Oral Bioavailability of Nonpolar Organic Chemicals in Soil for Use in Human Health Risk Assessment (HHRA)

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OUTLINE

- Background/Objectives
- Bioavailability and Factors Influencing Bioavailability
- Approaches to Measure Bioavailability
- Regulatory Uses of Bioavailability in HHRA
- PAH and PCB Bioavailability Summaries
- Data Gap and Additional Research

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BACKGROUND

Risk-based cleanup goals not adjusted to account for reduced bioavailability in soil

Higher remediation costs without more protection of public health

More meaningful and realistic risk management decisions derived from bioavailability adjustments in HHRAs

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OBJECTIVES

Summarize regulatory practice of using bioavailability in HHRAs among countries

Present findings from a comprehensive literature review of PAH and PCB oral bioavailability in soil

Evaluate feasibility of developing regulatory guidelines for *in vitro tests* of PAH and PCB bioavailability

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BIOAVAILABILITY DEFINITIONS

Absolute Bioavailability

- $$Absolute\ Bioavailability\ (fraction) = \frac{Absorbed\ Dose}{Administered\ Dose}$$

Relative Bioavailability

- $$RBA\ (fraction) = \frac{Absorbed\ Fraction\ from\ Exposure\ Medium\ (e.g.,Soil)}{Absorbed\ Fraction\ from\ Dosing\ Medium\ Used\ in\ Toxicity\ Study}$$

Bioaccessibility

- $$Bioaccessibility\ (fraction) = \frac{Mass\ Dissolving\ in\ In\ Vitro\ System}{Mass\ Administered}$$

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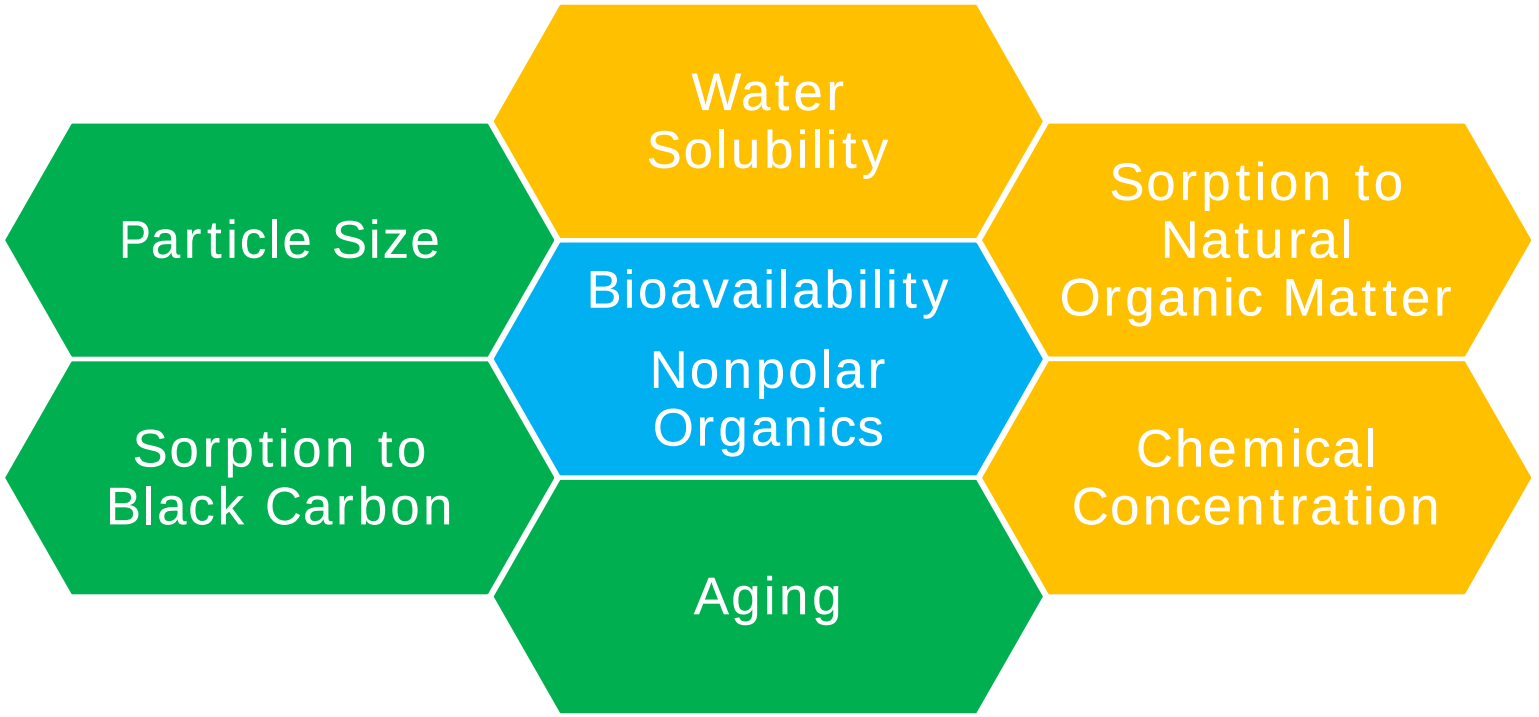
FACTORS INFLUENCING BIOAVAILABILITY



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IN VIVO APPROACHES TO MEASURE BIOAVAILABILITY

- Blood Concentrations
  - ✓ For chemicals readily absorbed and excreted quickly (e.g., arsenic) or slowly excreted chemicals at an approximate steady state (e.g., lead)
- Fecal Excretion
  - ✓ For chemicals without biliary excretion
- Urinary Excretion
  - ✓ For chemicals excreted primarily in urine
- Tissue Concentrations
  - ✓ For chemicals that accumulate in specific tissues

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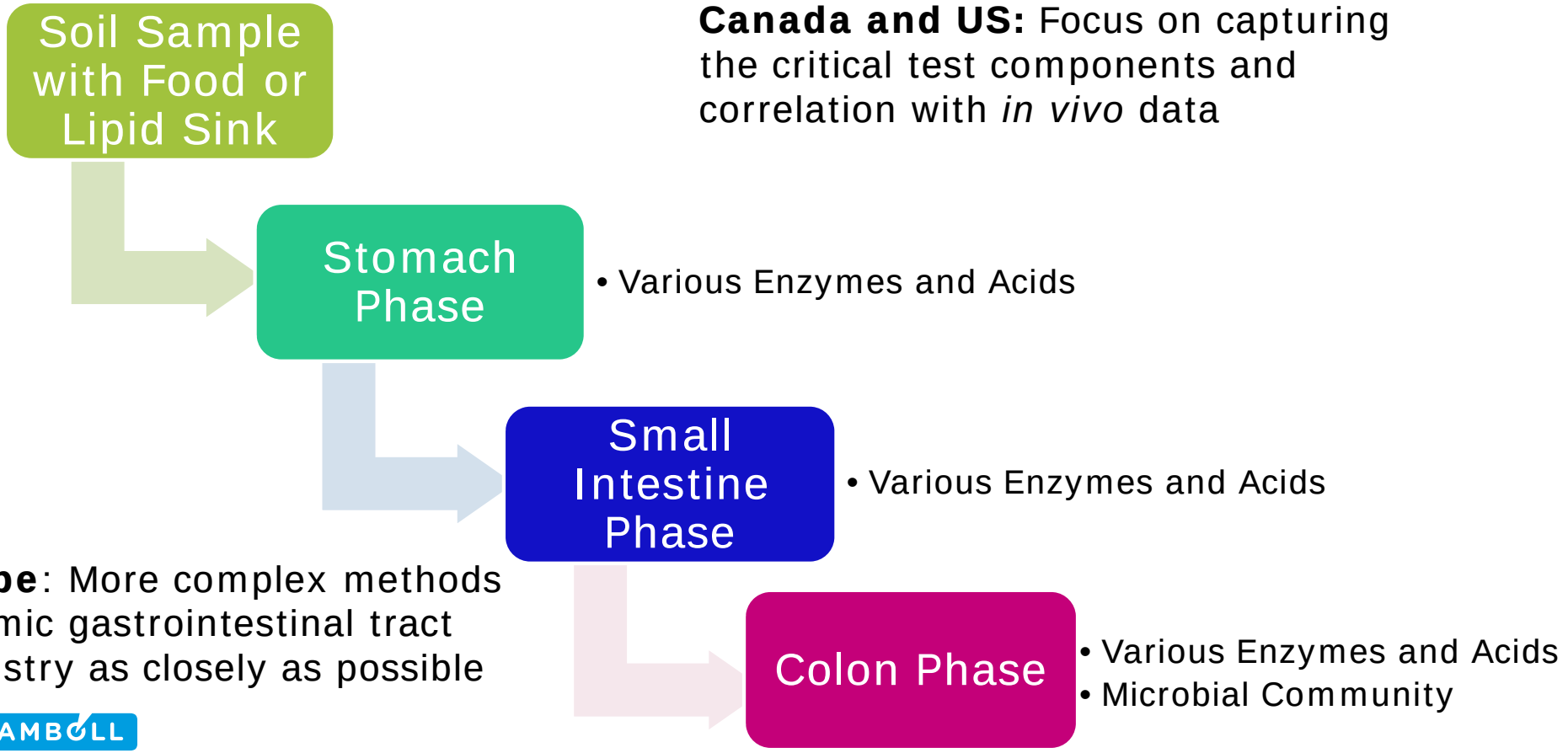
IN VITRO APPROACHES TO MEASURE BIOAVAILABILITY



Canada and US: Focus on capturing the critical test components and correlation with *in vivo* data

Europe: More complex methods to mimic gastrointestinal tract chemistry as closely as possible

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IN VITRO APPROACHES TO MEASURE BIOAVAILABILITY

- **P**hysiologically-**B**ased **E**xtraction **T**est (PBET) and **C**olon-**E**xtended PBET (CE-PBET)
- **S**imulator of the **H**uman **I**ntestinal **M**icrobial **E**cosystem (SHIME)
- Het **RI**jksinstituut voor **V**olksgezondheid en **M**ilieu (National Institute of Public Health and the Environment, Netherlands)(RIVM) Method
- **F**ed **OR**ganic **E**stimation **h**uman **S**imulation **T**est (FOREhST)
- ***I**n **V**itro* **G**astrointestinal (IVG) Method

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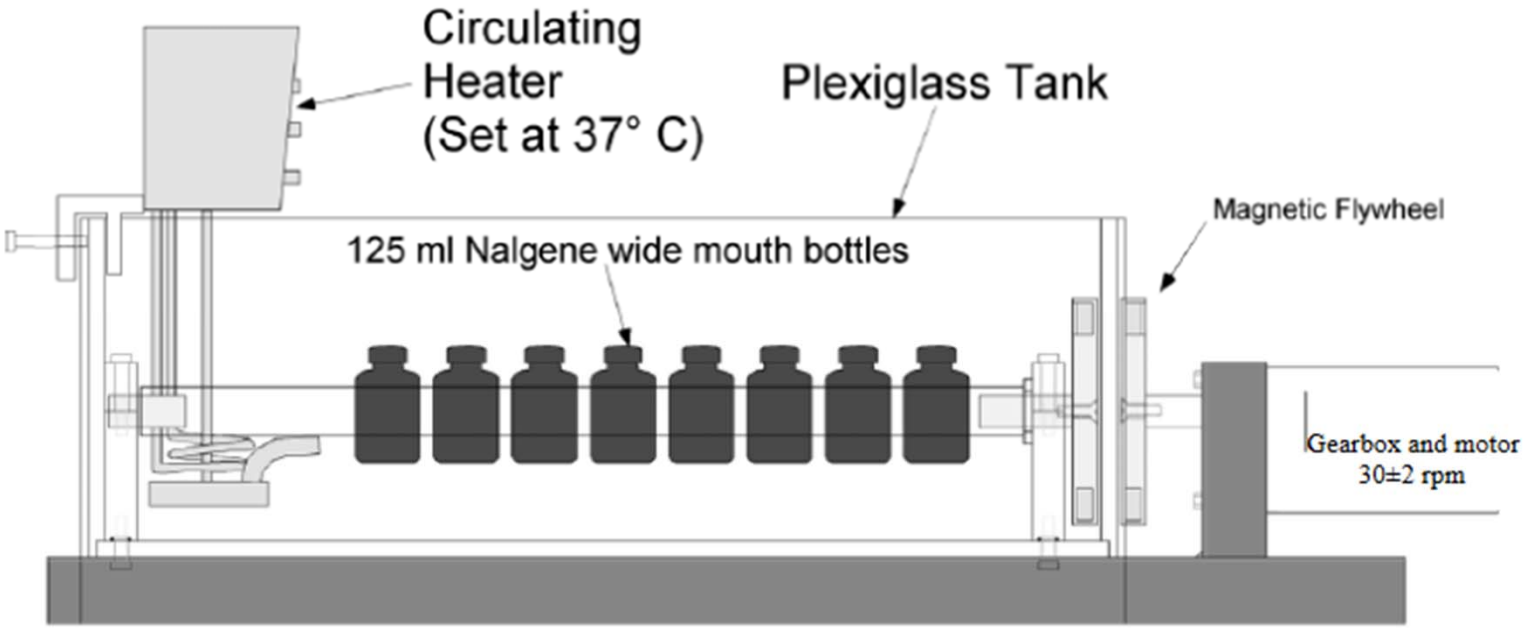
IN VITRO APPROACHES TO MEASURE BIOAVAILABILITY



Example of *In Vitro* Bioaccessibility Extraction Apparatus (USEPA 2017)

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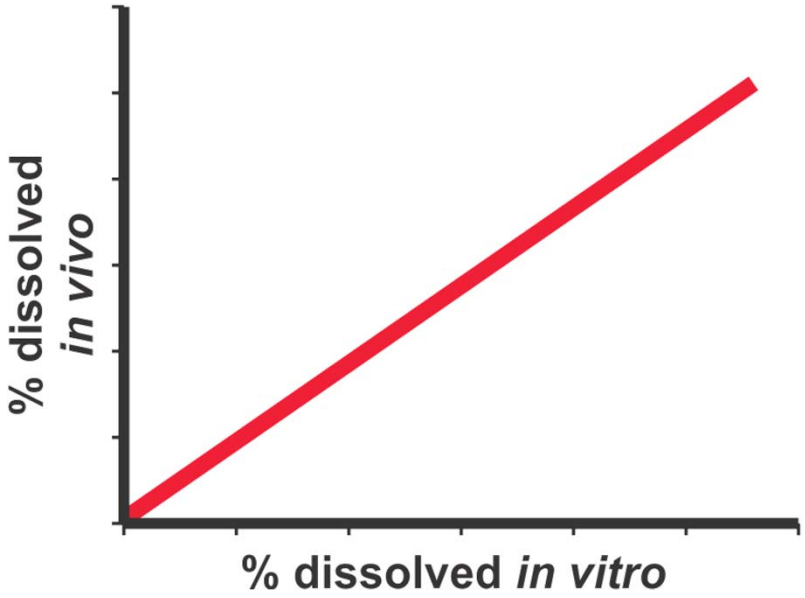
ROLE OF BIOAVAILABILITY IN RISK ASSESSMENT

$$Relative\ Bioavailability\ (fraction) = a * In\ Vitro\ Bioaccessibility\ (fraction) + b$$

$$Intake_{unadjusted} * RBA = Intake_{adjusted}$$

Soil bioavailability lower than diet bioavailability (USEPA critical toxicity studies) → RBA < 1.0

Very limited correlations between *in vitro* and *in vivo data* for organic chemicals → practically *in vitro* bioaccessibility directly used as RBA



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REGULATORY USES OF BIOAVAILABILITY IN HHRA

Country	Formal Guidance	HHRA Application	Standard *In Vitro* Method	Validation
US	Yes, 2007	Yes, lead, arsenic, dioxin/furan	Yes, lead, arsenic	Yes, lead, arsenic (underway)
UK	Yes, 2005 (under limited conditions)	Yes, arsenic, chromium, lead	Yes, arsenic, chromium, and lead	No
Netherlands	No	Yes, lead	Yes, lead, PAH	No
France	No	Yes, cadmium, lead, zinc	Yes, lead, cadmium, arsenic	Yes, lead, cadmium, arsenic
Canada	Yes, 2017	Yes, metals	No	Yes, lead, arsenic
Australia	Yes, 2013	Yes, lead, arsenic	No	No

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PAH BIOAVAILABILITY - TOXICOKINETICS

Complexity of toxicokinetics within human body leads to lack of a widely accepted *in vivo* method:

- Biliary excretion
- Extensive metabolism
- Enterohepatic recirculation
- Minor excretion in urine
- Accumulation in tissue

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PAH BIOAVAILABILITY – LITERATURE REVIEW

	***In Vivo* Study**	***In Vitro* Study**
No. Reviewed	23 studies	34 studies (13 studies with food/lipid sink)
Soil Type	field soil (21 studies), lab spiked soil (4 studies)	field soil (29 studies), lab spiked soil (6 studies)
Soil Concentration	<1 mg/kg to >4,000 mg/kg, a few <10 mg/kg	<1 mg/kg to 5,000 mg/kg, a few <10 mg/kg
Soil Particle Size	reported in 18 studies, much larger than <150 µm in 11 studies	reported in 26 studies, much larger than <150 µm to in 8 studies
Type of Organic Carbon in Soil	no characterization	characterized in a few studies
Bioavailability Result	RBA <0.6% to 100% (field soil), 50% to 100% (lab spiked soil)	bioaccessibility 0.1% to 76% (field soil), 2% to 89% (lab spiked soil), most <50%

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PAH BIOAVAILABILITY - STUDY DESIGN GUIDELINES

CE-PBET is recommended as the *in vitro* method for oral PAH bioavailability in soil

Study design consistent with a good practice established by BARGE:

- Three digestive compartments, including stomach, small intestine, and colon
- Fed state and a sorption sink
- Microbial community in colon compartment
- Aged/weathered site soil with particle size <150 µm

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PCB BIOAVAILABILITY - TOXICOKINETICS

- Different PCB congeners with a wide range of properties and behavior in human digestive system
- Distributed preferentially to adipose tissues
- Absorbed from gut primarily via lymphatic system, less likely than PAHs to exhibit liver first pass metabolism
- Biliary excretion

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PCB BIOAVAILABILITY – LITERATURE REVIEW

	***In Vivo* Study**	***In Vitro* Study**
No. Reviewed	9 studies	3 studies (1 study with food)
Soil Type	field soil (4 studies), lab spiked soil (5 studies)	field soil (1 study), lab spiked soil (2 studies)
Soil Concentration	< 0.1 mg/kg to 300 mg/kg, a few <10 mg/kg	< 1 mg/kg, 7 and 14 mg/kg, and 300 mg/kg
Soil Particle Size	reported in 5 studies, much larger than <150 µm in 3 studies	no study reported
Type of Organic Carbon in Soil	characterized in 4 studies	no characterization
Bioavailability Result	RBA 36% to 100% (field soil), 3% to 100% (lab spiked soil)	bioaccessibility 6% to 40% (field soil without food), 43% to 85% (field soil with food), 30% to 79% (lab spiked soil)

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PCB BIOAVAILABILITY - STUDY DESIGN GUIDELINES

A single standard *in vitro* method for PCB bioaccessibility cannot be recommended due to data limitations

Approaches being used for PAHs may provide a useful template with consideration of similar aspects in study design:

- At least two digestive compartments: stomach and small intestine
- Fed state and a sorption sink
- Aged/weathered site soil with particle size <150 µm

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DATA GAP AND ADDITIONAL RESEARCH

A variety of field soils (i.e., different types of organic carbon)

A range of environmentally relevant concentrations

A standard protocol of *in vitro* method

Inclusion of food or a lipid sink

Reliability of *in vivo* approach and feasibility of *in vitro* method validation against *in vivo* data

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DISCLAIMER

This study was conducted under contract to the Danish Environmental Protection Agency.

QUESTIONS?

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