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Review

A review on *in-vitro* oral bioaccessibility of organic pollutants and its application in human exposure assessment



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Meijuan Lu^a, Guiying Li^{a,b}, Yan Yang^{a,b}, Yingxin Yu^{a,*}

 ^a Guangdong Key Laboratory of Environmental Catalysis and Health Risk Control, Guangzhou Key Laboratory Environmental Catalysis and Pollution Control, School of Environmental Science and Engineering, Institute of Environmental Health and Pollution Control, Guangdong University of Technology, Guangzhou 510006, PR China
 ^b Synergy Innovation Institute of GDUT, Shantou 515041, PR China

HIGHLIGHTS

GRAPHICAL ABSTRACT

- Progress in *in-vitro* test for bioaccessibility of organic pollutants is reviewed.
- Factors influencing on the bioaccessibility of organic pollutants were focused.
- Validation of *in-vitro* methods by *in-vivo* assays was surveyed.
- Application of bioaccessibility in the human exposure assessment was highlighted.
- Faced challenges of validation and application were discussed and anticipated.

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* Corresponding author. *E-mail address:* yuyingxin@gdut.edu.cn (Y. Yu).



ABSTRACT

Generally, human oral exposure assessments of contaminants have not considered the absorption factor in the human gastrointestinal tract, thus overestimating human exposure and associated health risk. Currently, more researchers are adding the absorption factor into human exposure assessment, and bioaccessibility measured by *in-vitro* methods is generally replacing bioavailability for estimation because of the cheap and rapid determination. However, no single unified *in-vitro* method is used for bioaccessibility measurement of organic pollutants, although several methods have been developed for these pollutants and have shown good *in vitro-in vivo* correlation between bioaccessibility and bioavailability. The present review has focused on the development of *in-vitro* methods, validation of these methods through *in-vivo* assays, determination of factors influencing bioaccessibility, application of bioaccessibility in human exposure assessment, and the challenges faced. Overall, most *in-vitro* methods were validated using bioavailability, and better *in vitro-in vivo* correlations were obtained when absorption sinks were added to the digestion solution to mimic dynamic absorption of organic chemicals by small intestine. Incorporating bioaccessibility into the estimation of human exposure by oral ingestion significantly decreases the estimated exposure dose. However, more investigations on bioaccessibility of hydrophobic organic compounds are urgently needed because many challenges for *in-vitro* methods remain to be overcome.

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1. Introduction

With the development of industry and the economy, more and more pollutants (including organic compounds and heavy metals) have been discharged into the environment, which leads to potential adverse effects on the environment and human health and even some extremely harmful events (Mousavi et al., 2019; Palioura and Diamanti-Kandarakis, 2013; Yang et al., 2018). Among organic pollutants, persistent organic pollutants (POPs) and semi-volatile organic compounds (SVOCs) have attracted great attention because of their widespread occurrence in the environment and their highly toxic properties, although certain chemicals belong to both categories (Jones and Voogt, 1999; Raffy et al., 2018). General POPs are organic pollutants with the properties of high lipophilicity, bioaccumulation, long-range transport, long half-lives in environmental matrices or biota, and high toxicity to organisms, whereas special POPs are those listed in the Stockholm Convention (Chen et al., 2019; Ennour-Idrissi et al., 2019; Jones and Voogt, 1999; Sharma et al., 2014). As for SVOCs, the chemicals generally have boiling points of 240-400 °C and vapor pressures of 10^{-14} - 10^{-4} atm, which means they are less degraded and more able to be absorbed into particles further ingested or inhaled by human (Weschler and Nazaroff, 2008). SVOCs are attracting much attention because many of them are viewed as toxic materials and/or endocrine disruptors, causing adverse effects on the nervous and thyroid system and the development of the reproductive tract, and are even related to metabolic diseases like obesity and diabetes (Giulivo et al., 2016; Li et al., 2017b; Ren et al., 2011; Vuong et al., 2018).

SVOCs include many contaminants containing POPs. For example, polycyclic aromatic hydrocarbons (PAHs), polybromodiphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), organophosphorus flame retardants (OPFRs), organochlorine pesticides (OCPs), and perfluorinated compounds can all be classified as SVOCs. They exist in many environmental matrices such as soil, indoor dust, and food samples (Bonvallot et al., 2010; Mi et al., 2017; Tilston et al., 2011; Yu et al., 2012a). Taking PCBs as an example, the chemicals were first synthesized in 1881, were mainly produced during 1929–1993, and achieved global production rates up to 1.33×10^6 tons. Because of their neurotoxic and immunotoxic effects and links with liver and biliary tract cancer, the production of PCBs ceased after 1993 (Breivik et al., 2002, 2007). Similarly, PBDEs have been widely used in the manufacture of fire-resistant fabrics, textiles, electronics, and furniture, but studies have shown that these chemicals have adverse effects on reproductive function, endocrine activity, DNA structure, and the immune system (WHO, 1994; USEPA, 2010). Commercial Penta- BDEs and Oct-BDEs, and Deca-BDE were listed as the priority controlled POPs by the Stockholm Convention and were suggested for replacement by decabromodiphenyl ethane, aluminum trihydroxide, ethylene bis (tetrabromophthalimide), tris (2-chloroisopropyl) phosphate (TCPP), and other chemicals (UNEP, 2009, 2015).

A large number of pollutants discharged by human activities exist widely in the environment and cause potential adverse effects on ecological systems and even on human health (Giulivo et al., 2016; He et al., 2018a; Li et al., 2017b). Therefore, the health risks from these pollutants should be evaluated to reveal the human burden of pollutants and to understand human exposure. Normally, external and internal exposure are measured by two basic exposure assessment methods, which have been used by many researchers (Bramwell et al., 2016; Frederiksen et al., 2009; Jiang et al., 2019). Internal exposure is the pollutants in the human body measured by using urine, blood, human milk, and placental tissue, and other human tissues, to reveal the human burden of the pollutants (Chen et al., 2014; Guvenius et al., 2003; Jiang et al., 2019; Ma et al., 2017; Yu et al., 2019b). This method can accurately reflect the actual load levels of pollutants in the human body, but it involves ethical issues. It is also relatively difficult to collect samples for use in internal exposure, especially for blood, placenta, and other tissues (Jeong et al., 2018; Kim et al., 2019; McComb et al., 2019; Muller et al., 2019; Suarez-Lopez et al., 2019). In addition, exposure in the human body reflects the combined exposure through various pathways, including oral ingestion, inhalation, and dermal contact (Bramwell et al., 2016; Frederiksen et al., 2009; Jiang et al., 2019). Internal results can provide a body exposure extent, but cannot accurately reflect the contribution of a certain pathway, although one report used principal component analysis to analyze the possible contributions of inhalation, oral ingestion, and dermal contact using urinary organophosphate esters (Ding et al., 2019). Compared to internal exposure, external exposure assessment can solve this problem and provide clearer suggestions for pathways. Therefore, external exposure assessment, based on contaminant concentrations in matrices, the intake rate of the matrix, and body weight, is very important to understand exposure pathways. Many studies have shown that oral ingestion is a very important pathway for many organic pollutants, especially for SVOCs (Giovanoulis et al., 2018; Li et al., 2015c; Martínez et al., 2018; Yu et al., 2012c).

To date, most studies evaluating human exposure to contaminants through oral ingestion did not consider the complex absorption processes in the gastrointestinal tract, *i.e.*, absolute bioavailability (%) or relative bioavailability (%) which are generally less than 100%, did not added into the estimation (Fair et al., 2018; Ke et al., 2017; Toms et al., 2016). Obviously, it is not realistic because not all chemicals can be released from the matrix to digestive fluid, absorbed by the intestine and finally enter system circulation. Therefore, omitting the absorption factor would overestimate human exposure and the associated health risks (Jiang et al., 2019; Kang et al., 2013; Raffy et al., 2018; Yu et al., 2012a, 2012c). Absolute bioavailability means the proportion of pollutants (on total intake) that can be absorbed through the gastrointestinal tract and finally reach the bloodstream or the lymph tissue (that is, enter the circulation of the human body) (Dean and Ma, 2007), which equal to the concept of absorption factor in the human exposure or health risk assessment. Relative bioavailability (RBA) means the comparative bioavailability of a chemical in different exposure matrices or different chemical forms (Ruby et al., 1999). Bioavailability can be determined by *in-vivo* assays using animals such as swine and mice (Kang et al., 2018; Li et al., 2019; Pan et al., 2016; Yu et al., 2019a). However, in-vivo measurement is time-consuming and laborious, and also faces ethical challenges. Therefore, the bioaccessibility (%) of contaminants has been used to replace bioavailability for external exposure estimation. Bioaccessibility is the fraction of a contaminant released from matrices into the gastrointestinal digestion solution, which reflects the maximum fraction of the contaminant can be absorbed. Thus, the bioaccessibility of chemical is larger than or equal to the corresponding bioavailability value theoretically. It can be determined by in-vitro methods simulating the human gastrointestinal tract (Ruby et al., 1996; Yu et al., 2019a). Bioaccessibility, absolute and relative bioavailability can be calculated as follows (Fig. 1):

Bioaccessibility% =
$$\frac{M_E}{M_S} \times 100\%$$
 (1)

Absolute bioavailability% =
$$\frac{M_{[organism]}}{M_s} \times 100\%$$
 (2)

Relative bioavailability% =
$$\frac{M_{[organism-sample]}}{M_{[organism-reference]}} \times \frac{D_{[reference]}}{D_{[sample]}} \times 100\%$$
 (3)

where M_E means the amount of a chemical released into the digestive fluid (or the amount extracted in absorption sink); M_S is the total amount of the chemical in sample; $M_{[organism]}$ is the amount of the chemical detected in animal; $M_{[organism-sample]}$ and $M_{[organism-reference]}$ is the amount of the chemical detected in animal after dosed target sample and reference material, respectively; $D_{[sample]}$ and $D_{[reference]}$ means the total amount of the chemical in sample and reference material, respectively.

Currently, an increasing number of researchers believe that the absorption factor should be added to the human exposure and/or health risk assessment, and bioaccessibility is generally used (Juhasz et al., 2016a; Kang et al., 2018; Yu et al., 2012a, 2019a). Over the past twenty years, in-vitro methods have developed quickly. Many in-vitro methods, such as the simulator of the human intestinal microbial ecosystem (SHIME) (Van de Wiele et al., 2004), the physiologically based extraction test (PBET) (Ruby et al., 1993; Basta and Gradwohl, 2000), a method developed by the Dutch National Institute for Public Health and the Environment (RIVM) (Versantvoort et al., 2004, 2005; Smith et al., 2008), the unified BARGE method (UBM) (Li et al., 2015b), and others have been developed. Several of these methods or adapted methods have been validated against bioavailability through in-vivo assays. Historically, bioaccessibility was first used in food nutrition research and pharmacological research on drug absorption efficiency (Kondratenko et al., 2002; Miller et al., 1981). Later, it was applied to the environmental field and factored into estimations of human exposure including heavy metals, and then for organic pollutants (Cao et al., 2020; He et al., 2016; Hu et al., 2013; Luo et al., 2012; Nathanail and Smith, 2007; Ollson et al., 2009; Tian et al., 2018; Yu et al., 2011b, 2012b, 2012c). Compared with heavy metals, fewer studies have been conducted for organic pollutants. Currently, no unified in-vitro method exists to measure the bioaccessibility of organic pollutants, although several methods have been developed for organic pollutants and have shown good in vitro-in vivo correlations (IVIVCs), and although bioaccessibility has been added to human exposure and/or health risk assessment.

The present review has focused on development of *in-vitro* methods simulated human gastrointestinal tract for bioaccessibility measurement, validation of the methods by *in-vivo* assays, determination of the factors that influence on the bioaccessibility of organic pollutants, application of bioaccessibility to human exposure and/or health risk assessment, and identification of the challenges faced. This review aims at systematically and comprehensively summarize the research progress on the bioaccessibility studies on organic pollutants, calls for deeper researches on the complex digestion mechanism among human digestive system, hopes can help to set unified *in-vitro* method for special or even multiple organic pollutants in the future.

2. Methodology

In the present review, the Web of Science was systematically searched at the end of March 2020. Bioaccessibility, simulated gastrointestinal tract, and/or simulated digestive tract were used as for the article search, and the articles written in English were used in the present review. Articles reporting the bioaccessibility of organic pollutants as measured by gastrointestinal tract methods were further manual selected. Those articles reporting *in-vitro* experiments, not by simulated gastrointestinal methods, but using organic solutions (like sodium dodecyl sulfate or sequential supercritical fluid extraction, and cyclodextrin extraction) to extract organic pollutants from the matrix were not used in the present study because "abiotic" passive sampling methods like is too simple to mimic the complex bioaccessible progress in human body (Hilber et al., 2019). In addition, articles investigating



Fig. 1. Diagram of bioaccessibility and bioavailability (Bioa: bioaccessibility; Biov: bioavailability; M_{Released}: mass of released contaminants into the gastrointestinal digestion solution; M_{Total}: mass of total contaminants in the matrix; M_{Circulation}: mass of the contaminants entered into circulation system).

human exposure risk assessment, global POP production, human ingestion progress, and related topics supporting this review were used.

The bioaccessibility measurement of pollutants in environmental matrices using in-vitro gastrointestinal methods started with measurement for a nutritional study of the bioaccessibility of iron in food (Miller et al., 1981). Later, in-vitro methods were used in the environmental field for oral bioaccessibility measurement of heavy metals. At first, simple chemical extraction tests were used. These methods generally used acid solutions to extract heavy metals. For example, the European standard for toy safety used hydrochloric acid solution with pH values of 1.0-1.5 to simulate gastric juice and determined eight soluble metals in toy materials (EN71-3:1994+A1, 2000). Although these methods are relatively simple and easy to implement, they are quite different from the physiological conditions of the human digestive system, and the biological effectiveness values obtained are quite different from the actual situation in the human body. On the basis of these simple methods, more complex in-vitro methods based on human gastrointestinal physiological conditions have been developed for heavy metals (Basta and Gradwohl, 2000; Ruby et al., 1993; Schroder et al., 2004). The measurement of organic pollutants using in-vitro method was carried out in 1996 (Hack and Selenka, 1996). Until after 2002 (Ruby et al., 2002), more and more studies were carried out for organic pollutants (Abdallah et al., 2012; Cui et al., 2016; Li et al., 2015c; Smith et al., 2008; Tang et al., 2006). Thus, the present review mainly focused on the organic pollutants.

3. In-vitro methods simulating the human gastrointestinal tract

Currently, several *in-vitro* gastrointestinal methods have been used to determine the bioaccessibility of organic pollutants such as PAHs, PCBs, PBDEs, perfluorooctanoic acid (PFOA), and pesticides, and several of which have been successfully verified by *in-vivo* experiments using animals (Juhasz et al., 2014; Kang et al., 2018; Li et al., 2015b; Yu et al., 2019a). Most of the *in-vitro* methods can be classified as static methods, which only consider the release of pollutants from their matrices. However, in the actual human small intestine, the released pollutants are absorbed by the intestinal epithelium simultaneously with the release of pollutants from their matrices. Therefore, more and more studies have investigated dynamic *in-vitro* methods incorporating absorptive sinks using absorbents such as Tenax, silicone rod/sheet, C18 membrane, and ethylene vinyl acetate (EVA) membrane (Gouliarmou et al., 2013; Juhasz et al., 2016a; Kang et al., 2018; Yu et al., 2013).

3.1. Static in-vitro methods

Commonly used static gastrointestinal *in-vitro* methods include PBET (Ruby et al., 2016), colon-extended PBET (CE-PBET) (Tilston et al., 2011), SHIME (Van de Wiele et al., 2004), RIVM (Smith et al., 2008), the fed organic estimation human simulation test (FOREhST) (Cave et al., 2010), the *in-vitro* gastrointestinal method (IVG) method (Hurdzan et al., 2008), the German-Deutsches Institut fur Normung (DIN) method (Hack and Selenka, 1996), and UBM (Li et al., 2015b). Among these, PBET, CE-PBET, FOREhST, and SHIME are the most widely used *in-vitro* methods.

3.1.1. PBET

The PBET method was initially used to determine the bioaccessibility of organic pollutants (dioxins/furans), first by Ruby et al. (2002), who modified the method used for bioaccessibility measurement of Pb and As in soil samples (Ruby et al., 1996). The approach included sequential gastric and intestinal phases. Details of the parameters and the constituents of the simulated gastrointestinal digestion solution used in the PBET method are summarized in Table 1. Currently, this method has been used to determine the bioaccessibility of PAHs, PCBs, PBDEs, PFOA, dichlorodiphenyltrichloroethane and its metabolites (DDTs), phthalate esters (PAEs), and OPFRs in some matrices, including soil, indoor dust, and food. In addition, several experiments have been carried out, in which the bioaccessibility of certain organic compounds was compared with the bioavailability measured with an *in-vivo* method

Table 1	
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In-vitro gastrointestinal methods for organic pollutants.

	Specific	PBET	CE-PBET	RIVM	FOREhST	IVG	DIN	UBM	SHIME
Reference	-	Ruby et al., 2002;	Tilston et al., 2011	Smith et al., 2008	Juhasz et al., 2014	Hurdzan et al., 2008	Hack and Selenka,	Li et al., 2015b	Van de Wiele
Main		PCDDs/Fs,	PAHs	PAHs	PAHs	PAH (Phe)	PCBs, PAHs	PFOA	PAHs
Matrix		10 g soil (<250 μm)	1.2 g soil	0.6 g dry soil	0.3 g soil (<250 μm)	Cutan, cutin	1 g soil	0.6 g food	20 g soil
Organs mimicked	Oral cavity Stomach Small intestine	No Yes Yes	No Yes Yes	Yes Yes Yes	Yes Yes Yes (duodenal)	Yes Yes Yes (duodenal)	No Yes Yes	Yes Yes Yes	No Yes Yes
Oral cavity	Large intestine Volume Components	No No	Colon No	No 9 mL NA	No 4.5 mL Urea, uric acid, mucin, amylase	No 12 mL Urea, uric acid, mucin, amylase	No No	No 9 mL NA	Colon No
Stomach phase	pH Digestion time Volume	950 mL	NA	6.5 5 min 13.5 mL	6.8 ± 0.5 5 min 9.0 mL	6.5 ± 0.1 ~5 min 20 mL	105 mL	NA 0.5 min 13.5	200 mL
	Components	Pepsin, glycine, BSA, mucin, oleic acid, NaCl	Pepsin, mucin, HCl, NaCl	Pepsin, BSA	Pepsin, glucose, BSA, mucin, urea, glucuronic acid, HCl, NaCl	Pepsin, glucose, BSA, mucin, urea, glucuronic acid, HCl, NaCl	Pepsin, mucin, HCl, NaCl	Pepsin, mucin, BSA	(L/S: 10) Pepsin, NaCl
	pН	1.5 (fasting condition)	2.5	1.1	1.3 ± 0.5	2.0 ± 0.1	2.0	1.2	1.5
Intestinal phase	Digestion time Volume	1 h 960 mL (950 + 10)	1 h NA	2 h Duodenal juice 27.0 mL, bile juice 9.0 mL	2 h Duodenal juice 9.0 mL, bile juice 4.5 mL	2 h Duodenal juice 35 mL, bile juice 12 mL	2 h NA	1 h Duodenal juice 27.0 mL, bile juice 9.0 mL	2 h Duodenal juice 100 mL Colon suspension 100 mL
	Components	Porcine pancreatin, bile salts, lipase, BSA	Pepsin, pancreatin, mucin bile salts (1.78 g/L) bile salts	Pancreatin lipase, BSA, bile	Pancreatin, lipase, BSA, urea, bile, HCl, NaCl	Pancreatin, lipase, BSA, urea, bile, HCl, NaCl	Pancreatin, bile	Pancreatin lipase, BSA, bile	Pancreatin, NaHCO ₃ Anaerobe
			(400 mg/L)						and aerobe microbiota
	рН	7.2	7.0 6.5	7.8 (duodenal juice), 8 (bile juice)	8.1 ± 0.2 (duodenal juice), 8.2 ± 0.2 (bile juice)	5.5 ± 0.1	7.0	6.3 ± 0.5	6.3 NA
	Digestion time	4 h	4 h 8 h	2 h	2 h	2 h	6 h	4 h	5 h 18 h
Operating condition	Temperature Food components	37 °C No	37 °C No	37 °C No	37 °C S-26 Gold Toddler Formula, sunflower, oil	37 °C No	37 °C No/yes (dry milk)	37 °C No	37 °C Starch, xylan,
	Mechanic treatments	Mechanical stirring at	NA	Rotary shaker	End-over-end shaker at 30 rpm for	NA	Shaken at 200 rpm	End over end rotation at	150 rpm
	Centrifugation filtration	3000 g for 10 min	3000 g for 10 min	5 min	3000 g for 10 min	NA	7000 g for 10 min	3000 g for 5 min	3000 g for 5 min
	10tal S/L Fatio	1:100	INA	1:97.5	1.90	1.900	INA	1:100	1:25

BSA: bovine serum albumen; CE-PBET: colon extended physiologically based extraction test; DIN: the German-Deutsches Institut fur Normung; FOREhST: fed organic estimation human simulation test; GC: gas chromatography; GC–MS: gas chromatography coupled with mass spectrometry; HPLC-PDA: HPLC system fitted with a Water 996 photodiode array detector (PDA); IVG: *in vitro* gastrointestinal method; NA: not available; PAHs: polycyclic aromatic hydrocarbons; PBET: physiologically based extraction test; PCBs: polychlorinated biphenyls; PCDDs/Fs: polychlorinated dibenzo-p-dioxins and dibenzofurans; PFOA: perfluorooctanoic acid; Phe: phenanthrene; RIVM: Dutch National Institute for Public Health and the environment; SHIME: simulator of the human intestinal microbial ecosystem; SIM: single ion monitoring; UBM: the unified BARGE method; UPLC: ultraperformance liquid chromatography.

using animals (Juhasz et al., 2016a; Pan et al., 2016; Smith et al., 2012; Yu et al., 2019a).

Recently, the bioaccessibility of some flame retardants such as PBDEs and OPFRs has also been measured using the modified PBET from Ruby et al. (2002). For example, Pan et al. (2016) studied the bioaccessibility of decabromodiphenyl ether (BDE209) in house dust samples (<100 μ m) from Guangzhou using a modified PBET method in which the pH values of the gastric and intestinal phases were 2.5 and 7.0 respectively, unlike the values of 1.5 and 7.2 used by Ruby et al. (2002). In this case, the bioaccessibility of BDE209 ranged from 9.3% \pm 1.8% to 39.0% \pm 4.4% in the gastric phase and from 27.4% \pm 7.4% to 50.7% \pm 1.2% in the intestinal phase. A similar gastric pH of 2.5 was also used

by He et al. (2016), who measured the bioaccessibility of OPFRs in indoor dust samples with particle size <150 µm from office, house, dormitory, and public microenvironments. They found that the bioaccessibility of OPFRs varied between 8.18% for triphenyl phosphate (TPP) and 54.5% for TCPP. Furthermore, He et al. (2018b) carried out a more complete study on the bioaccessibility of 20 flame retardants, including PBDEs, OPFRs, dechlorane plus (DPs), and novel brominated flame retardants (NBFRs), in dust samples from different indoor environments including car, office, and public microenvironments in Nanjing.

Beside flame retardants, other organic pollutants, such as PAHs, DDT, and PAEs, have been investigated by the PBET method. PAHs have been

the most frequently investigated. The first study on PAHs was conducted by Tang et al. (2006), who found that the bioaccessibility of total PAHs in soil from several public areas in Beijing in the intestinal phase were 9.2%–60.5%, which were higher than those in the gastric phase (3.9%–54.9%). The bile in the intestinal solution could possibly promote the formation of micelles, which would decrease the surface tension of the digestion solution, causing PAHs to become more available for release from soil into the digestion solution. Recently, Kang et al. (2018) investigated the bioaccessibility of PAHs in house dust samples (<100 µm) in Guangzhou using PBET and showed that the bioaccessibility of phenanthrene (Phe), fluorene (Flu), pyrene (Pyr), and benzo(a)pyrene (BaP) were 15.0%-43.5%, 9.0%-38.8%, 10.0%-37.9%, and 6.0%-21.9%, respectively, which were slightly lower than those found by Tang et al. (2006). For DDTs, including DDT, dichlorodiphenyldichloroethylene (DDE), and chlorodiphenyldichloroethane (DDD), Juhasz et al. (2016a) and Smith et al. (2012) measured the bioaccessibility of DDTs in soil using PBET, and both found relatively low bioaccessibility of the pesticides (less than 5%). Moreover, Li et al. (2015b) measured the bioaccessibility of PFOA in food and found that the bioaccessibility of the chemicals ranged from 9.8% to 99.0%, which was the first report of PFOA bioaccessibility using the PBET method. In addition, He et al. (2016) measured the bioaccessibility of PAEs and found that they varied between 1.21% for di-2ethylhexyl phthalate (DEHP) and 81.1% for dimethyl phthalate in indoor dust samples with particle size <150 µm from offices, homes, dormitories, and public microenvironments. Currently, PBET is one of the most used in-vitro methods simulating the human gastrointestinal tract for bioaccessibility measurement of organic pollutants on the basis of the reported articles.

3.1.2. CE-PBET

With the development of the PBET method, the need for modifications soon became apparent because it did not behave well in testing the bioaccessibility of most hydrophobic organic compounds (HOCs). At the same time, because the time required for food to pass through the colon accounts for 80% of total food transit time in the human digestive tract, the rich presence of carbohydrates in the colon can improve HOC release from matrices to the digestion fluid, leading to a higher bioaccessibility. As a result, the CE-PBET method was developed by Tilston et al. (2011). The details of the components of the three phases (gastric, intestinal, and colon) and the operating conditions of CE-PBET method are listed in Table 1. An extend 8 h colon digestion of CE-PBET facilitated the release of HOCs from matrices compared with the original fed-PBET method, although it makes the work more complex and time consuming. It was found that PAH bioaccessibility in artificially contaminated soil increased several times after incorporating the colon phase, in which the digestion time was prolonged and carbohydrates were added, both of which could improve bioaccessibility.

Except for PAHs, the CE-PBET method has been used to investigate the bioaccessibility of brominated flame retardants (BFRs) and DDTs in some matrices including soil, dust, and food samples (Abdallah et al., 2012; Mi et al., 2017; Tilston et al., 2011). For instance, Abdallah et al. (2012) determined the bioaccessibility of tetrabromobisphenol A (TBBPA), hexabromocyclododecane (HBCD), and PBDEs in house dust samples from UK homes (25–500 µm), and found that the bioaccessibility was 72%–80% for HBCD, 94% for TBBPA, and 32%–58% for tri- to hepta-BDEs, with the lowest value of 14% for BDE209. However, the mean bioaccessibility of HBCD in house dust samples (<250 µm) from Belgium with comparatively lower HBCD concentration (compared by SRM-2585) were only 14%–37% measured using the CE-PBET method (S/L = 1:167 and colon phase: 16 h) (García-Alcega et al., 2016), a value that was lower than the data reported by Abdallah et al. (2012).

Fang and Stapleton (2014) used a modified CE-PBET method by adding porcine lipase in the intestinal phase to determine the bioaccessibility of BFRs and OPFRs in Standard Reference Material (SRM2585) (<53 µm) and found that the bioaccessibility ranged from less than 10% for bis (2-ethylhexyl) tetrabromophthalate to more than 80% for tris (2-chloroethyl) phosphate (TCEP) and less than 20% for PBDEs. For pesticides, Wang et al. (2018a) studied the bioaccessibility of eight pyrethroids in dust and soil samples using the CE-PBET method (colon phase: 16 h) and found values ranging from 18.2% to 35.7% for bifenthrin and from 6.0% to 48.0% for all eight pyrethroids. In addition to dust and soil samples, food items were also investigated. Mi et al. (2017) found that the oral bioaccessibility PBDEs in fish sample (yellow grouper) from coasts in Guangdong was 26%, which was lower than that of DDTs (60%), using CE-PBET. Comparatively, many more investigations have been conducted for soil or dust samples than for food samples. By the way, the small intestine is the main site of substance absorption, although studies have shown that the bioaccessibility with an added colon phase is improved, or even increased several times.

3.1.3. RIVM

The RIVM method was first introduced to measure Pb. As. and Cd. after which it was used for HOC bioaccessibility determination (Grøn et al., 2007; Oomen et al., 2002). Initially, the method was used to mimic the fasting ingestion condition (Oomen et al., 2002). Later, it was developed to mimic the fed condition (by adding food according to infant formula) by changing the gastric pH from 1.1 to 2–3, and it is a positive adjustment though makes the HOC distribution between fluid and matrices more complex (Grøn et al., 2007; Versantvoort et al., 2005). Compared with the PBET and CE-PBET methods, the major difference is the addition of an oral cavity phase for RIVM method (Table 1). This method simulated human ingestion progress more completely, but extractions in all phases were sequential, and therefore only total oral bioaccessibility data were available. Still, the RIVM method has more complex operating steps than most *in-vitro* methods; for example, the mimic digestive solutions (like bile juice) are less stable.

Hence, far fewer studies have used this method for the bioaccessibility measurement of organic pollutants. Smith et al. (2008) introduced an RIVM method with fasting condition and found that PAH bioaccessibility in standard spiked soil (OCED) was <30%–85%. For the fed RIVM method, an infant formula was adapted to serve as food components mimicking fed digestion condition of children. Grøn et al. (2007) applied such a formula including chicken and mashed potatoes to provide protein, carbohydrates, and fat to determine PAH bioaccessibility in contaminated soil from Denmark. It was found that the bioaccessibility of dibenz(*a*,*h*)anthracene (DBahA) and BaP ranged from $12\% \pm 9.1\%$ to $40\% \pm 24\%$ and from $5.7\% \pm 3.0\%$ to $38\% \pm 27\%$, respectively. The drawback is that only several samples were measured by Grøn et al. (2007).

3.1.4. FOREhST

The FOREhST method was modified from the fed-state RIVM method developed by Cave et al. (2010). Both FOREhST and RIVM had three digestion phases and contained infant formula. However, the two infant formulae were based on nutritional bases from different countries: the former was based on Great Britain (food mixed with sunflower oil), and the latter was based on The Netherlands (food mixed with vegetable oil). The FOREhST method includes three phases: an oral cavity, a gastric phase, and an intestinal phase (duodenal) (Table 1). Generally, urea is included in both the gastric and the intestinal phase in the FOREhST method, whereas it is not added in the RIVM method.

Specific information on this method was reported by Juhasz et al. (2014), who used the FOREhST method to test PAH bioaccessibility in soil ($<250 \mu$ m) polluted by creosote. They replaced the cheaper S-26 Gold Toddle Formula by the original HIPP porridge formula as food. As a result, the bioaccessibility of the seven PAH isomers was less than 4%. Notwithstanding, the food contents added in this method could enhance PAH bioaccessibility. The low PAH bioaccessibility may be explained by the PAHs partition equilibrium between soil and digestive fluid not reached due to the static nature of the method. Furthermore, James et al. (2018) investigated PAH bioaccessibility in polluted soil

using this method with a standard shaking condition of 30 rpm, which resulted in much higher bioaccessibility of 13%–29%.

In addition to PAHs, other HOCs, such as DDTs (DDT + DDE + DDD) and organophosphorus esters (OPEs), were also investigated using the FOREhST method. For example, Smith et al. (2012) investigated the bio-accessibility of DDTs in soil and found that it was less than 4%, which was similar to the results for DDTs (1.6%-3.8%) in soil obtained using the PBET method (Juhasz et al., 2016a). Moreover, Quintana et al. (2017) evaluated chlorinated organophosphate esters (Cl-OPEs) such as TCEP in indoor dust samples from houses and cabins using FOREhST (with organic cream as infant food) and found that the bioaccessibility of TCEP was highest, with a range of 69%–103%.

3.1.5. IVG

The IVG method was first used to determine the bioaccessibility of As in mining/smelter soil by Rodriguez et al. (1999). The method was initially only composed of gastric and intestinal phases. Later, it was used to measure organic phenanthrene (Phe) by Hurdzan et al. (2008). This model developed further to include an oral cavity, a gastric phase, and an intestinal phase (duodenal) within a short time, and no food components were added (Table 1). Compared with other in-vitro methods such as PBET, CE-PBET, RIVM, and FOREhST, this method had a relatively low pH in the intestinal phase. Hurdzan et al. (2008) used cutan and cutin from biopolymers as surrogates for natural organic matter (NOM) spiked with Phe and used the IVG method with the addition of a large intestinal phase and a C18 membrane to study the absorption of Phe onto the C18 membrane. As a result, after 72 h large-intestine incubation, the absorbed Phe in the C18 membrane was 83.1% \pm 4.7% in cutin and $35.7\% \pm 2.9\%$ in cutan. The data for the cutan were lower because the microporous structures in cutan can trap Phe better, which means that Phe release was tightly correlated with the constituents (*i.e.*, cutan and cutin) in NOM. In addition, Yu et al. (2019a) used the IVG method to determine PBDE bioaccessibility in e-waste contaminated soil samples and found that the results were generally less than 20%. Nevertheless, similarly to the RIVM method, the IVG method has not been widely used to measure HOC bioaccessibility, with only a limited number of reports in recent years.

3.1.6. DIN

The DIN method was developed by Hack and Selenka (1996) to test the bioaccessibility of PCBs and PAHs in contaminated soil, and it only has limited research of the bioaccessibility of HOCs compared with other methods. Similarly to the PBET and CE-PBET methods, this approach simulated only the gastric and intestinal phases (Table 1). However, it had longer digestion time in the intestinal phase than most in-vitro methods. Their main objective was to investigate the food effect on the bioaccessibility of PAHs and PCBs in soil. Their results showed that bioaccessibility ranged from 5%-40% for PAHs and PCBs, but increased to 40%-85% when lyophilized milk was added. Zhang et al. (2017) used the DIN, PBET, FOREhST, UBM, and IVD methods to determine the bioaccessibility of PAHs from contaminated soil (<250 µm) and observed that bioaccessibility (expressed as the BaP equivalent) was the highest when tested by the DIN (0.12%-5.47%) method, which was slightly higher than the results of 0.067%-1.98% for PBET, 0.34%-1.53% for FOREhST, 0.05%-1.11% for UBM, and 0.001%-0.49% for IVD. Recently, Yu et al. (2019a) investigated PBDE bioaccessibility in ewaste contaminated soil and compared the results with other in-vitro methods, including PBET, UBM, IVG, and Ad-SHIME. The authors found that the PBDE bioaccessibility (2%-16%) tested by DIN were similar to those from PBET (1%-6%), UBM (1%-14%), and IVG (1%-20%), but lower than those from Ad-SHIME (2%-42%). In addition, there was poor correlation between the bioaccessibility measured by DIN and the in-vivo bioavailability determined using female C57BL/6 mice. Overall, the DIN method has not been widely used, and scant information is available.

3.1.7. UBM

The UBM method was first used by Wragg et al. (2011) to study the bioaccessibility of trace elements (As, Pb, and Cd) in soil, which was an inter-laboratory trial. This method is consisted of three phases (saliva, gastric, and intestinal phases), similarly to the RIVM method (Table 1). Comparatively, less digestion time in the oral cavity (0.5 min vs. 5 min) and the gastric phase (1 h vs. 2 h) than in the RIVM method was used, although other conditions were the same (Li et al., 2015b). The UBM method was evaluated by an *in-vivo* assay. Li et al. (2015b) determined that PFOA bioaccessibility in food ranged from 8.7% to 73% using this method and that there was a strong linear relationship (r = 0.79, p < 0.01, slope = 0.79, *y*-intercept = 11.7) between bioaccessibility and RBA measured in mice. Their results suggested that the UBM method might be a potential useful *in-vitro* method for simulating human digestion to measure bioaccessibility and predict the RBA of PFOA in foods.

However, Smith et al. (2012) also used the UBM method to research DDTs in soil and found that the bioaccessibility of DDTs was less than 4%, which was lower than the results for RBA (2%–25%). Similar lower PBDE bioaccessibility in SRM2585 (approximately 1%–14%) were also observed by Yu et al. (2019a), which were lower than the oral bioavailability (3.9%–48.8%) determined using female C57BL/6 mice. The bioaccessibility was lower than the bioavailability mainly because of the static digestive procedure in the *in-vitro* method, which limited the release of these highly lipophilic substances, and because of the low bile concentrations in the UBM method, which can significantly affect the release of these chemicals (Yu et al., 2019a). Quintana et al. (2017) used the UBM-related (fasting ingestion condition) method to investigate Cl-OPEs in dust samples, and TCEP bioaccessibility was found to be 103% in cabin dust samples and 69% in house dust samples, as previously mentioned.

3.1.8. SHIME

The SHIME method was first proposed by Molly et al. (1993) to simulate the human gastro-intestinal microbial ecosystem. It was used for PAH bioaccessibility measurement by Van de Wiele et al. (2004). Unlike the other static methods mentioned earlier, SHIME mimics the total gastrointestinal tract more completely. It introduces a colon phase that not only has the corresponding organic and inorganic components, but also the colon microbiota, unlike CE-PBET. This helps scientists achieve a better understanding of the interaction between colon microbiota and chemicals. In addition, the SHIME method is widely used to evaluate HOC release from food and soil/dust matrices. Siciliano et al. (2010) studied PAHs in soil (<45 µm) from Canada using a SHIME reactor including gastric, intestinal, and colon phases and observed that PAH bioaccessibility was <8% in both the intestinal and gastric phases. In addition, PAH bioaccessibility had no correlation with PAH concentrations in soil. However, higher PAH bioaccessibility ranging from 1.2% to 21.0% in the colon phase were detected, which are strongly dependent on the fugacity capacity of soil to water (Z_{soil}/Z_{water}). Moreover, Yu et al. (2012a) used the SHIME model without fecal microbiota to research PAH bioaccessibility in animal-based foods and found that the mean bioaccessibility were 29.0%-61.2%, which were linearly correlated with the lipid contents ($R^2 = 0.752$, p = 0.005). In addition to PAHs, PBDE bioaccessibility was first investigated using the modified SHIME method by Yu et al. (2009a). Later, a series of PBDE bioaccessibility studies was carried out. For example, Yu et al. (2009a) studied the influence of digestion conditions and operating condition on PBDE bioaccessibility. Next, they investigated the influences of food components and dust characteristics on PBDE bioaccessibility (Yu et al., 2010, 2012b, 2013).

From the viewpoint of human health protection, measuring the bioaccessibility of a pollutant under the worst-case scenario is generally recommended. Therefore, an adapted fasting *in-vitro* digestion method modified from the SHIME method reported by Yu et al. (2011a) was used to optimize the digestion conditions to measure PBDE bioaccessibility in dust samples using a central composite design and response surface methodology. The results indicated that the worst-case scenario digestion conditions had a bile concentration of 5.5 g/L, an L/ S ratio of 200, and a digestion time of 6 h. Recently, the optimized method was validated by *in-vivo* assays by using female C57BL/6 mice, and the results were compared with another four *in-vitro* methods, including PBET, UBM, IGV, and DIN (Yu et al., 2019a). The results showed a significant linear relationship between the *in-vitro* bioaccessibility measured by the optimized method adapted from SHIME and the *invivo* bioavailability for several moderately brominated congeners, such as BDE99 and BDE153.

Comparatively, fewer reports on other organic pollutants, such as PCBs, pesticides, and bisphenol A (BPA), are available. Yu et al. (2009b) investigated the factors influencing PCB bioaccessibility using grass carp muscle. Wang et al. (2018b) found that the BPA bioaccessibility decreased with digestion progress (stomach, small intestine, and colon) using BPA-spiked samples in nutrition medium aged for 10 days. As for pesticides, Yu et al. (2012c) found that the bioaccessibility of DDTs and HCHs in animal-based foods were 31.5%-84.5% and 31.1%-59.6%, and these ranges were used as the absorption factor when estimating daily uptake of toxicants. Other pesticides such as triazolone, difenoconazole, hexaconazole, and spirodiclofen were also reported using the SHIME method. For example, the bioaccessibility of difenoconazole, hexaconazole, and spirodiclofen residues in apples were detected as 25.2%-76.3% in the gastric phase and 10.6%-79.6% in the intestinal phase (Shi et al., 2017), and those of triazolone in cherry tomatoes were 32.47%-67.4% in the gastric phase (pH = 1.68-4.97), which were relatively higher than those in the intestinal phase (31.0%–41.3%) (Liu et al., 2018b). It should be noted that the digestion conditions varied slightly different among the literature publications, although they were all SHIME-related methods.

3.2. Dynamic methods

In addition to static gastrointestinal methods, dynamic gastrointestinal methods have been developed because the release and absorption of pollutants in the small intestine occurred simultaneously, while static in-vitro methods cannot mimic this condition. They can be divided into dynamic operations or static methods modified by adding absorptive sinks, although there were studies considered the issue using mathematical model (Tao et al., 2009, 2010). The TNO gastrointestinal model (TIM) is a complex, computer-based method with dynamic operation that was first developed by Minekus in 1995 to mimic the lumen condition (including the components and flow rate of digestive fluids) in the gastrointestinal tract (Minekus et al., 1995; Minekus, 2015). TIM has been generally used in food nutrition and pharmaceutical studies, but only in limited research on the bioaccessibility of organic pollutants (Larsson et al., 1997; Oomen et al., 2002; Verwei et al., 2007). This is the only dynamic gastrointestinal method that works under a mechanically operated condition.

Currently, most dynamic methods are modified static methods. The motive to develop dynamic methods is to mimic the passive absorption of chemicals in the small intestine. Thus, the bioaccessibility determined by *in-vitro* methods may be more comparable to bioavailability measured through in-vivo assays. The first dynamic methods modified from a static method were introduced as Caco-2 and EVA by Vasiluck et al. (2007). However, these methods are not real dynamic methods because Caco-2 or EVA is added as a lipid sink to the digestion solution containing released pollutants after the digestion process has finished. In other word, the release and absorption of pollutants from the matrix do not occur at the same time. To overcome this shortcoming, Hurdzan et al. (2008) and James et al. (2011) used a C18 membrane as an absorptive sink immersed in the digestion solution during incubation. Later, a porous polymer resin, Tenax-TA, with stronger HOC adsorption capability and more convenient handling was first introduced in a study on PBDE bioaccessibility by Yu et al. (2013). Suitable absorption sink

materials should have great capability of maintaining the concentration gradient between the matrix and the digestion solution to facilitate HOC release sufficiently, trapping the release HOC fast and behaving well in back-extraction with solvent for bioaccessibility calculation (Gouliarmou et al., 2013). Before adding it in to simulated digestion fluid, sorption kinetics and capacity of it should be determined (Gouliarmou et al., 2013; Zhang et al., 2017). The final bioaccessibility after adding absorption material is the fraction of extractable HOC (found in digestive fluid and absorptive sink) in total HOC in matrix, *i.e.*, the ratio of total released HOC in the digestion solution and the absorbed HOC onto the absorptive sink to the target substance in the matrix. If the bioaccessibility data is comparable of the bioavailability from animals, the method is meaningful. In recent years, many studies have used absorptive sinks, including Tenax, silicone rods/sheets, and C18 membranes (Gouliarmou et al., 2013; Juhasz et al., 2016a; Kang et al., 2018; Li et al., 2015a; Pan et al., 2016; Yu et al., 2013).

3.2.1. Caco-2 cells and EVA

Caco-2 cells stem from human colon carcinoma, and their structure and function are similar to those of differentiated intestinal epithelial cells, which have microvilli and other structures and contain enzymes related to the brush border epithelium of the small intestine. This means that these cells can be used to mimic the dynamic absorption of chemicals from digestion fluid. To investigate whether EVA is an effective surrogate for simulating BaP uptake by the intestine, Vasiluck et al. (2007) first introduced Caco-2 as a lipid sink and compared the sorption of BaP after release from soil between the two sinks. They found that the data had a strong linear relationship ($R^2 = 0.92$), although the data tested by Caco-2 were 2.44 times those tested by EVA. However, Kang et al. (2018) found that EVA not only had similar elimination rate constants for several PAHs as determined by Caco-2, but also provided in-vitro bioaccessibility data with an excellent correlation with RBA measured in mice ($R^2 > 0.6$), which indicated that EVA had the potential to be a surrogate of Caco-2 cells. Considering the differences and the very limited applications of EVA to bioaccessibility measurement, more studies are warranted.

Intestinal absorption of mobilized PAHs occurs not only in digestive fluid, but PAHs are also absorbed in digestive residues. Wang et al. (2011) used Caco-2 to verify that if the dissolved PAHs and DDTs in digestive fluid were absorbed by Caco-2, a large amount of mobilized PAHs in the residues would release. In addition, Yu et al. (2017) investigated PBDE absorption and the associated mechanism in the human intestine using a Caco-2 cell monolayer model. They found that trans-cell transport, including the trans-pore process, was the rate-determining step during PBDE transport and that passive diffusion dominated transepithelial transport, although efflux and influx transporters might also participate in transport. The authors believe that investigating the mechanism of absorption and transport of contaminants using Caco-2 cells will be more meaningful than further investigation of the bioaccessibility.

3.2.2. Tenax improved method

Tenax is a porous and efficient material that also has excellent affinity with HOCs. It has been widely used to study HOC adsorption and desorption in soil and sediment in ecological risk assessment (Lydy et al., 2015; Mackenbach et al., 2012; Wang et al., 2019). It was first added to the digestion solution to simulate the dynamic process of measuring PBDE bioaccessibility in dust samples from air-conditioning filters by Yu et al. (2013). PBDE bioaccessibility was found to improve significantly. Later, Fang and Stapleton (2014) investigated the bioaccessibility of FRs (PBDEs and OPFRs) in different house dust samples with a modified CE-PBET method (by adding porcine lipase) and Tenax added to the digestion fluid. They found that the highest bioaccessibility (approximately 80%) was observed for OPFRs, which decreased with increasing log K_{OW} of the chemicals (when $logK_{OW} > 5$) and was <30% for BDE209. After this, an increasing number of studies used Tenax for HOC bioaccessibility determination (Kademoglou et al., 2018; Kang et al., 2018; Li et al., 2015a, 2016; Wang et al., 2018a).

Currently, there are approximately ten reports in the literature that describe studies with Tenax to improve bioaccessibility. For example, Li et al. (2015a) used the PBET method with Tenax as an absorptive sink to investigate PAH bioaccessibility in contaminated soil. They showed that Tenax could enhance bioaccessibility from 3.7%-6.92% to 16.3%-31.0%, which amounted to approximately a 4.4 times average improvement after incorporating Tenax, especially for isomers with high logK_{OW}. A similar tendency was observed for PBDEs in indoor dust samples by Kademoglou et al. (2018) with 0.5 g Tenax TA® as the absorptive sink with the CE-PBET method and for PCBs in soil using the PBET method (Li et al., 2017a). Moreover, after adding Tenax, Li et al. (2016) found a 3.4-22 times bioaccessibility improvement (27%-56% vs. 1.2%-15%) for DDTs in soil using the PBET method with Tenax addition. Zhang et al. (2017) found that adding 0.1 g Tenax in the DIN method could increase PAH bioaccessibility (expressed by the BaP equivalent) more than 16.6 times, from 0.12%-5.47% to 7.0%-34.8%, and that the enhancement was positively correlated with PAH hydrophobicity. In addition, a report on pesticides showed that 0.4 g Tenax enhanced the bioaccessibility of pyrethroids in dust and soil samples by 1.6-4.1 times with bioaccessibility of 21.5%-79.3% using the Tenaximproved CE-PBET method (Wang et al., 2018a). Overall, Tenax is the most widely used absorptive sink for HOC bioaccessibility measurement.

3.2.3. Silicone and C18 membranes

Silicone and C18 membranes have been used in some studies (Gouliarmou et al., 2013; Harris et al., 2013; Kang et al., 2018). Silicone is a polymer material with high partition properties and efficient sorption ability to act as an absorptive sink in a form of rod or sheet with a simple back-extraction procedure for HOCs before analysis. The silicone absorptive sink is supplemented by the PBET and CE-PBET methods. For example, Gouliarmou et al. (2013) observed that the capacity of a CE-PBET system to extract PAHs increased by 1-3 orders of magnitude after a silicone rod was incorporated. They also found that the rod could provide near-infinite sink capacity. The results of silicone rod elimination kinetics indicated that a silicone rod 2 m length was not only sufficient to maintain the diffusion gradient for PAH release from the matrix, but also could effectively absorb free PAHs in digestive solution. Zhang et al. (2015a) found that the presence of silicone sheet could sharply increase apparent PAH bioaccessibility (the ratio of chemicals in silicone and liquid to the initial mass in soot), and this increasing trend was positively correlated with the K_{OW} of the PAHs. Similar results were also observed in further studies on PAHs and their deuterated derivatives in soot samples (Zhang et al., 2018). In addition, a kind of silica powder has also been used, and the results were compared with other absorptive sinks such as Tenax-TA, poly(ethylene-*co*-vinyl acetate) (poly E), C18 membranes, and Caco-2 cells (Kang et al., 2018). The results suggested that poly E and silica can be used to simulate Caco-2 cells when added to the PBET method to predict PAH bioavailability in indoor dust samples as determined using BALB/c mice. The siliconeimproved method has also been used for DDTs. Juhasz et al. (2016a) found that DDT bioaccessibility tested by adding silicone cord (an extended 22 h extraction time) to the PBET method was 18.9%–56.3%, which was twenty times the bioaccessibility (1.6%–3.8%) determined without the absorptive sink. Currently, silicone sinks have been widely used to measure PAHs, although DDTs have also been investigated.

The C18 membrane is also a kind of material used as a lipid sink *invitro* methods. It showed a slower adsorption ratio and less affinity for DDTs than Tenax (Li et al., 2016). A slow adsorption ratio of $13.4\% \pm 0.65\%$ for Phe was found by Hurdzan et al. (2008) using a C18 membrane to absorb the chemical from water for 72 h. The C18 membrane also facilitated the release of HOCs like PAHs compared with single gastrointestinal methods, which further strengthened the relationship between bioavailability by pig and bioaccessibility *via* the IVG method (James et al., 2011). In comparison, Kang et al. (2018) found that silica powder and poly E were more suitable for predicting PAH bioavailability than the C18 membrane when added to the PBET method. It should be pointed out that silicone rods and C18 membranes need large surface areas for high-capacity HOC adsorption, which might limit the application of absorptive sinks in bioaccessibility improvement (Kang et al., 2018).

4. Factors influencing bioaccessibility

As mentioned earlier, bioaccessibility is the ratio of the chemicals released into a digestion solution to the total amount in the matrix. Therefore, it is obvious that every factor that influences (facilitates or restricts) the dissolution or release of target substances might change their bioaccessibility to various extents. This review discusses the factors that influence the bioaccessibility of contaminants from three aspects: *in-vitro* digestion conditions, pollutant characteristics (especially hydrophobicity), and matrices (including food, soil, soot, and dust) (Fig. 2). The first is an external factor, whereas the last two are internal factors. Currently, the uncertainty in bioaccessibility



Fig. 2. Factors influencing bioaccessibility (Bioa: bioaccessibility; Conc.: concentration).

evaluation is greatly influenced by digestion conditions, which can be mainly attributed to the fact that there is no global unified *in-vitro* measurement method. To obtain deep knowledge of influencing factors and the mechanisms behind them, a standardized protocol for bioaccessibility measurement would be of great significance.

4.1. Digestion conditions of in-vitro methods

4.1.1. Components and their concentrations in the digestion solution

Because bioaccessibility is a fraction of chemicals released from matrices to digestion fluid, it is limited by the partition equilibrium between the fluid and the matrices. The components of digestion solutions include organic and inorganic components. The organic components such as bile and all kinds of enzymes and their effect on HOC bioaccessibility have been thoroughly investigated, but research into the influence of inorganic components on it has been very limited. For example, Li et al. (2015b) proposed that PFOA would combine with cations (like Ca⁺, which was included only in the UBM method) as complexes, which would decrease PFOA bioaccessibility. Among the components, the influence of bile in the digestion solution on HOC bioaccessibility has been the most important and also the most studied.

Studies have shown that bile can promote HOC solubility in digestion solution, thus increasing bioaccessibility (Tao et al., 2011; Tang et al., 2006; Yu et al., 2011a). For the first time, Tang et al. (2006) reported that bile in the digestion solution performs like a surfactant that facilitates the formation of micelles and lessens the surface tension of the digestion solution. If the bile concentration were greater than the critical micelle concentration (0.15 g/L), it would facilitate PAH absorption in micelles, further enhancing their bioaccessibility. Later, Yu et al. (2011a) studied the influence of bile concentration on PBDE bioaccessibility in dust samples using response surface methodology in the context of a fasting SHIME method. The results showed an increasing PBDE bioaccessibility trend with increasing bile concentration. Similar results were also reported by Tao et al. (2011), who found that only bile salt could mobilize the remaining PAHs in soil (compared to other components in the intestine, like pancreatin and lipase) and that 2 g/L bile salt was enough to provide this mobilization. Still later, studies showed the positive influence of bile concentrations on HOC bioaccessibility (such as PFOA, OPFRs, DDT, and lindane) (Ertl and Butte, 2012; Li et al., 2015b; Zeng et al., 2019) and on that of pesticides and their metabolites, including fenpropathrin, imidacloprid, and thiamethoxam (Xiao et al., 2019).

Digestive enzymes other than bile, such as amylase, pepsin, and pancreatin, can also influence HOC bioaccessibility, although the effects are very limited compared with bile (Xiao et al., 2019; Zeng et al., 2019). For example, Zeng et al. (2019) found that pancreatin (lipase: α -amylase: trypsin = 64.3:1.81:1) enhanced the bioaccessibility of PAHs and halogenated flame retardants, excluding OPFRs in PM_{2.5}, and that α -amylase was the main contributor because of its higher hydrophobicity compared to other enzymes. Similarly, the existence of α -amylase increased the bioaccessibility of six pesticides, including phoxim, chlorpyrifos, and imidacloprid, in chaenomelis as reported by Xiao et al. (2019). Moreover, it was also found that pepsin not only facilitated to the release of pesticides, but also to their elimination through hydrolyzation and metabolism. The enzymes improved HOC bioaccessibility, perhaps because enzymes can hydrolyze carbohydrates and proteins, which can trap or bind HOCs.

4.1.2. pH

The influence of pH on bioaccessibility of organic pollutants was observed (Van de Wiele et al., 2004; Yu et al., 2009a; Zhang et al., 2015b). In a study involving PBDEs, the authors found that the pH of the intestinal digestion solution had a significant influence on PBDE bioaccessibility, as evidenced by a bioaccessibility increase from about 3% to 28% when the pH (intestinal phase) increased from 5.9 to 7.2, followed by a decrease to about 23% with a pH of 7.46 (Yu et al., 2009a). Similar results were reported by Zhang et al. (2015b), who found the PAH bioaccessibility in soot increased when intestinal pH rose from 5 to 7.35 for the PAHs with lower K_{OW} value (Van de Wiele et al., 2004).

The influence of pH on HOC bioaccessibility might be related to the occurrence of bile salts, which are the main component of bile and which are precipitated at low pH, decreasing micelle formation in the digestion solution and thus lowering HOC bioaccessibility (Wright et al., 2008; Yu et al., 2009a). For example, as reported by Zhang et al. (2015b), decreasing the pH of the digestion solution decreased the critical micelle concentration, in turn enhancing micelle disaggregation and favoring PAH partitioning into silicone sheets, leading to higher bioaccessibility. Therefore, pH can change the bioaccessibility of HOCs by affecting their solubility, release from matrices, and distribution in fluids or an absorptive sink.

4.1.3. S/L ratio

In different in-vitro methods, the S/L ratios have varied from 1:25 to 1:250 as generally used (Pan et al., 2016; Van de Wiele et al., 2004; Yu et al., 2011a). Undoubtedly, an influence of S/L ratio on bioaccessibility is to be expected because the more digestion solution the in-vitro method has, the more substances can be dissolved, whether the substances are metals or organic chemicals, before the bioaccessible chemicals are completely released from the matrices. Hence, a lower S/L ratio can lead to higher bioaccessibility under a certain range of the S/L ratio. For example, Yu et al. (2009a) found that high S/L (>1:90) might cause incomplete release of PBDEs and then reduced the S/L (to 1:100) until saturated release was achieved. Pan et al. (2016) determined that the bioaccessibility of BDE209 varied from 9.3% to 39.0% in the gastric phase and from 27.4% to 50.7% in the intestinal phase; these values were higher than those reported by He et al. (2018b). The choice of a lower S/L ratio (1:200) in the study by Pan et al. (2016) rather than the commonly used ratio (1:100) might have been the main reason.

Moreover, a slight increase in TCEP bioaccessibility in car dust samples was observed when the S/L ratio was decreased from 1:100 to 1:200 (He et al., 2018b), which might have occurred because a digestion solution with a ratio of 1:100 was enough to extract TCEP. This result is similar to those reported by Yu et al. (2009a), who found that PBDE bioaccessibility did not change when the ratio varied from 1:90 to 1:240. In addition, Shi et al. (2017) observed a significant negative logarithmic relationship ($R^2 > 0.919$) between the bioaccessibility of pesticides (including hexaconazole, difenoconazole, and spirodiclofen) and S/L ratios using the SHIME method, which was mainly attributed to the high S/L ratios used (from 1:4 to 1:2 in the gastric phase), causing insufficient release of the chemicals. Overall, when a substance was not completely released, there was a negative relationship between the released substance and the S/L ratio. However, the release was not affected by the S/L ratio once the bioaccessible substance was completely released.

4.1.4. Digestion time

Generally, extending digestion time can facilitate HOC release from a matrix until equilibrium is reached between the digestion solution and the matrix. Yu et al. (2009a) investigated the influence of digestion time on bioaccessibility of PBDEs in fish samples. They found that PBDEs released rapidly within the first 2 h, followed a slow-release phase from 2 to 4 h. PBDE bioaccessibility increased from approximately 5% at 0.5 h to about 25% at 4 h. After this time, there were no apparent changes in PBDE bioaccessibility, although prolonged digestion time was used, which can be attributed to PBDE equilibrium between the digestion solution and the matrix. More recently, there have been several reports on the influence of digestion time on bioaccessibility. For example, He et al. (2018b) observed a near-doubling of TPP bioaccessibility from 3.7% to 7.4% when the intestinal digestion time was varied from 4 to 8 h. Shi et al. (2017) observed that the bioaccessibility of pesticides (hexaconazole, difenoconazole, and spirodiclofen) in the gastric phase

reached its highest point at 90 min and only slightly changed when the time was prolonged to 150 min. However, for the intestinal phase, they observed high bioaccessibility at 210 min, followed by a sharp drop between 210 and 300 min. For example, the bioaccessibility of spirodiclofen decreased from 46%–70% before 210 min to approximately 35% after 300 min. However, the authors did not explain this phenomenon.

Actually, chemical release is an adsorption-desorption process. It first proceeds through a fast desorption process, then a slow process, and finally the apparent release is invisible when equilibrium is reached. Several models including the Elovich equation, pseudo-first-order, pseudo-second-order, and others can be used to explain the kinetics of the sorption process. Yu et al. (2009a) found that PBDE sorption in the digestion solution followed a pseudo-second-order process. In addition, they found that the Langmuir isotherm can be used to explain the adsorption and release process. This is the first report on the HOC release mechanism in simulated human digestion solution.

4.1.5. Shaking method

Energy input in shaking is also a factor that must be considered because it directly influences chemical release. Recently, James et al. (2018) used FOREhST with a silicone rod as a sink to investigate the influence of different shaking methods and energy inputs on PAH bioaccessibility. They found that the average PAH bioaccessibility was 13%-29% when using a high-energy shaking method (30 rpm end-over-end inside the solution), but only 1.6%-5.0% in a low-energy shaking method (a 2-1.5" rotating ball horizontally moving back and forth). Furthermore, the authors found that the bioaccessibility obtained from the high-energy method was significantly correlated ($r^2 = 0.81, p < 0.005$) with the bioavailability measured through in-vivo assays using swine. In literature publications, shaking methods are generally not mentioned. Their results indicated that reports on bioaccessibility should provide more information, including the shaking method used. Moreover, to develop a standard in-vitro method, the shaking method is a very important parameter, which should be considered.

4.2. Matrices

In addition to the digestion conditions, the composition of the matrix also has a great influence on HOC bioaccessibility. The present review classifies matrices into two types: dietary food and other matrices ingested accidently. For food, the components, such as lipid contents, protein, and carbohydrates, and cooking treatments have been widely discussed (Liu et al., 2018b; Shen et al., 2016; Yu et al., 2010), although there have also been reports on the influence of solid food size on PBDE bioaccessibility (Lou et al., 2016). For other matrices, generally house dust, surface soil, and soot have been studied, and particle size and organic matter content were important factors. Studies have observed the influences of particle size and organic components, although the latter accounted for only a small percentage compared to inorganic matter in the matrices (Wang et al., 2013a; Yu et al., 2013). Considering the development of studies on bioaccessibility for organic contaminants, this review discusses non-food matrix influence first and then that of food matrices.

4.2.1. Dust, soil, and soot

In the case of non-food matrices, they are generally ingested accidently, especially by hand-to-mouth behavior, or co-ingested by food in which the matrices reside. Particle size and organic matter content, especially for organic carbon and even black carbon, which significant influence desorption and absorption of chemicals in matrices, were generally found to affect HOC bioaccessibility. Particle size can influence HOC aggregation in matrices and their mobilization into digestion solution from matrices (Finley et al., 2009). To investigate the influence of particle size on bioaccessibility, Yu et al. (2013) collected dust samples from air-conditioner filters and determined PBDE bioaccessibility using size-specific dust samples. They found that the PBDE concentrations decreased with increasing dust particle size and that bioaccessibility also showed a similar trend for most PBDEs, that is, increasing dust particle size resulted in decreasing bioaccessibility. Part of this can be attributed to the fact that larger particles have smaller surface area per unit mass. In the study, they also observed that PBDE bioaccessibility tri- to hepta-brominated congeners was positively and significantly correlated with dust properties, including pore volume and surface area (Yu et al., 2013).

Similarly, studies showed that PAEs, PCBs, PAHs, and OCPs have higher bioaccessibility in dust samples with particle size <63 and 63–100 μ m than in dust samples with larger particles (100–150 μ m) (Wang et al., 2013a, 2013b, 2013c, 2013d). These results indicated that if only dust particles with 100–150 μ m were used to assess human health risk by oral ingestion, the resulting bioaccessibility would underestimate the associated risks because of the lower bioaccessibility of the chemicals in particles with these size ranges. As is well known, the digestion process is a kind of competition between absorption and desorption of chemicals onto and from the matrix during the digestion process. The larger pore volume and surface area at unit mass provide more sites where bile salt, which is the important improvement factor influencing bioaccessibility, can act on HOCs, thus leading to higher bioaccessibility.

In addition to particle size, organic matter (OM) also has an important influence. For example, Yu et al. (2012b) found that PBDE bioaccessibility in house dust was negatively correlated with OM content, or in other words, higher OM content led to lower bioaccessibility. A similar result was also observed in a later study, in which the observed linear relationship between PBDE bioaccessibility and OM content incorporated the pore volume of the dust as analyzed using multiple linear regression analysis and considering the size, pore volume, and surface area of particles, as well as the aromaticity and polarity of OMs (Yu et al., 2013). In fact, the results highlighted an essential observation that the influence of particle size on PBDE bioaccessibility is actually the effect of OM and pore volume size. Similar results were also reported by Pan et al. (2016), who found that the bioaccessibility of BDE209 in dust samples was negatively related with OM content.

However, some researchers have investigated the influence of organic carbon (OC) content on bioaccessibility and have found that PAH bioaccessibility in soil had no correlation with OC content (Juhasz et al., 2016b). This might have resulted from the complexity of total organic carbon composition and even that of black carbon. Black carbon (like soot, charcoal, and chars) has high affinity with HOCs such as PCBs and PAHs (McLeod et al., 2004; Meyer et al., 2014), mainly because the planar structure of these chemicals that facilitates their passage through narrow pores and their further combination with pore walls (Semple et al., 2013). For example, Meyer et al. (2014) used the PBET method to determine PAH bioaccessibility in geosorbents (sand, clay, peat, and charcoal) and found the lowest bioaccessibility (0.1% \pm 0.1%) in charcoal and the highest in sand (26.9% \pm 7.5%), indicating that black carbon had potential as an adsorbent to decrease health exposure risk. Biochar is one of the components of soil. Mayer et al. (2016) specially studied the absorption of PAHs by biochar material and competitive sorption between biochar and sorptive sink, and found biochar characterized with high distribution coefficients (K_D) (>10⁶ L/kg) making it as a PAH sink not source. Moreover, further studies on the influence of carbonaceous matter on HOC bioaccessibility and the underlying absorption and desorption mechanisms should be carried out, although it seems to belong to the scope of scientific research of adsorption and desorption.

4.2.2. Food

It is well known that except for water, animal-based food is mainly composed of lipids and proteins, whereas plant-based food is mainly composed of carbohydrates, proteins, and dietary fiber. Food composition has an important influence on HOC bioaccessibility. Yu et al. (2010) found that PBDE bioaccessibility in animal-based food measured by the SHIME method was positively correlated with lipid content and that the bioaccessibility of individual congeners was positively correlated with $\log K_{OW}$ when the lipid content was higher than 5.5%. This is not surprising because PBDEs are highly lipophilic chemicals. Higher lipid content in food would result in more lipids dissolved in the digestion solution containing bile salt, which would lead to high PBDE release and thus to higher bioaccessibility. Therefore, it is logical that higher HOC bioaccessibility would be observed for foods with higher lipid contents. Moreover, Chen et al. (2020) found that lipid (fat) could increase the micellarization and facilitate the chylomicron formation, which made the dilution and transposition of DDT in simulated gastrointestinal tract much easier.

Similarly, lipids (vegetable oil) facilitated the release of pyrethroids in dust and soil samples were also observed, although the authors hypothesized that lipids would decrease the bioaccessibility of pyrethroids. This can be explained by the fact that they used the fraction absorbed onto Tenax as bioaccessibility (Wang et al., 2018a). As is well known, higher lipid content in the digestion solution can facilitate the release of pyrethroids, but can also substantially absorb lipophilic pyrethroids, causing fewer pyrethroids to be absorbed onto the Tenax and thus leading to lower bioaccessibility. Similarly, a positive influence of lipid content on the bioaccessibility of PAHs and PFOA has also been reported (Li et al., 2015b; Yu et al., 2012a). However, Liu et al. (2018b) found that adding 0.4 mL oil had no effect on triazolone bioaccessibility. For plant-based food, the main components of carbohydrates had a positive correlation with PBDE bioaccessibility (Yu et al., 2010). This mainly contributed to the formation of hydrophobic micelles for carbohydrate during digestion, which increased the proportion of PBDEs in the digestion solution, thus improving PBDE bioaccessibility. A similar result was also observed by Wang et al. (2018a), who found that carbohydrates could enhance the bioaccessibility of pyrethroids in dust and soil samples. Therefore, lipids and carbohydrates have generally been found to enhance HOC release and thus lead to higher HOC bioaccessibility.

Unlike the influence of lipids and carbohydrates, negative or uncertain effects were observed for dietary fiber and proteins. For the influence of protein content on bioaccessibility, different results were observed for animal- and plant-based foods. Yu et al. (2010) found that protein in plant-based foods could negatively affect PBDE bioaccessibility, which might be attributed to the hydrolyzation of protein to amino acids, thus enhancing ionic strength against PBDE solubility in the digestion solution. However, Wang et al. (2018a) observed that protein could enhance the bioaccessibility of pyrethroids in dust and soil samples using the CE-PBET method with Tenax as a sink. The discrepancy might attribute to different properties of PBDEs and pyrethroids, although the underlying mechanism needs further study. Moreover, Yu et al. (2010) did not observe a similar influence of protein on PBDE bioaccessibility in animal-based foods. They found no obvious correlation between protein content and PBDE bioaccessibility for animalbased foods. This phenomenon can be mainly attributed to the effect of protein being masked by the influence of lipids in animal-based foods. A significantly positive correlation has been demonstrated between PBDE bioaccessibility and the ratio of protein to lipid content, or in other words, the lipid content-adjusted protein content of animal-based foods (Yu et al., 2010).

Comparatively few investigations of dietary fiber influence on bioaccessibility have been performed. According to a study by Yu et al. (2010), dietary fiber can decrease the bioaccessibility of PBDEs, possibly because dietary fiber consists mainly of insoluble and indigestible cellulose that is hard to digest. This resulted in PBDE adsorption onto the undigested substance, thus lowering bioaccessibility. In addition, because of binding of dietary fiber with bile acids and phospholipids (Orla et al., 2008), dietary fiber can decrease the formation of micelles that can improve HOC bioaccessibility as mentioned earlier. The resulting scarcity of micelles in the digestion solution can decrease HOC bioaccessibility. Similar results have also been reported for different types of dietary fiber, such as β -carotene, lycopene, and lutein, which can decrease the bioavailability of carotenoids in women (Riedl et al., 1999). Recently, Liu et al. (2018b) found that the bioaccessibility of triazolone in the gastric phase decreased as the amount of dietary fiber increased. Currently, our knowledge of the influence of dietary fiber on bioaccessibility is still limited, and more investigations are definitely warranted.

In addition, cooking methods have also been observed to have a significant influence on the bioaccessibility of contaminants. Studies of the influence of cooking methods were conducted early for heavy metals and nutrients (Bugianesi et al., 2004; Laparra et al., 2003). With the development of in-vitro methods to determine the bioaccessibility of pollutants, the first study of the influence of cooking method on HOC bioaccessibility were carried out in recent year. Shen et al. (2016) observed that the bioaccessibility of both PCBs and polychlorinated dibenzo-p-dioxins/furans significantly increased after frying (200-300 °C, 5 min) and boiling (100 °C, 5 min), and that this increasing trend was more clearly observed in vegetables than in animal-based foods because oil facilitates the dissolution of nonpolar contaminants. However, different results were found by Mi et al. (2017), who determined the bioaccessibility of DDTs and PBDEs in fish sample (yellow grouper) with three kinds of treatments (raw, raw with cooking oil, and cooked with oil) using the CE-PBET method. They found that the bioaccessibility of DDTs and PBDEs in raw fish samples increased after oil was added, from 60% to 83% and from 26% to 63%, respectively. However, the bioaccessibility of DDTs and PBDEs in oil-added raw fish samples decreased after cooking, from 83% to 66% and from 63% to 40%, respectively, because cooking facilitated the denaturation of proteins, which could affiliate with lipids.

Because people generally eat cooked food and because studies have used raw food for bioaccessibility determinations, it is necessary to measure the bioaccessibility of pollutants in cooked food and to investigate the influence of cooking methods on bioaccessibility to assess human health risk from contaminants more accurately. In addition, it should be mentioned that different cooking methods may not only affect pollutant concentrations in food (Rose et al., 2015), but also may affect their bioaccessibility. Therefore, in the future, studies of human health risks from pollutants through dietary intake should consider the overall risks by combining the dual effects of cooking methods on the concentrations and bioaccessibility of pollutants.

4.3. Properties of HOCs

It is obvious that HOC solubility can be affected by the hydrophobicity of the chemicals in the digestion solution. Thus, hydrophobicity affects HOC bioaccessibility. The literature offers various results, with some studies observing negative correlations between bioaccessibility and the logK_{OW} of HOCs and other investigations failing to do so. For example, individual PAH bioaccessibility decreased with increasing number of rings, as reported by Khan et al. (2008) and Tang et al. (2006). The higher K_{OW} and lower solubility of high-ring versus low-ring PAHs were the main factors. The same phenomenon has also been reported for PCBs ($r^2 = 0.65-0.93$, p < 0.05) (Kang et al., 2013) and PAEs (Kang et al., 2012) in dust samples. Compared to PAHs with lower hydrophobicity, Tao et al. (2010) observed that PAHs with higher hydrophobicity could bound more intensively with soil organic carbon *via* strong π - π and hydrophobic interactions, which leaded the lower mobility of them in digestive fluid. Moreover, further research discussed the bioaccessibility of PAHs in soils using PBET method (silicone rod as a sink) by Umeh et al. (2019), found that the PAHs with high molecular weight and hydrophobicity moved slower than with low molecular and hydrophobicity, in the interface of digestive fluid-silicone rod fluid, which means longer time (24 h used in this paper) was needed for allowing all the extractable PAHs absorbed into sink.

There are different results for PBDEs reported in the literature. A report by Abdallah et al. (2012) showed that PBDE bioaccessibility in dust samples was negatively correlated with log K_{OW} (p < 0.01), with the

lowest value being 14% for BDE209 and the highest being 32%–58% for tri- to hepta-BDEs. These results were different from those in a study by Yu et al. (2019a), who found that PBDE bioaccessibility in soil had a parabolic correlation with $\log K_{OW}$ ($R^2 = 0.757$). In other words, the bioaccessibility increased first then decreased with increasing $\log K_{OW}$. The discrepancy indicated that factors other than hydrophobicity, such as the original being status in the polymer matrix, affect PBDE bioaccessibility as explained by Yu et al. (2012b), who attributed the much lower bioaccessibility of BDE209 (measured by an adapted SHIME method) than those of lower brominated congeners to its low volatilization (not facilitating its release from matrix). Nevertheless, more attention should be paid on how properties of HOCs impact their bioaccessibility.

4.4. Others

Aging of chemicals in matrices happens under natural conditions over time, which might change the matrix structure and its physiochemical properties (Ltifi et al., 2014), thus influencing bioaccessibility. Actually, there have been studies of these aging effects, which showed that contaminants in aged soil and dust samples were difficult to release into digestive fluid, meaning that HOCs in aged samples usually had lower bioaccessibility than those in non-aged samples (Fang and Stapleton, 2014; Zhang et al., 2018). Fang and Stapleton (2014) investigated the bioaccessibility of FRs (PBDEs and OPFRs) in different house dust samples and found that dust samples collected in 2006 had significantly lower bioaccessibility (p < 0.001) than newly collected samples in 2010 for BDE100, TCIPP, and other chemicals. This might have been because the dust aging process decreased the mobility of HOCs, which was adsorbed onto organic matter. In another study, Zhang et al. (2018) found that aging facilitated the solution of soluble substance in soots, which enhanced their surface area and nanoporosity, so that the contaminants would be in a less labile situation in soot and would be difficult to release into digestion fluid.

In addition to aging, contaminant concentrations might affect bioaccessibility, and some studies have been carried out on this. For example, Yu et al. (2009a) spiked PBDEs into dry fish powders with concentrations of 10-200 ng/g and found that PBDE bioaccessibility was 24.3%-27.4%, which was not related to PBDE concentration. Similar observations were made by Yu et al. (2011a) and Zhang et al. (2015c). Yu et al. (2011a) studied PBDE bioaccessibility in dust samples from home, office, and laboratory floor, and dust samples from airconditioner filters. They found that although PBDE concentrations in filter dust $(6.6-1.32 \times 10^4 \text{ ng/g})$ were much higher than those in floor dust (0.4-30.3 ng/g), the mean bioaccessibility in filter dust was $42.0\% \pm 4.4\%$, which was not obviously different from those in floor dust (36.1% \pm 10.5% to 43.3% \pm 11.2%). Moreover, Zhang et al. (2015c) found that PBDE bioaccessibility in soil samples was not significantly related to spiked PBDE concentrations (100-400 ng/g) in soil. Generally, research results have shown that the bioaccessibility of HOCs are not correlated with their concentrations (Yu et al., 2009a, 2011a; Zhang et al., 2015c).

5. In vitro-in vivo correlations

In human health risk assessment, bioaccessibility and bioavailability are two commonly used absorption factors. In theory, bioaccessibility is greater than bioavailability. However, if bioaccessibility is introduced into health risk assessment, it will be better for the assessment if the bioaccessibility of a pollutant in a matrix measured using an *in-vitro* method is consistent with the bioavailability measured in animals, although there is uncertainty when the *in-vivo* bioavailability is extrapolated to humans. Therefore, to evaluate the human health risks of pollutants more accurately and to know whether bioaccessibility as measured by *in-vitro* methods can be introduced into health risk assessment, it is necessary to compare bioaccessibility with bioavailability obtained from animal assays. To verify an *in-vitro* method used for bioaccessibility measurement, the IVIVC between bioaccessibility and bioavailability is generally evaluated. If a unified *in-vitro* method is developed and evaluated by bioavailability, it may be used as a standard method for management decisions.

Generally, linear correlation analysis between bioaccessibility and bioavailability of a substance in the same matrix is used to evaluate the IVIVC. When bioaccessibility and bioavailability show a significant correlation with $R^2 > 0.8$, a slope of approximately one, and the intercept at nearly zero, this indicates that the in-vitro method would behave well with such a substance in a specific matrix (Wragg et al., 2011; Yu et al., 2019a). As far as current research is concerned, the bioaccessibility and bioavailability results for Pb as determined by the PBET method as modified by Ruby et al. (1996) are relatively consistent (Cadkova et al., 2015; Ngole-Jeme et al., 2016; Turner, 2011). Therefore, the invitro method is also recommended as a national standard method for bioaccessibility determination of Pb in soil in Germany (DIN 19738, 2004). However, there are relatively fewer studies on HOCs, although investigations have been carried out on the relationship between bioaccessibility by in-vitro methods and bioavailability by in-vivo assays (Tables 2-3). On the one hand, the bioaccessibility studies on organic pollutants were carried out later than those on heavy metals, and less data on this. On the other hand, the study on the in vitro-in vivo correlation for organic compounds is more difficult compared with heavy metals, especially for those organic substances that are easy to metabolize, such as PAHs, because it needs to trace all the metabolites of the chemicals.

5.1. PBET

For the PBET method, no significant or strong relationships have been observed between bioaccessibility and bioavailability for many HOCs except for BDE209. For instance, Kang et al. (2018) observed that the PAHs bioaccessibility in house dust (<100 µm) had a poor relationship with bioavailability by *in-vivo* assay using BALB/c mice ($r^2 =$ 0.28-0.38, p = 0.0604-0.1025). Moreover, because of the low bioaccessibility of DDTs (<4%) compared with their high RBA (8.3% \pm 1.1% to $24.3\% \pm 1.1\%$ in liver) with spiked sand using female mice, Smith et al. (2012) found no significant relationship between bioaccessibility and bioavailability. Similarly, Juhasz et al. (2016a) observed the low bioaccessibility (1.6%-3.8%) of DDTs in soil (<250 µm), whereas the RBA (compared with spiked sand) was relatively high (18.7% \pm 0.9% to $60.8\% \pm 7.8\%$). An IVIVC with slope > 15 indicated great discrepancy, even though $r^2 = 0.89$ (the slope between 0.8 and 1.2 and r > 0.8 was fitted). Moreover, Li et al. (2017a) determined the bioaccessibility of PCBs in spiked and aged soil (<250 µm) as 8.0%-40.9% and the RBA (compared with sand) tested in mice as 45%-119%. The relationship between these results was poor ($r^2 = 0.25$, p = 0.09). A similarly poor relationship was also observed for PBDEs (Yu et al., 2019a). These studies indicated that the PBET method does not behave well for predicting bioavailability by bioaccessibility.

However, some results have been slightly better. Li et al. (2015b) investigated the bioaccessibility of PFOA using spiked food (1 mg PFOA/kg) by the PBET method and found values ranging from 9.8% to 99%. Bioaccessibility was not significantly correlated with RBA (food/water) (results varying from $4.3\% \pm 0.80\%$ in corn oil to $69.0\% \pm 11.9\%$ in peas) measured in BALB/c mice. The peas significantly influenced the IVIVC of PBET (r = 0.11), unlike the other 10 types of foods. If the pea data were excluded, the correlation would be strengthened (r = 0.82, p < 0.001).

Furthermore, studies have also investigated the bioaccessibility of flame retardant and DDTs by PBET (Juhasz et al., 2016a; Pan et al., 2016). Pan et al. (2016) studied the bioaccessibility of BDE209 in house dust and found a strong relationship ($r^2 = 0.578$, p = 0.080 for gastric phase; $r^2 = 0.728$, p = 0.031 for intestinal phase) between bioaccessibility and RBA (compared to corn oil) in BALB/c mice. It seems

Table 2

Bioaccessibility of HOCs in various matrices by PBET and CE-PBET methods and related IVIVCs.

Method	Chemical	Sample	Bioaccessibility	IVIVC	Reference
PBET	PAHs	Soil from public areas; Beijing	Gastric phase: 3.9%–54.9%	No	Tang et al.,
PBET	PAHs	Dust of house (<100 µm); Guangzhou	Phe: 15%-43.5% Flu: 9.0%-38.8% Pyr: 10.0%-37.9%	BALB/c mice Poor relationship ($r^2 = 0.28-0.38, p = 0.0604-0.1025$)	2000 Kang et al., 2018
PBET+ Tenax	PAHs	Contaminated soils	3.7%-6.92% to 16.3%-31.0% (mean) without Tenax	No	Li et al., 2015a
PBET	DDTs	Soil	<4%	RBA in female mice: $8.3\% \pm 1.1\%$ – $24.3\% \pm 1.1\%$ in liver	Smith et al.,
PBET	DDTs	Soil (<250 µm)	1.6%-3.8% (<4%)	RBA in mice: $18.7\% \pm 0.9\%$ - $60.8\% \pm 7.8\%$; not good ($r^2 = 0.89$, slope > 15)	2012 Juhasz et al., 2016a
PBET+ silicone rod	DDTs		1.6%–3.8% without silicone rod, increased by 19 folds with silicone	RBA in mice; great related after using Tenax ($r^2 = 0.79$, slope = 0.94, y-intercept = 3.5)	Juhasz et al., 2016a
PBET+ Tenax	DDTs	Soil	27%-56% with Tenax, which is 3.4-22 times of the data without Tenax	No	Li et al., 2016
PBET	PCBs	Spiked and aging soil (<250 µm)	8.0%-40.9%	RBA in mice: 45%–119%; poor relationship ($r^2 = 0.25$, $p = 0.09$)	Li et al., 2017a
PBET+ Tenax	PCBs	Soil	3.0%–63.1% using Tenax	No	Li et al., 2017a
PBET	PFOA	11 types of foods	9.8%-99%	RBA in BALB/c mice: $4.3\% \pm 0.80\%$ (corn oil)– 69.0% $\pm 11.9\%$ (pea); r = 0.82, p < 0.01 (exclude the bioaccessibility of pea)	Li et al., 2015b
PBET	BDE209	Dust of house (<100 μm); Guangzhou	Gastric phase: $9.3\% \pm 1.8\%$ to $39.0\% \pm 4.4\%$ Intestinal phase: $50.7\% \pm 1.2\%$	No	Pan et al., 2016
PBET	PBDEs	Soil from e-waste	1%-6%	RBA in C57BL/6 mice: 1.7%–38.1% No significant relationship	Yu et al., 2019a
PBET	OPFRs and PAEs	Dust of indoor environments (office, house, dorm) (<150 µm)	OPFRs: 8.18% (TPP) to 54.5% (TCPP) PAEs: 1.21% (DEHP) to 81.1% (DMP)	No	He et al., 2016
PBET	FRs	Dust of indoor environments of different particle size	OPRFs:1.8%–82% (mean) NBFRs, DPs: not be detected for low hydrophobicity	No	He et al., 2018b
CE-PBET	BFRs	(~2000 μm); UK Dust (25–500 μm); UK	HBCD: 72%–80% TBBPA: 94% Tri- to hepta-BDE: 32%–58% BDF200•. 14%	No	Abdallah et al., 2012
CE-PBET	OPFRs and BFRs	SRM2585 (<53 μm)	10% (BEH-TEHP) to more than 80% (TCEP); <20% (PBDEs)	RBA in Sprague-Dawley rats No relationship for much lower bioaccessibility	Fang and Stapleton, 2014
CE-PBET+ Tenax	Pyrethroids	Dust and soil	Bifenthrin: 18.2%–35.7% (mean: 26.6%) without Tenax All 8 pyrethroids: 6.0%–48.0% (no Tenax), 21.5%–79.3% with Tenax (increased by 1.6–4.1 times)	No	Wang et al., 2018a
CE-PBET	DDTs and PBDEs	Yellow grouper fish from Guangdong	DDTs: 60% PBDEs: 26%	No	Mi et al., 2017
CE-PBET+ silicone rod	PAHs		Extract PAHs ability increased by 1–3 orders of magnitude with using silicone	No	Gouliarmou et al., 2013

BaP: benzo(*a*)pyrene; BDE209: decabromodiphenyl ether; BEH-TEHP: bis (2-ethylhexyl) tetra bromophthalate; BFRs: brominated flame retardants; CE-PBET: colon extended physiologically based extraction test; DDTs: DDT (dichlorodiphenyltrichloroethane) + DDE (dichlorodiphenyldichloroethylene) + DDD (chlorodiphenyldichloroethane); DEHP: di-2-ethylhexyl phthalate; DMP: dimethyl phthalate; DPs: dechlorane plus; Flu: fluorene; FRs: flame retardants; HBCD: hexabromocyclododecane; IVIVC: *in vitro-in vivo* correlation; NBFRs: novel brominated flame retardants; NOM: natural organic matter; OPFRs: organophosphorus flame retardants; PAEs: phthalate esters; PAHs: polycyclic aromatic hydrocarbons; PBDEs: polybromodiphenyl ethers; PBET: physiologically based extraction test; PCBs: polychlorinated biphenyls; PFOA: perfluorooctanoic acid; Phe: phenanthrene; Pyr: pyrene; RBA: relative bioaccessibility; SRM2585: standard reference material 2585; TBBPA: tetrabromobisphenol A; TCEP: tris (2-chloroethyl) phosphate; TCPP: tris(2-chloroisopropyl) phosphate; TPP: triphenyl phosphate; UK: United Kingdom.

that the PBET method is useful to predict the RBA of BDE209. To the authors' knowledge, the PBET method was derived from studies on heavy metals. If the method is not improved to measure HOC bioaccessibility, low IVIVC is generally to be expected. Fortunately, Juhasz et al. (2016a) introduced a silicone cord into the PBET method as an absorptive sink and found a significant correlation between the silicone cord-improved bioaccessibility of DDTs and the RBA in mice ($r^2 = 0.79$, slope = 0.94, *y*-intercept = 3.5). Considering the rarity of studies on this topic, further improvements and investigations should therefore be carried out so that the PBET method can be used to determine HOC bioaccessibility.

5.2. RIVM

The RIVM method is not widely used for HOCs, and therefore the number of IVIVC study is also limited. Still, there have been reports for PAHs in soil. Smith et al. (2008) used the RIVM method to determine PAH bioaccessibility using standard spiked soil and observed that the bioaccessibility of naphthalene, acenaphthene, acenaphthylene, anthracene, Phe, Flu, and DBahA were 60%–85%, in contrast to other priority controlled PAHs (<30%), which were comparable with *in-vivo* data from rats in the literature. The authors believed that the RIVM method was suitable to evaluate PAH bioaccessibility

Table 3

Bioaccessibility of HOCs in various matrices by other GI methods and related IVIVCs.

methou	Cheffical	Sample	bioaccessibility	IVIVC	Reference
RIVM	PAHs	Standard spiked soil (OCED, 1984)	<30% and 60%-85%	No But comparable to other researches <i>in vivo</i> rat	Smith et al., 2008
RIVM (fed: infant formula)	PAHs	Soils		RBA in mice; BaP: 36%–55% (linear relationship); DBahA: 7%–30% (no correlation because limited 3 camples)	Grøn et al., 2007
FOREhST (food: original HIPP porridge)	PAHs (7 types)	Soil remediated after polluted by creosote (<250 µm)	<4%	RBA in mice (84.0% ± 1.3%) No relationship	Juhasz et al., 2014
FOREhST	PAHs	Soil	13% to 29% (30 rpm energy input)	RBA in swine (AUC48); significantly correlation $(r^2 = 0.81, p < 0.005 \text{ and the slope} = 0.34)$	James et al., 2018
FOREhST	DDTs	Soil	<4%	RBA in mice (2%–25%) No correlation	Smith et al., 2012
FOREhST (food: organic cream)	Chlorinated organophosphate esters	Dust from indoor (house, car)	TCEP: 50%-103%	No	Quintana et al., 2017
IVG	PBDEs	Soil from e-waste contaminated spots	1%-20%	RBA in C57BL/6 mice: 1.7%–38.1%; No significant relationship	Yu et al., 2019a
IVG+ C18	Phe	NOM (cutin and cutan) spiked with Phe	83.1% \pm 4.7% in cutin; 35.7% $+$ 2.9% in cutan	No	Hurdzan et al., 2008
DIN	PAHs and PCBs	Soil	5%-40%	No	Hack and Selenka, 1996
DIN	PBDEs	Soil from e-waste contaminated spots	2%-16%	RBA in C57BL/6 mice: 1.7%–38.1% No significant relationship	Yu et al., 2019a
UBM	PBDEs	Soil from e-waste	1%-14%	RBA in C57BL/6 mice: 1.7%–38.1% No significant relationship	Yu et al., 2019a
UBM	PFOA	Food	8.7%-73%	RBA in mice Strong relationship ($r = 0.79, p < 0.01$, slope = 0.79, y-intercept = 11.7)	Li et al., 2015b
UBM	DDTs	Soil	<45	RBA in mice: 2%–25%	Smith et al., 2012
UBM-like (fast condition)	Chlorinated organophosphate esters	Dust from indoor (house, car)	TCEP: 103% (cabin dust), 69% (house dust)	No	Quintana et al., 2017
SHIME	PAHs	Soil	Gastric phase: 0.44% Small intestinal phase: 0.13% Large intestinal phase: 0. 3%	No	Van de Wiele et al., 2004
SHIME	PAHs	Soil (<45 µm); Canada	Gastric and small intestinal phase: <8% Colon phase: 1.2%-21%	No	Siciliano et al., 2010
SHIME	Bisphenol A	Nutritional medium (CK) spiked with bisphenol A for 10 davs	Decrease with digestion progress (stomach, small intestinal, colon)	No	Wang et al., 2018b
Ad-SHIME (Fa-VDM)	PBDEs	Soil from e-waste contaminated spots	2%-42%	RBA in C57BL/6 mice: 1.7% -38.1%; significant relationship: $\mathbb{R}^2 > 0.73$, slope = 0.83-1.16	Yu et al., 2019a
SHIME+ Caco-2	Pesticides	Apple	Gastric phase: 25.2%–76.3% Intestinal phase: 10.6%–79.6% Only difenoconazole can permeate cross the Caco-2 cell	No	Shi et al., 2017
SHIME	Triazolone	Cherry tomatoes	Gastric phase: 32.5%–67.4% Intestinal phase: 31.0%–41.3%	No	Liu et al., 2018b
	RIVM (fed: infant formula) FOREhST (food: original HIPP porridge) FOREhST FOREhST FOREhST (food: organic cream) IVG IVG+ C18 DIN UBM UBM UBM UBM UBM UBM UBM SHIME SHIME SHIME Ad-SHIME (Fa-VDM) SHIME+ Caco-2 SHIME	RIVMPAHsRIVM (fed: infant formula)PAHsFOREhST (food: original HIPP porridge)PAHs (7 types)FOREhSTPAHsFOREhSTDDTsFOREhST (food: organic cream)Chlorinated organophosphate estersIVGPBDEsIVG+ C18PheDINPAHs and PCBsUBMPBDEsUBMDDTsUBMDDTsUBMDDTsUBMDDTsSHIMEPAHsSHIMEPBDEsSHIMEPBDEsSHIMEPBDEsSHIMEPBDEsSHIMEPAHsSHIMEPBDEsSHIMEPBDEsSHIMEPAHsSHIMEPAHsSHIMEPAHsSHIMEPBDEsSHIMEPAHSSHIMESHIMESHIMETriazolone	RIVMPAHsStandard spiked soil (OCED, 1984)RIVM (fed: infant formula)PAHsSoilsFOREhST (food: original HIPP porridge)PAHs (7 types)Soil remediated after polluted by creosote (<250 µm)	RIVM PAHs Standard spiked soil (OCED, 1984) <30% and 60%-85%, 1984) RIVM (fed: infant formula) PAHs Soils FORENST (food: original HIPP porridge) PAHs (7 types) Soil remediated after polluted by creosote (<250 µm)	RVM PAHs Standard spiked soli (OCED, 1994) <30% and 60%-85% solis No Bat comparable to other researches <i>in vivo</i> rat results RDA in mice: BA? 55% (linear relationship); DBLA? 72-30% (no correlation because limited 3 samples) FOREIST (food: original HIPP portigie) PAHs Soil <4%

Ad-SHIME: advanced simulator of the human intestinal microbial ecosystem; BaP: Benzo(*a*)pyrene; BDE209: decabromodiphenyl ether; DBahA: dibenz(*a*,*h*)anthracene; DDT: DDT (dichlorodiphenyltrichloroethane) + DDE (dichlorodiphenyldichloroethylene) + DDD (chlorodiphenyldichloroethane); Fa-VDM: fasting *in vitro* digestion method; FOREhST: fed organic estimation human simulation test; FRs: flame retardants; IVIVC: *in vitro-in vivo* correlation; PAEs: phthalate esters; PAHs: polycyclic aromatic hydrocarbons; Phe: phenanthrene; RBA: relative bioaccessibility; RIVM: Dutch National Institute for Public Health and the environment; TCEP: tris (2-chloroethyl) phosphate.

in soil. However, different results were observed by Grøn et al. (2007), who used a fed RIVM method including infant formula to test relative PAH bioaccessibility (the bioaccessibility in soil *versus* data for wheat flour spiked with PAHs) in contaminated soil. The relative bioaccessibility of 36%–55% for BaP and 7%–30% for DBahA were found to be much higher than the RBA (polluted soil/soil mixed with power diet or gel diet) of 0.22%–3.9% for BaP and 0.08%–0.99% for DBahA. There were no significant linear relationships between bioaccessibility and RBA except for BaP. The RIVM method involves a complex preparation procedure, which has limited its application, and information on IVIVC is therefore scarce. Considering the poor correlations obtained, the FOREhST method (modified by RIVM) has been used instead.

5.3. FOREhST

The FOREhST method mimics a fed digestion condition, similar to fed-RIVM. There was, however, the dilemma that estimated HOC bioaccessibility was much lower than *in-vivo* data. Smith et al. (2012) found that DDT bioaccessibility in soil was less than 4%, which was lower than the RBA (2%–25%) because of the dynamic nature of digestion in the *in-vivo* assay. Similarly, Juhasz et al. (2014) tested PAH bioaccessibility in soil of <4% for seven PAHs, which was much lower than the RBA (soil/spiked sand) (84.0% \pm 1.3%) in mice. However, James et al. (2018) investigated PAH bioaccessibility in polluted soil and obtained a range of 13%–29%. These values were significantly correlated with the RBA (AUC48 swine), with $r^2 = 0.81$, p < 0.005, and slope = 0.34. The

variation in results suggests the need for more investigations. In addition, to the authors' best knowledge, there are no reports of the introduction of absorptive sinks into the FOREhST method. Further modifications of FOREhST are needed to enhance its usability.

5.4. Other in-vitro methods

As for other *in-vitro* gastrointestinal methods like SHIME, IVG, DIN, and UBM, *in-vivo* verification experiments have been carried out on the IVIVC for organic pollutants, but there are very few reports. For example, Yu et al. (2019a) determined PBDE bioaccessibility in SRM2585 and soil using five *in-vitro* methods (PBET, DIN, UBM, IVG, and adapted SHIME) and compared the results with PBDE bioavailability determined in female C57BL/6 mice. The results found that only the adapted SHIME (Fa-VDM) method showed a high correlation of results with *in-vivo* assays ($R^2 > 0.73$, slope = 0.83–1.16) for some congeners, including BDE47, BDE99, BDE100, and BDE153. Li et al. (2015b) found that the bioaccessibility of PFOA in foods tested by UBM was strongly correlated with *in-vivo* data for rats (r = 0.79), but results from PBET and IVD (r = 0.11-0.22) showed poor correlations with bioavailability.

Few researchers have carried out *in-vivo* experiments to verify the CE-PBET method, even though it is widely used. The same phenomenon was observed in the CE-PBET method provided with absorptive sinks like silicone rods and Tenax. Therefore, verifications on CE-PBET with absorptive sinks are urgently needed to evaluate the performance of these methods and their potential capabilities for bioavailability estimation. In addition, studies also have reported that colon components had a potential influence on the lipid sink, which will affect their performance.

6. Applications in human exposure and health risk assessments

It has been more than 30 years since *in-vitro* methods mimicking human digestion were first used to evaluate the bioaccessibility of pollutants in the human gastrointestinal tract. The associated bioaccessibility determined with these *in-vitro* methods has become an important parameter for assessing human daily exposure by oral ingestion and performing the associated health risk assessment. However, no uniform standard for these *in-vitro* methods currently exists for organic contaminants, and there are obvious differences between the bioaccessibility obtained from *in-vitro* methods and the bioavailability measured by animal assays, although some results have shown good IVIVC. To assess human exposure and health risk more accurately, many studies have introduced the bioaccessibility determined from *in-vitro* methods into the assessment. Incorporation of these bioaccessibility measures has attracted more and more attention.

6.1. Human exposure assessment

A human exposure assessment for pollutants is generally calculated from the intakes of pollutants from all kinds of exposure pathways, including dermal contact, inhalation, and oral ingestion, for one person per day. The assessment of pollutant exposure is usually calculated by the chemical concentration in a matrix, the mass of the matrix ingested per day, and the absorption factor of the chemical in the human body. Generally, the absorption factor by the gastrointestinal tract is replaced by bioaccessibility or bioavailability. With the development of the investigation of pollutants, two type of daily exposure data were reported. One is the data not considering the bioaccessibility (or bioavailability), i.e., estimated daily intake (EDI). Another is that the factor is factored into the estimation. For the latter, there are different names used in the literature. Both corrected estimated daily intake and estimated daily uptake (EDU) were used (Shen et al., 2016; Liu et al., 2018a). For better differentiation, EDI and EDU were used to indicate the daily exposure dose not added the absorption factor and that considered the bioaccessibility (or bioavailability), respectively, in the present review. Currently, daily intakes of HOCs, such as PBDEs, PAHs, PCBs, OPFRs, BFRs, and pesticides, in all kinds of matrices including food, dust, and soil have been studied (Liu et al., 2018a; Shen et al., 2016; Yu et al., 2011b, 2012b). A trend has developed that more and more researchers are adding the absorption factor into their assessments. The EDI and EDU can be calculated by the following equations:

$$EDI = C_{HOC} \times IngR \tag{4}$$

or

$$EDI = \frac{C_{HOC} \times IngR}{BW}$$
(5)

$$EDU = C_{HOC} \times IngR \times Bioa \text{ (or Biov)}$$
(6)

or

$$EDU = \frac{C_{HOC} \times IngR \times Bioa \text{ (or Biov)}}{BW}$$
(7)

where EDI (ng/day or ng/kg-bw/day) and EDU (ng/day or ng/kg-bw/ day) is the estimated daily intake and uptake, respectively; BW (kg) is the body weight; C_{HOC} (ng/g) represents the HOC concentration in the matrix; IngR (g/day) means the daily ingestion rate of the matrix; Bioa (%) and Biov (%) represents the bioaccessibility and bioavailability, respectively.

In 2008, Smith et al. (2008) proposed that some kind of bioaccessibility concept could be incorporated into site-specific PAH risk assessment, but that further development would be needed. Later, Yu et al. (2011b) first applied bioaccessibility to human health risk assessment from PBDEs in foods. After that, more and more studies have factored bioaccessibility into human HOC exposure assessment in some matrices, including food, dust, and soil (Table 4). As expected, the EDU of these chemicals was lower than EDI when bioaccessibility was added to the calculations. For example, the EDI of PAHs according to animalbased food consumption from Shanghai markets was 848 ng/day, whereas the EDU decreased to 297 ng/day, which amounted to a decrease of approximately 65% after PBDE bioaccessibility was considered (Yu et al., 2012b). Similarly, Shen et al. (2016) reported that the gross EDI of dioxin/PCBs from eating all kinds of foods (according to total dietary research in China) was 112 pg WHO-TEQ/day (World Health Organization-toxicity equivalent quantity), but the EDU decreased by 88% when foods were boiled and 63% when they were fried after bioaccessibility was considered.

Other than food, unintentional intake of dust and soil has been widely reported, especially for infants or children because they are more likely to ingest house dust unconsciously by hand-to-mouth behavior than adults. For example, Pan et al. (2016) used Caco-2 cells to evaluate the absorption factor through the intestinal wall of BDE209 in house dust and found that the EDU was 31.9–177 ng/day for children and 0.3–97.4 ng/day for adults when the absorption factor (42%) was added to the calculations. Yu et al. (2012b) found that the EDI of PBDEs ranged from 22.5 to 193 ng/day for children, but that the EDU decreased to 4.3-40.6 ng/day. Similar results were found for adults, although the values were lower than for children, which can be mainly attributed to less EDI of dust for adults than for children. Similarly, Liu et al. (2018a) investigated PAHs in dust samples of diverse particle sizes (<2000 µm) from various indoor environments. The average EDI of PAHs based on the TEQ of BaP was 1.09-15.0 ng/kg-bw/day, but the EDU decreased to 0.02-0.21 ng/kg-bw/day, or one or two orders of magnitude less after considering bioaccessibility. In fact, similar decreases in EDI after considering bioaccessibility have already been observed for other chemicals such as NBFRs, DP, FRs, and OPFRs (He et al., 2016; 2018).

Table 4

Estimated daily intake, estimate daily uptake and risk assessments of HOCs in various matrices.

Chemical	Sample	Bioaccessibility	EDI and EDU	Risk assessment	Suggestions	Reference
PAHs	Animal-based foods, Shanghai markets	29.0%-61.2%	847.8 ng/day; 297.2 ng/day (considering bioaccessibility), decreased by 65%	No	Induce the intake of snail is necessary for high PAHs exposure risk	Yu et al., 2012a
PAHs	Indoor dust (in different particles sizes)	Highest in 200–2000 μm, like in car dust, 57.6% (200–2000 μm), 20.1%–29.0% (other particle size)	1.09–15.0 ng/kg/d; 0.02–0.21 ng/kg/d (considering bioaccessibility)	No	Particle size is an essential factor when accessing bioaccessibility	Liu et al., 2018a
Dioxin/PCB	All foods eating normally	PCBs: $4.2\% \pm 0.9\%$ (cabbage)-72.3% \pm 1.6% (milk powder), boiling treatment; PCDD/Fs: $1.9\% \pm 0.7\%$ (cabbage)-28.4% \pm 1.2% (milk powder), boiling treatment	112 pg WHO-TEQ/day, decreased by 88% for boiled foods, and by 63% for frying food (considering bioaccessibility)	No	Applying bioaccessibility to modify TEQ can reduce the calculation uncertainty	Shen et al., 2016
OPFRs and PAEs	Indoor dust	OPFRs: 8.18%–54.5%; PAEs: 1.21%–81.1%	EDI of OPFRs for adults and infants < RfD, EDI of DEHP for infants > RfD (20 µg/kg'd), EDI of DEHP for infants > RfD (modified by bioaccessibility)	No	Considering bioaccessibility is important on risk assessment	He et al., 2016
PAHs	28 urban parks in Guangzhou	100%	No	22 of 28 parks (78.57%) soil showed high risk (> 10^{-4}) for users with various ages	Remediation measures should be taken based on such risk assessment	Ke et al., 2017
PAHs	8 PAHs contaminated soil in Lagos and Nigeria	0.1%-41%	Less than in foods	Cancer risk 5.5×10^{-10} - 4.1×10^{-7} (very low level, considering bioaccessibility)	No	Adetunde et al., 2018
PBDEs, PCBs, OCPs, PAHs	Meats, Shanghai markets		For multiple food, for adults 0.05–58.1 ng/kg/d, for children 0.06–66.6 ng/kg/d (considering bioaccessibility)	HQ for children 0.015–0.33, for adults 0.017–0.38; HQ for children 0.009–0.21, for adults 0.01–0.24 (considering bioaccessibility); No non-cancer risk for children and child (for HQ < 1)	No	Lei et al., 2015
PBDEs and DDTs	Fish, Guangdong	DDTs: 60% (raw fish), 83% (raw fish with oil), 66% (cooked); PBDEs: 26% (raw fish), 63% (raw fish with oil), 40% (cooked)	No	Non cancer risk for children (HQ: 0.76 (raw fish)–0.85 (cooked fish), <1)	less than 19 times a month (95% CI) for under accepted 10 ⁻⁵ cancer risk	Mi et al., 2017
PAEs	House dust, HK and Guangdong	Gastric phase: 0.68%-7.64% (mean: 3.21%) Intestinal phase: 1.44%-19.0% (mean: 7.71%)	EDI: for adults, higher than DEHP RfD (20 µg/kg'd) in moderate consumption rate, for children, less than DEHP RfD, in moderate consumption rate	Cancer risk 1.11×10^{-5} - 2.52×10^{-4} (high level), 2.23×10^{-6} - 3.77×10^{-5} (concerning level, after considering bioaccessibility)	Indoor dust for DEHP exposure should be noticed	Wang et al., 2013a

CI: confidence index; DDT: dichlorodiphenyltrichloroethane; DEHP: di-2-ethylhexyl phthalate; EDI: estimated daily intake; HK: Hong Kong; HQ: health quotient; OCPs: organochlorine pesticides; OPFRs: organophosphorus flame retardants; PAEs: phthalate esters; PAHs: polycyclic aromatic hydrocarbons; PBDEs: polybromodiphenyl ethers; PCBs: polychlorinated biphenyls; PCDD/Fs: polychlorinated dibenzo-p-dioxins/furan; RfD: reference dose; TEQ: toxicity equivalent quantity.

6.2. Human health risk assessment

As proposed by the United States Environmental Protection Agency, risk assessment can be divided into two groups: non-carcinogenic risk for non-carcinogens (usually acute exposure) by the hazard quotient (HQ) method, and cancer risk (CS) for carcinogens through the lifetime cancer risk approach (usually lifelong exposure for 70 years). HQ and CS can be calculated as follows:

$$HQ = \frac{EDI \text{ or } EDU}{RfD}$$
(8)

$$CS = CSF \times EDI (or EDU)$$
(9)

where HQ (dimensionless) and CS (dimensionless) is the hazard quotient and cancer risk considering the non-carcinogenic and carcinogenic effect endpoints, respectively; EDI and EDU is the estimated daily intake and uptake mentioned above, respectively; RfD (ng/kg-bw/day) is the reference dose meaning the maximum permissible risk for human to expose; CSF ((ng/kg-bw/day)⁻¹) is cancer risk factor. An HQ value <1 means no obvious exposure risk; cancer risk <10⁻⁶ means acceptable risk, 10⁻⁶–10⁻⁴ means a potential risk, but one that can be accepted, and >10⁻⁴ means unacceptable.

Undoubtedly, the estimated exposure risk to a chemical will be reduced after applying bioaccessibility into risk assessment. For example, Lei et al. (2015) found that the HQs of PAHs through livestock, poultry, fish, and shellfish consumption were 0.015–0.33 for children and 0.017–0.38 for adults in Shanghai, but they decreased to 0.009–0.21 and 0.01–0.24, respectively, when bioaccessibility was added to the assessment. Wang et al. (2013a) investigated the DEHP in house dust in Hong Kong and Guangzhou and found that the risk level was 1.11×10^{-5} – 2.52×10^{-4} for residents under high dust ingestion rate, but decreased to 2.23×10^{-6} – 3.77×10^{-5} after considering bioaccessibility. However, the accuracy of this evaluation method is questionable because certain problems remain to be faced for *in-vitro* methods measuring bioaccessibility.

6.3. Limitations and importance of application to health risk assessment

Nowadays, more and more studies are applying bioaccessibility to human exposure and health risk assessments of pollutants (Adetunde et al., 2018; He et al., 2016; Lei et al., 2015; Shen et al., 2016; Umeh et al., 2019; Wang et al., 2013a; Yu et al., 2011b, 2012b). However, at present, there is no standard unified method for bioaccessibility measurement of organic contaminants. Researchers have generally used various *in-vitro* methods that differ widely from one another, although some of these have been validated using animal assays. In order to evaluate the accuracy of the results, both for exposure assessment and for HOC risk assessment must keep be kept in perspective. The authors believe that investigation of relative HOC bioaccessibility from different matrices may be more meaningful than directly using bioaccessibility for exposure and risk assessment.

For example, Yu et al. (2011b) found that the contribution of PBDEs in different foods to human exposure varied because of different concentrations and consumption rates. When PBDE bioaccessibility was not considered, *i.e.*, the chemicals were assumed to be 100% absorbed by humans, the contributions of vegetables, fish, shellfish, and meat to human PBDE exposure were 49.2%, 34.0%, 4.4%, and 12.3%, respectively, which showed that vegetables were the most important source for human exposure to PBDEs. However, the contributions of vegetables, fish, shellfish, and meat were 38.3%, 51.8%, 2.4%, and 7.5%, respectively, when PBDE bioaccessibility was added to the estimation procedure. The most important source changed from vegetables to fish because of higher PBDE bioaccessibility in fish. The results indicated that if bioaccessibility effectiveness is not considered, the result may be incorrect source identifications of human exposure to pollutants. Similar results were found in other studies (Lei et al., 2015; Yu et al., 2012c).

7. Summary and perspective

At present, many *in-vitro* methods are used to study the bioaccessibility of organic contaminants. Studies have investigated various factors affecting bioaccessibility and have optimized and verified *in-vitro* methods on the basis of bioavailability obtained from *in-vivo* assays. Procedures to apply *in-vitro* methods to determine HOC bioaccessibility and to factor bioaccessibility into human exposure and risk assessment have been rapidly developed in the past two decades. The major advantages of *in-vitro* methods for bioaccessibility measurement are that they are convenient, cheap, and ethical. Still, further investigations of HOC bioaccessibility are urgently needed because many challenges for *in-vitro* methods remain to be overcome.

Firstly, it should notice that for chemical analysis, some researchers spiked certain concentration of standards into samples, further determined the bioaccessibility of the chemicals (Li et al., 2015b; Kang et al., 2018; Zhang et al., 2015c). However, there can be very large differences in the bioaccessible fraction between spiked and native compounds, mainly for the different being of them in samples and behaving when digested (Yu et al., 2013). Moreover, differences between high and low exposure concentrations should be considered, which had different effect on the microbial community of intestine (Wang et al., 2018b). So it has a great uncertainty to extrapolate the actual bioaccessibility of native contaminants at lower concentrations from the bioaccessibility of spiked contaminants, more researches are needed to solve this problem.

Secondly, almost all *in-vitro* methods are derived from methods that test the bioaccessibility of trace elements based on partition equilibrium. However, the properties of organic and inorganic materials are quite different, especially for HOCs, because simulated human gastrointestinal digestion solutions are a kind of aqueous solution. The solubility of HOCs in the digestion solution can have a significant influence on HOC bioaccessibility. In contaminated dust, soil, and sediment samples, the organic carbon and biochar carbon can significant influence the chemical distribution and desorption, related desorption and absorption mechanism studies between chemicals and matrices are needed. Further, if partition equilibrium is reached, but the bioaccessible HOCs have not yet been completely released, the result will be an underestimation of bioaccessibility.

Thirdly, as discussed earlier, many digestion conditions, including the composition and pH of the digestion solution, digestion time, and S/L ratio, have a significant influence on bioaccessibility. However, at present, there is no standard *in-vitro* method for HOCs, which poses a dilemma for researchers in that there are many *in-vitro* methods and various bioaccessibility data from different methods.

Fourthly, most currently available HOC bioaccessibility data have been determined for one type of compounds rather than under the condition of co-exposed HOCs. Interactions (desorption, solubility, and cellular response) can also influence bioaccessibility among chemicals, especially for those having similar molecular weight and structure (James et al., 2018). However, the number of studies on interactions is still far too limited.

Finally, even though the bioaccessibility of many HOCs has been determined using current *in-vitro* methods, their accuracies are still limited because many results have shown that the IVIVCs are generally poor, which indicates the limitations on using bioaccessibility to predict HOC bioavailability. To enhance the IVIVC, researchers must not only optimize digestion conditions, including adding absorptive sinks or developing new materials as sinks, but also must understand the dynamic process of ingestion and the mechanism of HOC transportation through intestinal cells. Furthermore, there are substantial differences between the human gastrointestinal tract and those of animals. If scientists obtain enough data, mathematical statistical methods to estimate bioavailability relationships between humans and animals may become possible. Uncertainty also requires further attention.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

- Abdallah, M.A.E., Tilston, E., Harrad, S., Collins, C., 2012. In vitro assessment of the bioaccessibility of brominated flame retardants in indoor dust using a colon extended method of the human gastrointestinal tract. J. Environ. Monit. 14 (12), 3276–3283. https://doi.org/10.1039/c2em30690e.
- Adetunde, O.T., Mills, G.A., Olayinka, K.O., Alo, B.I., 2018. Bioaccessibility-based risk assessment of PAHs in soils of different anthropogenic activities in Lagos, Nigeria using the fed organic estimation human simulation test method. Soil Sentiment Contam. 27 (6), 501–512. https://doi.org/10.1080/15320383.2018.1488239.
- Basta, N., Gradwohl, R., 2000. Estimation of Cd, Pb and Zn bioavailability in smeltercontaminated soils by a sequential extraction procedure. Soil and Sediment Contamination (formerly Journal of Soil Contamination) 9 (2), 149–164. https://doi.org/ 10.1080/10588330008984181.
- Bonvallot, N., Mandin, C., Mercier, F., Bot, B.L., Glorennec, P., 2010. Health ranking of ingested semi-volatile organic compounds in house dust: an application to France. Indoor Air 20 (6), 458–472. https://doi.org/10.1111/j.1600-0668.2010.00667.x.
- Bramwell, L., Glinianaia, S.V., Rankin, J., Rose, M., Fernandes, A., Harrad, S., Pless-Mulolli, T., 2016. Associations between human exposure to polybrominated diphenyl ether flame retardants via diet and indoor dust, and internal dose: a systematic review. Environ. Int. 92/93, 680–694. https://doi.org/10.1016/j.envint.2016.02.017.
- Breivik, K., Sweetman, A., Pacyna, J.M., Jones, K.C., 2002. Towards a global historical emission inventory for selected PCB congeners-a mass balance approach: 1. Global production and consumption. Sci. Total Environ. 290 (1/3), 181–198. https://doi.org/ 10.1016/S0048-9697(01)01075-0.
- Breivik, K., Sweetman, A., Pacyna, J.M., Jones, K.C., 2007. Towards a global historical emission inventory for selected PCB congeners a mass balance approach-3. An update. Sci. Total Environ. 377 (2/3), 296–307. https://doi.org/10.1016/j. scitotenv.2007.02.026.
- Bugianesi, R., Salucci, M., Leonardi, C., Ferracane, R., Catasta, G., Azzini, E., Maiani, G., 2004. Effect of domestic cooking on human bioavailability of naringenin, chlorogenic acid, lycopene and beta-carotene in cherry tomatoes. Eur. J. Nutr. 43 (6), 360–366. https://doi.org/10.1007/s00394-004-0483-1.
- Cadkova, Z., Szakova, J., Miholova, D., Horakova, B., Kopecky, O., Krivska, D., Langrova, I., Tlustos, P., 2015. Bioaccessibility versus bioavailability of essential (Cu, Fe, Mn, and Zn) and toxic (Pb) elements from phyto hyperaccumulator Pistia stratiotes: potential

risk of dietary intake. J. Agric. Food Chem. 63 (8), 2344-2354. https://doi.org/ 10.1021/jf5058099.

- Cao, P.Q., Fujimori, T., Juhasz, A., Takaoka, M., Oshita, K., 2020. Bioaccessibility and human health risk assessment of metal(loid)s in soil from an e-waste open burning site in Agbogbloshie, Accra, Ghana. Chemosphere 240, 124909. https://doi.org/10.1016/j. chemosphere.2019.124909.
- Cave, M.R., Wragg, J., Harrison, I., Vane, C.H., Van de Wiele, T., Groeve, E.D., Nathanail, C.P., Ashmore, M., Thomas, R., Robinson, J., Daly, P., 2010. Comparison of batch mode and dynamic physiologically based bioaccessibility tests for PAHs in soil samples. Environ. Sci. Technol. 44 (7), 2654–2660. https://doi.org/10.1021/es903258v.
- Chen, Z.J., Liu, H.Y., Cheng, Z., Man, Y.B., Zhang, K.S., Wei, W., Du, J., Wong, M.H., Wang, H.S., 2014. Polybrominated diphenyl ethers (PBDEs) in human samples of mothernewborn pairs in South China and their placental transfer characteristics. Environ. Int. 73, 77–84. https://doi.org/10.1016/j.envint.2014.07.002.
- Chen, H.B., Wang, C., Li, H., Ma, R.X., Yu, Z.L., Li, L.Z., Xiang, M.D., Chen, X.C., Hua, X., Yu, Y.J., 2019. A review of toxicity induced by persistent organic pollutants (POPs) and endocrine-disrupting chemicals (EDCs) in the nematode Caenorhabditis elegans. J. Environ. Manag. 237, 519–525. https://doi.org/10.1016/j.jenvman.2019.02.102.
- Chen, Y., Juhasz, A., Li, H.B., Li, C., Ma, L.Q., Cui, X.Y., 2020. The influence of food on the in vivo bioavailability of DDT and its metabolites in soil. Environ. Sci. Technol. 54 (8), 5003–5010. https://doi.org/10.1021/acs.est.9b06697.
- Cui, X.Y., Xiang, P., He, R.W., Juhasz, A.L., Ma, L.Q., 2016. Advances in in vitro methods to evaluate oral bioaccessibility of PAHs and PBDEs in environmental matrices. Chemosphere 150, 378–389. https://doi.org/10.1016/j.chemosphere.2016.02.041.
- Dean, J.R., Ma, R., 2007. Approaches to assess the oral bioaccessibility of persistent organic pollutants: a critical review. Chemosphere 68 (8), 1399–1407. https://doi.org/ 10.1016/j.chemosphere.2007.03.054.
- DIN, 19738-2004 (Deutsches Institut f
 ür Normung, 19738-2004). Soil Quality-Bioaccessibility of Organic and Inorganic Pollutants From Contaminated Soil Material.
- Ding, J.J., Deng, T.Q., Ye, X.Q., Covaci, A., Liu, J., Yang, F.X., 2019. Urinary metabolites of organophosphate esters and implications for exposure pathways in adolescents from Eastern China. Sci. Total Environ. 695, 133894. https://doi.org/10.1016/j. scitotenv.2019.133894.
- EN71-3:1994+A1, 2000. European Standard for Safety of Toys.
- Ennour-Idrissi, K., Ayotte, P., Diorio, C., 2019. Persistent organic pollutants and breast cancer: a systematic review and critical appraisal of the literature. Cancers 11 (8), 1063. https://doi.org/10.3390/cancers11081063.
- Ertl, H., Butte, W., 2012. Bioaccessibility of pesticides and polychlorinated biphenyls from house dust: in-vitro methods and human exposure assessment. J. Expo. Sci. Environ. Epidemiol. 22 (6), 574–583. https://doi.org/10.1038/jes.2012.50.
- Fair, P.A., White, N.D., Wolf, B., Arnott, S.A., Kannan, K., Karthikraj, R., Vena, J.E., 2018. Persistent organic pollutants in fish from Charleston harbor and tributaries, South Carolina, United States: a risk assessment. Environ. Res. 167, 598–613. https://doi.org/ 10.1016/j.envres.2018.08.001.
- Fang, M.L., Stapleton, H.M., 2014. Evaluating the bioaccessibility of flame retardants in house dust using an in vitro Tenax bead-assisted sorptive physiologically based method. Environ. Sci. Technol. 48 (22), 13323–13330. https://doi.org/10.1021/ es503918m.
- Finley, B., Fehling, K., Warmerdam, J., Morinello, E.J., 2009. Oral bioavailability of polychlorinated dibenzo-p-dioxins/dibenzofurans in industrial soils. Hum. Ecol. Risk. Assess. 15 (6), 1146–1167. https://doi.org/10.1080/10807030903304765.
- Frederiksen, M., Vorkamp, K., Thomsen, M., Knudsen, L.E., 2009. Human internal and external exposure to PBDEs-a review of levels and sources. Int. J. Hyg. Environ. Health 212 (2), 109–134. https://doi.org/10.1016/j.ijheh.2008.04.005.
- García-Alcega, S., Rauert, C., Harrad, S., Collins, C.D., 2016. Does the source migration pathway of HBCDs to household dust influence their bio-accessibility? Sci. Total Environ. 569/570, 244–251. https://doi.org/10.1016/j.scitotenv.2016.04.178.
- Giovanoulis, G., Bui, T., Xu, F., Papadopoulou, E., Padilla-Sanchez, J.A., Covaci, A., Haug, L.S., Cousins, A.P., Magnér, J., Cousins, I.T., Wit, C.A.D., 2018. Multi-pathway human exposure assessment of phthalate esters and DINCH. Environ. Int. 112, 115–126. https:// doi.org/10.1016/j.envint.2017.12.016.
- Giulivo, M., Alda, M.L.D., Capri, E., Barcelo, D., 2016. Human exposure to endocrine disrupting compounds: their role in reproductive systems, metabolic syndrome and breast cancer. A review. Environ. Res. 151, 251–264. https://doi.org/10.1016/j. envres.2016.07.011.
- Gouliarmou, V., Collins, C.D., Christiansen, E., Mayer, P., 2013. Sorptive physiologically based extraction of contaminated solid matrices: incorporating silicone rod as absorption sink absorptive sink for hydrophobic organic contaminants. Environ. Sci. Technol. 47 (2), 941–948. https://doi.org/10.1021/es303165u.
- Grøn, C., Oomen, A., Weyand, E., Wittsiepe, J., 2007. Bioaccessibility of PAH from Danish soils. J. Environ. Sci. Health: Part A 42 (9), 1233–1239. https://doi.org/10.1080/ 10934520701435619.
- Guvenius, D.M., Aronsson, A., Ekman-Ordeberg, G., Bergman, A., Nore'n, K., 2003. Human prenatal and postnatal exposure to polybrominated diphenyl ethers, polychlorinated biphenyls, polychlorobipheny polychlorobiphenylols, and pentachlorophenol. Environ. Health Perspect. 111 (9), 1235–1241. https://doi.org/10.1289/ehp.5946.
- Hack, A., Selenka, F., 1996. Mobilization of PAH and PCB from contaminated soil using a digestive tract method. Toxicol. Lett. 88 (1/3), 199–210. https://doi.org/10.1016/ 0378-4274(96)03738-1.
- Harris, K.L., Banks, L.D., Mantey, J.A., Huderson, A.C., Ramesh, A., 2013. Bioaccessibility of polycyclic aromatic hydrocarbons: relevance to toxicity and carcinogenesis. Expert Opin. Drug Metab. Toxicol. 9 (11), 1465–1480. https://doi.org/10.1517/ 17425255.2013.823157.
- He, R.W., Li, Y.Z., Xiang, P., Li, C., Zhou, C.Y., Zhang, S.J., Cui, X.Y., Ma, L.Q., 2016. Organophosphorus flame retardants and phthalate esters in indoor dust from different

microenvironments: bioaccessibility and risk assessment. Chemosphere 150, 528–535. https://doi.org/10.1016/j.chemosphere.2015.10.087.

- He, D.F., Luo, Y.M., Lu, S.B., Liu, M.T., Song, Y., Lei, L.L., 2018a. Microplastics in soils: analytical methods, pollution characteristics and ecological risks. Trends Anal. Chem. 10, 163–172. https://doi.org/10.1016/j.trac.2018.10.006.
- He, R.W., Li, Y.Z., Xiang, P., Li, C., C, X.Y., Ma, L.Q., 2018b. Impact of particle size on distribution and human exposure of flame retardants in indoor dust. Environ. Res. 162, 166–172. https://doi.org/10.1016/j.envres.2017.12.014.
- Hilber, I., Arrigo, Y., Zuber, M., Bucheli, T.D., 2019. Desorption resistance of polycyclic aromatic hydrocarbons in biochars incubated in cow ruminal liquid in vitro and in vivo. Environ. Sci. Technol. 53 (23), 13695–13703.
- Hu, J.L., Wu, F.Y., Wu, S.C., Cao, Z.H., Lin, X.G., Wong, M.H., 2013. Bioaccessibility, dietary exposure and human risk assessment of heavy metals from market vegetables in Hong Kong revealed with an in vitro gastrointestinal model. Chemosphere 91 (4), 455–461. https://doi.org/10.1016/j.chemosphere.2012.11.066.
- Hurdzan, C.M., Basta, N.T., Hatcher, P.G., Tuovinen, O.H., 2008. Phenanthrene release from natural organic matter surrogates under simulated human gastrointestinal conditions. Ecotoxicol. Environ. Saf. 69 (3), 525–530. https://doi.org/10.1016/j. ecoenv.2007.02.006.
- James, K., Peters, R.E., Laird, B.D., Ma, W.K., Wickstrom, M., Stephenson, G.L., Siciliano, S.D., 2011. Human exposure assessment: a case study of 8 PAH contaminated soils using in vitro digestors and the juvenile swine method. Environ. Sci. Technol. 45 (10), 4586–4593. https://doi.org/10.1021/es1039979.
- James, K., Peters, R.E., Cave, M.R., Wickstrom, M., Siciliano, S.D., 2018. In vitro prediction of polycyclic aromatic hydrocarbon bioavailability of 14 different incidentally ingested soils in juvenile swine. Sci. Total Environ. 618, 682–689. https://doi.org/10.1016/j. scitotenv.2017.07.244.
- Jeong, Y., Lee, S., Kim, S., Park, J., Kim, H., Choi, G., Choi, S., Kim, S., Kim, S.Y., Kim, S., Choi, K., Moon, H., 2018. Placental transfer of persistent organic pollutants and feasibility using the placenta as a non-invasive biomonitoring matrix. Sci. Total Environ. 612, 1498–1505. https://doi.org/10.1016/j.scitotenv.2017.07.054.
- Jiang, Y.F., Yuan, L.M., Lin, Q.H., Ma, S.T., Yu, Y.X., 2019. Polybrominated diphenyl ethers in the environment and human external and internal exposure in China: a review. Sci. Total Environ. 696, 133902. https://doi.org/10.1016/j.scitotenv.2019.133902.
- Jones, K.C., Voogt, D.P., 1999. Persistent organic pollutants (POPs): state of the science. Environ. Pollut. 100 (1/3), 209–221. https://doi.org/10.1016/s0269-7491(99)00098-6.
- Juhasz, A.L., Weber, J., Stevenson, G., Slee, D., Gancarz, D., Rofe, A., Smith, E., 2014. In vivo measurement, in vitro estimation and fugacity prediction of PAH bioavailability in post-remediated creosote-contaminated soil. Sci. Total Environ. 473/474, 147–154. https://doi.org/10.1016/j.scitotenv.2013.12.031.
- Juhasz, A.L., Herde, P., Smith, E., 2016a. Oral relative bioavailability of dichlorodiphenyltrichloroethane (DDT) in contaminated soil and its prediction using in vitro strategies for exposure refinement. Environ. Res. 150, 482–488. https://doi.org/10.1016/j. envres.2016.06.039.
- Juhasz, A.L., Tang, W., Smith, E., 2016b. Using in vitro bioaccessibility to refine estimates of human exposure to PAHs via incidental soil ingestion. Environ. Res. 145, 145–153. https://doi.org/10.1016/j.envres.2015.12.001.
- Kademoglou, K., Williams, A.C., Collins, C.D., 2018. Bioaccessibility of PBDEs present in indoor dust: a novel dialysis membrane method with a Tenax TA ® absorption sink. Sci. Total Environ. 621, 1–8. https://doi.org/10.1016/j.scitotenv.2017.11.097.
- Kang, Y., Man, Y.B., Cheung, K.C., 2012. Risk assessment of human exposure to bioaccessible phthalate esters via indoor dust around the Pearl River Delta. Environ. Sci. Technol. 46 (15), 8422–8430. https://doi.org/10.1021/es300379v.
- Kang, Y., Yin, Y., Man, Y., Li, L.S., Zhang, Q.Y., Zeng, L.X., Luo, J.W., Wong, M.H., 2013. Bioaccessibility of polychlorinated biphenyls in workplace dust and its implication for risk assessment. Chemosphere 93 (6), 924–930. https://doi.org/10.1016/j. chemosphere.2013.05.057.
- Kang, Y., Zeng, D.Y., Man, Y.B., Liu, J., Yang, Y., Li, S.W., Situ, K., Xiong, W., Zeng, L.X., Zhang, Q.Y., Luo, J.W., Pan, W.J., Jiang, F., Wong, M.H., 2018. Comparison of sorption kinetics of PAHs by sorptive sinks and Caco-2 cell and the correlation between bioaccessibility and bioavailability of PAHs in indoor dust. Sci. Total Environ. 645, 170–178. https:// doi.org/10.1016/j.scitotenv.2018.07.102.
- Ke, C.L., Gu, Y.G., Liu, Q., 2017. Polycyclic aromatic hydrocarbons (PAHs) in exposed-lawn soils from 28 urban parks in the megacity Guangzhou: occurrence, sources, and human health implications. Arch. Environ. Contam. Toxicol. 72 (4), 496–504. https://doi.org/10.1007/s00244-017-0397-6.
- Khan, S., Cao, Q., Lin, A.J., Zhu, Y.G., 2008. Concentrations and bioaccessibility of polycyclic aromatic hydrocarbons in wastewater-irrigated soil using in vitro gastrointestinal test. Environ. Sci. Pollut. Res. 15 (4), 344–353. https://doi.org/10.1007/s11356-008-0004-5.
- Kim, S., Cho, Y.H., Won, S., Ku, J.L., Moon, H.B., Park, J., Choi, G., Kim, S., Choi, K., 2019. Maternal exposures to persistent organic pollutants are associated with DNA methylation of thyroid hormone-related genes in placenta differently by infant sex. Environ. Int. 130, 104956. https://doi.org/10.1016/j.envint.2019.104956.
- Kondratenko, S.N., Starodubtsev, A.K., Blinkov, I.L., Shikh, E.V., Svetlyi, L.I., 2002. The effect of food intake on the bioaccessibility of foridon, acebutolol, and theophylline. Pharm. Chem. J. 36, 462–464. https://doi.org/10.1023/A:1021884419966.
- Laparra, J.M., Velez, D., Montoro, R., Barbera, R., Farre, R., 2003. Estimation of arsenic bioaccessibility in edible seaweed by an in vitro digestion method. J. Agric. Food Chem. 51 (20), 6080–6085. https://doi.org/10.1021/jf034537i.
- Larsson, M., Minekus, M., Havenar, R., 1997. Estimation of the bioavailability of iron and phosphorus in cereals using a dynamic in vitro gastrointestinal model. J. Sci. Food Agric. 74 (1), 99–106. https://doi.org/10.1002/(SICI)1097-0010(199705)74:1<99:: AID-JSFA775>3.0.CO;2-G.
- Lei, B.L., Zhang, K.Q., An, J., Zhang, X.Y., Yu, Y.X., 2015. Human health risk assessment of multiple contaminants due to consumption of animal-based foods available in the

markets of Shanghai, China. Environ. Sci. Pollut. Res. 22 (6), 4434-4446. https://doi. org/10.1007/s11356-014-3683-0.

- Li, C., Cui, X.Y., Fan, Y.Y., Teng, Y., Zhong, R.N., Ma, L.Q., 2015a. Tenax as sorption sink for in vitro bioaccessibility measurement of polycyclic aromatic hydrocarbons in soils. Environ. Pollut. 196, 47–52. https://doi.org/10.1016/j.envpol.2014.09.016.
- Li, K., Li, C., Yu, N.Y., Juhasz, A.L., Cui, X.Y., Ma, L.Q., 2015b. In vivo bioavailability and in vitro bioaccessibility of perfluorooctanoic acid (PFOA) in food matrices: correlation analysis and method development. Environ. Sci. Technol. 49 (1), 150–158. https:// doi.org/10.1021/es505075z.
- Li, C.L., Zhao, Z.S., Lei, B.L., An, J., Zhang, X.Y., Yu, Y.X., 2015c. Polybrominated diphenyl ethers in the air and comparison of the daily intake and uptake through inhalation by Shanghai residents with those through other matrices and routes. Environ. Sci. Pollut. Res. 22 (3), 1750–1759. https://doi.org/10.1007/s11356-014-3264-2.
- Li, C., Sun, H.G., Juhasz, A.L., Cui, X.Y., Ma, L.Q., 2016. Predicting the relative bioavailability of DDT and its metabolites in historically contaminated soils using a Tenax-improved physiologically based extraction test (TI-PBET). Environ. Sci. Technol. 50 (3), 1118–1125. https://doi.org/10.1021/acs.est.5b03891.
- Li, X.T., Gao, Y., Wang, J., Ji, G.X., Lu, Y., Yang, D.D., Shen, H.X., Dong, Q., Pan, L.P., Xiao, H., Zhu, B.L., 2017a. Exposure to environmental endocrine disruptors and human health. Public Health and Emergency 1, 8. https://doi.org/10.21037/jphe.2016.12.09.
- Li, C., Zhang, R.R., Li, Y.Z., Zhang, S.J., Gao, P., Cui, X.Y., Ma, L.Q., 2017b. Relative bioavailability and bioaccessibility of PCBs in soils based on a mouse method and Tenaximproved physiologically-based extraction test. Chemosphere 186, 709–715. https://doi.org/10.1016/j.chemosphere.2017.08.028.
- Li, H.B., Li, M.Y., Li, J., Li, S.W., Juhasz, A.L., Basta, N.T., Luo, Y.M., Ma, L.Q., 2019. Oral bioavailability of As, Pb, and Cd in contaminated soils, dust, and foods based on animal bioassays: a review. Environ. Sci. Technol. 53 (18), 10545–10559. https://doi.org/ 10.1021/acs.est.9b03567.
- Liu, R.Y., He, R.W., Cui, X.Y., Ma, L.Q., 2018a. Impact of particle size on distribution, bioaccessibility, and cytotoxicity of polycyclic aromatic hydrocarbons in indoor dust. J. Hazard. Mater. 357, 341–347. https://doi.org/10.1016/j.jhazmat.2018.05.058.
- Liu, Y.Y., Xiao, J.J., Fu, Y.Y., Liao, M., Cao, H.Q., Shi, Y.H., 2018b. Study of factors influencing the bioaccessibility of Triazolone in cherry tomatoes using a static SHIME method. Environ. Res. Public Health 15 (5), 993–1012. https://doi.org/10.3390/ ijerph15050993.
- Lou, S.F., Huang, N.B., Xu, Li, Yu, Y.X., 2016. Effect of food particle size and mixed methods on the bioaccessibility of polybrominated diphenyl ethers. Asian J. Ecotoxicol. (in Chinese) 11, 573–579.
- Ltifi, M., Abichou, T., Tisot, J.P., 2014. Effects of soil aging on mechanical and hydraulic properties of a silty soil. Geotech. Geol. Eng. 32 (4), 1101–1108. https://doi.org/ 10.1007/s10706-014-9784-1.
- Luo, X.S., Ding, J., Xu, B., Wang, Y.J., Li, H.B., Yu, S., 2012. Incorporating bioaccessibility into human health risk assessments of heavy metals in urban park soils. Sci. Total Environ. 424, 88–96. https://doi.org/10.1016/j.scitotenv.2012.02.053.
- Lydy, M.J., Harwood, A.D., Nutile, S.A., Landrum, P.F., 2015. Tenax extraction of sediments to estimate desorption and bioavailability of hydrophobic contaminants: a literature review. Integr. Environ. Assess. Manag. 11, 208–220. https://doi.org/10.1002/ ieam.1603.
- Ma, Y.L., Li, P., Jin, J., Wang, Y., Wang, Q.H., 2017. Current halogenated flame retardant concentrations in serum from residents of Shandong Province, China, and temporal changes in the concentrations. Environ. Res. 155, 116–122. https://doi.org/10.1016/ j.envres.2017.02.010.
- Mackenbach, E.M., Jing, Y., Mills, M.A., Landrum, P.F., Lydy, M.J., 2012. Application of a Tenax model to assess bioavailability of PCBs in field sediments. Environ. Toxicol. Chem. 31, 2210–2216. https://doi.org/10.1002/etc.1943.
- Martínez, M.A., Rovira, J., Sharma, R.P., Nadal, M., Schuhmacher, M., Kumar, V., 2018. Comparing dietary and non-dietary source contribution of BPA and DEHP to prenatal exposure: a Catalonia (Spain) case study. Environ. Res. 166, 25–34. https://doi.org/ 10.1016/j.envres.2018.05.008.
- Mayer, P., Hilber, I., Gouliarmou, V., Hale, S.E., Cornelissen, G., Bucheli, T.D., 2016. How to determine the environmental exposure of PAHs originating from biochar. Environ. Sci. Technol. 50, 1941–1948. https://doi.org/10.1021/acs.est.5b05603.
- McComb, J., Mills, I.G., Muller, M., Berntsen, H.F., Zimmer, K.E., Ropstad, E., Verhaegen, S., Connolly, L., 2019. Human blood-based exposure levels of persistent organic pollutant (POP) mixtures antagonise androgen receptor transactivation and translocation. Environ. Int. 132, 105083. https://doi.org/10.1016/j.envint.2019.105083.
- McLeod, P.B., Van Den Heuvel-Greve, M.J., Allen-King, R.M., Luoma, S.N., Luthy, R.G., 2004. Effects of particulate carbonaceous matter on the bioavailability of benzo[a]pyrene and 2,2',5,5'-tetrachlorobiphenyl to the clam, Macoma balthica. Environ. Sci. Technol. 38 (17), 4549–4556. https://doi.org/10.1021/es049893b.
- Meyer, W., Kons, S., Achten, C., 2014. Impact of reference geosorbents on oral bioaccessibility of PAH in a human in vitro digestive tract model. Environ. Sci. Pollut. Res. 22 (7), 5164–5170. https://doi.org/10.1007/s11356-014-3804-9.
- Mi, X.B., Bao, L.J., Tao, S., Zeng, E.Y., 2017. Significance of cooking oil to bioaccessibility of dichlorodiphenyltrichloroethanes (DDTs) and polybrominated diphenyl ethers (PBDEs) in raw and cooked fish: implications for human health risk. J. Agric. Food Chem. 65 (16), 3268–3275. https://doi.org/10.1021/acs.jafc.7b00505.
- Miller, D.D., Schricker, B.R., Rasmussen, R.R., Campen, D.V., 1981. An in-vitro method for estimation of iron availability form meals. Am. J. Clin. Nutr. 34 (10), 2248–2256. https://doi.org/10.1093/ajcn/34.10.2248.
- Minekus, M., 2015. The TNO gastro-intestinal model (TIM). The Impact of Food Bioactives on Gut Health, pp. 37–46 https://doi.org/10.1007/978–3–319–16104–4_5.
- Minekus, M., Marteau, P., Havenaar, R., 1995. A multicompartmental dynamic computercontrolled model simulating the stomach and small-intestine. ATLA-Altern Lab Anim 23 (2), 197–209.

- Molly, K., Van de Woestyne, M., Verstraete, W., 1993. Development of a 5-step multichamber reactor as a simulation of the human intestinal microbial ecosystem. Appl. Microbiol. Biotechnol. 39 (2), 254–258. https://doi.org/10.1007/BF00228615.
- Mousavi, S.E., Amini, H., Heydarpour, P., Chermahini, F.A., 2019. Air pollution, environmental chemicals, and smoking may trigger vitamin D deficiency: evidence and potential mechanisms. Environ. Int. 122, 67–90. https://doi.org/10.1016/j. envint.2018.11.052.
- Muller, M.H.B., Polder, A., Brynildsrud, O.B., Gronnestad, R., Karimi, M., Lie, E., Manyilizu, W.B., Mdegela, R.H., Mokiti, F., Murtadha, M., Nonga, H.E., Skaare, J.U., Solhaug, A., Lyche, J.L., 2019. Prenatal exposure to persistent organic pollutants in Northern Tanzania and their distribution between breast milk, maternal blood, placenta and cord blood. Environ. Res. 170, 433–442. https://doi.org/10.1016/j.envres.2018.12.026.
- Nathanail, C.P., Smith, R., 2007. Incorporating bioaccessibility in detailed quantitative human health risk assessments. J. Environ. Sci. Health: Part A 42 (9), 1193–1202. https://doi.org/10.1080/10934520701432095.
- Ngole-Jeme, V.M., Ekosse, G.I.E., Songca, S.P., 2016. An analysis of human exposure to trace elements from deliberate soil ingestion and associated health risks. J. Expo. Sci. Environ. Epidemiol. 28 (1), 55–63. https://doi.org/10.1038/jes.2016.67.
- Ollson, C.A., Koch, I., Smith, P., Knopper, L.D., Hough, C., Reimer, K.J., 2009. Addressing arsenic bioaccessibility in ecological risk assessment: a novel approach to avoid overestimating risk. Environ. Toxicol. Chem. 28 (3), 668–675. https://doi.org/ 10.1897/08-204.1.
- Oomen, A.G., Hack, A., Minekus, M., Zeijdner, E., Cornelis, C., Verstraete, W., Van de Wiele, T., Wragg, J., Rompelberg, C.J.M., Sips, A.J.A.M., Wijnen, J.H.V., 2002. Comparison of five in vitro digestion models to study the bioaccessibility of soil contaminants. Environ. Sci. Technol. 36 (15), 3326–3334. https://doi.org/10.1021/es010204v.
- Orla, O., Lisa, R., Laurie, O., Aisling, A.B.S., O'Brien, N.M., 2008. Carotenoid micellarization varies greatly between individual and mixed vegetables with or without the addition of fat or fiber. Int. J. Vitam. Nutr. Res. 78 (45), 238–246. https://doi.org/10.1024/0300-9831.78.45.238.
- Palioura, E., Diamanti-Kandarakis, E., 2013. Industrial endocrine disruptors and polycystic ovary syndrome. J. Endocrinol. Investig. 36 (11), 1105–1111. https://doi.org/10.1007/ BF03346762.
- Pan, W.J., Kang, Y., Zeng, L.X., Zhang, L.X., Zhang, Q.Y., Luo, J.W., 2016. Comparison of in vitro digestion method with in vivo relative bioavailability of BDE-209 in indoor dust and combination of in vitro digestion/Caco-2 cell method to estimate the daily intake of BDE-209 via indoor dust. Environ. Pollut. 218, 497–504. https://doi.org/ 10.1016/j.envpol.2016.07.029.
- Quintana, J.B., Rosende, M., Montes, R., Rodríguez-Álvarez, T., Rodil, R., Cela, R., Miró, M., 2017. In-vitro estimation of bioaccessibility of chlorinated organophosphate flame retardants in indoor dust by fasting and fed physiologically relevant extraction tests. Sci. Total Environ. 580, 540–549. https://doi.org/10.1016/j.scitotenv.2016.11.210.
- Raffy, G., Mercier, F., Glorennec, P., Mandin, C., Bot, B.L., 2018. Oral bioaccessibility of semivolatile organic compounds (SVOCs) in settled dust: a review of measurement methods, data and influencing factors. J. Hazard. Mater. 352, 215–227. https://doi. org/10.1016/j.jhazmat.2018.03.035.
- Ren, A.G., Qiu, X.H., Jin, L., Ma, J., Li, Z.W., Zhang, L., Zhu, H.P., Finnell, R.H., Zhu, T., 2011. Association of selected persistent organic pollutants in the placenta with the risk of neural tube defects. Proc. Natl. Acad. Sci. U. S. A. 108 (31), 12770–12775. https:// doi.org/10.1073/pnas.1105209108.
- Riedl, J., Linseisen, J., Hoffmann, J., Wolfram, G., 1999. Some dietary fibers reduce the absorption of carotenoids in women. J. Nutr. 129 (2), 2170–2176. https://doi.org/ 10.1093/jn/129.12.2170.
- Rodriguez, R.R., Basta, N.T., Casteel, S.W., Pace, L.W., 1999. An in vitro gastrointestinal method to estimate bioavailable arsenic in contaminated soils and solid media. Environ. Sci. Technol. 33 (4), 642–649. https://doi.org/10.1021/es980631h.
- Rose, M., Holland, J., Dowding, A., Petch, S., White, S., Fernandes, A., Mortimer, D., 2015. Investigation into the formation of PAHs in foods prepared in the home to determine the effects of frying, grilling, barbecuing, toasting and roasting. Food Chem. Toxicol. 78, 1–9. https://doi.org/10.1016/j.fct.2014.12.018.
- Ruby, M.V., Davis, A., Link, T.E., Schoof, R., 1993. Development of an in vitro screening test to evaluate the in vivo bioaccessibility of ingested mine-waste lead. Environ. Sci. Technol. 27 (13), 2870–2877. https://doi.org/10.1021/es00049a030.
- Ruby, M.V., Davis, A., Schoof, R., Eberle, S., Sellstone, C.M., 1996. Estimation of lead and arsenic bioavailability using a physiologically based extraction test. Environ. Sci. Technol. 30 (2), 422–430. https://doi.org/10.1021/es950057z.
- Ruby, M., Schoof, R., Brattin, W., Goldade, M., Post, G., Harnois, M., Mosby, D.E., Casteel, S.W., Berti, W., Carpenter, M., Edwards, D., Cragin, D., Chappell, W., 1999. Advances in evaluating the oral bioavailability of inorganics in soil for use in human health risk assessments. Environ. Sci. Technol. 33 (21), 3697–3705.
- Ruby, M.V., Fehling, K.A., Paustenbach, D.J., Landenberger, B.D., Holsapple, M.P., 2002. Oral bioaccessibility of dioxins/furans at low concentrations (50-350 ppt toxicity equivalent) in soil. Environ. Sci. Technol. 36 (22), 4905–4911. https://doi.org/10.1021/ es0206361.
- Ruby, M.V., Lowney, Y.W., Bunge, A.L., Roberts, S.M., Gomez-Eyles, J.L., Ghosh, U., Kissel, J.C., Tomlinson, P., Menzie, C., 2016. Oral bioavailability, bioaccessibility, and dermal absorption of PAHs from soil-state of the science. Environ. Sci. Technol. 50 (5), 2151–2164. https://doi.org/10.1021/acs.est.5b04110.
- Schroder, L., Basta, N.T., Casteel, S.W., Evans, T.J., Si, J., 2004. Validation of the in vitro gastrointestinal (IVG) method to estimate relative bioavailable lead in contaminated soils. J. Environ. Qual. 33 (2), 513–521. https://doi.org/10.2134/jeq2004.0513.
- Semple, K.T., Riding, M.J., McAllister, L.E., Sopena-Vazqueze, F., Bending, G.D., 2013. Impact of black carbon on the bioaccessibility of organic contaminants in soil. J. Hazard. Mater. 261, 808–816. https://doi.org/10.1016/j.jhazmat.2013.03.032.
- Sharma, B.M., Bharat, G.K., Tayal, S., Nizzetto, L., Cupr, P., Larssen, T., 2014. Environment and human exposure to persistent organic pollutants (POPs) in India: a systematic

review of recent and historical data. Environ. Int. 66, 48–64. https://doi.org/10.1016/j. envint.2014.01.022.

- Shen, H.T., Starr, J., Han, J.L., Zhang, L., Lu, D.S., Guan, R.F., Xu, X.M., Wang, X.F., Li, J.G., Li, W.W., Zhang, Y.J., Wu, Y.N., 2016. The bioaccessibility of polychlorinated biphenyls (PCBs) and polychlorinated dibenzo-p-dioxins/furans (PCDD/Fs) in cooked plant and animal origin foods. Environ. Int. 94, 33–42. https://doi.org/10.1016/j. envint.2016.05.003.
- Shi, Y.H., Xiao, J.J., Feng, R.P., Liu, Y.Y., Liao, M., Wu, X.W., Hua, R.M., Cao, H.Q., 2017. Factors affecting the bioaccessibility and intestinal transport of difenoconazole, hexaconazole and spirodiclofen in human Caco-2 cells following in vitro digestion. J. Agric. Food Chem. 65, 9139–9146. https://doi.org/10.1021/acs.jafc.7b02781.
- Siciliano, S.D., Laird, B.D., Lemieux, C.L., 2010. Polycyclic aromatic hydrocarbons are enriched but bioaccessibility reduced in brownfield soils adhered to human hands. Chemosphere 80 (9), 1101–1108. https://doi.org/10.1016/j. chemosphere.2010.04.061.
- Smith, R.P., Roberstson, A.M., Watchel, C.J., 2008. Measurement of polycylic aromatic hydrocarbon (PAH) bioaccessibility and their use in the assessment of human health risk. Geosci. South-West Engl. 12, 27–31.
- Smith, E., Weber, J., Rofe, A., Gancarz, D., Naidu, R., Juhasz, A.L., 2012. Assessment of DDT relative bioavailability and bioaccessibility in historically contaminated soils using an in vivo mouse method and fed and unfed batch in vitro assays. Environ. Sci. Technol. 46 (5), 2928–2934. https://doi.org/10.1021/es203030q.
- Suarez-Lopez, J.R., Clemesha, C.G., Porta, M., Gross, M.D., Lee, D.H., 2019. Organochlorine pesticides and polychlorinated biphenyls (PCBs) in early adulthood and blood lipids over a 23-year follow-up. Environ. Toxicol. Pharmacol. 66, 24–35. https://doi.org/ 10.1016/j.etap.2018.12.018.
- Tang, X.Y., Tang, L., Zhu, Y.G., Xing, B.S., Duan, J., Zheng, M.H., 2006. Assessment of the bioaccessibility of polycyclic aromatic hydrocarbons in soils from Beijing using an in vitro test. Environ. Pollut. 140 (2), 279–285. https://doi.org/10.1016/j. envpol.2005.07.010.
- Tao, S., Lu, Y., Zhang, D.Y., Yang, Y.F., Yang, Y., Lu, X.X., Sai, D.J., 2009. Assessment of oral bioaccessibility of organochlorine pesticides in soil using an in vitro gastrointestinal model. Environ. Sci. Technol. 43 (12), 4524–4529. https://doi.org/10.1021/ es900188c.
- Tao, S., Zhang, D.Y., Lu, Y., Li, L., Ding, J.N., Yang, Y., Yang, Y.F., Wang, X.L., Liu, W.X., Xing, B.S., 2010. Mobility of polycyclic aromatic hydrocarbons in the gastrointestinal tract assessed using an in vitro digestion model with sorption rectification. Environ. Sci. Technol. 44 (14), 5608–5612. https://doi.org/10.1021/es1010626.
- Tao, S., Li, L., Ding, J.N., Zhong, J.J., Zhang, D.Y., Lu, Y., Yang, Y.F., Cao, J., Lu, X.X., Liu, W.X., 2011. Mobilization of soil-bound residue of organochlorine pesticides and polycyclic aromatic hydrocarbons in an in vitro gastrointestinal method. Environ. Sci. Technol. 45 (3), 1127–1132. https://doi.org/10.1021/es1025849.
- Tian, K., Bao, H.Y., Zhang, X.C., Shi, T.R., Liu, X.P., Wu, F.Y., 2018. Residuals, bioaccessibility and health risk assessment of PAHs in winter wheat grains from areas influenced by coal combustion in China. Sci. Total Environ. 618, 777–784. https://doi.org/10.1016/j. scitotenv.2017.08.174.
- Tilston, E.L., Gibson, G.R., Collins, C.D., 2011. Colon extended physiologically based extraction test (CE-PBET) increases bioaccessibility of soil-bound PAH. Environ. Sci. Technol. 45 (12), 5301–5308. https://doi.org/10.1021/es2004705.
- Toms, L.L., Hearn, L., Mueller, J.F., Harden, F.A., 2016. Assessing infant exposure to persistent organic pollutants via dietary intake in Australia. Food Chem. Toxicol. 87, 166–171. https://doi.org/10.1016/j.fct.2015.12.018.
- Turner, A., 2011. Oral bioaccessibility of trace metals in household dust: a review. Environ. Geochem. Health 2011 (33), 331–341. https://doi.org/10.1007/s10653-011-9386-2.
- Umeh, A.C., Duan, L., Naidu, R., Esposito, M., Semple, K.T., 2019. In vitro gastrointestinal mobilization and oral bioaccessibility of pahs in contrasting soils and associated cancer risks: focus on PAH nonextractable residues. Environ. Int. 133, 105186. https:// doi.org/10.1016/j.envint.2019.105186.
- UNEP (United Nations Environment Programme), 2009. Report of the Persistent Organic Pollutants Review Committee on the Work of Its Fifth Meeting. UNEP/POPS/POPRC.5/ 10/Add.1.
- UNEP (United Nations Environment Programme), 2015. Report of the Persistent Organic Pollutants Review Committee on the Work of Its Eleventh Meeting. UNEP/POPS/ POPRC.11/10/Add.1.
- USEPA (United States Environmental Protection Agency), 2010. An Exposure Assessment of Polybrominated Diphenyl Ethers.
- Van de Wiele, T., Verstraete, W., Siciliano, S.D., 2004. Polycyclic aromatic hydrocarbon release from a soil matrix in the in vitro gastrointestinal tract. J. Environ. Qual. 33 (4), 1343–1353. https://doi.org/10.2134/jeq2004.1343.
- Vasiluck, L., Pinto, L.J., Walji, Z.A., Tsang, W.S., Gobas, F.A.P.C., Eickhoff, C., Moore, M.M., 2007. Benzo[a]pyrene bioavailability from pristine soil and contaminated sediment assessed using two in vitro models. Environ. Toxicol. Chem. 26 (3), 387–393. https://doi.org/10.1897/06-343R.1.
- Versantvoort, C.H.M., Kamp, E.V.D., Rompelberg, C.J.M., 2004. Development and applicability of an in vitro digestion model in assessing the bioaccessibility of contaminants from food. RIVM report 320102002/2004; https://www.doc88.com/p-118780635261.html; accessable 25 Oct, 2020.
- Versantvoort, C.H.M., Oomen, A.G., Kamp, E.V.D., Rompelberg, C.J.M., Sips, A.J.A., 2005. Applicability of an in vitro digestion model in assessing the bioaccessibility of mycotoxins from food. Food Chem. Toxicol. 43 (1), 31–40. https://doi.org/10.1016/j. fct.2004.08.007.
- Verwei, M., Freidig, A.P., Havenaar, R., Groten, J.P., 2007. Predicted serum folate concentrations based on in vitro studies and kinetic modeling are consistent with measured folate concentrations in humans. J. Nutr. 136 (12), 3074–3078. https://doi.org/10.1093/ jn/136.12.3074.

- Vuong, A.M., Braun, J.M., Webster, G.M., Zoeller, R.T., Hoofnagle, A.N., Sjodin, A., Yolton, K., Lanphear, B.P., Chen, A.M., 2018. Polybrominated diphenyl ether (PBDE) exposures and thyroid hormones in children at age 3 years. Environ. Int. 117, 339–347. https://doi.org/10.1016/j.envint.2018.05.019.
- Wang, B., Xue, M., Lv, Y., Yang, Y., Zhong, J.J., Su, Y.H., Wang, R., Shen, G.F., Wang, X.L., Tao, S., 2011. Cell absorption induced desorption of hydrophobic organic contaminants from digested soil residue. Chemosphere 83, 1461–1466. https://doi.org/10.1016/j. chemosphere.2011.03.008.
- Wang, W., Wu, F.Y., Huang, M.J., Kang, Y., Cheung, K.C., Wong, M.H., 2013a. Size fraction effect on phthalate esters accumulation, bioaccessibility and in vitro cytotoxicity of indoor/outdoor dust, and risk assessment of human exposure. J. Hazard. Mater. 261, 753–762. https://doi.org/10.1016/j.jhazmat.2013.04.039.
- Wang, W., Huang, M.J., Zheng, J.S., Cheung, K.C., Wong, M.H., 2013b. Exposure assessment and distribution of polychlorinated biphenyls (PCBs) contained in indoor and outdoor dusts and the impacts of particle size and bioaccessibility. Sci. Total Environ. 463, 1201–1209. https://doi.org/10.1016/j.scitotenv.2013.04.059.
- Wang, W., Wu, F.Y., Zheng, J.S., Wong, M.H., 2013c. Risk assessments of PAHs and Hg exposure via settled house dust and street dust, linking with their correlations in human hair. J. Hazard. Mater. 263, 627–637. https://doi.org/10.1016/j. ihazmat.2013.10.023.
- Wang, W., Huang, M.J., Wu, F.Y., Kang, Y., Wang, H.S., Cheng, K.C., Wong, M.H., 2013d. Risk assessment of bioaccessible organochlorine pesticides exposure via indoor and outdoor dust. Atmos. Environ. 77, 525–533. https://doi.org/10.1016/j. atmosenv.2013.04.071.
- Wang, J., Lin, K.D., Taylor, A., Gan, J., 2018a. In vitro assessment of pyrethroid bioaccessibility via particle ingestion. Environ. Int. 119, 125–132. https://doi.org/10.1016/j. envint.2018.05.043.
- Wang, Y.H., Rui, M., Nie, Y., Lu, G.H., 2018b. Influence of gastrointestinal tract on metabolism of bisphenol A as determined by in vitro simulated system. J. Hazard. Mater. 355, 111–118. https://doi.org/10.1016/j.jhazmat.2018.05.011.
- Wang, B., Jin, Z.X., Xu, X.Y., Zhou, H., Yao, X.W., Ji, F.Y., 2019. Effect of Tenax addition amount and desorption time on desorption behaviour for bioavailability prediction of polycyclic aromatic hydrocarbons. Sci. Total Environ. 651, 427–434. https://doi. org/10.1016/j.scitotenv.2018.09.097.
- Weschler, C.J., Nazaroff, W.W., 2008. Semivolatile organic compounds in indoor environments. Atmos. Environ. 42 (40), 9018–9040. https://doi.org/10.1016/j. atmosenv.2008.09.052.
- WHO (World Health Organization), 1994. Environmental Health Criteria 162. Brominated Diphenyl Ethers, Environmental Health Criteria. pp. 1–347.
- Wragg, J., Cave, M., Basta, N., Brandon, E., Casteel, S., Denys, S., Gron, C., Oomen, A., Reimer, K., Tack, K., Van de Wiele, T., 2011. An inter-laboratory trial of the unified BARGE bioaccessibility method for arsenic, cadmium and lead in soil. Sci. Total Environ. 409 (19), 4016–4030. https://doi.org/10.1016/j.scitotenv.2011.05.019.
- Wright, A.J., Pietrangelo, C., MacNaughton, A., 2008. Influence of simulated upper intestinal parameters on the efficiency of beta carotene micellarisation using an in vitro model of digestion. Food Chem. 107 (3), 1253–1260. https://doi.org/10.1016/j. foodchem.2007.09.063.
- Xiao, J.J., Fu, Y.Y., Ye, Z., Liu, Y.Y., Shi, Y.H., Liao, M., Cao, H.Q., 2019. Analysis of the pesticide behavior in Chaenomelis speciosa and the role of digestive enzyme in vitro oral bioaccessibility. Chemosphere 231, 538–545. https://doi.org/10.1016/j. chemosphere.2019.05.172.
- Yang, Q.Q., Li, Z.Y., Lu, X.N., Duan, Q.N., Huang, L., Bi, J., 2018. A review of soil heavy metal pollution from industrial and agricultural regions in China: pollution and risk assessment. Sci. Total Environ. 642, 690–700. https://doi.org/10.1016/j. scitotenv.2018.06.068.
- Yu, Y.X., Han, S.Y., Zhang, D.P., Van de Wiele, T., Lu, M., Wang, D.Q., Yu, Z.Q., Wu, M.H., Sheng, G.Y., Fu, J.M., 2009a. Factors affecting the bioaccessibility of polybrominated diphenyl ethers in an in vitro digestion method. J. Agric. Food Chem. 57 (1), 133–139. https://doi.org/10.1021/jf802659u.
- Yu, Y.X., Chen, L., Yang, D., Pang, Y.P., Zhang, S.H., Zhang, X.Y., Yu, Z.Q., Wu, M.H., Fu, J.M., 2012a. Polycyclic aromatic hydrocarbons in animal-based foods from Shanghai: bioaccessibility and dietary exposure. Food Addit. Contamin.: Part A 29 (9), 1465–1474. https://doi.org/10.1080/19440049.2012.694121.
- Yu, Y.X., Han, S.Y., Li, J.L., Zhang, D.P., Wu, M.H., Sheng, G.Y., Fu, J.M., 2009b. Factors affecting the bioaccessibility of polychlorinated biphenyls using in vitro test. 2009 3rd International Conference on Bioinformatics and Biomedical Engineering. vols. 1–11, pp. 4241–4244. https://doi.org/10.1109/ICBBE.2009.5162846.
- Yu, Y.X., Li, J.L., Zhang, X.Y., Yu, Z.Q., Van de Wiele, T., Han, S.Y., Wu, M.H., Sheng, G.Y., Fu, J.M., 2010. Assessment of the bioaccessibility of polybrominated diphenyl ethers in foods and the correlations of the bioaccessibility with nutrient contents. J. Agric. Food Chem. 58 (1), 301–308. https://doi.org/10.1021/jf9036358.
- Yu, Y.X., Pang, Y.P., Zhang, X.Y., Li, C., Yu, Z.Q., Fu, J.M., 2011a. Optimization of an in vitro method to measure the bioaccessibility of polybrominated diphenyl ethers in dust using response surface methodology. J. Environ. Sci. 23 (10), 1738–1746. https:// doi.org/10.1016/S1001-0742(10)60571-2.
- Yu, Y.X., Huang, N.B., Zhang, X.Y., Li, J.L., Yu, Z.Q., Han, S.Y., Lu, M., Van de Wiele, T., Wu, M.H., Sheng, G.Y., Fu, J.M., 2011b. Polybrominated diphenyl ethers in food and associated human daily intake assessment considering bioaccessibility measured by simulated gastro-intestinal digestion. Chemosphere 83 (2), 152–160. https://doi.org/ 10.1016/j.chemosphere.2010.12.049.
- Yu, Y.X., Pang, Y.P., Li, C., Li, J.L., Zhang, X.Y., Yu, Z.Q., Feng, J.L., Wu, M.H., Sheng, G.Y., Fu, J.M., 2012b. Concentrations and seasonal variations of polybrominated diphenyl ethers (PBDEs) in in- and out-house dust and human daily intake via dust ingestion corrected with bioaccessibility of PBDEs. Environ. Int. 42, 124–131. https://doi.org/ 10.1016/j.envint.2011.05.012.

- Yu, Y.X., Li, C.L., Zhang, X.L., Zhang, X.Y., Pang, Y.P., Zhang, S.H., Fu, J.M., 2012c. Routespecific daily uptake of organochlorine pesticides in food, dust and air by Shanghai residents, China. Environ. Int. 50, 31–37. https://doi.org/10.1016/j. envint.2012.09.007.
- Yu, Y.X., Yang, D., Wang, X.X., Huang, N.B., Zhang, X.Y., Zhang, D.P., Fu, J.M., 2013. Factors influencing on the bioaccessibility of polybrominated diphenyl ethers in size-specific dust from air conditioner filters. Chemosphere 93 (10), 2603–2611. https://doi.org/ 10.1016/j.chemosphere.2013.09.085.
- Yu, Y.X., Wang, M.M., Zhang, K.Q., Yang, D., Zhong, Y.F., An, J., Lei, B.L., Zhang, X.Y., 2017. The transepithelial transport mechanism of polybrominated diphenyl ethers in human intestine determined using a caco-2 cell monolayer. Environ. Res. 154, 93–100. https://doi.org/10.1016/j.envres.2016.12.024.
- Yu, Y.X., Lou, S.F., Wang, X.X., Lu, S.Y., Ma, S.T., Li, G.Y., Feng, Y., Zhang, X.Y., An, T.C., 2019a. Relationships between the bioavailability of polybrominated diphenyl ethers in soils measured with female C57BL/6 mice and the bioaccessibility determined using five in vitro methods. Environ. Int. 123, 337–344. https://doi.org/10.1016/j. envint.2018.12.022.
- Yu, Y.X., Li, W.B., Lu, S.Y., Wu, S.Y., Wang, F., Tse, L.A., Kang, L., Ma, S.T., 2019b. Urinary parabens in adults from South China: implications for human exposure and health risks. Ecotoxicol. Environ. Saf. 182, 109419. https://doi.org/10.1016/j. ecoenv.2019.109419.
- Zeng, Y., Fan, Y., Yan, X., Zheng, J., Chen, S.J., Mai, B.X., 2019. In vitro oral and inhalation bioaccessibility of hydrophobic organic contaminants (HOCs) in airborne particles

and influence of relevant parameters. Environ. Res. 170, 134–140. https://doi.org/10.1016/j.envres.2018.12.025.

- Zhang, Y.Y., Pignatello, J.J., Tao, S., Xing, B.S., 2015a. Bioaccessibility of PAHs in fuel soot assessed by an in vitro digestive model: effect of including an absorptive sink. Environ. Sci. Technol. 49 (6), 3905–3912. https://doi.org/10.1021/es505898v.
- Zhang, Y.Y., Pignatello, J.J., Tao, S., Xing, B.S., 2015b. Bioaccessibility of PAHs in fuel soot assessed by an in vitro digestive method with absorptive sink: effect of food ingestion. Environ. Sci. Technol. 49 (24), 14641–14648. https://doi.org/10.1021/acs. est.5b04342.
- Zhang, S., Li, C., Li, Y., Zhang, R.R., Gao, P., Cui, X.Y., Ma, L.Q., 2017. Bioaccessibility of PAHs in contaminated soils: comparison of five in vitro methods with Tenax as a sorption sink. Sci. Total Environ. 601/602, 968–974. https://doi.org/10.1016/j. scitotenv.2017.05.234.
- Zhang, Y.H., Liu, W.J., Cheng, F.F., Xiong, G.N., Yang, X.H., Wang, X., Tao, S., Xin, B.S., Liu, W.X., 2015c. Variations and influencing factors of oral bioaccessibility of polybrominated diphenyl ethers in soils using an in-vitro gastrointestinal model. Environ. Sci. 36, 2292–2298 (in Chinese).
- Zhang, Y.Y., Pignatello, J.J., Tao, S., 2018. Bioaccessibility of PAHs and PAH derivatives in a fuel soot assessed by an in vitro digestive method with absorptive sink: effects of aging the soot in a soil-water mixture. Sci. Total Environ. 615, 169–176. https://doi. org/10.1016/j.scitotenv.2017.09.227.