nessel et al., 1992; Ramesh et al., 2002, 2001; Withey et al., 1993, 1992). Samples have been taken of blood, lung tissues, and liver tissues. The bioavailability of particle-phase 2,3,7,8-tetrachlorodibenzo-p-dioxin was found to be 100% (Nessel et al., 1992), while the bioavailability of particle-phase BaP was found to vary between 25% (Ramesh et al., 2002) and 65% (Ramesh et al., 2001). When the concentration of the particle-phase pyrene ranged between 200 and 800 mg/m^3, the pyrene concentration in the blood ranged between 2.5 and 23.4 μg/g (Withey et al., 1992).

Fouchécourt et al. housed 4 rats in cages containing PAH-contaminated soil for 3 days to study the exposure *via* inhalation, ingestion, and dermal absorption (Fouchécourt et al., 1999). The rat lungs were exposed to PAHs directly by the inhalation of contaminated soil and indirectly by blood circulation. However, the contribution of each route was not quantified or distinguished. While the soil contained 13 PAHs, only 3 (BaP, fluoranthene, and pyrene) were detected in the lung after sacrificing the exposed rats. The cytochrome P450-dependent monooxygenase activity, followed by 7-ethoxyresorufin O-deethylase (EROD) activity measurement, a biomarker of chemical exposure (Whyte et al., 2000) in the lungs, showed that the composition of the carrier particles can affect the absorption and bioavailability of the particle-phase SVOCs (Fouchécourt et al., 1999).

The SVOC bioavailability can also be measured *ex vivo* in an isolated and perfused lung (IPL) (Tornquist et al., 1988). Ewing et al. measured the bioavailability of the inhaled particle-phase BaP in 10 rats (Ewing et al., 2006). The inhaled particles were BaP-coated silica in powder form containing 1.3 ng BaP per μg silica powder. The rat lungs were excised and kept ventilated *ex vivo* in an artificial thoracic chamber at 37 °C and perfused with albumin buffer. The particles were pushed into the IPL over a one-minute period while rebreathing was prevented by maintaining a constant downstream flow in the lungs. The lung lobes were dissected, and the amount of BaP deposited in the lung tissues was analyzed. The bioavailability of the inhaled particle-phase BaP was dose-dependent and was approximately 100% under sub-saturation dosing regimens. It has been noted by the U.S. Food and Drug

Table 1
Measurements of the SVOC bioaccessibility *via* inhalation.

Reference	SVOC	Vapor pressure (Pa)	Particle	Particle size (μm)	SVOC content (ng/mg particle)	Synthetic lung medium	Leaching temperature (°C)	Leaching time	Extraction medium	Extraction temperature (°C)	Extraction time	Agitation	Analytical instrument	Bioaccessibility
(Bevan and Yonda, 1985)	BaP	7.3×10^{-7}	Woodstove particle	NA	1.5 ± 0.1	Phospholipid vesicles	37	18 h	Ethyl acetate	50	NA	Bath-type sonicator	HPLC	25%
(Gerde et al., 2001)	BaP	7.3×10^{-7}	Diesel soot	1.3 ± 0.2	14,500	1-octanol (120 μg particle in 17 ml liquid)	37	20 s	1-octanol	37	8 min	Two-bladed impeller (15 mm diameter, 12 mm height, 400 rpm)	HPLC	36%
(Ewing et al., 2006)	BaP	7.3×10^{-7}	Silica	3.5	1300 ± 60	1-octanol (100 mg particle in 17 ml 1-octanol)	37	5 min	1-octanol	37	NA	Stirring	HPLC	> 85%
(Bevan and Yonda, 1985)	BkF	1.3×10^{-7}	Woodstove particle	NA	0.22 ± 0.02	Phospholipid vesicles	37	18 h	Ethyl acetate	50	NA	Bath-type sonicator	HPLC	68%
(Borm et al., 2005)	Phe	1.6×10^{-2}	Diesel or carbon black particle	NA	0.001–191	Dipalmitoylphosphatidylcholine (3–60 mg particle in 3 ml saline)	37	24 h	Tertiary butylmethyl ether	NA	60 s	Shaking water bath	HPLC	< 1.2%
(Borm et al., 2005)	Pyr	6.0×10^{-4}	Diesel or carbon black particle	NA	0.001–191	Dipalmitoylphosphatidylcholine (3–60 mg particle in 3 ml saline)	37	24 h	Tertiary butylmethyl ether	NA	60 s	Shaking water bath	HPLC	< 0.4%
(Borm et al., 2005)	Ant	8.7×10^{-4}	Diesel or carbon black particle	NA	0.001–191	Dipalmitoylphosphatidylcholine (3–60 mg particle in 3 ml saline)	37	24 h	Tertiary butylmethyl ether	NA	60 s	Shaking water bath	HPLC	< 1%
(Borm et al., 2005)	Chr	8.3×10^{-7}	Diesel or carbon black particle	NA	0.001–191	Dipalmitoylphosphatidylcholine (3–60 mg particle in 3 ml saline)	37	24 h	Tertiary butylmethyl ether	NA	60 s	Shaking water bath	HPLC	< 1.3%
(Borm et al., 2005)	Flu	1.2×10^{-3}	Diesel or carbon black particle	NA	0.001–191	Dipalmitoylphosphatidylcholine (3–60 mg particle in 3 ml saline)	37	24 h	Tertiary butylmethyl ether	NA	60 s	Shaking water bath	HPLC	< 1.3%

BaP: benzo[*a*]pyrene, BkF: benzo[*k*]fluoranthene, Phe: phenanthrene, Pyr: pyrene, Ant: anthracene, Chr: chrysene, Flu: fluoranthene, NA: not available, HPLC: high-performance liquid chromatography. Vapor pressures were calculated at 25 °C using the EPI Suite program developed by the U.S. Environmental Protection Agency.

Table 2
Measurements of the SVOC bioavailability *via* inhalation.

Reference	SVOC	Vapor pressure (Pa)	Particle	Particle diameter (μm)	SVOC content (ng/mg particle)	Animal	Method	Exposure time	Biological endpoints	Sampling period	Analytical instrument	Bioavailability
(Nessel et al., 1992)	TCDD	2.0×10^{-7}	Soil	< 20	72.2 ppm	Female Sprague-Dawley rats (200–250 g)	*In vivo*	1, 7, or 28 d	Liver tissue	After exposure	GC–MS	100%
(Gardiner et al., 1992)	Pyr	6.0×10^{-4}	Carbon black	NA	8 mg/m^3	Humans	*In vivo*	5 d	Urine	After exposure	HPLC	0.3 μmol 1-hydroxy-pyrene per molcreatinine
(Withey et al., 1992)	Pyr	6.0×10^{-4}	Micro-condensation aerosol	1.6–2.7	200 mg/m^3	Pregnant Wistar rats (250–300 g)	*In vivo*	95 min	Blood	After exposure	HPLC	2.5 ± 0.7 μg/g blood
(Withey et al., 1992)	Pyr	6.0×10^{-4}	Micro-condensation aerosol	1.6–2.7	200 mg/m^3	Pregnant Wistar rats (250–300 g)	*In vivo*	95 min	Lung	After exposure	HPLC	1.6 ± 0.4 μg/g organ
(Withey et al., 1992)	Pyr	6.0×10^{-4}	Micro-condensation aerosol	1.6–2.7	350 mg/m^3	Pregnant Wistar rats (250–300 g)	*In vivo*	95 min	Blood	After exposure	HPLC	5.4 ± 0.9 μg/g blood
(Withey et al., 1992)	Pyr	6.0×10^{-4}	Micro-condensation aerosol	1.6–2.7	350 mg/m^3	Pregnant Wistar rats (250–300 g)	*In vivo*	95 min	Lung	After exposure	HPLC	4.7 ± 0.7 μg/g organ
(Withey et al., 1992)	Pyr	6.0×10^{-4}	Micro-condensation aerosol	1.6–2.7	500 mg/m^3	Pregnant Wistar rats (250–300 g)	*In vivo*	95 min	Blood	After exposure	HPLC	12.1 ± 1.4 μg/g blood
(Withey et al., 1992)	Pyr	6.0×10^{-4}	Micro-condensation aerosol	1.6–2.7	500 mg/m^3	Pregnant Wistar rats (250–300 g)	*In vivo*	95 min	Lung	After exposure	HPLC	9.4 ± 1.8 μg/g organ
(Withey et al., 1992)	Pyr	6.0×10^{-4}	Micro-condensation aerosol	1.6–2.7	650 mg/m^3	Pregnant Wistar rats (250–300 g)	*In vivo*	95 min	Blood	After exposure	HPLC	19.2 ± 3.1 μg/g blood
(Withey et al., 1992)	Pyr	6.0×10^{-4}	Micro-condensation aerosol	1.6–2.7	650 mg/m^3	Pregnant Wistar rats (250–300 g)	*In vivo*	95 min	Lung	After exposure	HPLC	14.8 ± 2.4 μg/g organ
(Withey et al., 1992)	Pyr	6.0×10^{-4}	Micro-condensation aerosol	1.6–2.7	800 mg/m^3	Pregnant Wistar rats (250–300 g)	*In vivo*	95 min	Blood	After exposure	HPLC	23.4 ± 4.4 μg/g blood
(Withey et al., 1992)	Pyr	6.0×10^{-4}	Micro-condensation aerosol	1.6–2.7	800 mg/m^3	Pregnant Wistar rats (250–300 g)	*In vivo*	95 min	Lung	After exposure	HPLC	14.8 ± 1.9 μg/g organ
(Fouchécourt et al., 1999)	Pyr	6.0×10^{-4}	Coke plant soil	< 10	54	Male adult Sprague-Dawley rats (200-220 g)	*In vivo*	88 ± 2 h	Lung tissue	After exposure	HPLC	327 ng/g organ
(Withey et al., 1993)	BaP	7.3×10^{-7}	Micro-condensation aerosol	0.61–0.88	200 mg/m^3	Pregnant Wistar rats (250–350 g)	*In vivo*	95 min	Blood	After exposure	HPLC	2.7 μg/g blood
(Withey et al., 1993)	BaP	7.3×10^{-7}	Micro-condensation aerosol	0.61–0.88	350 mg/m^3	Pregnant Wistar rats (250–350 g)	*In vivo*	95 min	Blood	After exposure	HPLC	4.4 μg/g blood
(Withey et al., 1993)	BaP	7.3×10^{-7}	Micro-condensation aerosol	0.61–0.88	500 mg/m^3	Pregnant Wistar rats (250–350 g)	*In vivo*	95 min	Blood	After exposure	HPLC	13.7 μg/g blood
(Withey et al., 1993)	BaP	7.3×10^{-7}	Micro-condensation aerosol	0.61–0.88	650 mg/m^3	Pregnant Wistar rats (250–350 g)	*In vivo*	95 min	Blood	After exposure	HPLC	18.8 μg/g blood
(Withey et al., 1993)	BaP	7.3×10^{-7}	Micro-condensation aerosol	0.61–0.88	800 mg/m^3	Pregnant Wistar rats (250–350 g)	*In vivo*	95 min	Blood	After exposure	HPLC	21.9 μg/g blood

(*continued on next page*)

Table 2 (*continued*)

Reference	SVOC	Vapor pressure (Pa)	Particle	Particle diameter (μm)	SVOC content (ng/mg particle)	Animal	Method	Exposure time	Biological endpoints	Sampling period	Analytical instrument	Bioavailability
(Gøtze et al., 1994)	BaP	7.3×10^{-7}	Urban air particle	NA	NA	Male Sprague-Dawley rats (350 g)	*In vivo*	NA	Lung tissue	After exposure	HPLC	29–60%
(Fouchécourt et al., 1999)	BaP	7.3×10^{-7}	Coke plant soil	< 10	21	Male adult Sprague-Dawley rats (200-220 g)	*In vivo*	88 ± 2 h	Lung tissue	After exposure	HPLC	648 ng/g organ
(Gerde et al., 2001)	BaP	7.3×10^{-7}	Diesel soot	1.3 ± 0.2	14,500	1-year-old beagle dogs	*In vivo*	4–5 s	Blood	Within 1 h after exposure	HPLC	18% in 4.3 min, 36% in 5.6 months
(Ramesh et al., 2001)	BaP	7.3×10^{-7}	Carbon black	NA	0.1–2.5 mg/m^3	10-week-old male and female F344 rats	*In vivo*	4 h	Blood and lung tissue	0.5–4 h after exposure	HPLC	65% in 2 h
(Ramesh et al., 2002)	BaP	7.3×10^{-7}	Carbon black	NA	100 μg/m^3	8-week-old male Fisher-344 rats (200 g)	*In vivo*	4 d	Lung tissue	Within 72 h after exposure	Reverse-phase HPLC and fluorescence detector	25%
(Ewing et al., 2006)	BaP	7.3×10^{-7}	Silica	3.5	1300 ± 60	Female Sprague-Dawley rats (325 ± 19 g)	*Ex vivo*	1 min	Lung tissue	After exposure	HPLC	95–100%
(Fouchécourt et al., 1999)	Flu	1.2×10^{-3}	Coke plant soil	< 10	78	Male adult Sprague-Dawley rats (200-220 g)	*In vivo*	88 ± 2 h	Lung tissue	After exposure	HPLC	284 ng/g organ
(Fouchécourt et al., 1999)	BbF	6.7×10^{-5}	Coke plant soil	< 10	39	Male adult Sprague-Dawley rats (200-220 g)	*In vivo*	88 ± 2 h	Lung tissue	After exposure	HPLC	< 40 ng/g organ
(Fouchécourt et al., 1999)	BkF	1.3×10^{-7}	Coke plant soil	< 10	14	Male adult Sprague-Dawley rats (200-220 g)	*In vivo*	88 ± 2 h	Lung tissue	After exposure	HPLC	< 40 ng/g organ
(Fouchécourt et al., 1999)	BgP	1.3×10^{-8}	Coke plant soil	< 10	12	Male adult Sprague-Dawley rats (200-220 g)	*In vivo*	88 ± 2 h	Lung tissue	After exposure	HPLC	< 40 ng/g organ
(Fouchécourt et al., 1999)	IP	4.0×10^{-8}	Coke plant soil	< 10	15	Male adult Sprague-Dawley rats (200-220 g)	*In vivo*	88 ± 2 h	Lung tissue	After exposure	HPLC	< 40 ng/g organ
(Fouchécourt et al., 1999)	Phe	1.6×10^{-2}	Coke plant soil	< 10	97	Male adult Sprague-Dawley rats (200-220 g)	*In vivo*	88 ± 2 h	Lung tissue	After exposure	HPLC	< 40 ng/g organ
(Fouchécourt et al., 1999)	Ace	2.9×10^{-1}	Coke plant soil	< 10	141	Male adult Sprague-Dawley rats (200-220 g)	*In vivo*	88 ± 2 h	Lung tissue	After exposure	HPLC	< 40 ng/g organ
(Fouchécourt et al., 1999)	Ant	8.7×10^{-4}	Coke plant soil	< 10	33	Male adult Sprague-Dawley rats (200-220 g)	*In vivo*	88 ± 2 h	Lung tissue	After exposure	HPLC	< 40 ng/g organ
(Fouchécourt et al., 1999)	Chr	8.3×10^{-7}	Coke plant soil	< 10	< 0.1	Male adult Sprague-Dawley rats (200-220 g)	*In vivo*	88 ± 2 h	Lung tissue	After exposure	HPLC	< 40 ng/g organ
(Fouchécourt et al., 1999)	BaA	4.1×10^{-5}	Coke plant soil	< 10	2	Male adult Sprague-Dawley rats (200-220 g)	*In vivo*	88 ± 2 h	Lung tissue	After exposure	HPLC	< 40 ng/g organ
(Fouchécourt et al., 1999)	DaA	1.3×10^{-7}	Coke plant soil	< 10	3	Male adult Sprague-Dawley rats (200-220 g)	*In vivo*	88 ± 2 h	Lung tissue	After exposure	HPLC	< 40 ng/g organ

TCDD: 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, Flu: fluoranthene, BbF: benzo[*b*]fluoranthene, BkF: benzo[*k*]fluoranthene, BaP: benzo[*a*]pyrene, BgP: benzo[*g*, *h*, *i*]perylene, IP: Indeno[1,2,3,-c,d]pyrene, Phe: phenanthrene, Ace: acenaphthene, Ant: anthracene, Pyr: pyrene, Chr: chrysene, BaA: benzo[*a*]anthracene, DaA: dibenz[*a*,*h*]anthracene, NA: not available, GC–MS: gas chromatography–mass spectrometry, HPLC: high-performance liquid chromatography. Vapor pressures were calculated at 25 °C using the EPI Suite program developed by the U.S. Environmental Protection Agency.

Administration and other associations that data from unrestrained animals that are chronically instrumented for telemetry are preferable to data from restrained animals (U.S. Food and Drug Administration, 2001).

The results reported in Table 2 suggest that the bioavailability following an inhalation exposure to particle-phase SVOCs depends on the content of SVOCs on the carrier particles as well as the substrate and diameter of the particles. The ratio of the SVOC concentration in the organs or blood to the SVOC content in the particles increases with the SVOC content in the particles. The exposed subject, exposure protocol, dosing regimen, and sampling method differ from one study to another, resulting in difficulties in interpreting and comparing the results. Some test conditions, such as stuffing particles down the lung and remaining apneic after exposure, differ from normal breathing. Although animal tests are often considered relevant to human exposure assessment, the translation of animal data to equivalent human data remains challenging (Kastury et al., 2017). Moreover, animal testing raises ethical concerns. As a conclusion, data on bioaccessibility and bioavailability *via* inhalation are available only for very few SVOCs.

3. Modeling of SVOC bioaccessibility and bioavailability following inhalation

The modeling approaches to address the bioaccessibility and bioavailability of compounds *via* inhalation are shown in Fig. 1. For inhaled compounds in the gas phase, the deposition rate along the respiratory tract (the GD mechanism) should be considered. Inhaled compounds in the particle phase may evaporate into the gas phase and then deposit together with the other inhaled gas-phase compounds (the EGD mechanism), or they may be retained in the particles. The compounds in the deposited particles may transfer into the mucus of the respiratory tract *via* evaporated gas deposition (the PDEGD mechanism) or diffusion (the PDD mechanism). The fraction of an inhaled compound that is deposited along the respiratory tract due to the four abovementioned mechanisms is the bioaccessible fraction. Models addressing each of the four mechanisms were reviewed. The models on the inhaled gas- and particle-phase compounds are presented in Sections 3.1 and 3.2, respectively. The fraction of a bioaccessible compound that can transfer across the tissue to reach the blood circulation is defined as being bioavailable. Models addressing this mass transfer process were reviewed and are presented in Section 3.3. Overall, forty-four articles have been found on the modeling of the bioaccessibility and bioavailability *via* inhalation; twenty-nine of them were published after the year 2000, and six of them were published over the past five years.

3.1. Deposition of inhaled gas-phase compounds

No specific model has been developed to address the deposition of inhaled gas-phase SVOCs along the respiratory tract, *i.e.*, the GD mechanism. Some mass transfer models did not target any specific compound (Davies, 1985; Kimbell et al., 1997). Other models were originally developed for formaldehyde, ozone, chlorine, or VOCs (Bush et al., 2001; Kepler et al., 1998; Padaki et al., 2009).

Davies considered inhaled gas-phase compounds absorbed in the respiratory tract through the diffusion of the gas molecules to the surface of the airway and assumed a tube shape of the respiratory tract (Davies, 1985). Therefore, the dynamic concentration of the inhaled compounds along the respiratory tract depends on the geometry and diffusion coefficient of the tube, and the flow rate of the inhaled gas. Moreover, the absorption of the inhaled gas into the fluid of the respiratory tract depends on the physicochemical properties of the inhaled compounds, particularly the octanol/water partition coefficient and water solubility (Nielsen et al., 2008). Compounds that are very soluble in water absorb rapidly into the fluid of the upper airways and can reach the deeper airways and lungs after the diffusion of the inhaled compounds into upper airways reaches equilibrium (Davies, 1985).

Although the human respiratory tract is three-dimensional, it is difficult to specify the air velocity everywhere within the respiratory tract (Miller et al., 1985). Therefore, a one-dimensional airway was assumed to simplify the three-dimensional equation of continuity to simulate the concentrations of inhaled gas-phase ozone and chlorine along the respiratory tract (Bush et al., 2001; Miller et al., 1985). The radial flux of the inhaled gas towards the mucus of an airway was considered, and the one-dimensional mass transport along the airway was described as

$$\frac{\partial \overline{C}}{\partial t} + \overline{U}\frac{\partial \overline{C}}{\partial x} = D\frac{\partial^2 \overline{C}}{\partial x^2} - \frac{2}{R}k_g(\overline{C} - C_R) \tag{1}$$

where t is the time, x is the distance along the x-axis, $\overline{C}$ is the average airway concentration of the compound at x and t, R is the airway radius, $\overline{U}$ is the average air velocity through the cross section of the airway, D is the effective dispersion coefficient, k_g is the gas-phase mass transfer coefficient, and C_R is the concentration of the compound in the gas phase immediately adjacent to the mucus. Since SVOCs are different from ozone and chlorine, the mass transfer parameters, *e.g.*, D and k_g, should be determined for each SVOC, and the one-dimensional model should be modified accordingly to simulate the gas-phase SVOC deposition.

Although the one-dimensional model may be reasonable for the lower respiratory tract, it is not valid in nasal passages due to the shape of the nasal passages and the airflow patterns. Thus, Kimbell et al. developed a three-dimensional computational fluid dynamics (CFD) model that incorporated airflow patterns and the diffusion of the inhaled gas to quantify the delivery of a compound to a rat's nasal passages (Kimbell et al., 1997, 1993). Kepler et al. used this method to model the nasal absorption of formaldehyde in rhesus monkeys and concluded that the total nasal wall uptake of formaldehyde was 90% (Kepler et al., 1998). This value may vary among SVOCs since they are generally much less soluble in water than formaldehyde. Moreover, the use of the one-dimensional model is restricted to symmetrically branched airways, and the mass transfer parameters are applied to idealized geometric and flow conditions (Keshavarzi et al., 2009). To overcome these disadvantages, CFD technology has been used to construct three-dimensional airway models (Padaki et al., 2009; Taylor et al., 2007).

Combining the CFD nasal model and the one-dimensional airway model, dynamic models of the whole respiratory system were developed (Overton et al., 2001; Schroeter et al., 2013). Human respiratory tracts were divided into 24 generations (the division point where one airway branches into multiple airways) from the trachea to the alveolar sacs, and in each generation, one-dimensional symmetrically branched airways were constructed. The absorption of inhaled gas-phase formaldehyde and hexamethylene diisocyanate was analyzed using nasal-airway models. These models may be used to predict the absorption of SVOCs along the human respiratory tract if some characteristic parameters, *e.g.*, the dispersion and overall mass transfer coefficients of the SVOCs, are determined.

In conclusion, the abovementioned models were all developed originally for general compounds or specific compounds, such as ozone and formaldehyde; none were developed particularly for SVOCs. Therefore, the mass transfer parameters for SVOCs need to be determined before using the models. Three limitations of the abovementioned models may be addressed in the future. First, a respiratory cycle includes both inhalation and exhalation. Inhaled compounds are absorbed in the fluid of the respiratory tract, but 30% of them may desorb during exhalation (Medinsky and Bond, 2001), *i.e.*, the washin-washout effect (Johanson, 1991). This bi-directional transport of inhaled gas-phase compounds between the inhaled air flow and the airway tissue has not been well characterized. Thus, the amount of inhaled compounds that is bioaccessible or bioavailable may be overestimated. Second, in the abovementioned models, only nasal inhalation was considered, while oral inhalation was neglected. In real life, a fraction of air may be inhaled through the mouth, especially by

children, the elderly, and people with diseases or performing physical activities. Finally, the properties of the airway mucus and alveolar surfactant have not been considered in the models. Thus, the fate of the inhaled SVOCs in the mucus and surfactant has not been modeled. SVOC concentrations in airway and alveolar tissues may decrease with time due to the fate of SVOCs, which may enhance the mass transfer of SVOCs from the inhaled airflow to the respiratory tract.

3.2. Deposition of inhaled particle-phase compounds

While GD is the direct deposition of the inhaled gas-phase compounds along the respiratory tract, EGD, PDEGD, and PDD are associated with the deposition of the inhaled particle-phase compounds along the respiratory tract and the desorption of the compounds from the inhaled particles to the fluid of the respiratory tract (Fig.1).

3.2.1. Particle deposition along the respiratory tract

The deposition of inhaled particles along the respiratory tract has been well modeled in past decades. Mechanisms of particle deposition include inertial impaction, sedimentation, diffusion, interception, and electrostatic precipitation, which are related to the particle's momentum, gravity, size, shape, and electrostatic charges, respectively (Carvalho et al., 2011). The existing models can be generally classified into five categories. First, the typical-path lung models (Schum and Yeh, 1980; Yeh and Schum, 1980) consider the dynamic deposition of particles in anatomical respiratory tracts. Respiratory tracts are divided into a number of generations, *e.g.*, 25 generations for humans (Yeh and Schum, 1980), and in each generation, all the airways are assumed to have the same geometric parameters. Second, considering the variation in the geometric parameters of airways in the same generation, stochastic models incorporating Monte Carlo simulation were developed (Koblinger and Hofmann, 1990, 1985) in which the geometric parameters of airways are randomly selected in accordance with their distributions in each generation. Third, to simplify the calculation of the stochastic models, multiple-path models use a number of structurally different airways derived from the stochastic model to represent the geometry of the airways (Asgharian et al., 2010, 2001). Moreover, with the development of computational technologies, the dynamic deposition of inhaled particles can be modeled in 3-dimensional respiratory tracts using the computational fluid-particle dynamics (CFPD) method (Koullapis et al., 2017). Finally, empirical models of the steady-state deposition of particles for the general population were developed based on *in vivo* tests of the particle deposition in human airways (Cheng et al., 1996) and lungs (Asgharian et al., 1995). A number of individuals should be measured to reduce the variability in an empirical model. Models of the deposition of inhaled particles in the human respiratory tract have been reviewed and presented elsewhere (Hofmann, 2011; Sturm, 2012). Therefore, we do not present detailed models of particle deposition in the present review.

The deposited fraction of inhaled particles is size-dependent. Inhaled ultrafine particles can efficiently deposit in the respiratory tract during spontaneous breathing. For particles < 100 nm in diameter, the mean deposited fraction for the total respiratory tract is 0.66 by particle number and 0.58 by particle mass concentration for healthy people at rest (Daigle et al., 2003). Swift et al. used radon progeny aerosols for a deposition study and found that the nasal deposition rate can be > 95% for particles < 1 nm in diameter (Swift et al., 1992). Moreover, nasally deposited ultrafine particles can subsequently translocate *via* the olfactory nerve and accumulate in the olfactory bulb of the brain (Mistry et al., 2009; Oberdörster et al., 2004; Peters et al., 2006).

3.2.2. Desorption of particle-phase compounds into airway fluid

The desorption rate of the particle-phase compounds in the respiratory tract depends on the gas/particle and liquid/particle partition coefficients (Pankow, 2001). For small-molecule compounds with high volatility, *e.g.*, nicotine in tobacco smoke, the fraction deposited into the respiratory tract due to the EGD mechanism is much larger than that due to the PDEGD and PDD mechanisms (Pankow, 2001). This process can be simplified by compound deposition in a denuder tube (Liu et al., 2017) and described as (Lipowicz and Piadé, 2004)

$$2v\left(1-\frac{r^2}{R^2}\right)(1-\varnothing)\frac{\partial C_g}{\partial x}=\frac{D}{r}(1-\varnothing)\frac{\partial}{\partial r}\left(r\frac{\partial C_g}{\partial r}\right)-2\pi NDdF(C_g-C_{eq}) \tag{2}$$

$$2v\left(1-\frac{r^2}{R^2}\right)\varnothing\frac{\partial C_p}{\partial x}=2\pi NDdF(C_g-C_{eq}) \tag{3}$$

where v is the air flow velocity, C_g and C_p are the gas- and particle-phase concentrations of the inhaled compound, respectively, C_{eq} is the gas-phase concentration if the equilibrium partitioning of the inhaled compound between the gas and particle phases is reached, r and x are the radial and axial dimensions, respectively, R is the tube radius, N is the particle number concentration, D is the gas diffusion coefficient, d is the particle diameter, ϕ is the volume fraction of particles, and F is the Fuchs-Sutugin correction factor. A major limitation of the model is that deposition of particle-phase compounds is neglected in the model because the EGD mechanism is the dominant deposition mechanism for small-molecule compounds with high volatility. However, the EGD mechanism may not be dominant compared to the PDEGD and PDD mechanisms for SVOCs due to their low volatility.

Therefore, Liu et al. took into account the dynamic partitioning of inhaled SVOCs between the gas and particle phases in the human head, tracheobronchial, and alveolar regions and developed a model to address the SVOC deposition associated with the GD, EGD, and PDEGD mechanisms (Liu et al., 2017). The model considered both inhalation and exhalation. During inhalation, the concentrations of the gas- and particle-phase SVOCs in the airflow of a region are described as

$$V_1\frac{dC_{g1}}{dt}=Q(C_{g0}-C_{g1})+h_{m1}A_1\left(\frac{C_{s1}}{K_{s1}}-C_{g1}\right)+\frac{V_1v_tC_{mp1}A_p}{V_p\rho_p}\left(\frac{C_{sp1}\rho_p}{C_{mp1}K_p}-C_{g1}\right) \tag{4}$$

$$V_1\frac{dC_{sp1}}{dt}=Q(C_{sp0}-C_{sp1})-Q\frac{D_1C_{mpout}}{C_{mp1}}C_{sp1}+\frac{V_1v_tC_{mp1}A_p}{V_p\rho_p}\left(C_{g1}-\frac{C_{sp1}\rho_p}{C_{mp1}K_p}\right) \tag{5}$$

$$V_1\frac{dC_{mp1}}{dt}=Q(C_{mp0}-C_{mp1})-QD_1C_{mpout} \tag{6}$$

where V_1 and V_p are the volumes of the present region and of a single particle, respectively, C_{g1} and C_{g0} are the gas-phase SVOC concentrations in the present and previous regions, respectively, t is the time, Q is the breathing rate, h_{m1} is the mass transfer coefficient over the surface of the respiratory tract, A_1 and A_p are the surface areas of the present region and of a single particle, respectively, C_{s1} and C_{sp1} are the SVOC concentrations in the present region in the airway wall and particle phase, respectively, K_{s1} is the gas-mucus partition coefficient, v_t is the mass transfer coefficient around the inhaled particles, C_{mp0} and C_{mp1} are the particle mass concentrations in the present and previous regions, respectively, ρ_p is the particle density, C_{sp0} is the particle-phase SVOC concentration in the previous region, D_1 is the deposition fraction of the inhaled particles in the present region, and C_{mpout} is the particle mass concentration of the inhaled particles.

The results show that most of the gas-phase SVOCs are deposited (the GD mechanism) in the head region, while the particle-phase SVOCs travel deeper into the respiratory tract. As the particles go deeper, the SVOC content on the particles decreases due to the evaporation of the particle-phase SVOCs into the gas phase (the EGD mechanism). The evaporation effect is more significant for particles of small size and SVOCs with high volatility. The study provided the gas- and particle-

deposition values in each region, but the bioaccessibility value was not provided because the desorption of SVOCs from deposited particles into the mucus (the PDD mechanism) was not modeled. This model has three limitations. First, the geometry of the respiratory system was largely simplified. For example, the alveolar region was modeled as a sphere. This simplification lacks anatomical support. Second, the SVOC concentrations in the gas and particle phases in each of the three regions were assumed to be uniform. However, due to the complexity of the human respiratory system and the progressive deposition of the inhaled compounds, the gradient of the SVOC concentration in each region may not be neglected. Finally, the model does not consider the mucociliary clearance and alveolar macrophage clearance of particles, which influences the particle mass concentration. Also, the model does not consider the fate of SVOCs in the airway and alveolar walls, which can influence the SVOC concentration in the tissue and the mass transfer of the inhaled SVOCs in the respiratory system.

Desorption of particle-phase compounds from the deposited particles into the respiratory fluid (the PDD mechanism) has rarely been studied. This process depends on the solubility of the compound in the fluid (Gerde and Scholander, 1989) and is associated with energy changes (Risby et al., 1988). Considering a particle as a sphere, the desorption of a particle-phase PAH from the outer surface into an aqueous phase was described by Gerde and Scholander (1989)

$$\frac{C_s(t)}{C_s(t=0)} = 1 - \frac{2D_L C_{Lsat} t}{d_s C_s(t=0)}, \quad \text{for } 0 < t < t_{iso} \tag{7}$$

$$\frac{C_s(t)}{C_s(t=0)} = \frac{K_L C_{Lsat}}{C_s(t=0)} \exp\left\{\frac{-2D_L(t - t_{iso})}{K_L d_s}\right\}, \quad \text{for } t > t_{iso} \tag{8}$$

where C_s is the surface concentration of the PAH on the deposited particles, t is the time, t_{iso} is the time to reach the linear adsorption isotherm of the saturated solution, D_L is the diffusion coefficient of the PAH in the fluid, C_{Lsat} is the saturated PAH concentration in the fluid, d_s is the diameter of the sphere, and K_L is the coefficient of the linear adsorption isotherm in the fluid. Moreover, the desorption of a particle-phase PAH from a pore into an aqueous phase was described by Gerde and Scholander (1989)

$$\frac{dQ}{dt} = \frac{-\pi d_p^2 D_L C_{Lsat}}{4x} \tag{9}$$

where Q is the amount of the PAH in the pore, d_p is the pore diameter, and x is the distance into the pore. When the fluid was water, the PAHs on the outer surface and in the pores of the deposited particles desorbed within 4 s and 10 min, respectively (Gerde and Scholander, 1989). This model should be integrated in a particle-deposition model in future studies to provide a full understanding of SVOC deposition due to the PDD mechanism.

3.3. Mass transfer of inhaled compounds across the tissue

Modeling the mass transfer of inhaled compounds across the epithelium into the blood circulation corresponds to a bioavailability evaluation. Two types of models exist for gas-phase and particle-phase compounds.

For gas-phase compounds, all the studies focused on the exchange of oxygen at the level of the alveolar region. Two geometric structures for the alveolar sac were assumed, *i.e.*, the spherical model (Suresh et al., 2005) and the layered model (Reynolds et al., 2010; Roy and Secomb, 2014). Suresh et al. studied the liquid breathing of human lungs for treating acute lung injuries and developed a spherical model of alveolar gas exchange in partial liquid ventilation (Suresh et al., 2005). The spherical model considers an alveolar sac as a spherical shell with a variable volume encapsulated by a tissue layer and surrounded by a capillary blood compartment (Fig. 2). For the partial liquid ventilation, the volume encapsulated by the tissue is filled with a liquid layer of perfluorocarbon and the inhaled gas (Suresh et al., 2005). For the breathing of a healthy lung, the volume encapsulated by the tissue is filled with only gas (Pavelka and Roth, 2005). The mass transfer in the alveolar tissue was assumed to be driven by diffusion (Suresh et al., 2005). The spherical structure of the alveolar sac has not been validated using measured data because the model describes the mass transfer in a single alveolar sac. An expanded model on the whole alveolar region has not been developed yet. The layered model considers three layers in the alveolar region: the air space, the tissue, and the blood (Fig. 2) (Reynolds et al., 2010; Roy and Secomb, 2014). The mass transfer of compounds across the tissue was assumed to be driven by diffusion. The simplification of the geometric structure compared to the spherical model allows the expansion of the layered model to the whole alveolar region. However, compared to the measured values, the layered model tends to overestimate the concentrations of compounds in the blood (Roy and Secomb, 2014).

For particle-phase compounds, a study on the transport of particle-phase nicotine in the lungs assumed a 3-layer structure of the alveolar region: the airway fluid containing nicotine desorbed from the inhaled particles, the tissue, and the blood (Gowadia and Dunn-Rankin, 2010). The mass transfer of nicotine across the tissue was assumed to be driven by diffusion (Gowadia and Dunn-Rankin, 2010). The mass transfer of the deposited compounds in the mucus through the airway tissue has been modeled in many studies (George and Hlastala, 2011; Tian and Longest, 2010a, 2010b). The compound concentration in the airway tissue (C_t) at any time (t) can be described by the reaction-diffusion equation (Asgharian et al., 2012, 2011; Schroeter et al., 2006)

$$-\frac{\partial C_t}{\partial t} + D_t \frac{\partial^2 C_t}{\partial r^2} = K_f C_t + \frac{V_{max} C_t}{V_t(K_m + C_t)} \tag{10}$$

where D_t is the diffusion coefficient of the compound in the tissue, r is the radial dimension of the tissue, K_f is the first-order rate constant if the reaction of the compound in the tissue initiates, V_t is the tissue volume, and V_{max} and K_m are Michaelis-Menten rate constants. In these models, the permselectivity of the epithelium is not considered, which allows the development of a simplified physical model. However, the errors in the results due to the simplification have never been studied.

4. Perspectives on determining the bioaccessibility and bioavailability of inhaled SVOCs

Many studies have reported the bioaccessibility and bioavailability of SVOCs *via* the ingestion of soil or settled dust (Fang and Stapleton, 2014; He et al., 2016; Quintana et al., 2017; Wang et al., 2013), and the bioaccessibility and bioavailability of PAHs *via* dermal contact have been reviewed and presented elsewhere (Beriro et al., 2016), but the literature on inhalational exposure remains scarce. The existing studies on the bioaccessibility or bioavailability of inhaled SVOCs involved 2,3,7,8-tetrachlorodibenzo-p-dioxin and some PAHs, especially BaP. However, no data are available for the other SVOCs present in indoor environments, such as phthalate esters, flame retardants, and PCBs. Specific experimental conditions known to influence the results are of crucial importance, such as the temperature, agitation, extraction duration, composition of the lung lining fluid, extraction method and solid/liquid ratio in the bioaccessibility tests (Basta and Juhasz, 2014; Stefaniak et al., 2010; Turner, 2011) and in the biological endpoints (blood, tissue or urine) in bioavailability tests. Analytical methods to determine the bioaccessibility and bioavailability differ widely from one study to another (Carbonell-Capella et al., 2014; Wiseman, 2015).

Within modeling, the model developed by Liu et al. focused on SVOCs and considered the deposition of both gas- and particle-phase inhaled SVOCs (Liu et al., 2017), while the model developed by Gerde and Scholander focused on PAH desorption from the deposited particles into the surrounding liquid (the PDD mechanism) (Gerde and Scholander, 1989). Due to these pioneering works, the SVOC deposition associated with the GD, EGD, PDEGD, and PDD mechanisms can be quantitatively predicted under some assumptions and simplifications.

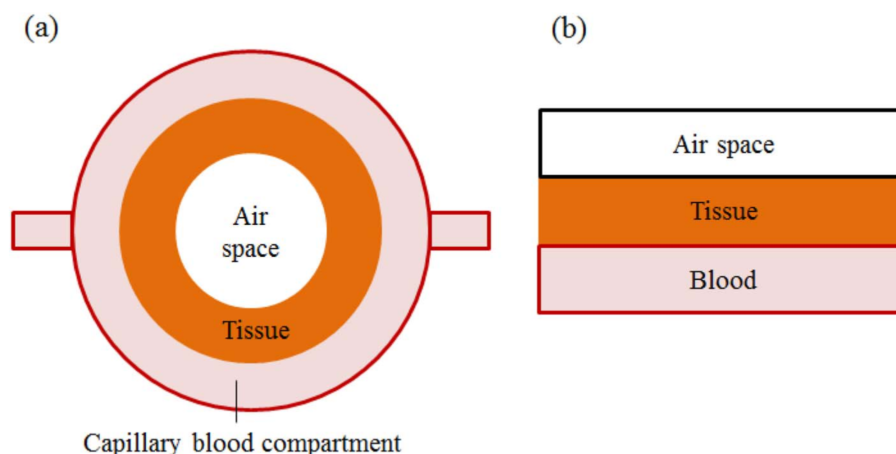

Fig. 2. Schematics of the alveolar sac (a) spherical model (b) layered model.

The other existing models in the literature frequently consider only one phase because they do not focus on modeling SVOCs. A number of parameters should be determined before applying these models to SVOCs. Four mechanisms exist for characterizing gas- and particle-phase SVOC deposition (GD, EGD, PDEGD, and PDD) and estimating the bioaccessibility of the inhaled SVOCs in both gas and particle phases. These mechanisms have not yet been considered together in one model. The following four points may be considered in future modeling approaches for improvements.

First, mass transfer models may be developed for the whole respiratory system or for different regions, *e.g.*, the extrathoracic, tracheobronchial and alveolar regions (Hofmann, 2011). However, for the purpose of bioaccessibility and bioavailability studies, a model considering the whole respiratory system is needed because the concentration of an inhaled compound in one region can interfere with that in another region. Moreover, an empirical model of the deposition of inhaled particles considered both the nasal and oral airways (Cheng et al., 1996), while other models considered nasal inhalation to be the only inlet of air. A calculation of the SVOC bioavailability and bioaccessibility including both the nasal and oral airways may be developed.

Second, the washin-washout effect plays an important role in the respiratory uptake of inhaled compounds (Johanson, 1991). The inhaled compounds absorbed on the surface of the respiratory epithelium may not be able to diffuse across the epithelium by the end of inhalation. For example, the time for nicotine to diffuse across the epithelium differs from one region to another, *e.g.*, 10^{-5} s in the pulmonary region and 0.7 s in the tracheobronchial region (Gowadia and Dunn-Rankin, 2010). A fraction of the inhaled nicotine deposited on the epithelium may be lost in the exhaled breath due to the slow diffusion rate, leading to a reduction in the amount of compound that is bioaccessible or bioavailable. As suggested by Medinsky and Bond, up to 30% of inhaled gas is exhaled (Medinsky and Bond, 2001). For inhaled particles, Heyder suggested that their deposition fraction increases with the particle size, particle density, and respiratory cycle period (Heyder, 2004). The impact of the respiratory cycle period on the availability and accessibility of inhaled SVOCs in the gas and particle phases may be quantified in models.

Third, the mucociliary clearance and alveolar macrophage clearance of inhaled particles may be considered to better address the deposited particle mass concentration along the respiratory tract. The deposition of particle-phase SVOCs may depend on the substrate of the particles, as mentioned above for diesel and silica particles. The properties of the airway mucus, alveolar surfactant, and inhaled particle-phase SVOCs may be considered to characterize the fate of inhaled SVOCs in airway and alveolar tissues to improve the existing mass transfer model.

Finally, a large variation in the deposited amount of inhaled particles exists across individuals, which is influenced by the morphological factors of the airways, distribution factors of inhaled particles, and breathing patterns among human individuals (Cuddihy et al., 1979; Heyder et al., 1982). Hofmann et al. studied the variation among individuals caused by differences in the airway morphology and concluded that the variation in the extrathoracic deposition was a major source of the difference in the total deposition (Hofmann et al., 2002). A variation in the deposition due to variations in the respiratory cycle period and volumetric flow rate of the air also exists within an individual (Cuddihy et al., 1979; Heyder et al., 1982). Although some studies investigated the influence of individuals' biological variability on the deposition of particles, the influence of this variation on the absorption of the inhaled gas and the desorption of the deposited particle-phase SVOCs into the fluid of the respiratory tract has never been studied. This variability may be addressed using probabilistic models that incorporate physical mass transfer models.

5. Conclusion

Bioaccessibility and bioavailability of SVOCs in the gas and particle phases along the human respiratory tract are essential to evaluate the uptake of inhaled SVOCs and to more accurately assess the associated health risks. The existing *in vitro*, *in vivo*, and *ex vivo* methods have been carried out for 2,3,7,8-tetrachlorodibenzo-p-dioxin and a few PAHs. Valid methods should be developed for the quantification of other SVOCs. Regarding the modeling of the SVOC bioaccessibility and bioavailability, we suggest developing modeling approaches based on the whole respiratory system. The model should incorporate mechanisms of the gas- and particle-phase SVOC mass transfer, particle deposition, gas- and particle-phase SVOC absorption to the respiratory tract, and respiratory cycle period. Additionally, the model should account for individual differences, such as the lung morphology and breathing pattern. Lastly, the model and the measurement method of bioaccessibility should be validated using data from *in vivo* studies.

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