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Oral bioaccessibility of PTEs in soils: A review of data, influencing factors and application in human health risk assessment

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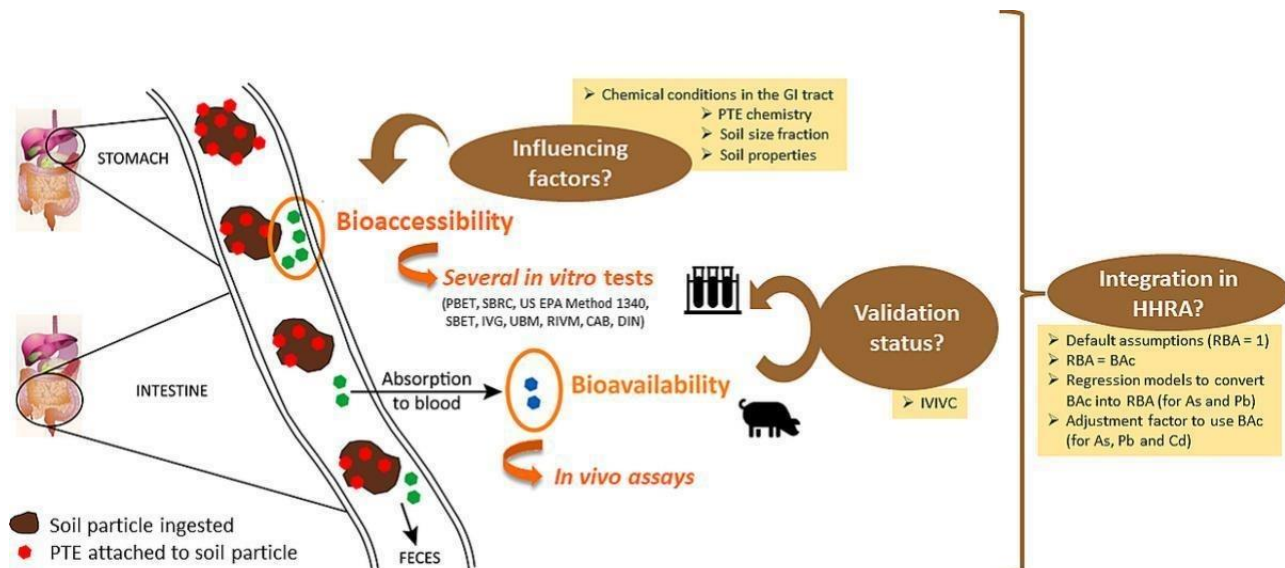
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Highlights

- Use of bioaccessibility under appropriate conditions to refine exposure
- Bioaccessibility assessed by the most appropriate in vitro protocol based on IVIVC
- Official recommendations for integrating bioaccessibility in HHRA are hardly used.
- Choice of soil size fraction in accordance with the test and its in vivo validation
- Influencing parameters of bioaccessibility are site-dependent.

Graphical abstract



Abstract

Understanding the behavior of metal(loid)s transported from soil to humans is critical for human health risk assessment (HHRA). In the last two decades, extensive studies have been conducted to better assess human exposure to potentially toxic elements (PTEs) by estimating their oral bioaccessibility (BAc) and quantifying the influence of different factors. This study reviews the common *in vitro* methods used to determine the BAc of PTEs (in particular As, Cd, Cr, Ni, Pb, and Sb) under specific conditions (particularly in terms of the particle size fraction and validation status against an *in vivo* model). The results were compiled from soils derived from various sources and allowed the identification of the most important influencing factors of BAc (using single and multiple regression analyses), including physicochemical soil properties and the speciation of the PTEs in question. This review presents current knowledge on integrating relative bioavailability (RBA) in calculating doses from soil ingestion in the HHRA process. Depending on the jurisdiction, validated or non-validated bioaccessibility methods were used, and risks assessors applied different approaches: (i) using default assumptions (i.e., RBA of 1); (ii) considering that bioaccessibility value (BAc) accurately represents RBA (i.e., RBA equal to BAc); (iii) using regression models to convert BAc of As and Pb into RBA as proposed by the USA with the US EPA Method 1340; or (iv) applying an adjustment factor as proposed by the Netherlands and France to use BAc from UBM (Unified Barge Method) protocol. The findings from this review should help inform risk stakeholders about the uncertainties surrounding using bioaccessibility data and provide recommendations for better interpreting the results and using bioaccessibility in risk studies.

Keywords: Contaminated soils; Metal(loid)s; Bioaccessibility; Bioavailability; Soil parameters; Human health risk assessment

1. Introduction

Soils serve as sinks for many metallic elements derived from human activities, including past or present mining activities, industrial activities (such as steel manufacturing, plating, dyeing, battery manufacturing, smelting, coal, or fossil fuel combustion), waste disposal, and agricultural practices (such as the use of fertilizers or pesticides), depending on the soil type and soil use. Additionally, soils may inherit metallic elements from natural geochemical origin, volcanic eruptions or parent materials, because many minerals contain high concentrations of elements that are released into the environment through actions such as weathering and erosion (Ayangbenro and Babalola, 2017; FAO and UNEP, 2021; He et al., 2015). These potentially toxic elements (PTEs) pose a risk to human health because of their toxicity, especially in sensitive populations such as children. Compared with inhalation and dermal contact, unintentional ingestion of soil particles, especially for children through outdoor activities (i.e., hand-to-mouth contact), is considered the primary route of exposure for PTEs (Paustenbach, 2000; Ruby et al., 1996; Zingaretti and Baciocchi, 2021).

Over 10 million soil contamination sites have been reported worldwide, half contaminated with PTEs (He et al., 2015). In the context of managing contaminated sites, there is now a consensus that human health risk assessment (HHRA) may overestimate exposure and risk based on total (or pseudo-total) PTE concentrations in the soil (i.e., considering that the entire amount of a contaminant is available to human organs) (Ikegami et al., 2014; Izquierdo et al., 2015; Monneron-Gyurits et al., 2020). A lack of realism can result in excessive management costs. Soil particles ingested by humans enter the digestive system, where they encounter several compartments with different properties that affect the dissolution and absorption of contaminants in the soil matrix. Only the bioavailable fraction, the quantity of PTEs that reaches the bloodstream and human organs, can generate toxic effects (Ruby et al., 1999; Semple et al., 2004). However, measuring oral bioavailability requires *in vivo* experiments, that are time-consuming, expensive, and ethically questionable. Therefore, oral bioaccessibility can be used to incorporate the concept of bioavailability into human health risk assessments (HHRA). It is defined as the fraction of PTEs soluble in the gastrointestinal tractus and potentially available for absorption (Oomen et al., 2002; Ruby et al., 1999). Research on bioaccessibility related to contaminated site management has gained international attention as it can lead to a more balanced risk assessment (Babaahmadifooladi et al., 2020; Darko et al., 2017; Li et al., 2014; Mehta et al., 2019; Wang et al., 2023a).

In the last two decades, numerous *in vitro* extraction methods have been developed for application into PTE-contaminated soils. However, to refine the exposure method and HHRA, the bioaccessible concentrations of PTEs obtained from validated and standardized protocols (i.e., *in vivo* and interlaboratory assays) are recommended. Priority PTEs have been identified as As and Pb (Denys et al., 2012; González-Grijalva et al., 2019; Karadaş and Kara, 2011; Pelfrène et al., 2011; Ruby et al., 1996; Zapusek and Lestan, 2009) because of their adverse effects on human health (Table 1) and their prevalence in soils worldwide. Studies have also been conducted on other elements, such as Cd, which exhibits high toxicity even at very low concentrations (Kumar and Sharma, 2019; FAO and UNEP, 2021). Other PTEs, such as Cr, Ni, and Sb, have received less attention; however, their interest is increasing because they can also have adverse effects on human health (Table 1), and their bioaccessibility is often estimated to be relatively low (Amponsah et al., 2022; Bourliva et al., 2021; Cavonas et al., 2023; Denys et al., 2008; Guillen et al., 2021; Kirman et al., 2016; Laha et al., 2020; Li et al., 2014; Ning et al., 2021; Pascaud et al., 2014; Pereira et al., 2020). The toxicities of certain PTEs are influenced by their speciation. When ingested, Cr (III) is absorbed less by the human body than carcinogenic Cr (VI) (Kerger et al., 1996), underscoring the importance of studying Cr speciation in the HHRA (Yu et al., 2012). As and Sb are primarily present as As/Sb (V) and As/Sb (III), with the latter being more toxic than As/Sb (V) (Bagherifam et al., 2019; Filella et al., 2002). Therefore, this review focuses on PTEs such as As, Cd, Cr, Ni, Pb, and Sb, which are essential in HHRA. Studies have also been conducted on Hg (e.g., Bavec and Gosar, 2016; Rodrigues et al., 2014; Vasques et al., 2020; Welfringer and Zagury, 2009). However, this PTE was excluded from the review because of its volatile nature and the difficulty in estimating its bioaccessible and bioavailable fractions. Because only a fraction of contaminants in the soil may reach the bloodstream and cause toxic effects, and to improve the

representativeness of the characterization of human exposure, it is essential to incorporate the oral bioaccessibility of these PTEs in HHRA. A site-specific approach is also necessary because bioaccessibility depends on the contaminant and soil type (Oomen et al., 2002). Two ISO standards, ISO 17402 (2011) and ISO 17924 (2019) are based on bioavailability and(or) bioaccessibility for exposure or risk assessment. However, some existing frameworks for the use of oral bioaccessibility in contaminated soil management (Environment Agency, 2009; Grøn and Andersen, 2003; Health Canada, 2017; MTES, 2017; Ng et al., 2015; Oomen et al., 2006; US EPA, 2007) recommend using bioaccessibility as a corrective factor for the total concentration, allowing for a more realistic estimation of exposure in risk calculations. Nevertheless, several aspects have not been sufficiently explained, including the appropriate conditions and good practices for using bioaccessibility.

Table 1. Effects of studied PTEs on human health

PTE	Effect on Human
Antimony	Cancer, cardiovascular diseases, conjunctivitis, dermatitis, liver diseases, nasal ulceration, blood, gastrointestinal and neurological dysfunction
Arsenic	Circulatory diseases, acute toxicity, dermatitis, skin cancer, blackfoot disease, proximal tubule degeneration, papillary and cortical necrosis, peripheral neuropathy, encephalopathy, hepatomegaly, cirrhosis, altered heme metabolism, diabetes, bone marrow depression, brain damage, cardiovascular disorder, conjunctivitis.
Cadmium	Adverse effects on kidneys, nephrotoxicity, bone disease, emphysema, headache, hypertension, itai-itai, kidney diseases, prostate cancer, lymphocytosis, microcytic hypochromic anemia, testicular atrophy, vomiting
Chromium	Emphysema, irritation of the skin, liver diseases, nausea, renal failure, reproductive toxicity, vomiting, skin rashes, weakened immune systems, kidney failure, alteration in genetic material, cardiovascular collapse in humans
Lead	Neurotoxic response, damage to neurons in children, impaired IQ, anorexia, chronic nephropathy, high blood pressure, hyperactivity, insomnia, learning deficits, reduced fertility, renal system damage, shortened attention span, various deleterious effects on the hematopoietic and central nervous system.
Nickel	Increased reactivity in Ni allergic persons, cardiovascular diseases, chest pain, dermatitis, dizziness, headache, kidney diseases, nausea Ni can be substitute to oligo-elements and disrupt metabolic pathways

Abdul et al., 2015; Assi et al., 2016; Ayangbenro and Babalola, 2017; Blais et al., 2008; FAO and UNEP, 2021; Flora et al., 2012; Grøn and Andersen, 2003; Raj and Maiti, 2020; Wang et al., 2023b; Zhitkovich, 2005

After presenting the common *in vitro* methods used to determine the oral bioaccessibility of PTEs, the objective of this review is to provide an overview of the current state of knowledge regarding (i) the ranges of PTEs bioaccessibility in soils; (ii) the factors that influence the oral bioaccessibility of As, Cd, Cr, Ni, Pb, and Sb in soils; and (iii) the use of bioaccessibility in HHRA and contaminated soil management on an international scale. This literature review aims to inform risk stakeholders about some points of attention surrounding the use of bioaccessibility data, mainly the information that should be collected and the links between factors and bioaccessibility, and to interpret better the results and use of bioaccessibility in risk studies.

1. Common *in vitro* extraction procedures for predicting bioaccessibility of PTEs

In vitro chemical extraction methods have been developed to substitute *in vivo* animal assays (Li et al., 2021). The most commonly used methods (Table 2) include the Physiologically Based Extraction Test (PBET; Ruby et al., 1996), the Solubility/Bioavailability Research Consortium method or Relative Bioavailability Leaching Procedure (SBRC or RBALP; Kelley et al., 2002), the US EPA Method 1340 (US EPA, 2017a, 2017b, 2021) derived from SBRC (only the gastric phase) and SBET (the Simple Bioaccessibility Extraction Test; Medlin, 1997), the *In vitro* Gastrointestinal test (IVG; Rodriguez et al., 1999) and its modified version (Basta et al., 2007) without dosing vehicle, the Deutsches Institut für Normung method (DIN 19738; Hack et al., 2002), and the Unified BARGE Method (UBM; Denys et al., 2012; ISO 17924, 2019) which is derived from the Dutch National Institute for Public Health and the Environment method (RIVM; Oomen et al., 2003). Moreover, more recently, a modified extraction procedure (the California Arsenic Bioaccessibility Method, CAB; California DTSC, 2015) was developed to improve the prediction of As bioavailability (Whitacre et al., 2017). Previous studies have compared the results of different *in vitro* tests using the same soil samples and have concluded that bioaccessibility values could vary significantly (De Miguel et al., 2012; Kierulf et al., 2022; Koch et al., 2013; Li et al., 2021; Oomen et al., 2002; Van de Wiele et al., 2007; Wragg et al., 2003; Zingaretti and Baciocchi, 2021). Indeed, the results are not generally comparable between tests, and data on the quality of bioaccessibility test methods are limited. The differences, which can sometimes be high (a factor of two between bioaccessibility estimated with a different method is highlighted), can be explained by variations in the protocols used, including (i) the physiological compartments included and their residence time, (ii) the pH of each compartment, (iii) the composition of the simulated digestive fluids, (iv) the solid-liquid (S: L) ratio of the soil sample and digestive fluids, (v) the inclusion of food during the test, and (vi) other sensitive parameters (e.g., mode of agitation, aerobic or anaerobic conditions, soil sample preparation, and the fraction considered). Differences in the pH of the acidic gastric digestion phase are given as the most likely explanation for the poor correspondence obtained with different *in vitro* tests (Bagherifam et al., 2019; Li et al., 2019; Oomen et al., 2002; Smith et al., 2014).

As previously mentioned, *in vitro* tests vary according to different parameters. Some are important because they influence the bioaccessibility results, ultimately impacting the strength of the *in vivo* - *in vitro* correlation (IVIVC). The IVIVC is crucial for determining the validity of bioaccessibility assays as surrogate measures for refining bioavailability for human exposure and risk. The validation of these *in vitro* methods involves comparing the bioaccessibility and bioavailability results obtained from animal experiments. The exact definitions and prerequisites for validation are still under debate, although an approach has been published by the US EPA (2007). The objective was to determine whether there was a sufficiently robust linear correlation to estimate the bioavailability of a PTE from its bioaccessibility in solutions simulating digestive fluids. Criteria for validity were identified to judge the robustness of the

Table 2. Overview of the common *in vitro* tests used to assess bioaccessibility of PTEs in soils

Method	Phase	Fluid composition (L ⁻¹)	pH	S:L ratio	Duration	PTEs	Particle size fraction	Reference
SBRC	Gastric	30.03 g glycine	1.5	1:100	1 h	As, Cd, Pb	<250 µm	Kelley et al. (2002)
	Intestinal	1.75 g bile, 0.5 g pancreatin	7	1:100	4 h			
PBET	Gastric	1.25 g pepsin, 0.5 g sodium malate, 0.5 g sodium citrate, 0.42 mL lactic acid, 0.5 mL acetic acid	2.5	1:100	1 h	As, Pb	<250 µm	Ruby et al. (1996)
	Intestinal	1.75 g bile, 0.5 g pancreatin	7	1:100	4 h			
IVG	Gastric	10 pepsin, 8.77 g NaCl	1.8	1:150	1 h	As, Pb	<250 µm	Rodriguez and Basta, 1999
	Intestinal	3.5 g bile, 0.35 g pancreatin	5.5	1:150	1 h			
DIN	Gastric	1 g pepsin, 3 g mucin, 2.9 g NaCl, 0.7 g KCl, 0.27 g KH ₂ PO ₄	2	1:100	2 h	As, Pb, Cd, Cr, Ni, Hg	<2 mm	Hack et al. (2002); DIN 19738
	Intestinal	9.0 g bile, 9.0 g pancreatin, 0.3 g trypsin, 0.3 g urea, 0.3 g KCl, 1 g NaHCO ₃ , 0.5 g CaCl ₂ , 0.2 g MgCl ₂	7.5	1:100	3 h			
UBM	Saliva	0.45 g KCl, 0.44 g NaH ₂ PO ₄ , 0.1 g KSCN, 0.28 g Na ₂ SO ₄ , 0.15 g NaCl, 0.1 g urea, 0.15 g amylase, 50 mg mucin, 15 mg uric acid, NaOH	6.5	1:15	10 s	As, Cd, Pb	<250 µm	Denys et al. (2012); ISO 17924 (2019)
	Gastric	1.85 g NaCl, 0.163 g NaH ₂ PO ₄ , 0.41 g KCl, 0.2 g CaCl ₂ , 0.15 g NH ₄ Cl, 0.32 g glucose, 20 mg glucuronic acid, 40 mg urea, 165 mg glucosamine hydrochloride, 1.0 g BSA, 3.0 g mucin, 1.0 g pepsin, HCl	1.2	1:37.5	1 h			
	Intestinal	Duodenal: 3.5 g NaCl, 2.8 g NaH ₂ PO ₄ , 40 mg KH ₂ PO ₄ , 0.28 g KCl, 25 mg MgCl ₂ , 50 mg urea, 0.2 g CaCl ₂ , 1.0 g BSA, 3 g pancreatin, 0.5 g lipase Bile: 2.6 g NaCl, 2.9 g NaHCO ₃ , 0.18 g KCl, 0.12 g urea, 0.2 g CaCl ₂ , 1.8 g BSA, 6.0 g Bile, HCl	6.3	1:97.5	4 h			
Method 1340	Gastric	30.03 g glycine, HCl	1.5	1:100	1 h	As, Pb	<150 µm	US EPA (2017a)

SBRC: Solubility/Bioavailability Research Consortium; PBET: Physiologically Based Extraction Test; IVG: *In vitro* Gastrointestinal test; DIN: Deutsches Institut für Normung; UBM: Unified Barge Method; Method 1340: *in vitro* bioaccessibility test from US EPA

correlation. These are (i) a statistically significant linear correlation (close to 1, in practice $R^2 > 0.6$); (ii) a sufficiently wide range of bioavailability values tested (an interval of approximately 70 % between the minimum and maximum values), which should make it possible to validate the correlation for different types of soil, thus theoretically enabling its use regardless of the study site; (iii) a good distribution of values in the range of bioavailability. In addition, the *in vitro* bioaccessibility test must be repeatable and reproducible, similar to any other experimental protocol. The criteria are intralaboratory repeatability (RSD or CV) < 10 % and interlaboratory reproducibility (RSD or CV) < 20 %. Wragg et al. (2011) adapted these guidelines to evaluate regression parameters and determine an acceptable IVIVC. Acceptable parameters included a slope close to 1 (in practice, between 0.8 and 1.2), r value >0.8, and $R^2 > 0.6$. In addition to the slope and R^2 , Juhasz et al. (2013) suggested that the y-intercept should be zero. Table 3 summarizes several studies' comparisons between the *in vitro* and *in vivo* methods. Linear regression models were also provided for predicting the *in vivo* relative bioavailability of PTEs (As, Cd, and Pb) in contaminated soils using *in vitro* bioaccessibility tests. Relative bioavailability was measured as the contaminant uptake in the target organ from the soil matrix relative to the uptake from a readily soluble salt of the contaminant (reference matrix). In general, methods for measuring the bioaccessibility of Pb have been validated with good results for the US EPA Method 1340 (RBALP or SBET), PBET, UBM, RIVM, and IVG tests. Among these tests, the Method 1340 met the maximum criteria for validation, and the RIVM and UBM tests. For As, validations were observed for the Method 1340, IVG, CAB, RIVM, PBET, and DIN tests. Similarly, for Cd, the methods listed for As yielded valid results. These results are consistent with those reported by Li et al. (2019), where IVIVC were established based on large sample sizes from different studies. For As, linear regression coefficient of determination (R^2) values are for the best extraction phase of each *in vitro* test: SBRC-G (0.73, n =107) > UBM-GI (0.71, n =63) > IVG-G (0.65, n = 102) > PBET-G (0.54, n = 60) > DIN-G (0.52, n = 47). For Pb, UBM-G (0.75, n = 36) > PBET-G (0.73, n =27) > SBRC-G (0.52, n =94) > IVGG(0.48,n = 138). For Cd, UBM-G (0.72, n =22) > DIN-G (0.65, n = 7) > PBET-GI (0.59, n =19) > SBRC-GI (0.44, n = 19) > IVG-G (0.39, n = 29). The study by Li et al. (2019) is critical for validating *in vitro* tests, as some have only been validated for a few soils (even if $R^2 > 0.6$) (i.e., DIN-G for Cd, $R^2 =0.65$ and n=7). This is consistent with the report of Basta et al. (2016), which was a comprehensive study comparing key *in vitro* methods (Method 1340, UBM, IVG without dosing vehicle, PBET and CAB), based on 27 As-contaminated soils and two animal models (adult mouse and juvenile swine). The *in vivo-in vitro* correlation analysis showed that the five methods predicted the relative bioavailability for both bioassays. More specifically, linear regression coefficient of determination (R^2) values were IVG (0.89) > UBM (0.84), PBET = Method 1340 (0.82) > CAB (0.74) using the mouse method, and IVG (0.73) > UBM (0.67), PBET (0.63) > Method 1340 (0.60) > CAB (0.54) using the swine method. In this report (Basta et al., 2016), swine As RBA (relative bioavailability) was greater than mouse As RBA but variability is larger for swine than mouse. This highlights the issue of the choice of animal model. *In vivo* tests on the closest models to humans (primates or piglets) are more expensive and difficult to carry out than those on rodents (mouse). Studies agree that mouse model can serve as a highly cost-effective alternative to swine assays for As RBA

Table 3. Linear regression models for predicting *in vivo* PTE relative bioavailability (RBD) in contaminated soils using *in vitro* bioaccessibility (BAc) in both gastric and gastrointestinal phases (GP and GIP, respectively).

PTE	Number of soils	<i>In vitro</i> method	<i>In vivo</i> model	RBD equation in GP	RBD equation in GIP	Reference
As	10	IVG with food (dough)	Juvenile swine	1.299 BAc + 5.12 (R ² = 0.92)	1.887 BAc + 3.96 (R ² = 0.90)	Basta et al. (2007)
	10	IVG with food	Juvenile swine	1.07 BAc + 5.81 (R ² = 0.96)	1.22 BAc + 4.94 (R ² = 0.82)	Basta et al. (2007)
	40	SBRC	Mouse	0.65 BAc + 7.8 (R ² = 0.81)	-	Bradham et al. (2015)
	20	SBET (Method 1340)	Swine	0.62 BAc + 19.7 (R ² = 0.72)	-	Brattin et al. (2013)
	13	UBM	Juvenile swine	1.0 BAc + 0.01 (R ² = 0.98)	0.99 BAc - 0.04 (R ² = 0.97)	Denys et al. (2012)
	49	RBALP (or SBET)	Swine	0.93 BAc (mg/kg) + 14.19 (R ² = 0.92)	-	Juhasz et al. (2007b)
	12	SBRC	Swine	0.992 BAc + 1.656 (R ² = 0.75)	1.644 BAc + 5.626 (R ² = 0.65)	Juhasz et al. (2009a)
	12	IVG	Swine	0.853 BAc + 14.323 (R ² = 0.57)	1.105 BAc + 13.971 (R ² = 0.57)	Juhasz et al. (2009a)
	12	PBET	Swine	1.162 BAc + 10.096 (R ² = 0.64)	1.762 BAc + 5.682 (R ² = 0.66)	Juhasz et al. (2009a)
	12	DIN	Swine	1.774 BAc + 5.732 (R ² = 0.546)	1.46 BAc + 9.2 (R ² = 0.53)	Juhasz et al. (2009a)
	13	SBRC	Swine	0.62 BAc + 5.4 (R ² = 0.90)	0.51 BAc + 19.1 (R ² = 0.61)	Juhasz et al. (2014b)
	13	IVG	Swine	0.59 BAc + 12.4 (R ² = 0.79)	0.59 BAc + 17.5 (R ² = 0.67)	Juhasz et al. (2014b)
	13	PBET	Swine	0.56 BAc + 13.7 (R ² = 0.78)	0.56 BAc + 14.6 (R ² = 0.85)	Juhasz et al. (2014b)
	13	DIN	Swine	0.6 BAc + 11.1 (R ² = 0.90)	0.61 BAc + 12.6 (R ² = 0.88)	Juhasz et al. (2014b)
	13	UBM	Swine	0.59 BAc + 9.8 (R ² = 0.90)	0.55 BAc + 12.6 (R ² = 0.89)	Juhasz et al. (2014b)
	13	SBRC	Swine	0.69 BAc + 5.24 (R ² = 0.75)	1.02 BAc + 6.85 (R ² = 0.71)	Juhasz et al. (2014a, 2015)
	13	IVG	Swine	0.89 BAc + 5.14 (R ² = 0.69)	0.91 BAc + 6.06 (R ² = 0.62)	Juhasz et al. (2015)
	13	PBET	Swine	0.60 BAc + 10.20 (R ² = 0.59)	0.66 BAc + 8.42 (R ² = 0.56)	Juhasz et al. (2015)
	13	UBM	Swine	0.54 BAc + 4.53 (R ² = 0.70)	0.58 BAc + 5.91 (R ² = 0.74)	Juhasz et al. (2015)
	13	DIN	Swine	0.64 BAc + 9.03 (R ² = 0.63)	0.88 BAc + 5 (R ² = 0.53)	Juhasz et al. (2015)
	12	UBM	Mouse	-4.40 BAc + 0.97 (R ² = 0.66)	4.43 BAc + 1.09 (R ² = 0.80)	Li et al. (2015a)
	12	SBRC	Mouse	-0.60 BAc + 0.96 (R ² = 0.67)	8.22 BAc + 1.35 (R ² = 0.5)	Li et al. (2015a)
	12	IVG	Mouse	-1.06 BAc + 1.29 (R ² = 0.83)	2.28 BAc + 1.35 (R ² = 0.81)	Li et al. (2015a)
	12	DIN	Mouse	12.1 BAc + 0.79 (R ² = 0.61)	4.52 BAc + 1.36 (R ² = 0.53)	Li et al. (2015a)
	12	PBET	Mouse	8.59 BAc + 1.08 (R ² = 0.56)	9.46 BAc + 1.04 (R ² = 0.5)	Li et al. (2015a)
	5	IVG	Mouse	0.87 BAc + 9.16 (R ² = 0.94)	-	Nagar et al. (2009)

	8	RIVM (S:L ratio of 1:1000)	Juvenile swine	0.802 BAc ($R^2 = 0.9083$)	0.957 BAc ($R^2 = 0.796$)	Oomen et al. (2006)
	8	RIVM (S:L ratio of 1:100)	Juvenile swine	1,88 BAc ($R^2 = 0.94$)	5.18 BAc ($R^2 = 0,23$)	Oomen et al, (2006)
	13	IVG	Juvenile swine	1.136 BAc + 2.02 ($R^2 = 0.83$)	1.316 BAc + 1.36 ($R^2 = 0.82$)	Rodriguez and Basta (1999)
	13	PBET	Juvenile swine	1.724 BAc - 1.724 ($R^2 = 0.51$)	2.564 BAc - 0.07 ($R^2 = 0.75$)	Rodriguez and Basta (1999)
Cd	10	UBM	Juvenile swine	1.04 BAc - 2.66 ($R^2 = 0.97$)	1.06 BAc - 1.43 ($R^2 = 0.91$)	Denys et al. (2012)
	7	SBRC	Mouse	0.991 BAc - 51.388 ($R^2 = 0.58$)	1.522 BAc - 50.842 ($R^2 = 0.80$)	Juhasz et al. (2010)
	7	IVG	Mouse	0.936 BAc - 29.141 ($R^2 = 0.42$)	1.578 BAc - 22.985 ($R^2 = 0.58$)	Juhasz et al. (2010)
	7	PBET	Mouse	0.778 BAc - 14.765 ($R^2 = 0.75$)	1.091 BAc - 5.14 ($R^2 = 0.835$)	Juhasz et al. (2010)
	7	DIN	Mouse	0.863 BAc - 20.764 ($R^2 = 0.58$)	1.805 BAc - 2.159 ($R^2 = 0.55$)	Juhasz et al. (2010)
	10	IVG with food (dough)	Juvenile swine	5.263 BAc - 27.5 ($R^2 = 0.55$)	7.692 BAc - 5.07 ($R^2 = 0.80$)	Schroder et al. (2003)
	10	IVG without food	Juvenile swine	1.667 BAc - 25.4 ($R^2 = 0.86$)	4.762 BAc - 25.8 ($R^2 = 0.54$)	Schroder et al. (2003)
Pb	14	UBM	Juvenile swine	0.91 BAc - 1.86 ($R^2 = 0.93$)	1.92 BAc - 1.09 ($R^2 = 0.89$)	Denys et al. (2012)
	19	Method 1340 (RBALP or SBET)	Juvenile swine	0.878 BAc - 0.028 ($R^2 = 0.924$)	-	Drexler et al. (2007)
	5	SBRC	Juvenile swine	-0.18 BAc + 25.26 ($R^2 = 0.12$)	4.07 BAc + 6.84 ($R^2 = 0.14$)	Juhasz et al. (2009b)
	10	RIVM (S:L ratio of 1:100)	Juvenile swine	1.27 BAc ($R^2 = 0.95$)	1.45 BAc ($R^2 = 0.81$)	Oomen et al. (2006)
	10	RIVM (S:L ratio of 1:1000)	Juvenile swine	0.93 BAc ($R^2 = 0.68$)	0.86 BAc ($R^2 = 0.66$)	Oomen et al. (2006)
	7	PBET	Rat	1.4 BAc + 3.2 ($R^2 = 0.93$)	-	Ruby et al. (1996)
	18	IVG with food (dough)	Juvenile swine	2.56 BAc - 2.97 ($R = 0.93$)	100 BAc - 0.0002 ($R = 0.80$)	Schroder et al. (2004)
	18	IVG without food	Juvenile swine	1.54 BAc + 1.44 ($R = 0.89$)	100 BAc - 0.52 ($R = 0.38$)	Schroder et al. (2004)

RBA and BAc are expressed in %PBET: Physiologically Based Extraction Test; SBET: Simple Based Extraction Test; US EPA Method 1340: *in vitro* bioaccessibility test from US EPA; SBRC: Solubility/Bioavailability Research Consortium; RBALP: Relative Bioavailability Leaching Procedure; IVG: *In vitro* Gastrointestinal test; RIVM: Dutch Rijksinstituut voor Volksgezondheid en Milieu; UBM: Unified Barge Method; DIN: Deutsches Institut für Normung

assessment (Diamond et al., 2022) because for most soil samples they showed that RBA of swine was similar to mouse (Basta et al., 2016; Bradham et al., 2013; Diamond et al., 2016; Li et al., 2017). These studies also showed that sometimes the RBA estimated using the mouse model underestimates the RBA estimated using the swine model. This suggests that we should remain cautious of tests validated by a large number of *in vivo* tests, depending on the models used. Even if the study of Bradham et al. (2016) showed that the use of mouse model for Pb RBA assessment is promising, more tests are needed, in particular for other PTEs than As, to compare RBA obtained through mouse and swine model before starting using the mouse model for RBA assessment.

Initially, these tests were developed for one or few PTEs (mostly Pb, As, and Cd); however, they have been extended to various PTEs for which they have not yet been shown to be suitable analogs of *in vivo* conditions. An attempt to validate the UBM test for Sb was made but was incomplete (Denys et al., 2012), as the small bioaccessibility range covered in the study did not make the dataset suitable for calibrating Sb bioaccessibility measurements from *in vitro* testing methods.

2. Ranges of PTEs bioaccessibility data in soils

The gastric and gastrointestinal bioaccessibility ranges of the six PTEs of interest (As, Cd, Cr, Ni, Pb and Sb) are presented in Fig. 1, and are based on the results pooled from different *in vitro* tests. The bioaccessibility values can range from 0 to 100 %, depending on the study, the *in vitro* protocol, and the considered element. Specifically, for each PTE, the bioaccessibility ranges in both G and GI phases were considered in 10 % increments, and the graphs show the percentages of studies that reported bioaccessibility values at each step. Further details are provided in the Supplementary Material (SM). The most available data were for Pb and As. Nearly half of the studies found As bioaccessibility values below 30 % in both G and GI phases. These results follow those of the analysis of As RBA estimates in soils from various sites of regulatory interest (US EPA, 2012a), which showed that <5 % of the RBA estimates exceeded 60 %. In that way, in cases where the development of site-specific RBA estimates is not feasible, US EPA recommends using a default value of 60 %. More than half of the studies found bioaccessibility ranges of Pb and Cd below 50 % and 60 % in the G phase and below 30 % and 40 % in the GI phase respectively. Low bioaccessibility ranges were observed for Cr, Ni and Sb. Less than three-quarters of the studies reported values below 20 %, 30 %, and 40 % in the G phase and 30 %, 20 %, and 30 % in the GI phase for Cr, Ni, and Sb respectively. The bioaccessibility ranges were usually larger for As, Cd, and Pb than for Cr, Ni, and Sb. The bioaccessibility tended to be higher in the G phase than in the GI phase for Cd, Ni, Pb, and Sb. Their solubility depends on pH and greatly increases in acidic environments (Sintorini et al., 2021)(e.g., stomach or simulated gastric phase). However, in the near-neutral pH and carbonate-rich environment of the intestinal phase (depending on the *in vitro* test used), PTEs may be stabilized in solution by complexation, re-adsorption on remaining particles or other insoluble constituents of chyme, and(or)

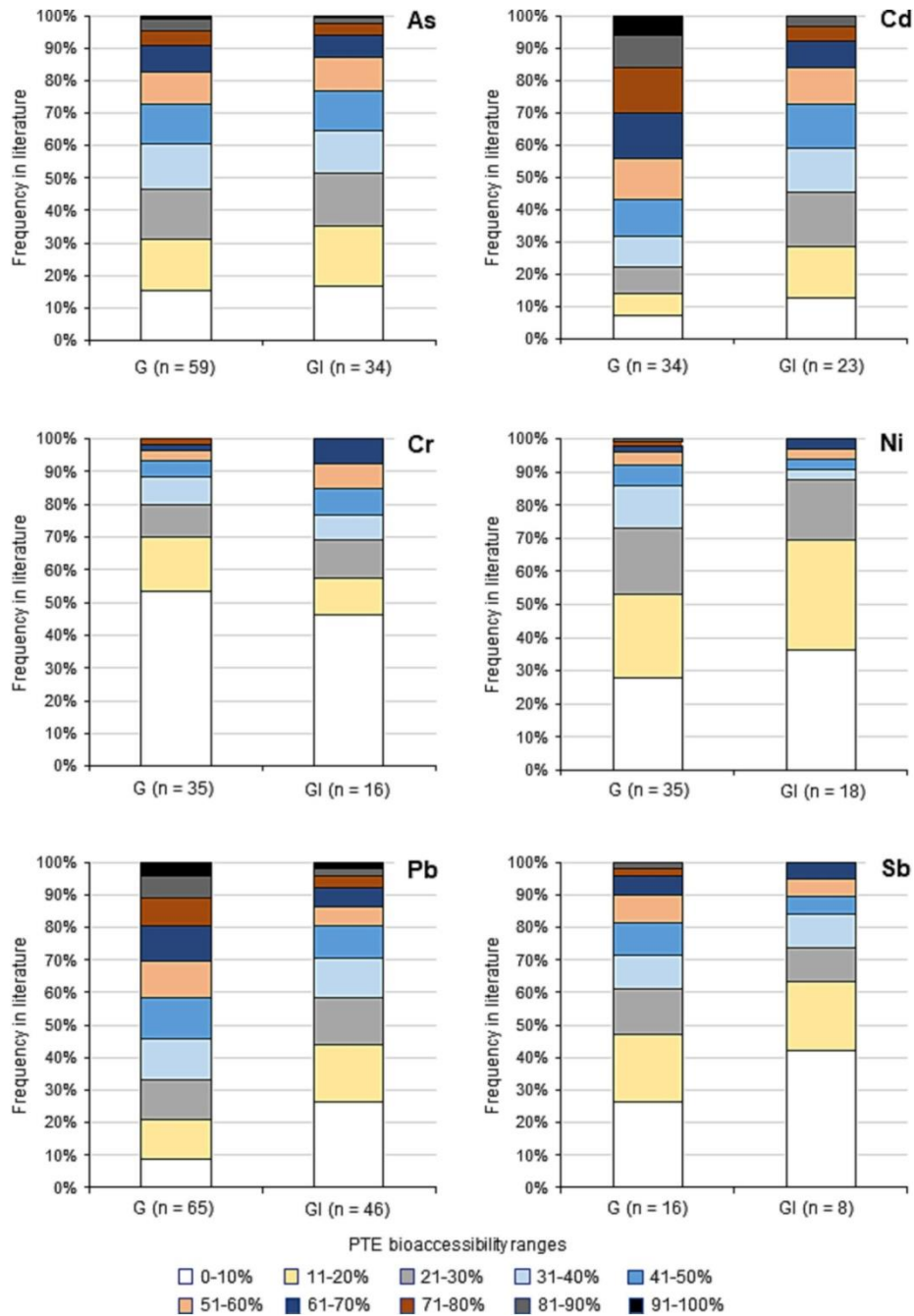


Fig. 1. Bioaccessibility ranges of As, Cd, Cr, Ni, Pb, and Sb in gastric (G) and gastrointestinal (GI) phases according to their frequency of occurrence in the literature.

precipitation as relatively insoluble compounds, making them less bioaccessible (Bagherifam et al., 2019; Cao et al., 2020; Grøn and Andersen, 2003). The distribution of As was similar in both phases. For Cr, in contrast to other PTEs, the bioaccessibility ranges reported in the literature appear slightly higher in the GI phase than in the G phase. As and Cr can be found in both anionic and cationic forms, indicating that these elements can behave differently in response to pH variations. A high pH can provoke the desorption of negatively charged species (anions) owing to a decrease in the positive charges of soil matrix compounds (De Miguel et al., 2012), or it may be associated with the formation of oxosoluble species at higher pH (Sialelli et al., 2011). Regarding the patterns, the differences between Ni and the other cationic elements (Cd and Pb) can be explained by their often geogenic origin, leading to a larger percentage of undissolved Ni in the G phase compared to Cd or Pb, which are mainly derived from anthropogenic sources (Ljung et al., 2007). Sb is similar to As, as both occur mainly as oxides, hydroxides, or oxo-anions and share the same major oxidation states (+III, +V) (Wilson et al., 2010), but their behavior in soils differs. The lower bioaccessibility values observed for some PTEs (particularly Cr, Ni, and Sb) suggest that further studies should consider their bioaccessibility and incorporate the data into HHRA; however, *in vivo* validations should first be established.

3. Factors influencing oral bioaccessibility of PTEs

Soils are complex matrices whose constituents can interact with PTEs and modify their mobility and bioavailability. Measuring the total (or pseudototal) concentration of PTEs is insufficient for estimating the associated risk. It is necessary to consider bioavailability through bioaccessibility to account for the influence of the soil matrix. This review identified the most important influencing factors, including the source of contamination, physicochemical soil properties, chemical form (i.e., speciation), and solid phase distribution of the element in question.

3.1. Influence of the source of PTEs in soils

PTE environmental concentrations are related to natural phenomena such as weathering, biological activity, volcanic activity, and anthropogenic inputs such as agriculture, industry, mining, and urban sources. However, their bioaccessibility tends to be much lower when their origin in soils is geogenic compared with recent anthropogenic contamination (Bagherifam et al., 2019; Barsby et al., 2012; Morman et al., 2009; Madrid et al., 2008; Wang et al., 2020). In the case of geogenic contamination, PTEs tend to be sequestered over time, mainly through maturation processes, such as adsorption and trapping in soil micropores and organic matter (Diquattro et al., 2021; Fendorf et al., 2004; Stewart et al., 2003b). PTEs such as Cr, Ni, and Sb are often incorporated into the crystal lattice (i.e., assessed in the residual fraction by chemical sequential extractions), explaining their low bioaccessibility (Chu et al., 2022; Ding et al., 2022; Wang et al., 2023b).

The correlation between the total concentration of a PTE and its bioaccessibility may reflect a common source of contamination (Barsby et al., 2012; Darko et al., 2019).

PTEs derived from anthropogenic sources are generally more soluble in the gastrointestinal environment than naturally occurring PTEs (Ljung et al., 2007). However, with anthropogenic contamination, bioaccessibility can vary depending on the source. For example, a meta-analysis by Kierulf et al. (2022) highlighted a higher gastric bioaccessibility of As in industrial soils than mining and rural soils and a high gastric bioaccessibility of Cd in agricultural soils. In contrast, the bioaccessibility of Cr in the gastric phase was higher than that in both industrial and urban soils. If the origin of contamination is known (geogenic or anthropogenic), it can be an indicator to get an initial idea of PTE bioaccessibility. However, predicting bioaccessibility becomes more complex when the contamination origin of PTEs is both geogenic and anthropogenic or only anthropogenic.

3.2. Influence of soil properties

The bioaccessibility of soil-bound PTEs depends on soil properties and contaminants. The influence of these different parameters on the bioaccessibility of PTEs is shown in Table 4, with total PTE concentration, pH, CEC, organic matter (OM), oxides, carbonates, and phosphate content, and granulometry. This table summarizes studies that have shown significant (positive or negative) correlations between the bioaccessibility of PTE and a given parameter. Studies that showed no significant influence of a parameter on bioaccessibility were also included. This table presents soil parameters and bioaccessibility correlations, expressed in mg kg^{-1} or percentage. The results of statistical analyses of bioaccessibility in both units are not always consistent (Cox et al., 2013; Liu et al., 2016). The correlations obtained with percentage bioaccessibility were included for clarity in this case. When significance test information was unavailable, the influence was considered if the correlation coefficient was higher than 0.5 (Pearson R² or Spearman Rho >0.5). When several soil fractions were tested, the fraction <250 μm recommended by most tests was used. Correlations were also read graphically (if the principal component analysis was used) when no other information was available but only when the correlations were excellent. Each reference has been numbered to facilitate the understanding of the table, and Table 5 presents each study in more detail, including its location, context, number of soils, and *in vitro* assay used.

3.2.1. Soil pH

The pH of the soil solution controls many reactions in the soil, such as solubilization/precipitation, adsorption/desorption on the soil matrix, or speciation in the soil solution and can influence the surface charges of soil particles. The pH of the soil solution is linked to the soil pH and its compounds. Soil pH is one of the significant parameters controlling the availability of PTEs directly or indirectly by influencing other soil properties (e.g., the charge of Al and Fe oxides and the exchange capacity of clays) and has a direct effect on absorption (Basta et al., 1993; Du et al., 2020; Lake et al., 2021). Soil pH is linked to the soil's redox potential (Eh), which controls the oxidation state of PTEs and subsequently affect their mobility

Table 4. Summary of PTE bioaccessibility studies addressing correlations with soil properties

	As						Cd					
	Gastric phase			Gastro-intestinal phase			Gastric phase			Gastro-intestinal phase		
	Negative correlation	No significant correlation	Positive correlation	Negative correlation	No significant correlation	Positive correlation	Negative correlation	No significant correlation	Positive correlation	Negative correlation	No significant correlation	Positive correlation
Soil matrix												
Total concentration	[9]	[19]	[1] [2] [3] [6] [7] [16] [21] [24]			[1] [2] [3] [7] [16] [21] [24] [31]	[22]	[9]	[2] [3] [4] [7] [14] [20] [21] [27]	[30]		[2] [3] [4] [7] [20] [21] [27]
pH		[1] [12] [16] [19]	[6] [9] [15] [23] [35]		[1] [12] [16] [35]			[9] [12] [20] [22] [29] [35]	[23]	[30]	[12] [20] [29] [35]	
CEC		[15] [35]			[35]	[31]		[29] [35]		[29]	[35]	
OM content / TOC	[6] [11] [16] [35]	[1] [9] [12] [15]	[19] [23]	[16] [35]	[1] [12] [31]		[23]	[12] [20] [22] [29] [35]	[9] [30] [36]	[21] [35]	[12] [20] [29]	
Oxides Fe / Fe tot	[6] [12] [15] [16] [23]	[1] [9] [35] [19]		[12] [16] [35]	[1]		[9] [12] [22] [23]	[20] [29] [35]		[35]	[12] [20] [29]	
Oxides Mn / Mn tot	[1] [12] [16]	[1] [6] [19] [23] [35]		[1] [12] [16]	[1] [35]		[12] [22]	[29] [20] [23] [35]			[12] [20] [29] [35]	
Oxides Al / Al tot	[12] [16] [23] [15]	[35] [19] [1]	[9]	[12] [16] [35]	[1]		[12] [22]	[20] [35] [9] [23]		[35]	[12] [20]	
Oxides Mg / Mg tot												
Carbonates			[12]						[12]			[12]
Phosphorus		[16]	[9]		[16]			[9] [20]			[20]	
Clay	[6] [11] [15]	[12] [35]			[12] [35]		[20]	[12] [35]	[36]	[20] [30]	[12] [35]	
Silt		[12] [35]			[12] [35]			[12] [20] [35]			[12] [35] [20]	
Sand		[12] [35]	[11]		[12] [35]			[12] [20] [35]			[12] [35] [20]	
Solid phase distribution												
Acid-exchangeable phase			[1] [18]			[1] [18]		[29]	[17] [29]		[17] [29]	[17]
Reducible phase	[18]		[1]	[18]		[1]	[29]	[17]	[17]	[29]	[17]	[17]
Oxidable phase	[18]		[1]		[18]	[1]	[29]	[17]	[17]	[29]	[17]	
Residual fraction		[18]			[18]			[29]			[29]	

(continued on next page)

Table 4. (continued)

	Cr						Ni					
	Gastric phase			Gastro-intestinal phase			Gastric phase			Gastro-intestinal phase		
	Negative correlation	No significant correlation	Positive correlation	Negative correlation	No significant correlation	Positive correlation	Negative correlation	No significant correlation	Positive correlation	Negative correlation	No significant correlation	Positive correlation
Soil matrix												
Total concentration		[4] [7] [9] [22] [33]	[2] [5] [38]		[4] [7]	[2] [5] [30]	[25] [22]	[2] [5] [7] [8] [9] [26] [33]	[4] [14]	[25]	[2] [7] [26]	[4] [5]
pH	[9] [38]	[5] [12] [13] [33]	[22] [23]	[30]	[5] [12]		[25] [36]	[5] [8] [9] [12] [13] [22] [23] [26] [32] [33]			[12] [26] [25]	[5]
CEC	[36]	[13]	[38]					[8]	[13]			
OM content / TOC		[5] [12] [13] [22] [23]	[9] [30] [33] [38] [36]		[12] [5]			[5] [8] [12] [13] [22] [23] [33]	[9] [25] [26] [32] [33] [36]	[5]	[12]	[25] [26]
Oxides Fe / Fe tot	[22] [23]	[9] [12] [13]	[5]		[12]	[5]	[9] [13] [22] [23] [25]	[5] [8] [12]	[32]	[25]	[5] [12]	
Oxides Mn / Mn tot	[22] [23]	[12]	[5]		[12]	[5]	[25]	[5] [12] [22] [23]		[25]	[5] [12]	
Oxides Al / Al tot	[22] [23]	[9] [12]	[5]		[12]	[5]	[9] [22] [25] [23]	[5] [12]		[25]	[12]	[5]
Oxides Mg / Mg tot		[13]	[5]			[5]	[25]	[5] [13]		[25]		[5]
Carbonates		[12]			[12]			[12]			[12]	
Phosphorus		[5] [9] [33]	[5]		[5]	[5]	[5]	[5] [25] [9]		[5]	[5] [25]	
Clay		[12]		[30]	[12]		[26]	[12] [33]	[32]	[26]	[12]	
Silt		[12]			[12]		[26]	[12]			[12]	[26]
Sand		[12]			[12]			[12]	[26]		[12]	[26]
Solid phase distribution												
Acid-exchangeable phase		[33]						[33]	[8] [33]			
Reducible phase		[33]							[8] [33]			
Oxidable phase		[33]	[13]				[33]	[33]	[8] [13]			
Residual fraction	[38]	[33]					[8]	[33]				

(continued on next page)

Table 4. (continued)

	Pb						Sb					
	Gastric phase			Gastro-intestinal phase			Gastro-intestinal phase			Gastro-intestinal phase		
	Negative correlation	No significant correlation	Positive correlation	Negative correlation	No significant correlation	Positive correlation	Negative correlation	No significant correlation	Positive correlation	Negative correlation	No significant correlation	Positive correlation
Soil matrix												
Total concentration		[22] [28] [37] [38]	[2] [3] [4] [7] [9] [14] [20] [21] [27] [26]		[31]	[2] [3] [4] [7] [10] [20] [21] [26] [27] [30]			[16] [24] [34]			[16] [24]
pH	[9]	[12] [15] [20] [22] [23] [26] [37] [38]	[28]		[12] [20] [26]			[12] [16] [34]			[12] [16]	
CEC	[28] [15]	[38]	[37]		[31]	[10]	[28]					
OM content / TOC	[28]	[12] [15] [20] [22] [23] [37] [38]	[9] [26]	[10]	[12] [20] [30] [31]	[26]	[16]	[12]	[34]	[16]	[12]	
Oxides Fe / Fe tot	[9] [12] [15] [28]	[20] [22] [23]			[12] [20]		[16] [28]	[12] [34]		[16]	[12]	
Oxides Mn / Mn tot		[12] [20] [22] [23]			[12] [20]		[16]	[12] [34]		[16]	[12]	
Oxides Al / Al tot	[9] [15]	[12] [20] [22] [23]			[12] [20]		[16]	[12]		[16]	[12]	
Oxides Mg / Mg tot												
Carbonates		[12]			[12]	[10]		[12]			[12]	
Phosphorus		[20] [9]			[20]			[16]			[16]	
Clay	[15] [20] [26]	[12] [37]		[10] [26]	[12] [20]			[12] [34]			[12]	
Silt	[26]	[12] [20] [37]		[26]	[12] [20]		[34]	[12]			[12]	
Sand		[12] [20] [37]	[26]		[12] [20]	[26] [30]		[12]	[34]		[12]	
Solid phase distribution												
Acid-exchangeable phase		[18]	[10]		[18]							
Reducible phase	[18]		[10]			[18]						
Oxidable phase	[10] [18]			[18]								
Residual fraction	[38]	[18]		[18]								

Numbers from [1] to [38] correspond to studies from literature listed in Table 5

Table 5. List of studies cited in Table 4

Study	Reference	Location	Context	Number of soils	<i>In vitro</i> test
1	Bari et al. (2021)	Australia	Abandoned mine locations	7	SBRC / PBET
2	Barsby et al. (2012)	Ireland	Rural and urban soils	91	UBM
3	Boisa et al. (2013)	Kosovo	Mining and smelting area	128	UBM
4	Chu et al. (2022)	China	Nonferrous smelting area	32	PBET
5	Cox et al. (2013)	Ireland	Overlying Palaeogene basalt lavas	12	UBM
6	Das et al. (2013)	India	As-enriched soil	7	SBET
7	Ding et al. (2014)	China	Urban soils	43	PBET
8	Ding et al. (2022)	China	Natural soils containing serpentine minerals and anthropogenically contaminated soils	48	SBRC
9	Dodd et al. (2017)	Canada	Background soils	532	Method 1340
10	Finžgar et al. (2007)	Slovenia	Mining and smelting area	18	PBET
11	Girouard et Zagury (2009)	Canada	Chromated copper arsenate contaminated soils	20	IVG
12	Hiller et al. (2022)	Slovakia	Urban garden	33	PBET
13	Kelepertzis and Stathopoulou (2013)	Greece	Non anthropogenic contamination	15	PBET
14	Laha et al. (2020)	India	Playgrounds	16	SBET
15	Lake et al. (2021)	-	-	19	Method 1340
16	Li et al. (2014)	China	Mining area	29	SBET / PBET
17	Li et al. (2022)	-	-	12	UBM/SBRC/IVG/PBET
18	Liang et al. (2016)	China	Spiked soils	3	PBET
19	Liu et al. (2016)	China	Rural and urban soils	80	SBET
20	Liu et al. (2018)	China	Mining soils	33	PBET
21	Louzon et al. (2020)	France	Urban, industrial, agricultural, soils	30	UBM
22	Ma et al. (2019)	China	Urban school/kindergarten soil	3	SBET
23	Ma et al. (2020)	China	Schools or kindergartens urban and rural areas	58	SBET
24	Ning et al. (2021)	China	Farming area / mining and smelting area	29	SBET
25	Palmer et al. (2013)	Ireland	Bedrock soils	91	UBM
26	Poggio et al. (2009)	Italy	Agricultural and residential soils	66	PBET
27	Roussel et al. (2010)	France	Urban soils	27	UBM
28	Sanderson et al. (2012)	Australia	Shooting range soils	4	SBET
29	Tang et al. (2006)	China	Unpolluted soils	5	PBET
30	Tian et al. (2020)	China	Urban soils	124	PBET
31	Van der Kallen et al. (2020)	Canada	Chromated copper arsenate contaminated soils	10	IVG
32	Vasiluk et al. (2019)	Canada	Ultramafic soils	8	SBRC
33	Wang et al. (2020)	Taiwan	Natural soils containing serpentine minerals and anthropogenically contaminated soils from farmlands	27	Method 1340
34	Wang et al. (2023b)	China	Farmland soil	269	SBRC
35	Xia et al. (2016)	Australia	-	7	UBM
36	Xia et al. (2022)	China	Industrial sites	27	PBET
37	Yan et al. (2019)	Australia	Mining, shooting ranges, smelting soils	31	RBALP
38	Yang et al. (2018)	China	Urban soils	12	PBET

and toxicity. Although Eh is a parameter governing the speciation of PTEs, only pH is measured by stakeholders because of the variation in Eh over time. Negative correlations between the soil pH and PTEs bioaccessibility were found in the literature for both phases (Table 4). Indeed, a low soil pH can lead to the desorption of PTEs from organic, clay, or other sorbent compounds (Rinklebe and Shaheen, 2017) and whereas an alkaline pH can promote substantial and(or) sometimes irreversible adsorption (Grøn and Andersen, 2003; Yang et al., 2006). Therefore, cationic PTEs may be less strongly adsorbed in acidic soils and are thus more bioaccessible because of their global positive charge. The behavior of PTEs that can be found in both anionic and cationic forms (As, Cr and Sb) in response to pH changes is more complex, as they are found to change their affinities with soil matrix compounds. Studies have generally found positive correlations for Cr and As (Table 4), indicating that a lower soil pH leads to lower bioaccessibility, and vice versa. A neutral to basic soil pH, together with assumed high Eh value, can favor the appearance of soluble Cr (VI), whereas the opposite would enhance the appearance of less soluble Cr (III) (De Miguel et al., 2012; Wolf et al., 2007). In several studies, there was a consensus on the fact that there was a positive relationship between soil pH and the bioaccessibility of As, using UBM, PBET or USEPA Method 1340 (Lake et al., 2021). Furthermore, high soil pH can promote the desorption of negatively charged species owing to the higher number of negative sites on the surface of iron oxides (Das et al., 2013; Juhasz et al., 2009a). Conversely, acidification of the soil in the G phase can cause an increase in the adsorption of negatively charged PTE on iron oxides, decreasing the bioaccessibility in the same way (Xia et al., 2016).

3.2.2. *Soil organic matter*

Soil organic matter (OM) content varies widely among soils. OM includes non-humic (i.e., unaltered biochemicals that have not been degraded through production by living organisms) and humic compounds (i.e., formed by secondary synthesis reactions involving microorganisms). Dissolved organic carbon (DOC) is the fraction of organic carbon dissolved in soil water or extracted from soil samples. DOC is an essential component of soil OM and can affect the mobilization of PTEs (Kalbitz and Wennrich, 1998). Soil OM can act as a negatively charged surface, depending on the pH of the soil solution. OM contains functional groups such as carboxyl, phenolic, enolic and alcoholic groups (Zhou and Haynes, 2010), which can ionize and become negatively charged under certain pH conditions. Negative charges on soil OM particles allow them to attract and retain positively charged ions, including PTE. The soil OM's functional groups can form covalent bonds with cationic PTEs, leading to the immobilization or reduced mobility of these elements in the soil. Moreover, OM (as well as some clays and oxides) has a variable charge depending on the pH of the soil solution, explicitly referring to the point of zero charges (PZC). At pH values below the PZC, the surfaces of the particles became positively charged, whereas, at pH values above the PZC, the surfaces became negatively charged. This charge variability may affect the interactions between soil components, including the adsorption and desorption of ions, as well as the overall chemical properties of the soil. Thus, the mechanisms that control the bioaccessibility of PTEs in the presence of soil OM and DOC are complex and simultaneous involve (i) the adsorption and complexation of cations on negatively charged sites (ion

exchange), (ii) the mobility of some PTEs ions from adsorption through the formation of low molecular weight chelates, and (iii) the retention of many higher molecular weight contaminants in the solid forms of humus (Selinus et al., 2013; Zhou and Haynes, 2010). Soil OM can reduce the bioaccessibility of metals by immobilizing them in the soil matrix, making them less available. Covalent bonding between functional groups on soil OM and metal ions can form stable complexes, reducing their mobility and bioaccessibility. The binding of PTEs to soil OM and DOC sequesters them in OM aggregates or humic substances. This sequestration process limits the bioavailability of PTEs. Moreover, the pH-dependent charge of the soil OM can influence the bioaccessibility of PTEs. At low pH values, the positively charged surfaces of soil particles and OM may enhance metal adsorption and reduce bioaccessibility. Conversely, negatively charged surfaces can repel metals at higher pH values, potentially increasing their bioaccessibility. The literature shows that OM can decrease or increase the bioaccessibility of PTEs in soils (Table 4). For example, Cai et al. (2016) found that the bioaccessibility of Pb decreased with increasing OM content because of its high affinity for each other. In some cases, the retention mechanisms may be weaker, inducing easier release by digestive fluids. De Miguel et al. (2012) found that polar groups of OM probably fixed the small bioaccessible fraction of Cr. Therefore, the influence of OM may depend on the affinity and intensity of the retention mechanisms between the OM and PTEs.

3.2.3. Mineral constituents

The inorganic constituents of soils typically constitute most of the soil mass. The interaction between PTEs and the surfaces of these compounds is a critical process that governs their bioaccessibility. The mineralogical properties that affect the bioaccessibility of PTEs include encapsulation in insoluble matrices; formation of insoluble alteration or precipitation rinds; and formation of iron oxide, PTE oxide, and PTE phosphate cement, which reduce the surface area available for dissolution (Davis et al., 1996). Oxides of iron, manganese, aluminum, clays, carbonates, and phosphates have been identified as having the most significant influence on the bioaccessibility of PTEs. All these constituents affect the cation exchange capacity (CEC), a correlation parameter reported in the literature. Fe, Mn, and Al are often referred to as hydrous oxides, and similar to clays, they are mainly derived from the weathering reactions of rock minerals. These minerals have vast reactive surface areas and similar modes of action to bind contaminants, including cation and anion exchange and specific adsorption. PTEs are electrostatically bound to clay or oxide surface sites with opposite cation- and anion-exchange charges. As mentioned previously, OM can also act as an ion exchanger. CEC represents the ability of the soil to attract and retain cations, and it mainly measures the number of sorption sites available on the soil matrix compounds (Finžgar et al., 2007). However, the literature indicates that the influence of CEC can be both positive and negative (see Table 4). An increase in bioaccessibility related to an increase in CEC can occur, because a higher CEC can improve the solubility of PTEs in an exchangeable form in the soil (Kelepertzis and Stathopoulou, 2013; Yan et al., 2019). The bioaccessibility of cationic and anionic PTEs may be less affected by CEC.

Specific adsorption involves the exchange of cations and anions with surface ligands on solids to form partially covalent bonds with lattice ions. As with cation and anion exchange, specific adsorption highly depends on pH, charge, and ionic radius. However, this binding mechanism is much stronger. Several studies have confirmed the importance of oxides in the bioaccessibility of contaminants, which play a critical role in controlling soil chemical reactions and may retain significant quantities of PTEs in the soils. Moreover, soil pH and Eh determine the soil's distribution of Fe and Mn oxide fractions (Bagherifam et al., 2019). Similar to OM, the surface charge of oxides can vary with pH. The surface has a net positive charge at pH values lower than the PZC (Zhou and Haynes, 2010). Overall, the literature shows that the presence of oxides or total Fe, Al, Mn, and Mg reduces the bioaccessibility of all PTEs (Table 4). Associations (adsorption and coprecipitation) with oxides tend to be relatively stable and, therefore, more resistant to dissolution by digestive fluids (Diquattro et al., 2021; Lake et al., 2021; Li et al., 2014; Niyommaneerat and Aung, 2010; Rinklebe and Shaheen, 2017). In some cases, the bioaccessibilities of PTEs and oxide compounds were positively correlated. One explanation may be that weathering transforms primary iron oxides into secondary oxides over time, and PTEs tend to be more bioaccessible (Cox et al., 2017). Although geogenic PTEs are often not bioaccessible because of sequestration mechanisms, mineral weathering can increase their bioaccessibility over time (Fendorf et al., 2004).

The effect of phosphorus (P) on bioaccessibility has received little attention in the literature, although some studies have highlighted the relationships between the two; for Cr and As, phosphorus appeared to be positively correlated with gastric bioaccessibility, whereas for Ni and Pb, the opposite was observed (Table 4). Soluble phosphorus is often associated with As mobilization, as both can be found in anionic species. The addition of P has been shown to increase As bioaccessibility (Basta et al., 2007; Basta and Juhasz, 2014) because of the similarity between P and As, which makes it possible for P to desorb As from the soil (Li et al., 2017). Phosphorus is an essential component of soil when considering As chemistry. In contrast, Pb bioaccessibility decreased when phosphorus was added to Pb-contaminated soils due to the formation of Pb–P minerals during the acidic gastric *in vitro* test phase (Li et al., 2017; Tian et al., 2020). The effect of soluble phosphorus can vary between elements with cationic and anionic behavior.

Clay, sand, and silt contents also appeared to influence the bioaccessibility of PTEs. Similarities were found for some elements, where the clay content and bioaccessibility of As, Cd, Cr, Ni, and Pb were generally negatively correlated, and the sand content and bioaccessibility of As, Ni, Pb, and Sb were positively correlated (Table 4). The uptake of PTEs by clay minerals in soils may limit their mobility through stronger bonds (Tian et al., 2020). In contrast, the association with sand content induced weaker associations, making the elements more bioaccessible. The literature review highlights the critical influence of inorganic compounds, which can resist the dissolution of digestive fluids through strong retention mechanisms (oxides and clays).

PTEs associated with carbonates are generally relatively bioaccessible because of the acidic pH of the gastric phase. Cox et al. (2013) found that bioaccessible Ni is often present in carbonates and that Cr is only weakly bound to carbonates. PTEs contained in carbonates are quickly released in the acidic gastric phase,

which could partly explain the lower bioaccessibility of Cr than that of Ni. However, the total amount of carbonates is not always sufficient to understand bioaccessibility because, some elements may have variable affinities depending on chemical speciation. Denys et al. (2008) found no association between Sb and carbonates. This may be due to the prevalence of Sb (V), which has a lower affinity for carbonates than Sb (III).

3.2.4. *Solid phase distribution and chemical form*

The adsorption of contaminants onto different solid phases is a key factor determining the bioaccessibility of PTEs. Several analytical methodologies are available for measuring the physical and chemical forms of soil PTEs. Spectroscopic methods, such as X-ray diffraction (XRD) and scanning electron microscopy (SEM), are used to characterize the mineralogy of soil and possibly specify the distribution of PTEs in these minerals (MonneronGyurits et al., 2022). A relatively simple and well-adopted method to assess phases, including PTEs, is chemical sequential extractions with reagents of increasing dissolution strength. Each reagent targets a specific solid phase associated with the PTE. The residual fraction often comprises primary and secondary silicates (Cornu and Clozel, 2000) and is less bioaccessible. Several studies have shown that low bioaccessibility is often coupled with a high fraction of PTEs carried by the residual phase, particularly Ni, Cr, and Sb, and(or) those of geogenic origin (Denys et al., 2008; Ding et al., 2022; Poggio et al., 2009). In contrast, PTEs with higher bioaccessibility (As, Cd, and Pb) are often bound to exchangeable, carbonate, or amorphous Fe/Al hydroxides fractions rather than to the residual fraction (Bari et al., 2021; Li et al., 2015b; Li et al., 2022). Therefore, chemical sequential extraction is an exciting tool for understanding bioaccessibility (Table 4). In addition to the solid phase distribution of PTEs, their chemical form (i.e., speciation) can affect their bioaccessibility and toxicity. Some PTEs have different toxic effects depending on redox states (As, Cr, and Sb). Given the potential risks associated with chemical speciation, it is crucial to understand the redox states better. Some authors have investigated whether the speciation of these redox-sensitive PTEs changes during the human gastrointestinal digestion of soils. In a study conducted by Denys et al. (2008) on Sb bioaccessibility in four soil samples collected from a former Pb mining site, the results showed that for each soil, the pentavalent form was present, and no change in speciation occurred during the digestion process. However, Wolf et al. (2007), Broadway et al. (2010), and Yu et al. (2012) observed a reduction in Cr (VI) to Cr (III) in digestive fluids, which was a consequence of both low pH in the gastric phase and the contribution of OM from the soil samples (Bulgariu et al., 2008; Jardine et al., 2013; Pettine and Capri, 2005). Ruby et al. (1999) illustrated the effects of chemical composition (in particular, As and Pb species and morphologies) on PTE bioavailability and bioaccessibility. Mineral phases such as lead sulfate or iron-lead sulfate, which form under acidic conditions, are more stable and hence less bioaccessible in the acidic gastric compartment. In contrast, mineral phases such as lead carbonate or lead oxide, which form under alkaline conditions, are less stable and hence more bioaccessible in the stomach. Phosphate minerals have highly variable compositions and a wide range of bioaccessibility values. Pb may also be bound to carboxyl and sulfhydryl ligands on OM, sorbed to the clay and mineral surfaces of Fe, Al or Mn

oxides, dissolved, and complexed with ionic species. Depending how Pb is bound or complexed, these species may have a different bioaccessibility (Ruby et al., 1999). As is substantially different from Pb, it occurs in natural environments in valence states: As(III) and As(V). In soils, As may be present in an anthropogenic form in which it was deposited (e.g., lead and calcium arsenates, arsenic pentoxide, and arsenic disulfide), or as various soil alteration phases of variable composition, such as arsenic in iron and manganese oxides and in phosphate minerals. It commonly co-occurs with Pb during several phases of soil alteration. Studies have shown that soil arsenic phases, such as arsenic sulfides or arsenopyrite, have lower relative bioavailability than iron-arsenic oxides, manganese-arsenic oxides, or lead-arsenic oxides (Ruby et al., 1999; Meunier et al., 2010; Stevens et al., 2018). Toujaguez et al. (2013) reported that the main factors influencing As bioaccessibility were the frequent occurrence of amorphous Fe arsenate and Fe oxyhydroxides and the stability of mineral phases in the gastrointestinal compartment. The influence of solid phase speciation in soil on the bioaccessibility and bioavailability of As and Sb was studied in details by Bagherifam et al. (2019).

3.2.5. *Statistical modeling of bioaccessibility*

The study of the parameters that influence the bioaccessibility of PTEs has made it possible to highlight some of the most critical factors. Soils are complex matrices in which each parameter can potentially affect the others. Several studies have performed multiple regression analyses to predict the oral bioaccessibility of PTEs based on soil properties (Table 6). Similarities in soil properties may be a prerequisite for creating a standard predictive model (Zhu et al., 2016). Occasionally, the soil type has been found to increase the explained variance in soil properties (Du et al., 2020). It should be noted that different statistical approaches and assumptions have been used to develop these models. However, in general, the most common soil predictors of PTE bioaccessibility are a combination of the total concentration of PTEs, soil pH, soil texture (clay, sand, and silt), and(or) the contents of Fe and Al (total and oxides), OM, and organic carbon. For example, a simple regression of As bioaccessibility vs. $\log(\text{FeOx} + \text{AlOx})$, including soil pH and the percentage of clay, can significantly improve the regression (Lake et al., 2021). Similarly, the inclusion of clay in combination with Fe and Al oxides resulted in a better explanation of the variability in Pb bioaccessibility (Lake et al., 2021). These results show that the prediction of PTE bioaccessibility resulted from a multitude of site-dependent influencing parameters (soil use, origin, or source of contamination).

Table 6. Overview of predictive models of PTE bioaccessibility in the gastric (G) and gastrointestinal (GI) phases from soil properties

PTE	Context	N	In vitro test	Phase	Log Bac	Equation	R ²	Reference
As	Railway corridors, dip and mine sites	50	SBET	G	-	0.409 As - 4.579 Fe + 67.85	0.96	Juhasz et al. (2007a)
As	Railway corridors	18	SBET	G	-	0.498 As - 3.764 Fe - 31.86	0.9	Juhasz et al. (2007a)
As	Dip sites	13	SBET	G	-	0.358 As - 9.803 Fe + 131.91	0.7	Juhasz et al. (2007a)
As	Mine sites	8	SBET	G	-	0.762 As - 20.544 Fe + 72.877	0.98	Juhasz et al. (2007a)
As	-	19	Method 1340	G	-	29 + 12.9 pH - 0.402 clay - 38.9 log (Fe oxide + Al oxide)	0.85	Lake et al. (2021)
As	-	19	Method 1340	G	-	-1.66 + 12 pH - 0.145 clay - 1.3 Al oxide	0.90	Lake et al. (2021)
As	-	19	Method 1340	G	-	97.1 - 25.5 log (Fe oxide + Al oxide)	0.69	Lake et al. (2021)
As	Urban, industrial, agricultural soils	30	UBM	GI	-	-2.06 + 0.905As + 0.644 silt	0.72	Louzon et al. (2020)
As	Urban, industrial, agricultural soils	30	UBM	G	-	-2.09 + As + 0.623 silt	0.71	Louzon et al. (2020)
As	Urban, industrial, agricultural soils	30	UBM	G	-	-0.422 + 0.952 As	0.65	Louzon et al. (2020)
As	Urban, industrial, agricultural soils	30	UBM	GI	-	-0.337 + 0.851As	0.63	Louzon et al. (2020)
As	Urban soils	25	IVG	G	-	2.78 pH + 0.07 OM - 11.74	0.45	Lu et al. (2011)
As	Urban soils	25	IVG	GI	-	2.64 + 0.027 OM - 0.13 silt - 0.097	0.6	Lu et al. (2011)
As	Former dipping vat sites	12	IVG	G	-	250.9 + 0.15 P - 3.36 clay - 40.5 pH - 0.34 CEC + 0.66 Ca+Mg	0.85	Sarkar et al. (2007)
As	Former dipping vat sites	12	IVG	GI	-	- 11 + 0.14 P - 1.57 clay - 0.15 CEC + 0.044 Ca+Mg	0.86	Sarkar et al. (2007)
As	Spiked soils	22	PBET	GI	-	10.1 pH + 13.1 TIC - 32.7 log Fe	0.81	Yang et al. (2002)
As	Spiked soils	36	PBET	GI	-	11.3 pH - 30.5 log Fe	0.74	Yang et al. (2002)
As	Mining area	76	SBET	G	-	-1.907 + 0.896 log As + 0.13 pH	0.44	Zhu et al. (2016)
Cd	Mining soils	33	PBET	G	Log	- 0.226 + 0.35 log TOC - 0.20 log Mn + 1.18 log Cd	0.93	Liu et al. (2018)
Cd	Mining soils	33	PBET	GI	Log	0.33 - 0.27 log Mn + 0.98 log Cd	0.77	Liu et al. (2018)
Cd	Urban, industrial, agricultural soils	30	UBM	G	-	-0.054 + 0.996 Cd	0.99	Louzon et al. (2020)
Cd	Urban, industrial, agricultural soils	30	UBM	GI	-	-0.144 + 0.833 Cd	0.95	Louzon et al. (2020)
Cd	Urban, industrial, agricultural soils	30	UBM	GI	-	0.160 + 0.893 Cd + 0.193 OM	0.96	Louzon et al. (2020)
Cd	Coal mining area	36	UBM	G	-	-0.96 + 0.0025 sand + 2.33 Al oxide + 0.61 Cd	0.83	Pelfrène et al. (2011)
Cd	Coal mining area	36	UBM	GI	-	0.98 + 0.0013 sand - 0.0051 OM + 0.24 Cd	0.72	Pelfrène et al. (2011)
Cd	Coal mining area	280	UBM	G	-	-0.053 + 0.012 Al + 0.75 Cd	0.90	Pelfrène et al. (2012)
Cd	Coal mining area	280	UBM	GI	-	0.56 - 0.0024 CaCO ₃ + 0.035 Fe oxide + 0.24 Cd	0.46	Pelfrène et al. (2012)
Cd	Urban/Industrial/Rural/Mining	223	SBET	G	-	-0.07 + 1.1 log Cd NHO ₃	0.92	Rodrigues et al. (2013)
Cd	Coal mining area	27	UBM	G	-	1.23 - 2.25 Fe + 0.79 Cd - 0.00102 Pb	0.98	Roussel et al. (2010)

Cd	Coal mining area	27	UBM	GI	-	$0.68 - 0.55 N + 0.39 Cd$	0.87	Roussel et al. (2010)
Cd	Vegetable plots	6	PBET	GI	Log	$- 1.345 - 0.209 \log Cd + 2.321 \log P$	0.88	Tian et al. (2020)
Cd	Industrial	26	PBET	GI	Log	$2.062 + 0.011 \log Cd - 0.080 pH + 0.265 \log OM$	0.41	Tian et al. (2020)
Cd	Roadside area	25	PBET	GI	Log	$1.396 - 0.363 \log Cd$	0.28	Tian et al. (2020)
Cr	Urban soils	3	SBET	GI		$5.15 Cr_{red} + 0.0818 Cr_{ox} + 18.01$	0.97	Jorge Mendoza et al. (2017)
Cr	non anthropogenic contamination	15	PBET	G		$- 36.8 + 1.79 Cr_{AOx} + 4.9 pH$	0.80	Kelepertzis and Stathopoulou (2013)
Cr	Roadside area	25	PBET	GI	Log	$2.283 - 1.121 \log Cr + 0.651 \log N - 0.264 \log P$	0.81	Tian et al. (2020)
Cr	Solid waste landfill	9	PBET	GI	Log	$- 0.006 - 0.069 \log Cr - 0.005 clay + 0.253 pH$	0.89	Tian et al. (2020)
Cr	Vegetable plots	6	PBET	GI	Log	$- 0.236 - 2.337 \log Cr + 2.033 \log OM + 3.065 \log P$	0.99	Tian et al. (2020)
Cr	Industrial	28	PBET	GI	Log	$1.589 - 0.792 \log Cr + 0.819 \log OM - 0.002 clay$	0.49	Tian et al. (2020)
Cr	Industrial	25	PBET	GI	Log	$1.085 - 0.060 \log Cr - 0.003 clay$	0.15	Tian et al. (2020)
Cr	Industrial	26	PBET	GI	Log	$1.211 + 0.239 \log Cr + 1.304 \log OM - 1.332 \log K$	0.3	Tian et al. (2020)
Cr (III)	-	35	PBET	G	-	$16.02 + 0.426 clay - 9.56 TIC$	0.72	Stewart et al. (2003a)
Cr (III)	-	35	PBET	G	-	$15.54 + 0.408 clay - 3.78 TOC$	0.67	Stewart et al. (2003a)
Ni	Urban soils	3	SBET	G	-	$-0.425 CEC + 0.953 Ni - 6.679$	0.93	Jorge Mendoza et al. (2017)
Ni	non anthropogenic contamination	15	PBET	G	-	$53.7 + 8.42 TOC + 0.0326 Ni - 6.18 Ca$	0.86	Kelepertzis and Stathopoulou (2013)
Ni	Agricultural and residential sites	56	PBET	G	-	$0.58 pH + 0.41 OM + 0.01 sand + 0.02 clay + 0.03 Ni - 1.6$	0.22	Poggio et al. (2009)
Ni	Agricultural and residential sites	56	PBET	GI	-	$0.38 pH + 0.21 OM - 0.01 sand + 0.01 Ni + 9.8$	0.33	Poggio et al. (2009)
Pb	Urban soils	144	UBM	-	-	$- 34 + 0.695 Pb$	0.96	Appleton et al. (2012)
Pb	Mining soils	15	UBM	G	-	$-18.9 CEC + 1.14 Mn - 2.82 Fe - 3.6 OM$	0.81	Caboche et al. (2010)
Pb	Smelting soils	10	UBM	G	-	$-2.2 clay + 4.9 P + 4.6 Mn$	0.73	Caboche et al. (2010)
Pb	Mining and smelting soils	25	UBM	G	-	$-7.7 clay + 21.1 Mn$	0.58	Caboche et al. (2010)
Pb	Community gardens and urban farms	20	PBET	G	-	$47.8 - 2.78 OM$	0.53	Cai et al. (2016)
Pb	Community gardens and urban farms	20	PBET	GI	-	$17.6 - 0.994 OM$	0.52	Cai et al. (2016)
Pb	Urban soils	10	SBET	G	-	$-107 + 0.327 Pb + 13.6 pH$	0.99	Dehghani et al. (2018)
Pb	Farming and mining soils	78	PBET	G	-	$27.87 + 0.01 Pb + 0.77 Clay$	0.25	Du et al. (2020)
Pb	Farming and mining soils	78	PBET	GI	-	$-2.05 + 1.62 pH - 0.002 Pb + 0.16 Pb G$	0.28	Du et al. (2020)
Pb	Urban soils	3	SBET	G	-	$0.409 CEC + 2.98 Pb_{red} + 0.935 Pb_{ox} - 2.26$	0.99	Jorge Mendoza et al. (2017)
Pb	Urban soils	45	SBET	G	-	$1.75 + 0.769 Pb + 0.394 Ca$	0.81	Kelepertzis et al. (2015)

Pb	-	19	Method 1340	G	-	103.8 - 0;245 clay - 11.9 log (Fe oxide + Al oxide)	0.686	Lake et al. (2021)
Pb	Mining soils	33	PBET	G	Log	1.74 - 1.07 log Fe - 1.12 log pH - 0.30 log silt + 1.23 log Pb	0.91	Liu et al. (2018)
Pb	Mining soils	33	PBET	GI	Log	- 0.53 + 0.79 log Pb	0.37	Liu et al. (2018)
Pb	Urban, industrial, agricultural soils	30	UBM	G	-	-0.350 + 1.07 Pb	0.95	Louzon et al. (2020)
Pb	Urban, industrial, agricultural soils	30	UBM	GI	-	-1.68 + 1.18 Pb	0.75	Louzon et al. (2020)
Pb	Coal mining area	36	UBM	G	-	56.6 - 0.5 CaCO ₃ - 101.7 Al oxide + 0.64 Pb	0.82	Pelfrène et al. (2011)
Pb	Coal mining area	36	UBM	GI	-	60.4 - 3.95 Fe + 25.1 Cd - 0.14 Zn	0.64	Pelfrène et al. (2011)
Pb	Coal mining area	280	UBM	G	-	6.06 - 0.25 CaCO ₃ - 0.42 OM + 16.08 P ₂ O ₅ - 0.88 Al + 0.67 Pb	0.9	Pelfrène et al. (2012)
Pb	Coal mining area	280	UBM	GI	-	- 5.12 + 17.07 P ₂ O ₅ + 0.19 Pb	0.65	Pelfrène et al. (2012)
Pb	Agricultural and residential sites	56	PBET	G	-	- 1.5 OM - 1.1 clay + 0.31 Pb + 12.7	0.53	Poggio et al. (2009)
Pb	Agricultural and residential sites	56	PBET	GI	-	0.51 pH + 0.35 OM + 0.03 sand + 0.02 Pb - 3.9	0.49	Poggio et al. (2009)
Pb	Urban/Industrial/Rural/Mining	223	SBET	G	-	-0.18 + log Pb HNO ₃ - 0.08 log TOC + 0.02 pH	0.99	Rodrigues et al. (2013)
Pb	Coal mining area	27	UBM	G	-	171.7 - 1.09 CaCO ₃ - 225.9 Fe + 0.68 Pb	0.97	Roussel et al. (2010)
Pb	Coal mining area	27	UBM	GI	-	1020.6 - 32.6 N - 131.1 pH + 0.39 Pb	0.95	Roussel et al. (2010)
Pb	Urban green land	5	PBET	GI	Log	2.232 - 0.098 log Pb - 0.962 log P	0.9	Tian et al. (2020)
Pb	Industrial	28	PBET	GI	Log	- 0.075 + 0.632 log Pb	0.42	Tian et al. (2020)
Pb	Mining area	76	SBET	G	-	-2.675 + 0.969 log Pb + 0.567 log silt + 0.903 log sand	0.87	Zhu et al. (2016)
Pb	Playground	27	SBET	G	-	0.312 + 0.472 log Pb + 0.486 log OM - 0.157 log clay	0.93	Zhu et al. (2016)

As, Cd, Pb, Ni, Cr, Ca, Fe, Mn, Zn: total or pseudototal concentrations; OM: soil organic matter; P or P₂O₅: available phosphorus; CEC: cationic exchange capacity; Ca+Mg: calcium and magnesium content; TIC: total inorganic carbon; TOC: total organic carbon; CaCO₃ : total carbonates; Cd HNO₃ or Pb HNO₃: extractable concentrations by nitric acid; Cr red or Pb red: chromium or lead bound to reducible fraction; Cr ox or Pb ox: chromium or lead bound to oxidable fraction; N: nitrogen ; Cr AOx : extractable ammonium oxalate (NH₄)₂C₂O₄ chromium

4. Use of bioaccessibility in human health risk assessment

For the soil ingestion pathway and chronic exposure, human intake is calculated as follows (US EPA, 1989):

$$ADI = \frac{C \times IngR \times EF \times ED}{BW \times AT} \times 10^{-6}$$

Where *ADI* is the average daily intake (mg PTE kg⁻¹ bw day⁻¹); *C* is the total concentration of PTE in soil (mg kg⁻¹); *IngR* is the ingestion rate of soil (mg day⁻¹); *EF* is the exposure frequency (days year⁻¹); *ED* is the exposure duration (years); 10⁻⁶ corresponds to the conversion factor (kg mg⁻¹); *BW* is the body weight (kg); and *AT* is the averaging time (days) equal to *ED* x 365 for threshold effects of the substances and lifetime (70 years) x 365 for non-threshold effects.

Subsequently, the risk is quantified using the hazard quotient (HQ, unitless) or cancer risk (CR, unitless) depending on the effect type (USEPA, 2002), as follows:

$$HQ = \frac{ADI}{TRV}$$

$$CR = ADI \times TRV$$

Where *TRV* is the oral toxicity reference value expressed in mg PTE kg⁻¹ bw day⁻¹ for threshold effects and (mg kg⁻¹ bw day⁻¹)⁻¹ for non-threshold effects. In the exposure assessment, the integration of bioavailability is involved in the calculation of *ADI* according to the following equation:

$$ADI = \frac{C \times IngR \times EF \times ED}{BW \times AT} \times BA$$

Where *BA* is the bioavailability of PTE in the soil matrix (unitless).

In the literature, the ADI calculated by directly considering bioaccessibility compared with the TRV. French agencies questioned this comparison's relevance (InVS and INERIS, 2012) because TRVs were defined as a reference matrix (aqueous solution or food) that served as a vector for pollutant administration. It is necessary to integrate the relative bioavailability or bioaccessibility of the pollutant in the soils compared to that of the same pollutant in the reference matrix to calculate risk. However, there is a lack of data concerning these values, so assumptions must be made to integrate the relative bioavailability or bioaccessibility. Therefore, the integration of these concepts must be justified, and the assumptions must be explained clearly. Using absolute oral bioavailability in HHRA requires construction of TRVs from absorbed (or internal) doses, which is not always possible. Hence, it is currently impossible to use the absolute bioavailability. However, relative bioavailability can be used to quantify the difference in the bioavailability of a PTE between the soil matrix and the reference matrix (origin of the TRV) used for risk calculation:

$$RBA = \frac{ABA_{soil}}{ABA_{TRV}} = \frac{BAC_{soil} \times fa_{soil}}{BAC_{TRV} \times fa_{TRV}}$$

where *RBA* is the relative bioavailability (unitless); *ABA* is the absolute bioavailability of the PTE in the soil or in the reference matrix used for TRV construction; *BAC* is the absolute bioaccessibility of the

contaminant in the soil or the reference matrix used for TRV construction; f_a is the factor of absorption of PTE from the soil or the reference matrix. RBA could therefore be used to calculate the adjusted ADI corresponding to the internal exposure to the PTE contained in the soil, considering its bioavailability in the matrix used to construct the TRV and in the soil studied. Thus, this adjusted ADI is directly comparable to the TRV reported in the literature (an external dose):

$$ADI_{adj} = ADI \times RBA = EDI \times \frac{BAC_{soil} \times f_{a_{soil}}}{BAC_{TRV} \times f_{a_{TRV}}}$$

Two alternatives can be used to refine the assumption that RBA is equal to 1 and to integrate the calculation of this parameter: (i) determine the ABA of the PTE in both the soil and the reference matrix, or (ii) determine the BAc (relative or absolute) and f_a of the PTE. This review provides an overview of recent articles incorporating RBA or BAc into risk calculations (Table 7). Other existing national frameworks are also used to consider BAc or ABA in contaminated soil management (e.g. generic assessment criteria derived in the UK using the Contaminated Land Exposure Assessment CLEA model; Environment Agency, 2009; and guidance for state regulatory agencies in the US from Interstate Technology & Regulatory Council; ITRC, 2017). Risk calculations are often performed for elements not validated by *in vivo* tests. In most studies, BAc was directly integrated into the calculation of ADI by adjusting the total concentration instead of the RBA without explaining the validity of this substitution. This lack of explanation occurs even though several countries have developed guides or decision trees to help researchers ask the right questions before using *in vitro* bioaccessibility data for HHRA (Grøn and Andersen, 2003; Health Canada, 2017; InVS and INERIS, 2012; LABO, 2020; Ng et al., 2015; US EPA, 2012b). The most frequently asked questions were as follow: (i) Are the estimated risks (HQ or CR) exceeding the acceptable risk levels for soil ingestion exposure? (ii) Is the adjustment of the ADI by the RBA appropriate for this site and would it reduce the estimated risk? (iii) Is there a validated *in vitro* method for detecting contaminants of interest? These decision trees can guide the suitability of bioaccessibility. There are clear methodologies and equations for determining the bioaccessibility in HHRA. Two recent methodologies (from the US EPA and France, based on The Netherlands) for which information is readily available are detailed below. The US EPA provides precise and comprehensive guidance on integrating the bioavailability and bioaccessibility (BAc) for HHRA. They recommended using RBA based on the bioaccessibility of As and Pb in the soil to improve the characterization of site-specific risk assessments (US EPA, 2017b, 2021). US EPA Method 1340 is currently the recommended test for integrating BAc directly into the RBA calculation (US EPA, 2017a). This test simulated the gastric phase extraction of As and Pb from the soil in a relatively simple extraction medium (glycine and pH adjustment with HCl). The regression models used to convert the BAc of As and Pb into RBA are as follows (Diamond et al., 2016; US EPA, 2007):

$$RBA_{As} \% = 0.79 \times BAc \% + 3$$

$$RBA_{Pb} \% = 0.878 \times BAc \% - 2.8$$

Table 7. Overview of recent articles using bioaccessibility (BAc) or bioavailability (RBA) data in risk calculation for HHRA

Reference	Country	PTE	<i>In vitro</i> test	Information about BAc integration in HHRA or RBA adjustment
Amponsah et al. (2022)	Ghana	As, Cd, Cr, Cu, Hg, Ni, Pb, Sb, Zn	US EPA Method 1340	RBA As (%) = 0.79 BAc (%) + 3 RBA Pb (%) = 0.878 BAc (%) - 2.8 Due to the lack of <i>in vivo/in vitro</i> equations for the remaining metals, RBA = BAc
Bari et al. (2021)	Australia	As	SBRC/PBET	In EDI calculation, BAc instead of C (i.e. RBA = BAc)
Cao et al. (2020)	Ghana	Cu, As, Cd, Pb, Sb	PBET	RBA = BAc
Darko et al. (2017)	Ghana	Zn, Pb, Cu, Co, Ni, As, Cr	US EPA Method 1340	RBA = BAc
Darko et al. (2019)	Ghana	As, Cr, Ni, Fe, Co, Mn, Cu, Zn	US EPA Method 1340	RBA = BAc
Das et al. (2013)	India	As	SBET	RBA = BAc
Dehghani et al. (2018)	Iran	Cu, Pb, Zn	SBET	RBA = BAc
Diquattro et al. (2021)	Italy	Sb	SBRC	RBA = BAc
Dodd et al. (2023)	Ghana	Ag, As, Cd, Cr, Cu, Mo, Ni, Pb, Sb, Sn, Zn	US EPA Method 1340	RBA As = 0.79 BAc + 3 RBA Pb = 0.878 BAc - 2.8 Due to the lack of <i>in vivo/in vitro</i> equations for the remaining metals, RBA = BAc
Fang et al. (2023)	China	As, Zn	PBET	RBA = BAc
Fernandez-Caliani et al. (2019)	Spain	As, Cu, Pb	UBM	RBA As = 0.59 BAc - G + 9.8 BAc-G Pb = 1.1 RBA Pb + 1.86
Girardeau et al. (2018)	France	As	UBM	RBA = BAc
Gu et al. (2016)	China	Cd, Pb, Cr, Ni, Cu, Zn, Fe, Mn	SBET	RBA = BAc
Guillén et al. (2021)	Spain	As, Cd, Co, Cr, Ni, Cu, Pb, Zn	SBET	BAc As = 1.0 RBA - 0.01 BAc Pb = 1.1 RBA + 1.86
Helser et al. (2022)	Belgium, Germany and Portugal	As, Cd, Cu, Pb, Zn	PBET/US EPA Method 1340	RBA = BAc
Hiller et al. (2017)	Slovak Republic	Cd, Cu, Hg, Pb, Zn	SBET	RBA = BAc
Izquierdo et al. (2015)	Spain	Ca, Co, Cr, Cu, Fe, Mn, Ni, Pb, Zn	SBET	RBA = BAc
Kasemodel and Rodrigues (2022)	Brazil	Cd, Pb	US EPA Method 1340	RBA = BAc
Laha et al. (2020)	India	As, Cd, Co, Cu, Fe, Mn, Ni, Pb, Sb, Zn	SBET	RBA = BAc
Li et al. (2014)	China	As, Sb	SBET/PBET	RBA = BAc (which corresponds to the sum of the BAc obtained through PBET G and PBET I extraction)
Li et al. (2020)	China	As, Ba, Co, Cr, Cu, Mn, Ni, Pb, Zn	SBET/PBET/UBM/SBRC/IVG	RBA = BAc
Liu et al. (2018)	China	Pb, Cd, Zn	PBET	EDI x BAc
Luo et al. (2012)	China	Cd, Co, Cr, Cu, Mn, Ni, Pb, Zn	SBET	RBA = BAc

Ma et al. (2019)	China	Cd, Cr, Cu, Ni, Pb, Zn	SBET	RBA = BAc
Ma et al. (2020)	China	As, Cd, Cr, Cu, Ni, Pb, Zn	SBET	RBA = BAc
Mehta et al. (2020)	Italy	As, Cd, Co, Cr, Cu, Ni, Pb, Zn	UBM	RBA = ABA_{soil}/ABA_{ref} and ABA_{ref} assumed equal to 1 and $ABA_{soil} = BAc$ as conservative proxi
Monneron-Gyurits et al. (2020)	France	Pb	UBM	RBA = BAc G
Moreira et al. (2018)	Brazil	Cr	US EPA Method 1340	RBA = BAc
Ning et al. (2021)	China	Tl, As, Sb, Hg	SBET/PBET	RBA = BAc
Wang (2023a)	China	As, Cd, Cr, Cu, Ni, Pb, Zn, Hg	SBET/PBET	RBA = BAc
Wang (2023b)	China	Sb	SBET	RBA = BAc
Yang et al. (2018)	China	Cr, Cu, Pb, Zn	SBET	RBA = BAc
Yin et al. (2021)	China	As, Cd, Cr, Cu, Fe, Mn, Ni, Pb, and Zn	PBET/SHIME	RBA = BAc
Yu et al. (2012)	China	Cr	IVG	RBA = BAc
Zhong and Jiang (2017)	China	Ni	UBM	RBA = BAc

RBA: relative bioavailability; BAc: bioaccessibility; ABA_{soil} : absolute bioavailability in the soil matrix; ABA_{ref} : absolute bioavailability in the reference matrix; G: gastric phase;

EDI: estimated daily intake; SBRC: Solubility/Bioavailability Research Consortium; SBET: Simple Based Extraction Test; PBET: Physiologically Based Extraction Test; UBM:

Unified Barge Method; IVG: *In vitro* Gastrointestinal Test; SHIME: the Simulator of the Human Intestinal Microbial Ecology

In France, InVS and INERIS (2012) issued an approach based on the RIVM report (Oomen et al., 2006) for bioaccessibility in HHRA, making calculating the RBA possible. For As and Cd, equal absorptions were retained regardless of whether they came from the soil matrix or the reference matrix (i.e., drinking water used for TRV construction), which means that fa_{soil} was equal to fa_{TRV} . This allowed the following simplification of the adjusted ADI:

$$ADI_{adj} = ADI \times \frac{BAC_{soil}}{BAC_{TRV}}$$

It has also been shown that the absolute bioaccessibilities of As and Cd in the G phase of drinking water are close to 100 %, meaning that BAC_{TRV} equals 1. This result allows for the following simplification:

$$ADI_{adj} = ADI \times BAC_{soil}$$

Thus, measuring the bioaccessibility of As and Cd is sufficient to adjust the estimated daily intake. A similar approach was conducted for Pb, considering the TRV established by WHO in 2012, which considered all sources of Pb (i.e., water, air, food) with the objective of not exceeding a blood Pb level of $50 \mu\text{gL}^{-1}$ in children. Anses the French agency recommends a value of $15 \mu\text{gL}^{-1}$ for all exposure pathways (i.e., water, air, food) and children and adults (Anses, 2013). Despite the revision of the TRV value used by HHRA in France, the approach applied for Pb remains valid. The adjusted exposure dose for Pb was calculated using assumptions regarding its bioavailability and absorption. In particular, studies have shown the absorption of Pb from food from 20 to 80 % in children, depending on their age (Ziegler et al., 1978; DeMichele, 1984). Therefore, the maximum absorption value ($fa_{soil} = 0.8$) was selected. Additionally, the absolute bioavailability of Pb in the reference matrix was estimated to be 40 % on average (Oomen et al., 2006). As Pb is not metabolized, the absorbed fraction is considered equal to the bioavailable fraction. This allows the following simplification of the adjusted ADI:

$$ADI_{adj} = ADI \times \frac{BAC_{soil} \times 0.8}{0.4} = ADI \times 2 \times BAC_{soil}$$

This methodology and the proposed ADI adjustment for As, Cd and Pb apply only to the BAc values from the UBM protocol. Moreover, depending on the objective of the study and the pollutant under consideration, the current French recommendation to integrate BAc into the calculation is to make a conservative choice for health by retaining the highest bioaccessibility value of the two phases or the one that presents the best correlation with the measured bioavailable fraction.

5. Knowledge gaps, points for attention and future perspectives

- There are advantages and disadvantages associated with different methodologies currently available for estimating bioaccessibility. Decisions regarding the applicability of bioaccessibility estimates and the most appropriate protocol should consider the validation statues of any method and the associated IVIVC. The IVIVC is crucial for determining the validity of bioaccessibility assays as surrogate measures for refining bioavailability for human

exposure and risk. The maximum criteria for validation were observed for US EPA Method 1340, PBET, UBM, RIVM, CAB, and IVG.

- The mouse assay can serve as a highly cost-effective alternative to more expensive assays (swine) for assessments of As RBA in soils, but it is important to remain cautious because results are not always consistent. In addition, comparison studies between mouse and piglet models are needed for PTEs other than As before mouse tests can also be used to estimate RBA.
- This highlights the issue of the choice of animal model. *In vivo* tests on models most similar to humans (primates or piglets) are more expensive and take longer than those on rodents (mice). Although some studies showed that RBA of swine is similar to mice (Diamond et al, 2016; Li et al., 2016), this is not always the case for all samples tested (Basta et al, 2016; Bradham et al. 2013). Comparison tests are also required for PTEs other than As. This suggests that we should remain critical of tests validated by a large number of *in vivo* tests, depending on the models used.
- Common *in vitro* extraction procedures for predicting the bioaccessibility of PTEs were developed for one or a few PTEs (mostly Pb, As, and Cd) and have been extended in numerous articles to various PTEs (e.g., Co, Cr, Cu, Hg, Ni, Sb, and Zn), for which they have not yet been shown to be good analogs of *in vivo* conditions, suggesting the need for further studies to extend the validation of the most relevant *in vitro* tests to other PTEs of interest.
- The current study will significantly help researchers for better use and integration of bioaccessibility in HHRA. Some guides and official recommendations are well-documented and squarely focused on this use. At the same time, there is a certain vagueness in articles where bioaccessibility is directly integrated into HHRA without explanation, without considering the relative bioavailability or validity of the test. Moreover, risk calculations are often performed for PTEs not validated by *in vivo* tests.
- When choosing the soil size fraction, *in vitro* tests usually used < 2 mm, < 250 µm, or < 150 µm. In most cases, < 250 µm is the fraction of choice because it is considered the optimal size for adherence to children's hands. However, US EPA has shown that the fraction < 150 µm is more suitable. In addition, it seems inappropriate to use the < 2 mm size fraction commonly used for soil analysis. However, the recommendation to use this size fraction in the German method (DIN) is explained by the fact that the trigger values in the German Federal Soil Protection and Contaminated Sites Ordinance for this particle size fraction were derived from < 2 mm. The DIN method was validated by an *in vivo* model that considered this specific fraction. Specific attention must be paid to the particle-size fraction under the selected test and *in vivo* validation.
- The bioaccessibility of soil contaminants depends on the PTE chemistry, soil properties, and chemical parameters of the simulated gastrointestinal fluids. Regarding this last point,

differences in the pH of the acidic gastric digestion phase are the most likely explanation for the poor correspondence obtained with the different *in vitro* tests.

- The physico-chemical characteristics of soil have varying impacts on the bioaccessibility of PTEs. Soil particle size, physico-chemical properties such as OM content, sand and clay percentages, soil pH and complexing agents (Mn, Fe, and Si) can affect bioaccessibility. However, the results are highly variable. Moreover, numerous models and equations have been proposed demonstrating that the influence of the soil matrix is site-dependent. Depending on the *in vitro* test selected, it is easier to measure bioaccessibility directly.
- Chemical speciation should be considered because the toxicity of certain PTEs varies according to their oxidation states (As, Cr, and Sb). It would be interesting to study the reactions that occur when they encounter digestive fluids in a living being and to compare whether the simulated fluids are representative, as this will give us a better idea of the actual risk.

6. Conclusions

Managing contaminated soils of geogenic and (or) anthropogenic origins poses various challenges, and assessing the exposure of populations to PTEs is a significant concern. The ingestion of soil particles, particularly among sensitive populations such as children (hand-to-mouth behavior), is one of the main exposure routes. Regarding the HHRA, the exposure doses are often calculated by considering the total concentration of PTE in the soil. However, only the fraction of PTE extracted from the matrix, ingested, and absorbed by the organism (i.e., the bioavailable fraction) can induce a toxic effect. Therefore, many studies have considered the bioavailability of PTEs by determining their bioaccessibility and integrating this parameter into risk calculations. Several *in vitro* tests have been developed to estimate the bioaccessibility of PTEs, including PBET, SBET, SBRC, the US EPA Method 1340, CAB, IVG, UBM, and RIVM. A test is helpful in HHRA if it adequately represents the RBA. However, at present, most of the tests have only been validated for As and Pb, and to a lesser extent for Cd (except for the DIN test, which has also been validated for Cr, Ni, and Hg), despite being widely used for other PTEs. This review emphasizes the importance of considering the bioaccessibility and the need for validated tests for other PTEs of interest. As per the literature, the physicochemical parameters of soils, total concentrations of PTEs, and their chemical forms influence the gastric and gastrointestinal bioaccessibility of PTEs. Correlations between different parameters and PTE bioaccessibility in soil varied from one study to another for the same element, indicating a multifactorial aspect governing PTE bioaccessibility in soils. This variability is due to the complexity of the soil matrix, different interactions between its constituents, and protocols used. Nevertheless, these factors affect bioaccessibility, and their study is essential for a better understanding of the mechanisms of direct bioaccessibility, which can help manage contaminated sites and soils more efficiently. The literature review also revealed disparities between the official recommendations and the methods used by researchers, which tend to incorporate bioaccessibility

values into exposure or risk calculations without considering the RBA or test's validity. Therefore, there is a need to develop methodologies and guidelines that are more accessible, applicable, and understandable for incorporating bioaccessibility into health risk assessments.

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