Asia-Pacific Economic Cooperation

APEC PHILIPPINES 2015

ICMM International Council on Mining & Metals

Bioavailability Tools for Human Health Risk Assessment of Metals in Soil

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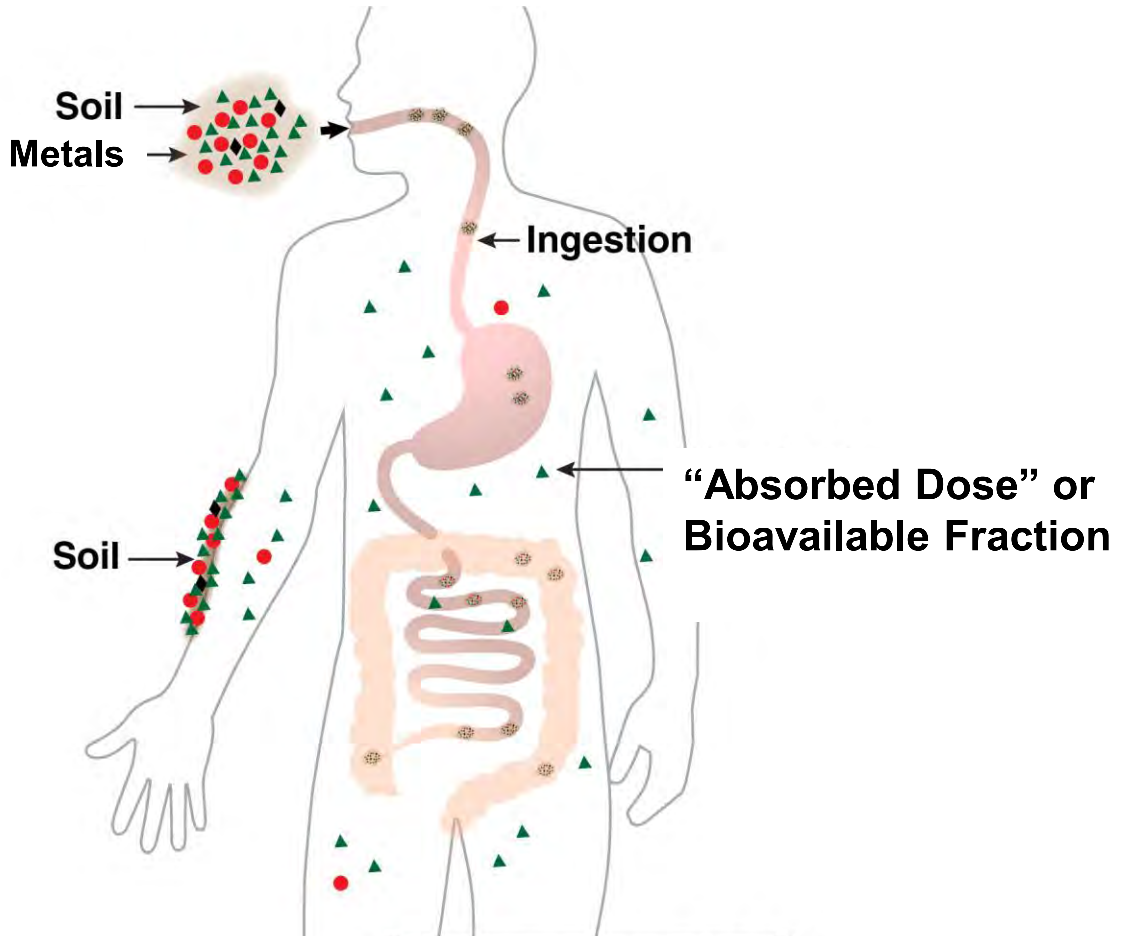
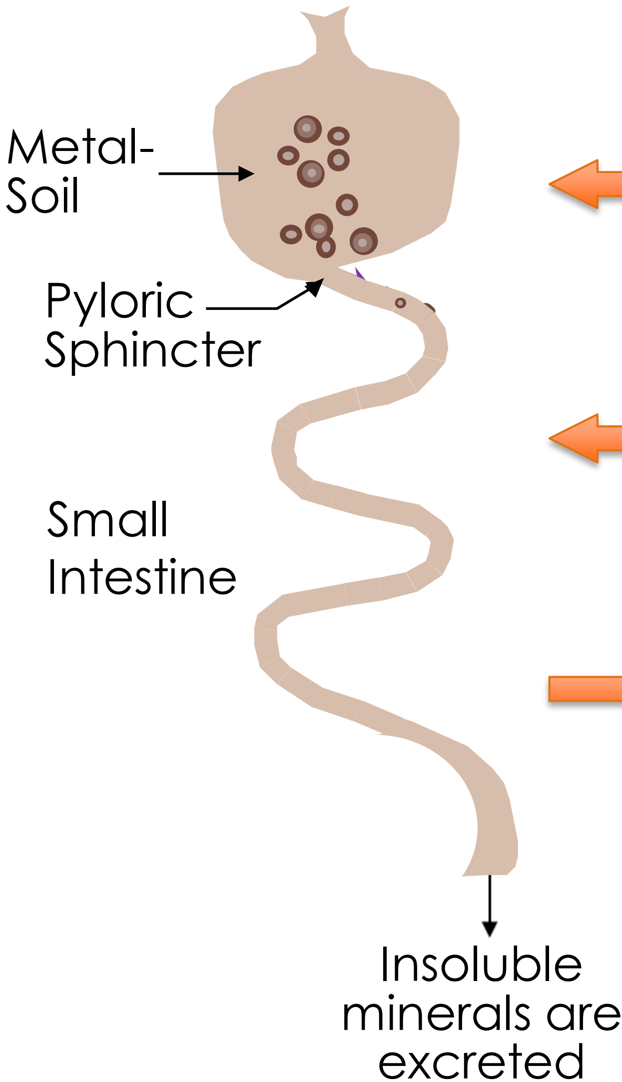
Bioavailability Tools for Human Health Risk Assessment of Metals in Soil

- Why bioavailability considerations belong in the risk assessment process?
- Where in human health risk assessment should we account for bioavailability?
- How a simple benchtop extraction tests ("in vitro" or "bioaccessibility") can be a useful tool for estimating bioavailability for HHRA
- Case studies
  - Arsenic – example of the process for a contaminated site
  - Lead – where bioavailability fits into blood lead modeling

Gastro-Geochemistry of Metals



Gastro-Geochemistry of Metals



- pH of 1.5 – 4 (fasting vs. fed)
- Metals desorb from soil
- Some metal minerals dissolve

- pH increases to 7

- Soluble metals absorbed into bloodstream
- Metals precipitate/adsorb

Incorporating Relative Oral Bioavailability into Human Health Risk Assessment

$$\text{Risk (non cancer)} = \frac{\text{Exposure}}{\text{Safe Dose}}$$

$$\text{Cancer Risk} = \text{Exposure} \times \text{Cancer Slope Factor}$$

Where:

"Safe Dose" is based on threshold for toxicity, including uncertainty factors (e.g., Reference Dose or "RfD")

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Determined based on Toxicity Studies

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Incorporating Relative Oral Bioavailability into Human Health Risk Assessment

$$\text{Risk}_{(\text{non cancer})} = \frac{\text{Exposure}}{\text{Safe Dose}}$$

Determined based on Toxicity Studies

Toxicity is related to absorbed dose (bioavail-ability)

$$\text{Cancer Risk} = \text{Exposure} \times \text{Cancer Slope Factor}$$

Incorporating Relative Oral Bioavailability into Human Health Risk Assessment

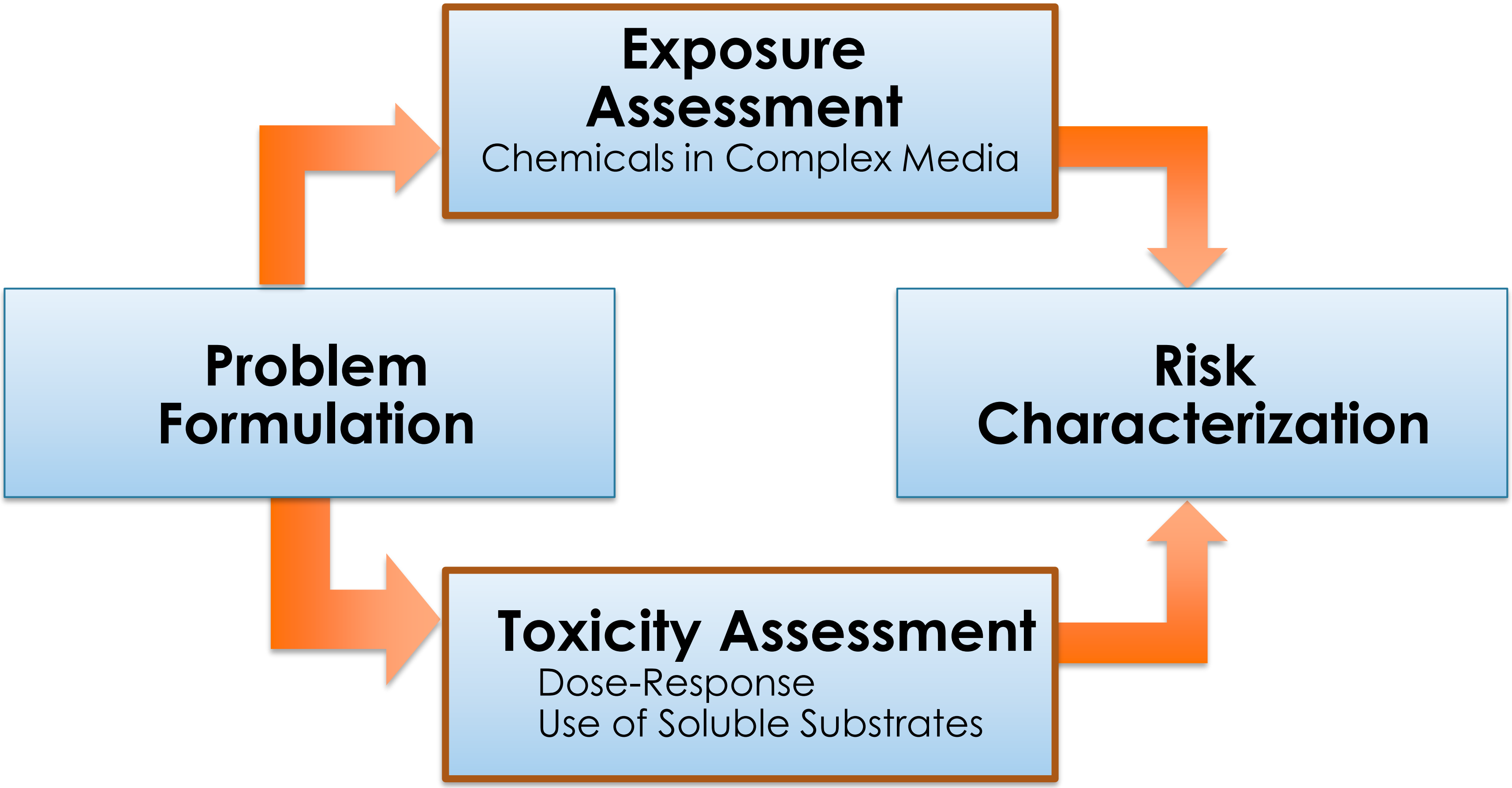
$$\text{Risk}_{\text{(non cancer)}} = \frac{\text{Exposure}}{\text{Safe Dose}}$$

May Affect Bioavailability

- Concentration
- Contact rate
- Soil chemistry
- Source of metal

Cancer Risk = Exposure x Cancer Slope Factor

Incorporating Bioavailability Adjustments in Risk Assessment



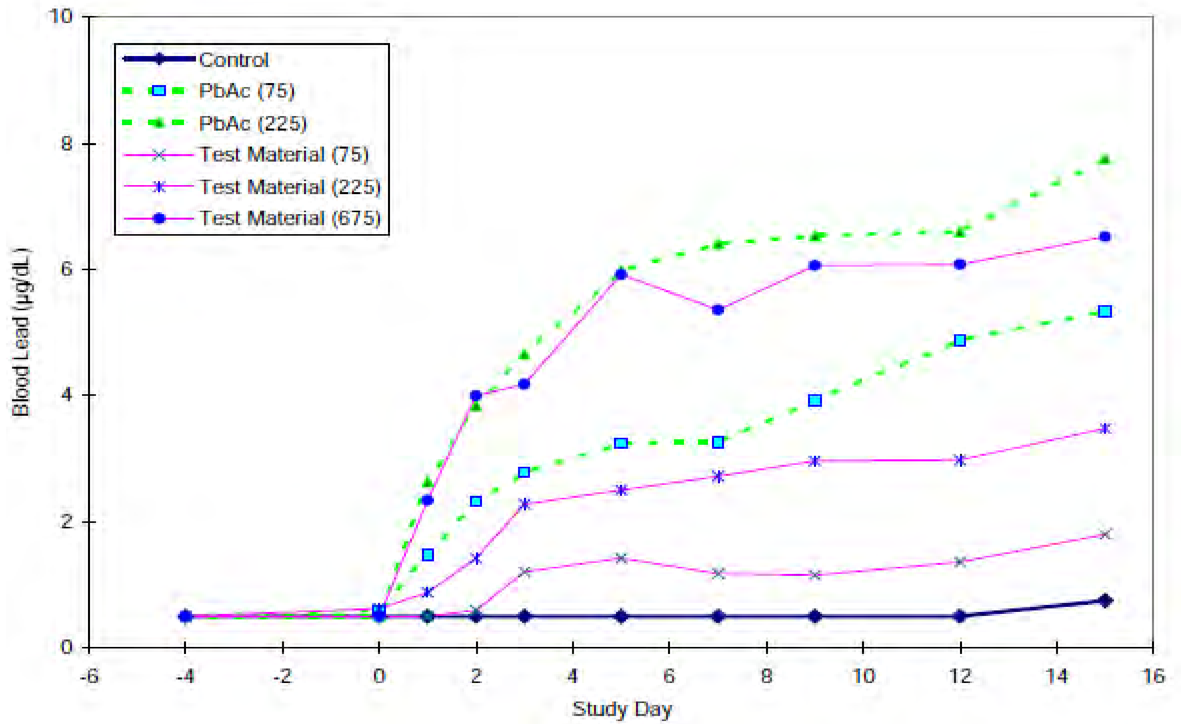
Incorporating Bioavailability Adjustments in Risk Assessment

Exposure Assessment

Relative Oral Bioavailability (RBA) Adjustment ensures that assumptions about bioavailability in the toxicity assessment aren't inconsistent with bioavailability from the exposure medium of interest

Toxicity Assessment

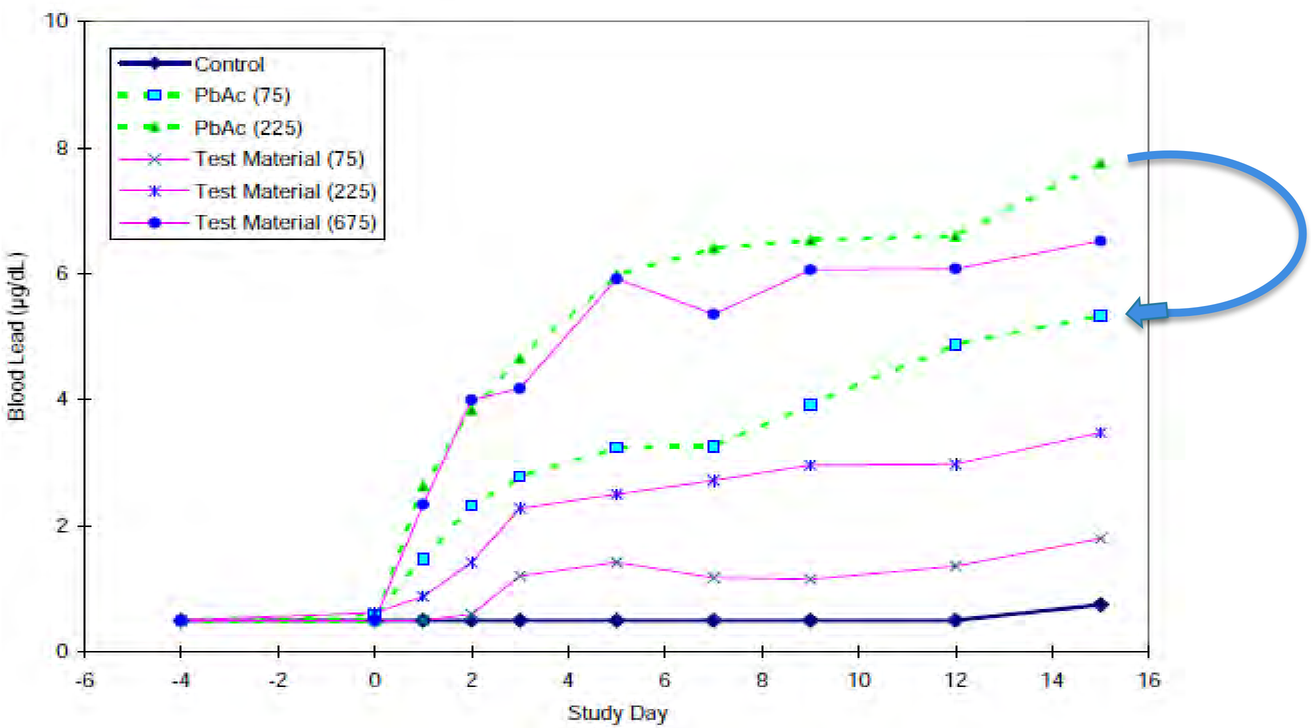
Bioavailability of Lead in Soil: Assessing RBA in Animal Studies



Example time course of blood lead measurements in swine dosed with lead as lead acetate and soil

Source: U.S. EPA OSWER 9285.7-77 2007.

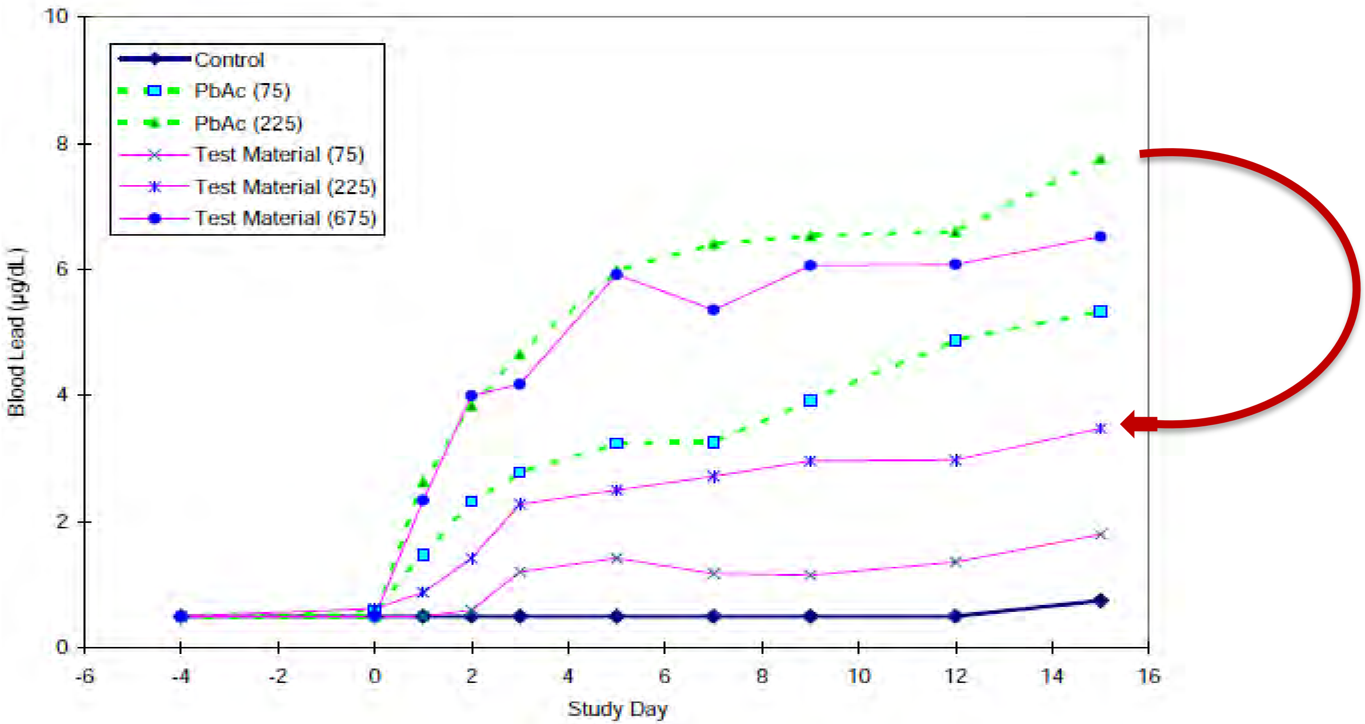
Bioavailability of Lead in Soil: Assessing RBA in Animal Studies



Lower dose of lead acetate results in lower blood lead level

Source: U.S. EPA OSWER 9285.7-77 2007.

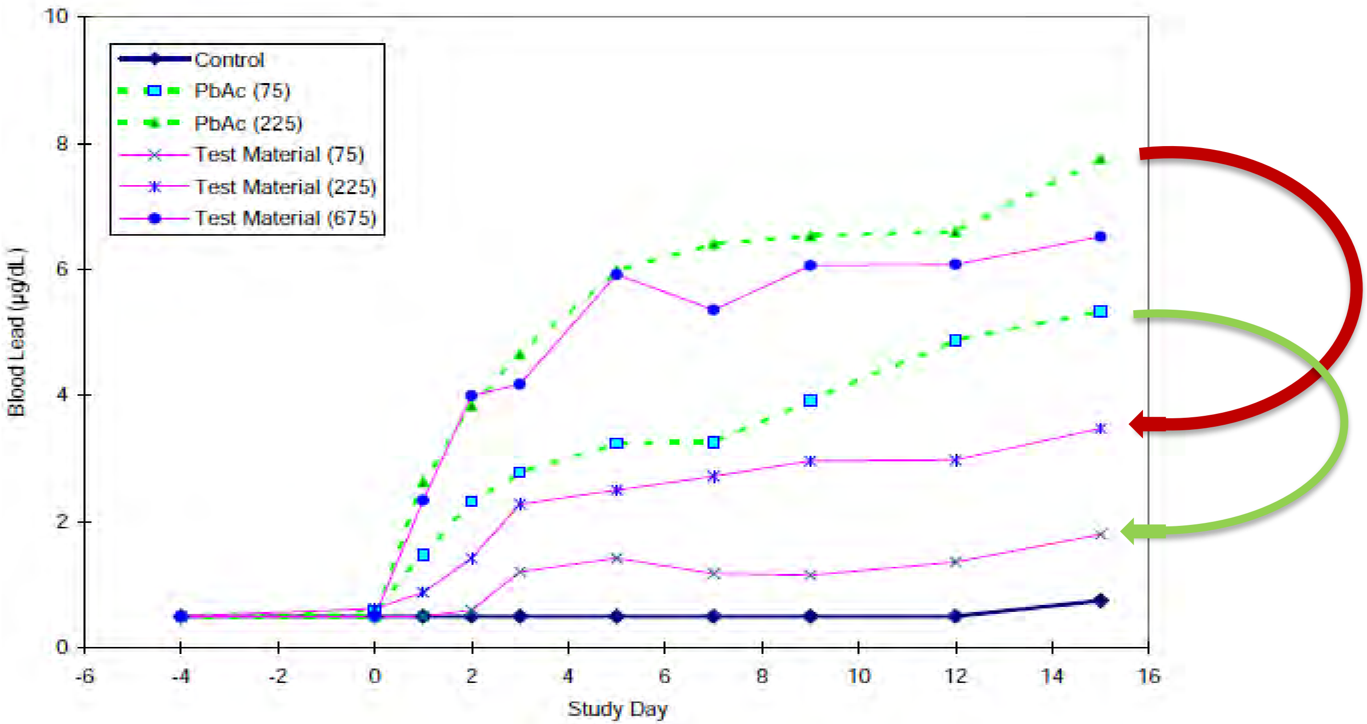
Bioavailability of Lead in Soil: Assessing RBA in Animal Studies



Dose of lead in soil results in lower blood lead than same dose (225) of lead as lead acetate

Source: U.S. EPA OSWER 9285.7-77 2007.

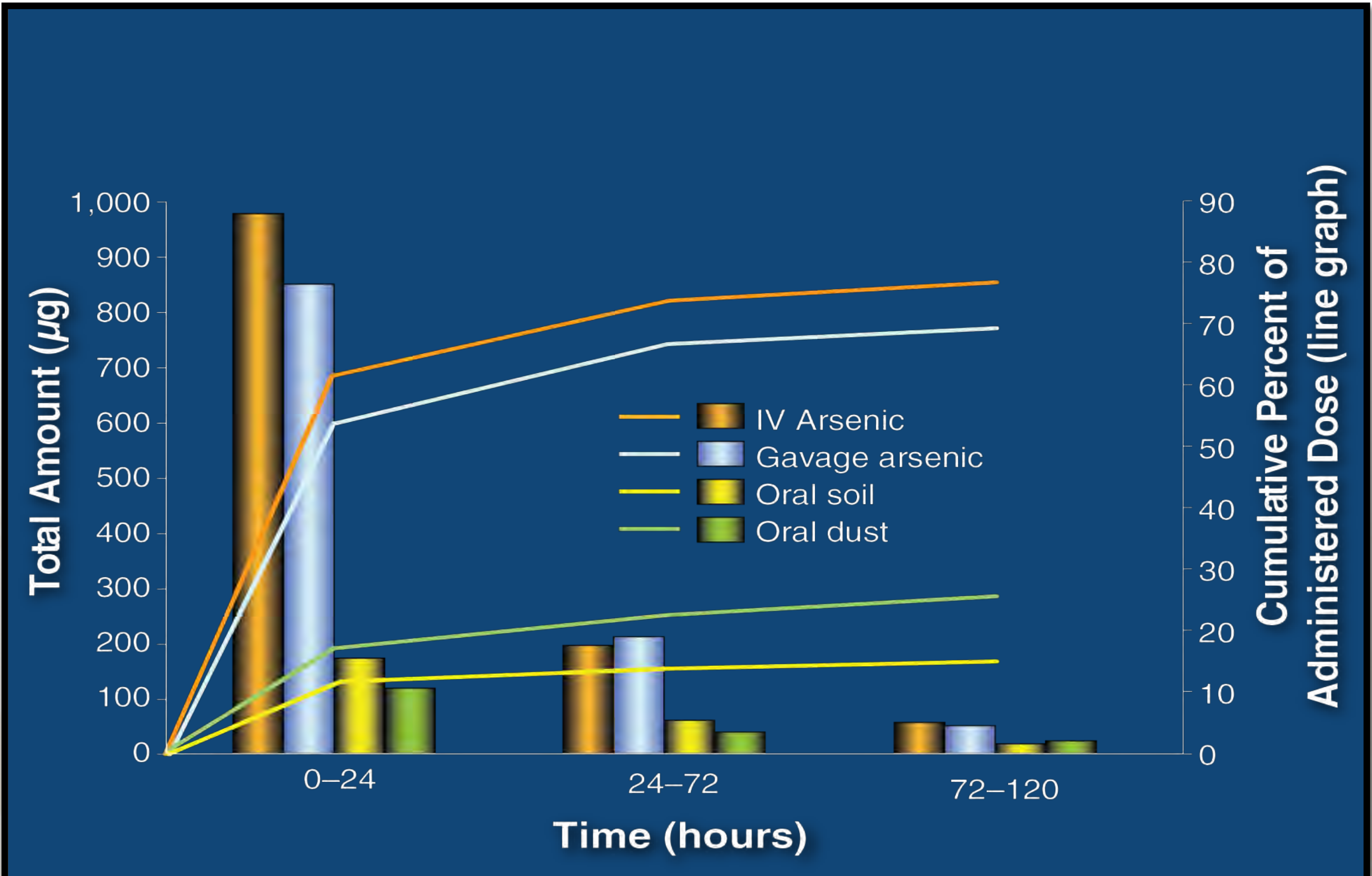
Bioavailability of Lead in Soil: Assessing RBA in Animal Studies



Dose of lead in soil results in lower blood lead than same dose (225) of lead as lead acetate

Source: U.S. EPA OSWER 9285.7-77 2007.

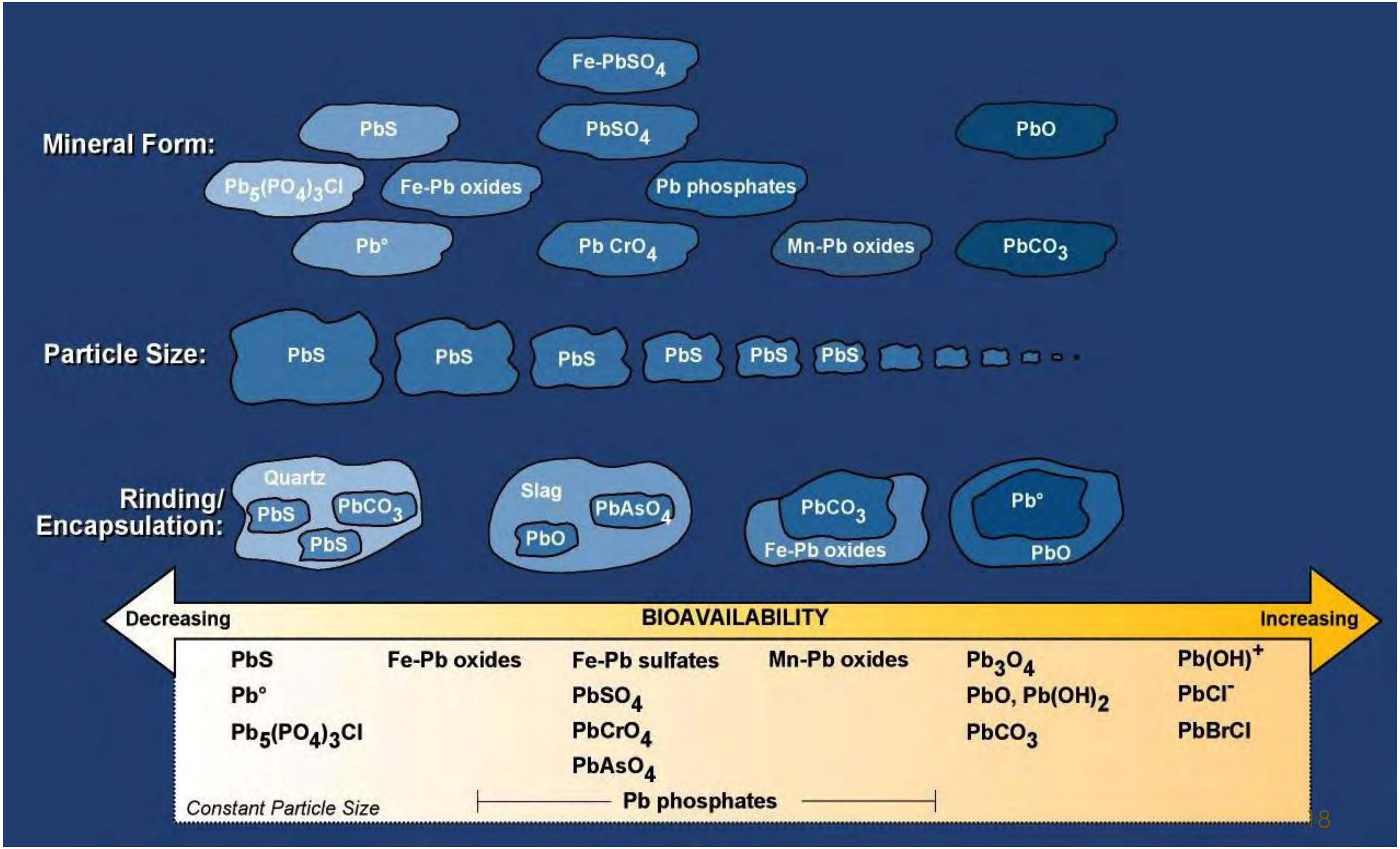
Monkey Bioavailability Study: Arsenic Excretion in Urine



Basis for Oral Toxicity Values for Selected Metals

Chemical	Toxicity Value		Toxicity Endpoint	Species, Study Type	Exposure from Chemical Form
Arsenic Inorganic	RfD CSF	$3x10^{-4}$ mg/kg-d	Hyperpigmentation keratosis, possible vascular complications Skin Cancer	Human, chronic oral	Drinking water, food/dissolved arsenic
Cadmium	RfD–water RfD–food	$5x10^{-4}$ mg/kg-d $1x10^{-3}$ mg/kg-d	Significant proteinuria	Human, number of chronic studies	Water, food
Chromium (III) insoluble salts	RfD	1.5 mg/kg-d	NOAEL	Rat, chronic feeding study Rat, 1-year drinking study	Diet/Cr_2O_3
Chromium (VI)	RfD	$3x10^{-3}$ mg/kg-d	NOAEL	Rat, 1-year drinking study	Water/K_2CrO_4
Mercury	RfD	$3x10^{-4}$ mg/kg-d	Autoimmune effects	Rat, subchronic feeding and subcutaneous studies	Gavage, subcutaneous mercuric chloride
Nickel	RfD	$2x10^{-2}$ mg/kg-d	Decreased body and organ weights	Rat, chronic oral	Diet/nickel sulfate

Factors Affecting the Relative Oral Bioavailability of Lead



Incorporating Relative Oral Bioavailability into Human Health Risk Assessment

Bioavailability from soil can be addressed in the site **Exposure Assessment**

$$\text{Exposure}_{(\text{RBA-adjusted})} = \frac{CS \times IR \times EF \times ED \times FI \times \mathbf{RBA}}{BW \times AT}$$

Where:

CS = soil concentration
IR = soil ingestion rate
EF = exposure frequency
FI = fraction ingested from site
ED = exposure duration
BW = bodyweight
AT = averaging time

Incorporating Relative Oral Bioavailability into Human Health Risk Assessment

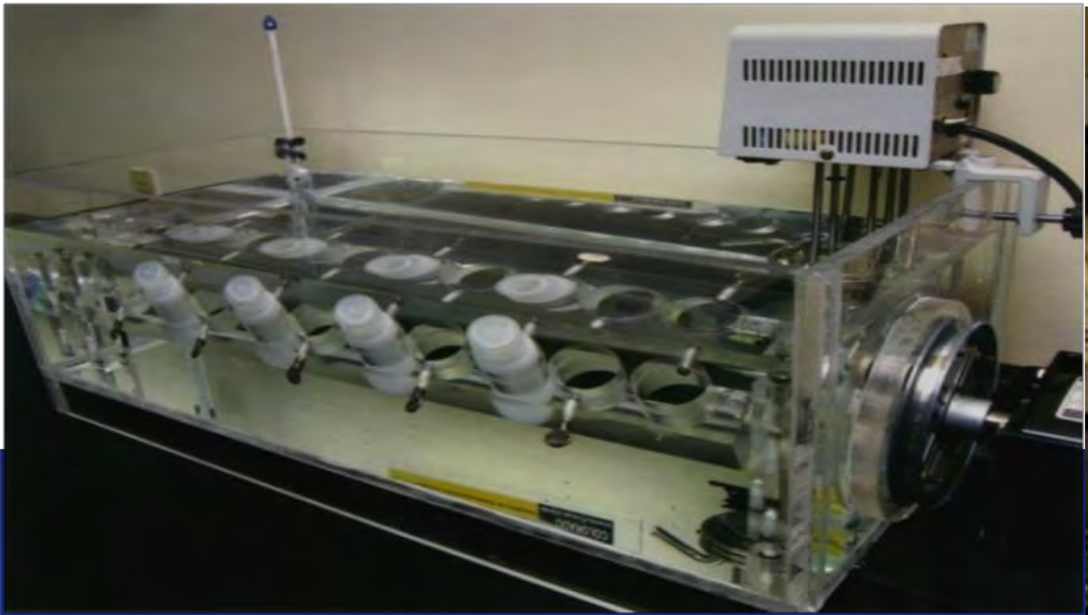
Bioavailability from soil can be addressed in the site-specific **Screening Values**

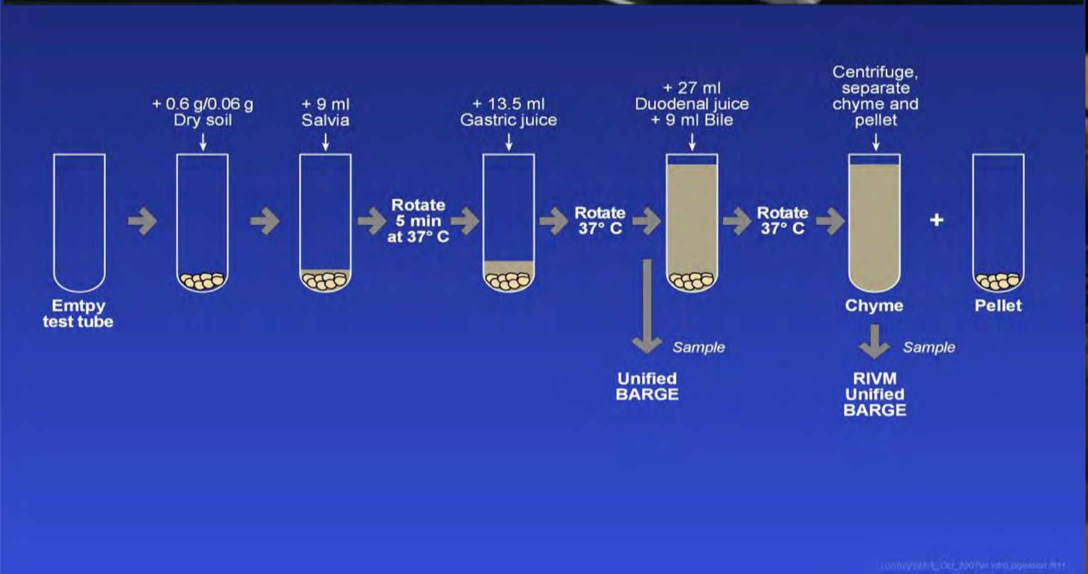
$$\text{Screening Value}_{(\text{RBA-adjusted})} = \frac{\text{Screening Value}}{\textbf{RBA}}$$

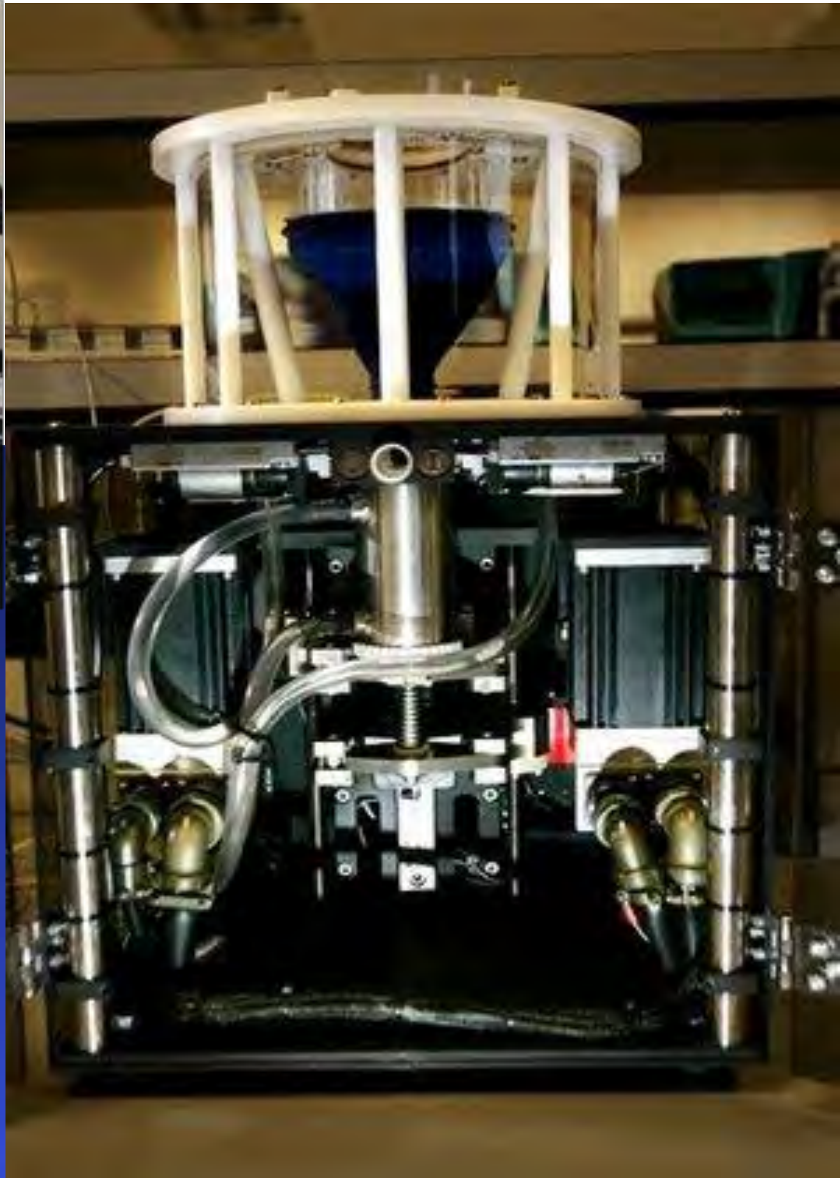
Example:

- Soil Screening Value for Lead = 400mg/kg
- Site-Specific RBA = 50%
- Site-Specific Screening Value = $\frac{400}{50\%} = \frac{400}{0.5} =$ 800 mg/kg

In vitro Methods for Bioaccessibility Testing

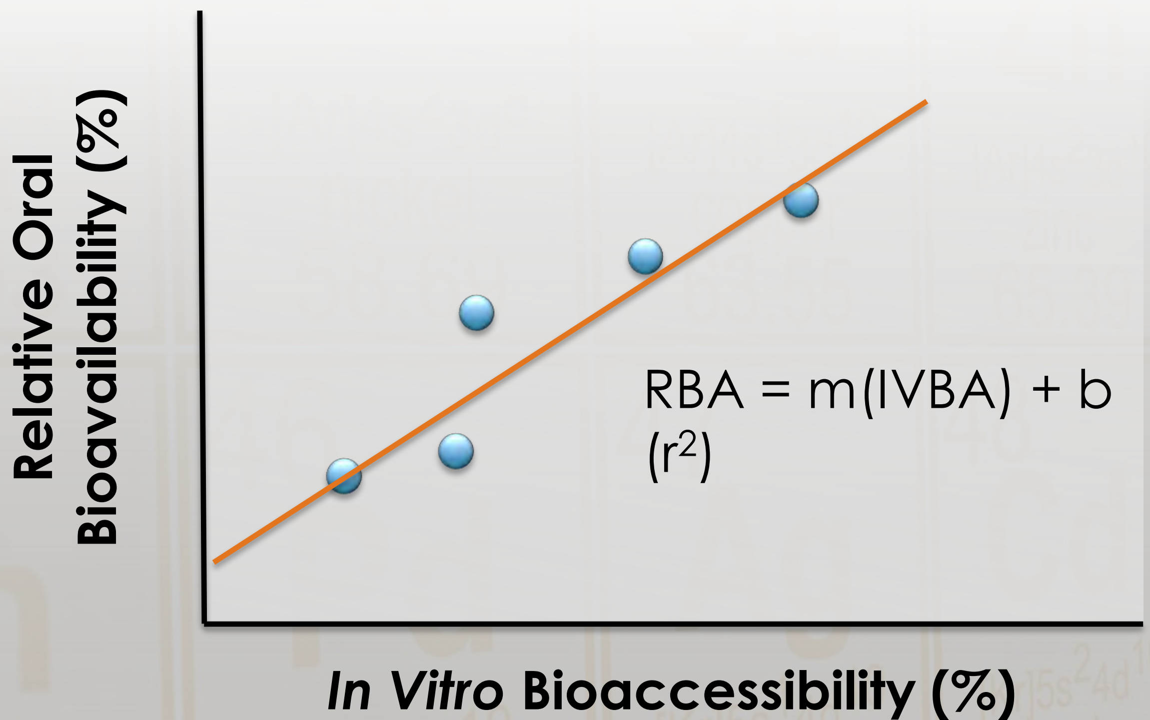






Predicting RBA with In Vitro Bioaccessibility Data

- *In vitro bioaccessibility data may be used to predict RBA*
- *In vivo : in vitro* correlation (IVIVC)



Different terms but same concept

- *"In vitro"*
- *"bioaccessibility"*
- *"IVBA"*

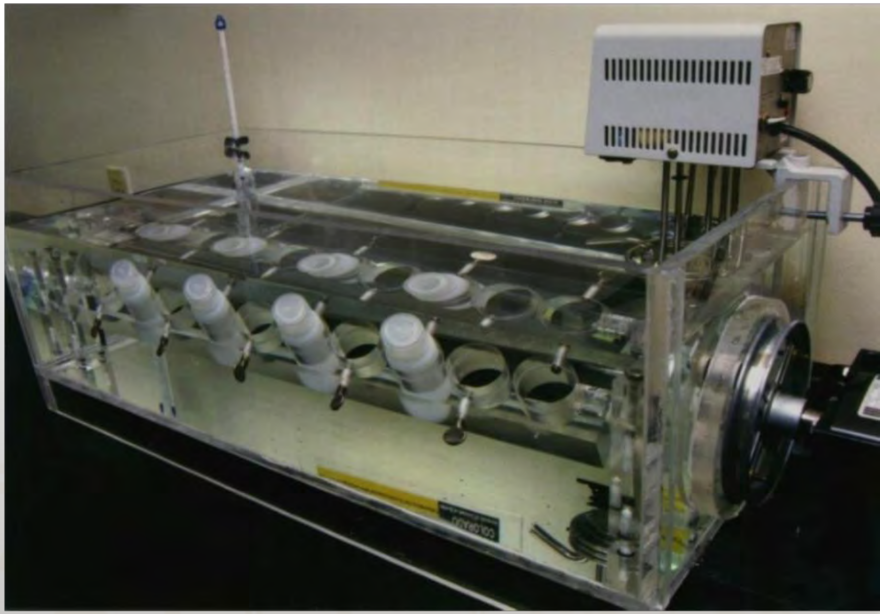
Predicting RBA with In Vitro Bioaccessibility Data

Advantages of using in vitro bioaccessibility data:

- Cost
  - 3 soils for $100,000 vs. 10 soils for $1,000
- Schedule
  - ~1 year for data vs. 3 weeks
- Informative
  - Provides estimate of RBA
  - Can evaluate many soils from one site
  - Characterize variability across site
  - Characterize possible different sources

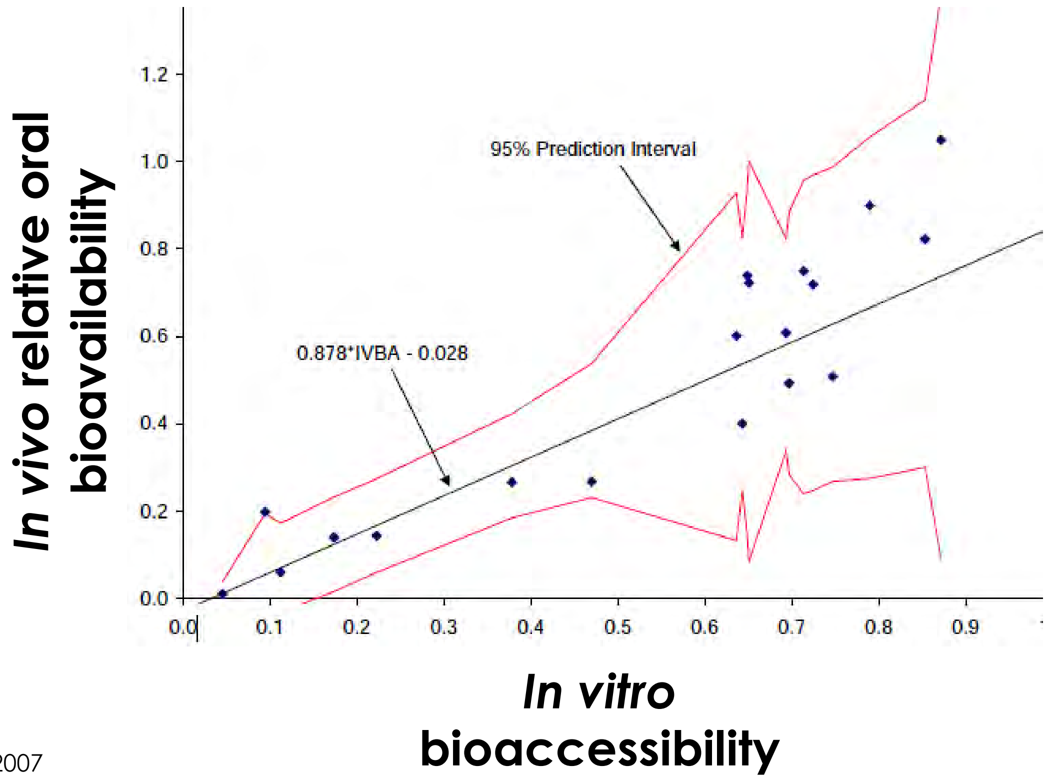
In Vitro Methods to Estimate the RBA of Metals in Soil

- **Evaluation of factors that affect solubility of metals under laboratory conditions**
- **Physiologically-based, then simplified**
  - 1 gram soil
  - 100 mL fluid
    - 0.4 M Glycine
    - pH 1.5
  - 37°C
  - End-over-end rotation
  - 1 hour



Development of *In Vitro* Methods to Estimate Bioavailability of Lead in Soil

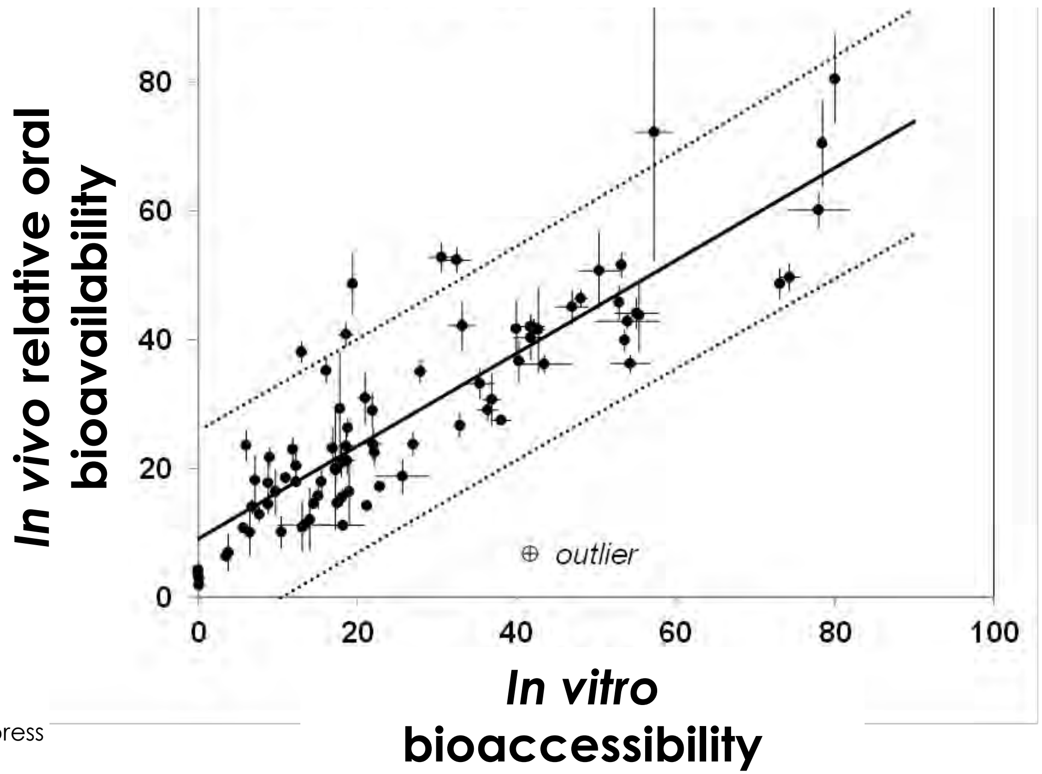
- ***In vitro*** **method "validated" for use in risk assessment**
- **19 soils with RBA measured in swine**
- **RBA = (0.89)IVBA – 0.028 (r^2 = 0.92)**



Source: OSWER 9285.7-77 2007

Development of *In Vitro* Methods to Estimate Bioavailability of Lead in Soil

- Arsenic *in vitro* bioaccessibility
- Pooled data from three laboratories (USA and Australia) using same method (total of 83 samples)
- RBA = (0.79)IVBA + 3 ($r^2 = 0.87$)



Source: Diamond et al., in press

RBA: State of the Science for Use in Human Health Risk Assessment

Lead and Arsenic:

- **Clear evidence that site- and source-specific factors control bioavailability**
- **Factors controlling bioavailability well characterized**
  - Chemical form
  - Particle size
  - Soil characteristics
- ***In vitro* methods developed and "validated"**
  - Predictive of RBA as measured in animals
  - Good reproducibility within and across laboratories
- **RBA adjustments widely accepted in risk assessment**

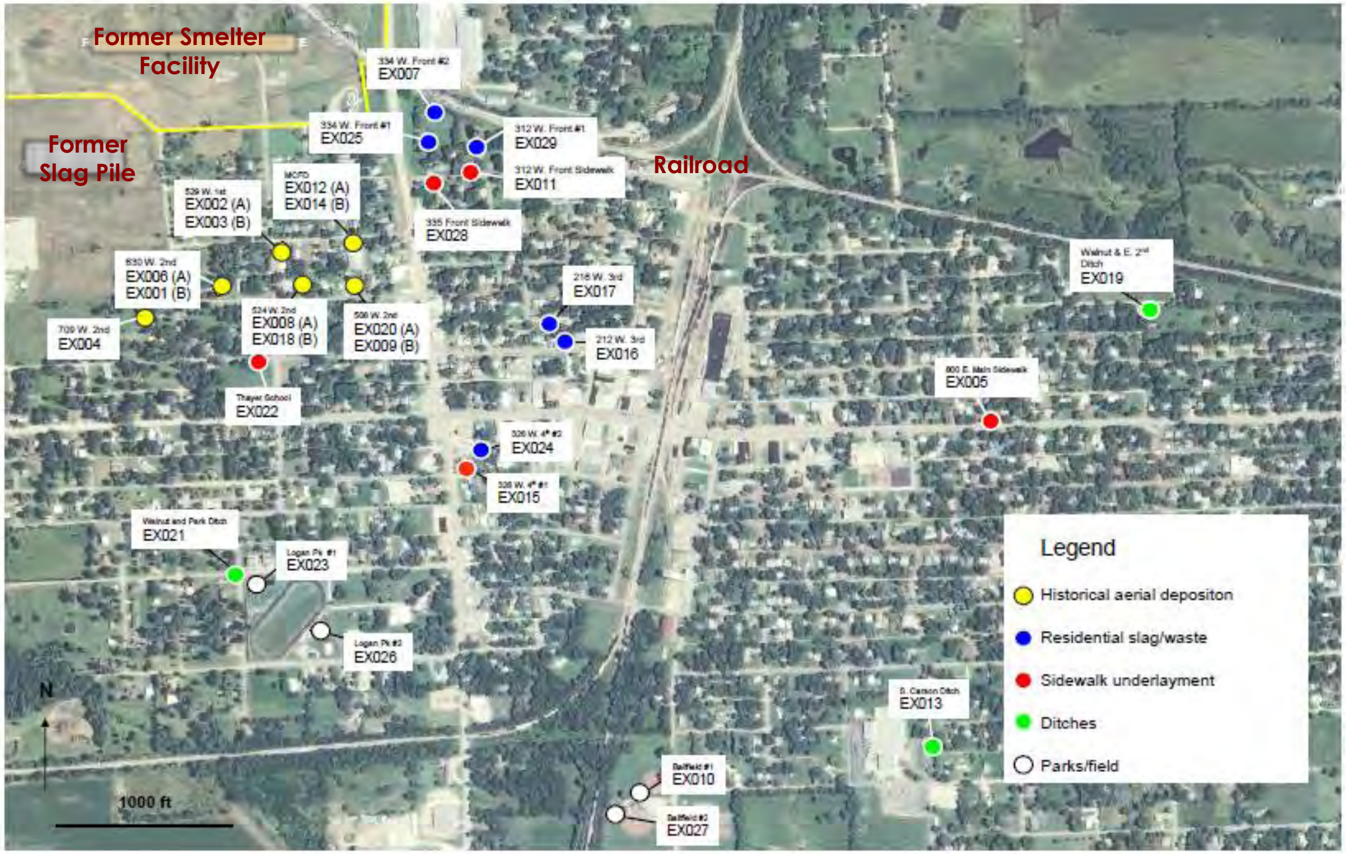
Case Study:

Using bioaccessibility data to adjust for RBA in HHRA

- Moving from site data to bioavailability data
- Selecting samples for bioaccessibility testing
- Interpreting bioaccessibility data
- Deriving RBA for use in HHRA
- Bioavailability adjustments in risk assessment for lead (IEUBK pharmacokinetic modeling)

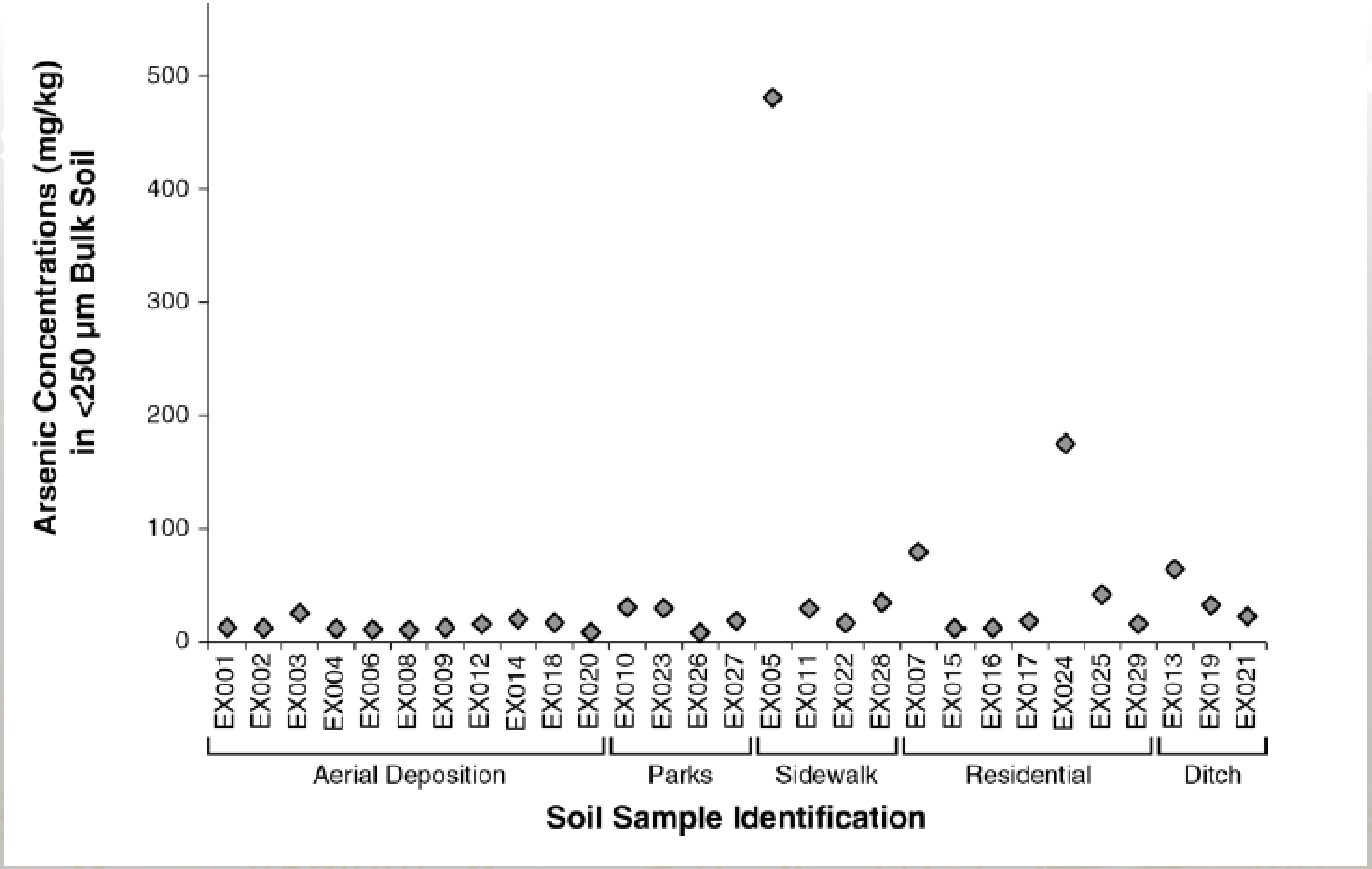
Case Study: Residential Impacts from Former Smelter Site

- **Example: Soil sampling to characterize different source materials**



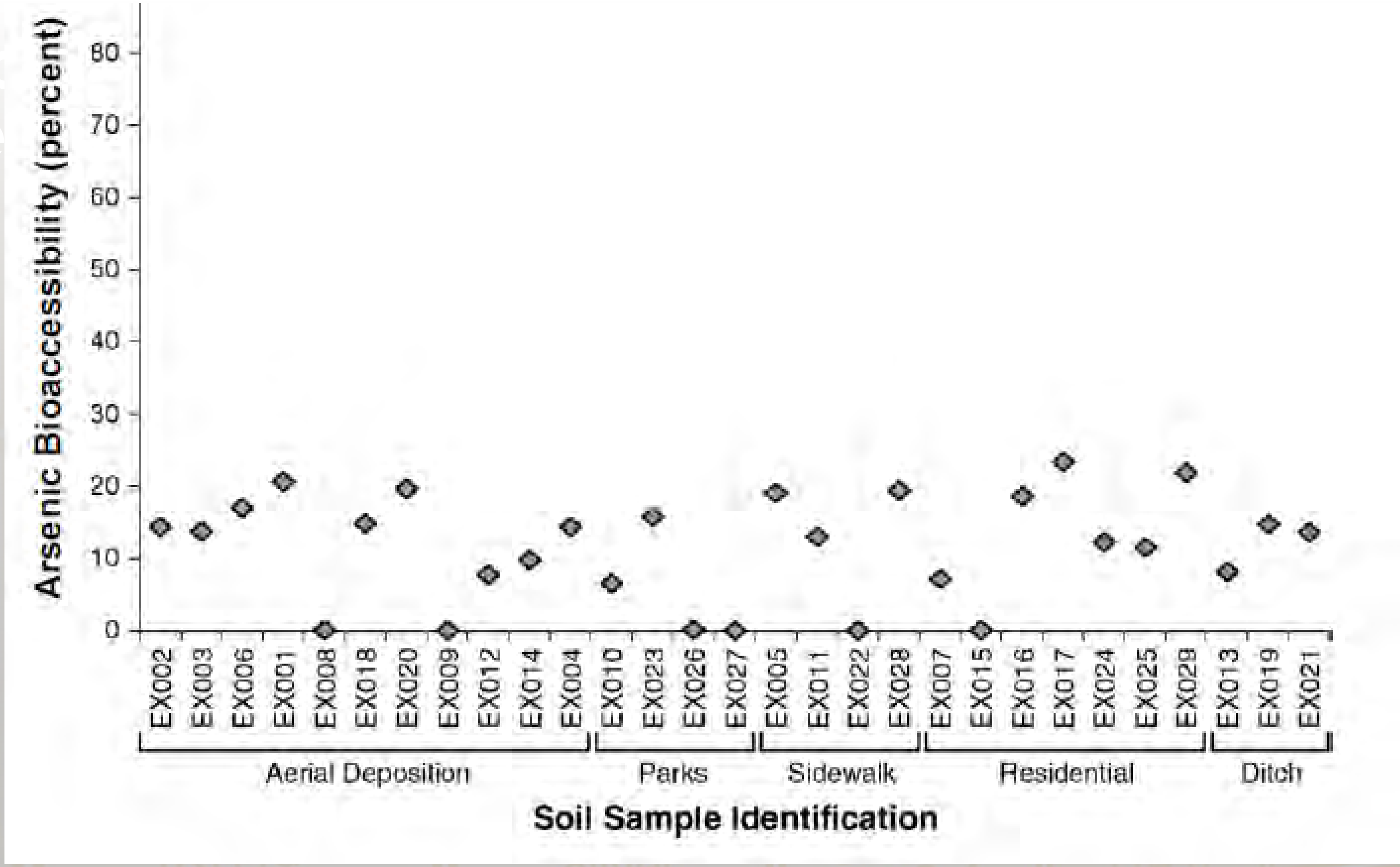
Case Study: Residential Impacts from Former Smelter Site

- Characterize <u>concentration</u> in soil



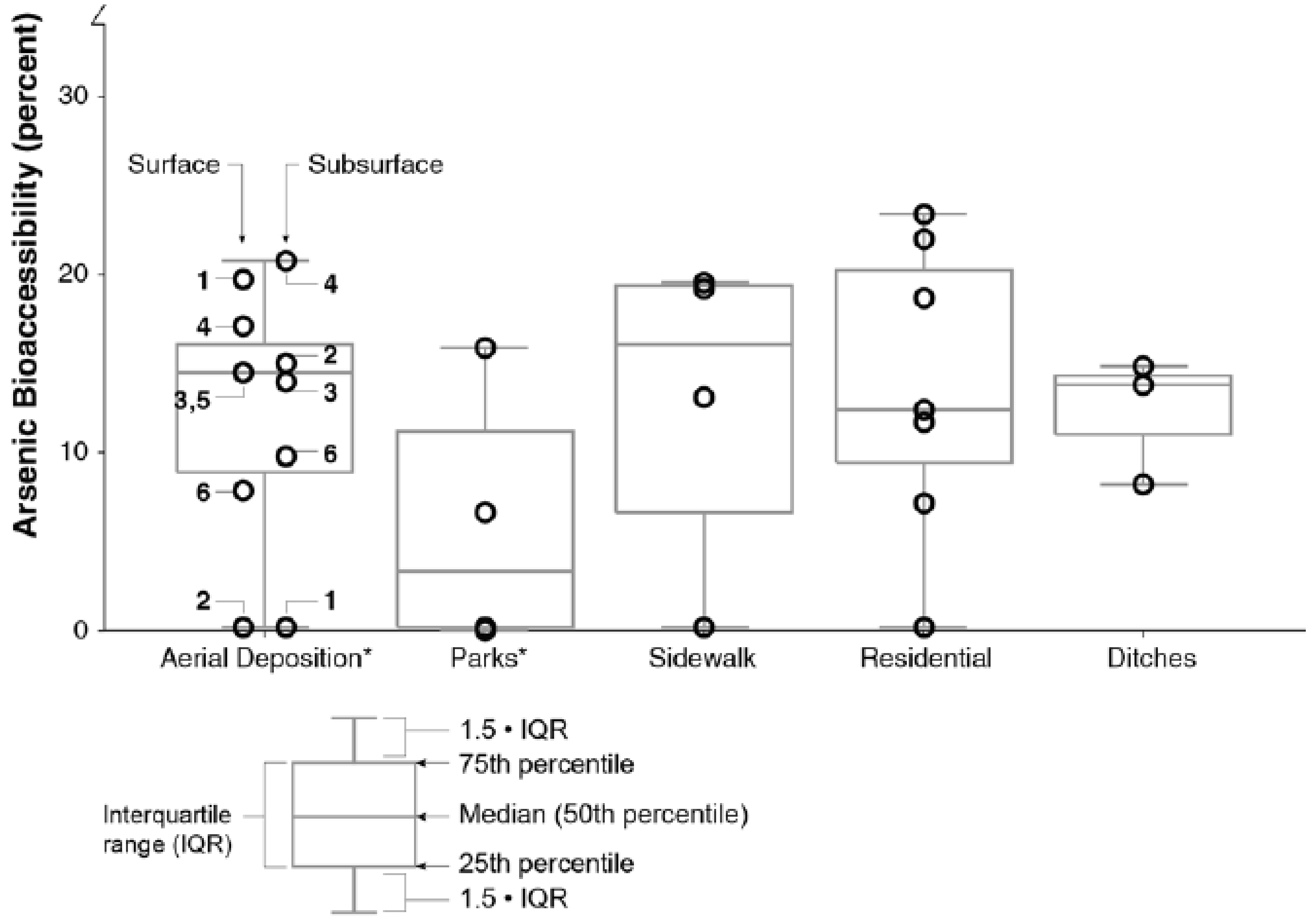
Case Study: Residential Impacts from Former Smelter Site

- Characterize <u>bioaccessibility</u>



Case Study: Residential Impacts from Former Smelter Site

- **Reported bioaccessibility by source type**



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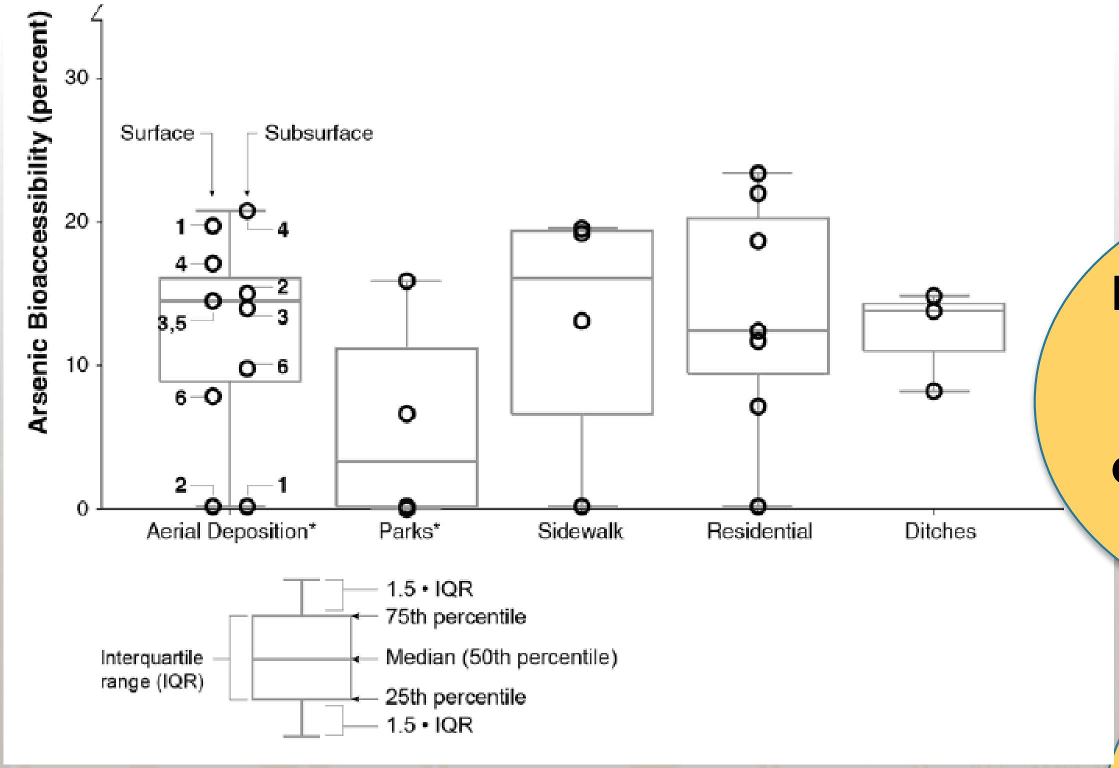
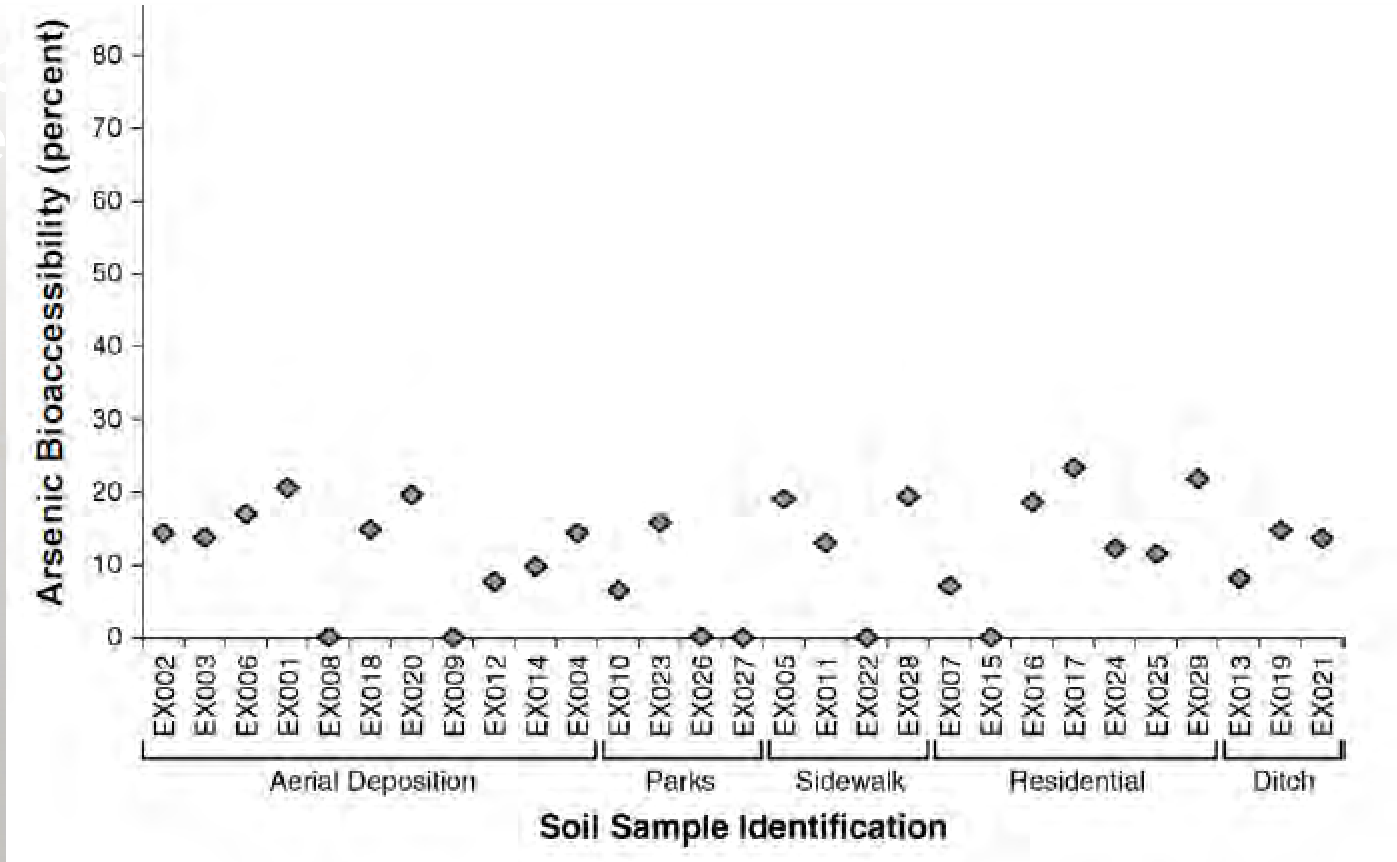


Data were used to support a bioavailability adjustment of 21% across the site.

Used to adjust soil screening level for the site $SSL_{adj} = SSL \div 0.21$

Case Study: Residential Impacts from Former Smelter Site

- Characterize bioaccessibility



Case Study: Residential Impacts from Former Smelter Site

Example:
what bioaccessibility data look like

- **Soil data**
  - Arsenic concentration in soil
  - Mass of soil tested
  - Calculate mass in soil
- **Extraction results**
  - Arsenic concentration in extract
  - Volume of extract
  - Calculate mass extracted
- **Bioaccessibility (% As IVBA)**

$$\frac{(\text{mass extracted})}{(\text{mass in soil})} \times 100$$

Represents the fraction extracted from soil under physiological conditions

Sample Type	Sample ID	Soil Horizon	As in <250-µm Bulk Soil (mg/kg)	Mass Soil (g)	Mass As in Soil Tested (µg)	ICP As (µg/L)	Solution Amount (L)	%As IVBA
Historical Aerial Deposition	EX001	B	12.4	1.0122	12.57	26	0.1	21
	EX002	A	11.9	1.0083	11.99	17	0.1	14
	EX003	B	25.2	1.0021	25.21	35	0.1	14
	EX004	A	11.4	1.0131	11.54	17	0.1	15
	EX006	A	10.6	1.0109	10.73	18	0.1	17
	EX008	A	10.2	1.0265	10.45	0.212	0.1	0
	EX009	B	12.2	1.0231	12.50	0.212	0.1	0
	EX012	A	15.5	0.9871	15.33	12	0.1	8
	EX014	B	19.8	1.0077	19.95	20	0.1	10
	EX018	B	16.8	1.0135	17.00	25	0.1	15
	EX020	A	8.4	1.0076	8.44	17	0.1	20
Parks/Fields	EX010		30.5	1.0229	31.17	21	0.1	7
	EX023		29.6	1.0095	29.84	47	0.1	16
	EX026		8.1	1.0261	8.29	0.212	0.1	0
	EX027		18.3	1.0186	18.66	0.212	0.1	0
Sidewalk Underlayment	EX005		480.5	1.0137	487.12	933	0.1	19
	EX011		29.3	1.0217	29.88	39	0.1	13
	EX022		16.5	0.9972	16.44	0.212	0.1	0
	EX028		34.5	1.0162	35.11	68	0.1	19
Residential slag/waste	EX007		79.3	1.0041	79.63	57	0.1	7
	EX015		11.7	1.0216	12.00	0.212	0.1	0
	EX016		12.0	1.0164	12.23	23	0.1	19
	EX017		18.1	1.0246	18.51	43	0.1	23
	EX024		174.9	0.9870	172.64	214	0.1	12
	EX025		41.7	1.0233	42.67	50	0.1	12
	EX029		15.7	1.0210	15.98	35	0.1	22
Ditches	EX013		64.1	1.0136	65.02	53	0.1	8
	EX019		32.2	1.0092	32.53	48	0.1	15
	EX021		22.4	1.0061	22.51	31	0.1	14

Case Study: Residential Impacts from Former Smelter Site

Example: what bioaccessibility data look like

Quality control demonstrates that the system is working

- Duplicates
- Blanks
- Spikes
- Reference material

Sample ID	Extraction Date	pH (s.u.)	Spike Conc. (mg/L)	Arsenic Conc. in Extract (mg/L)	Arsenic Conc. in Soil (mg/kg	Relative Percent Difference[a] (%)	Percent Recovery (%)	Control Limits
Duplicate Extractions								
EX010	09/09/13	1.628	--	0.021	--	--	--	--
EX010-DUP	09/09/13	1.613	--	0.017	--	20%	--	20%
EX020	09/09/13	1.609	--	0.017	--	--	--	--
EX020-DUP	09/09/13	1.617	--	0.013	--	24%	--	20%
Duplicate Soil Split Samples								
EX010	09/09/13	1.628	--	--	30.5	--	--	--
EX010-DUP	09/09/13	1.613	--	--	31.9	4.7%	--	20%
EX020	09/09/13	1.609	--	--	8.4	--	--	--
EX020-DUP	09/09/13	1.617	--	--	8.5	1.7%	--	20%
QC Samples								
Bottle Blank 1	09/09/13	--	--	DL	--	--	--	<0.01 mg/L
Bottle Blank 2	09/09/13	--	--	DL	--	--	--	<0.01 mg/L
BLANK-1	09/09/13	1.53	--	DL	--	--	--	--
BLANK-SPK-1	09/09/13	1.528	2.5	2.81	--	--	112%	85-115%
BLANK-2	09/09/13	1.5	--	DL	--	--	--	--
BLANK-SPK-2	09/09/13	1.49	2.5	2.80	--	--	112%	85-115%
EX010-SPK	09/09/13	1.613	2.5	2.42	--	--	--	--
EX020-SPK	09/09/13	1.62	2.5	2.45	--	--	--	--
NIST-2711 (SRM)[b]	09/09/13	1.62	--	0.58	--	--	--	0.50 - 0.68
NIST-2711 (SRM)[b]	09/09/13	1.62	--	--	105.0	--	100%	97 - 113

Notes: -- – Not available or not applicable
DL – undetected (below reporting limit)

[a] Relative percent difference = ((absolute value(c1 – c2))/average) × 100

[b] Certified values for NIST 2711 are 105 mg/kg for arsenic, and 1162 mg/kg for lead

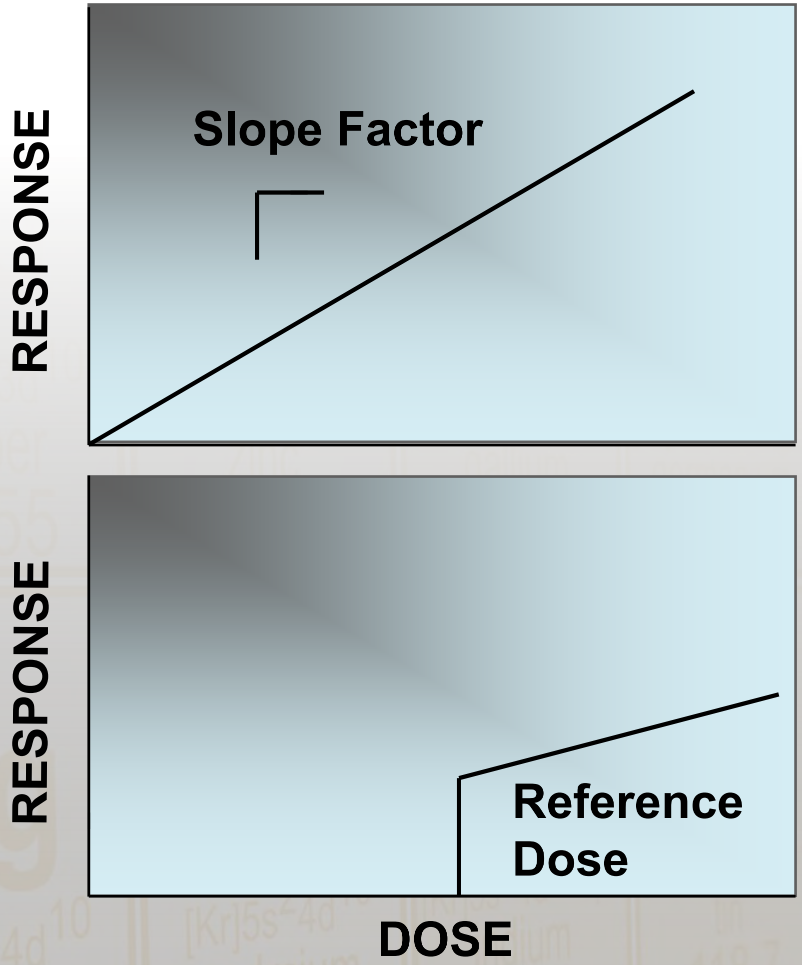
Bioavailability in Lead Risk Assessment

- Unique characteristics of HHRA of lead in soil
- Use of pharmacokinetic models
- Incorporating bioavailability considerations in modeling of blood lead levels
- Impact on results

Comparison of Dose – Response Assessments

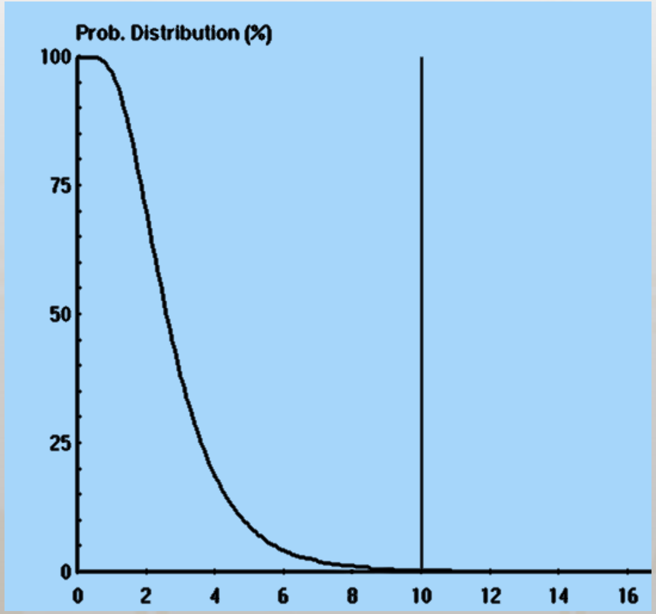
Carcinogens

Non-Carcinogens



Comparison of Dose – Response Assessments

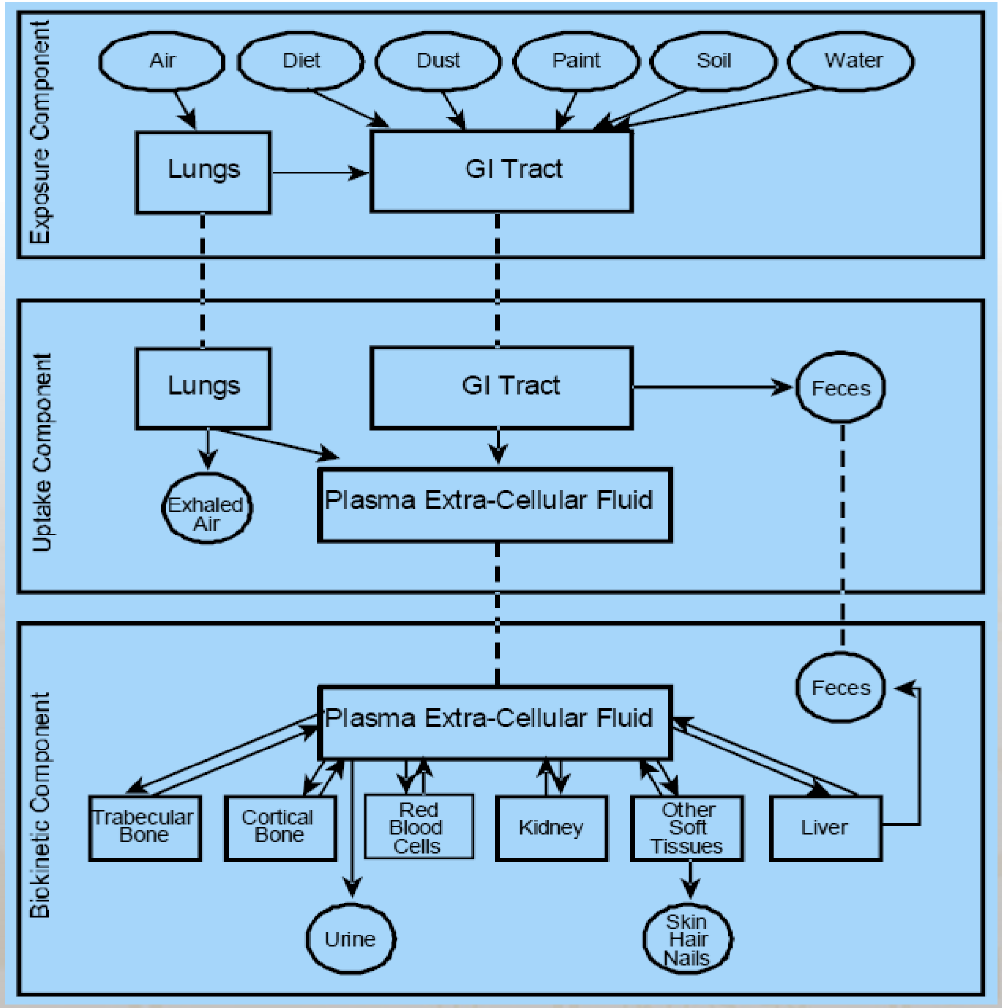
Lead

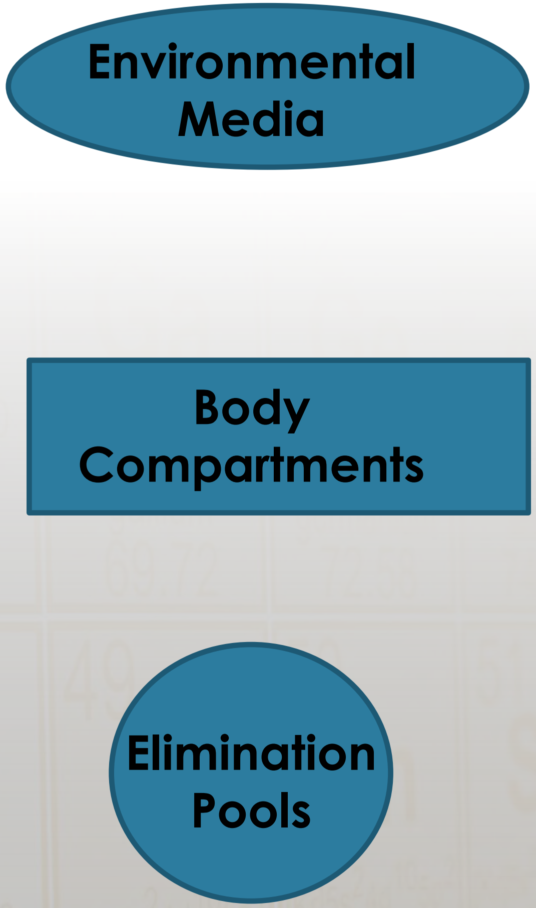


Blood Lead Conc (ug/dL)

- Risks evaluated based on blood lead levels (internal dose) rather than exposure level (external dose)
- Pharmacokinetic models used to assess exposure and determine blood lead levels
    - IEUBK Model for Children
    - Adult Lead Models

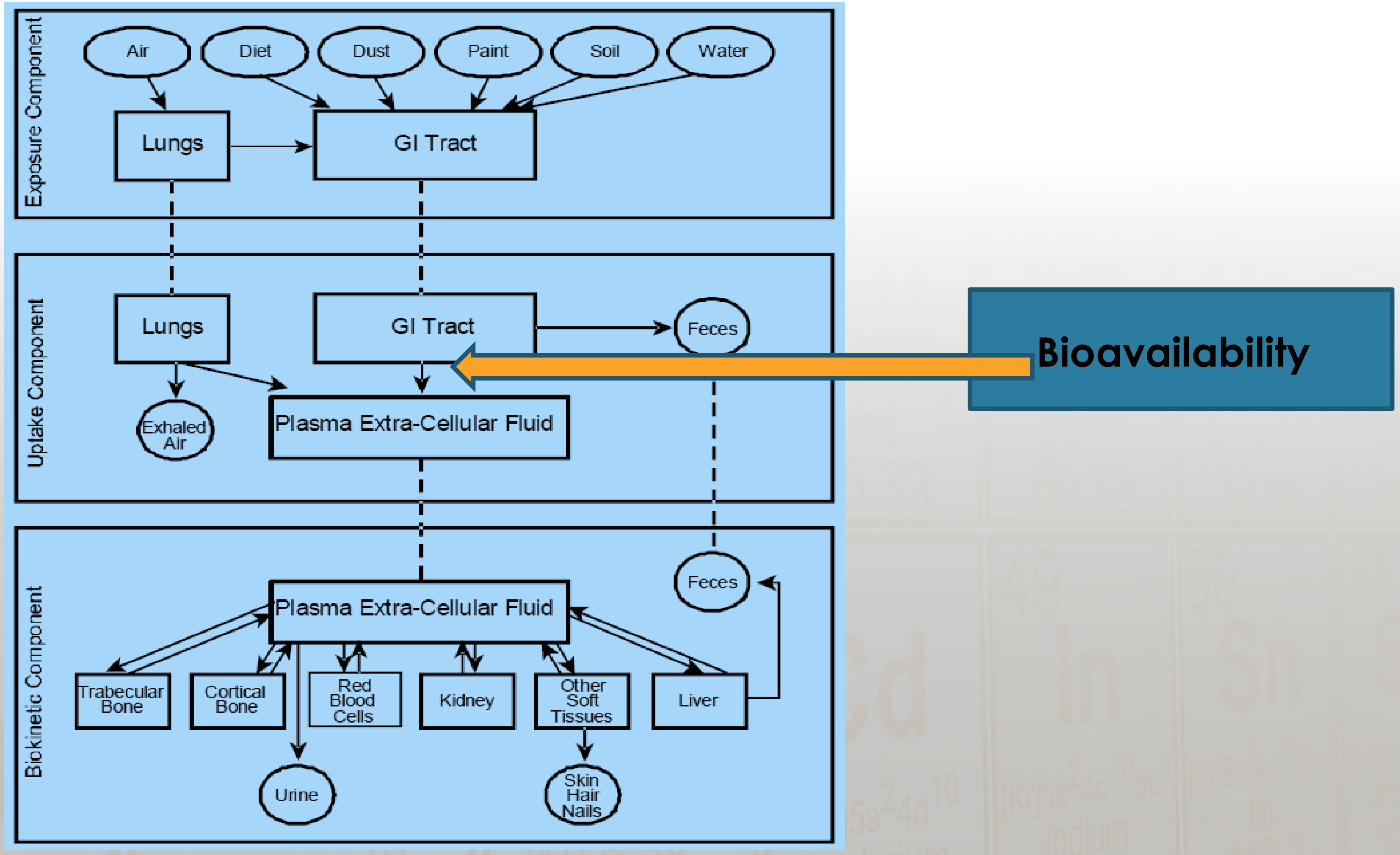
IEUBK Model for Lead Exposure



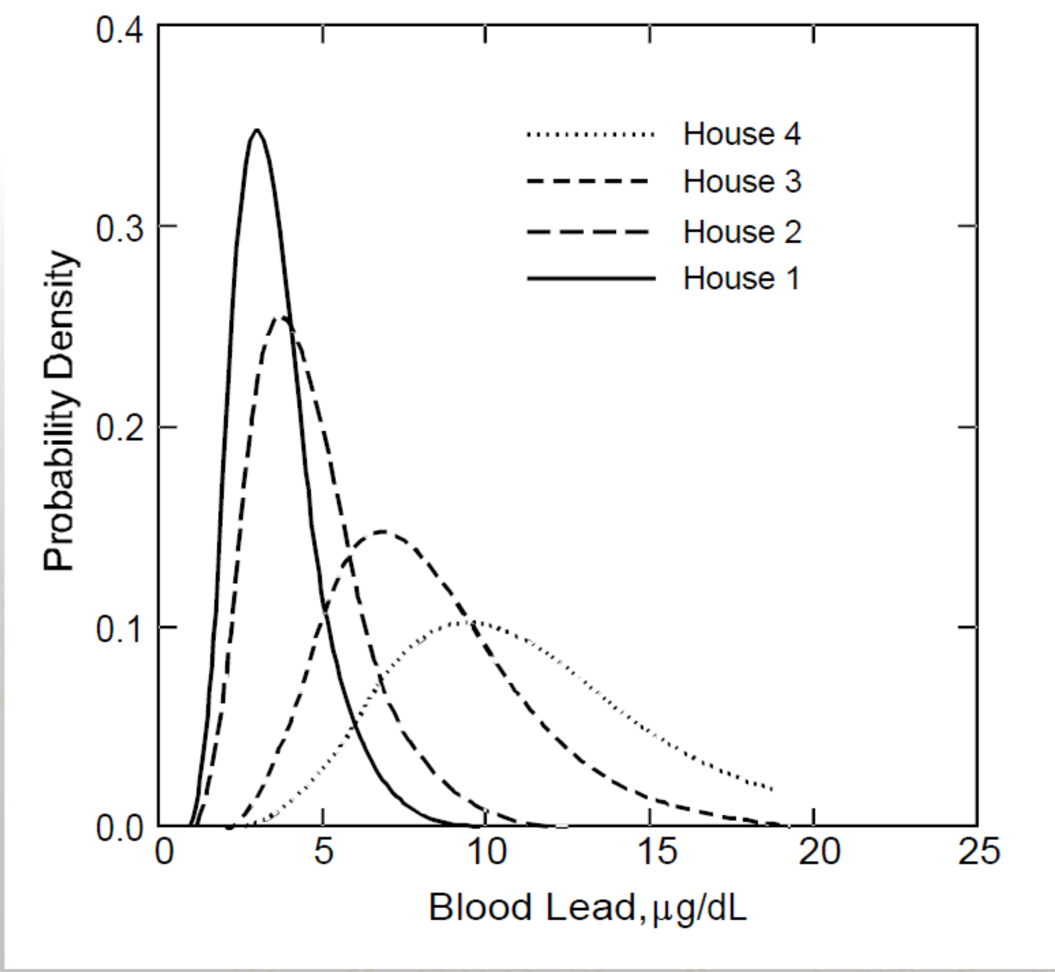


From U.S. EPA

IEUBK Model for Lead Exposure



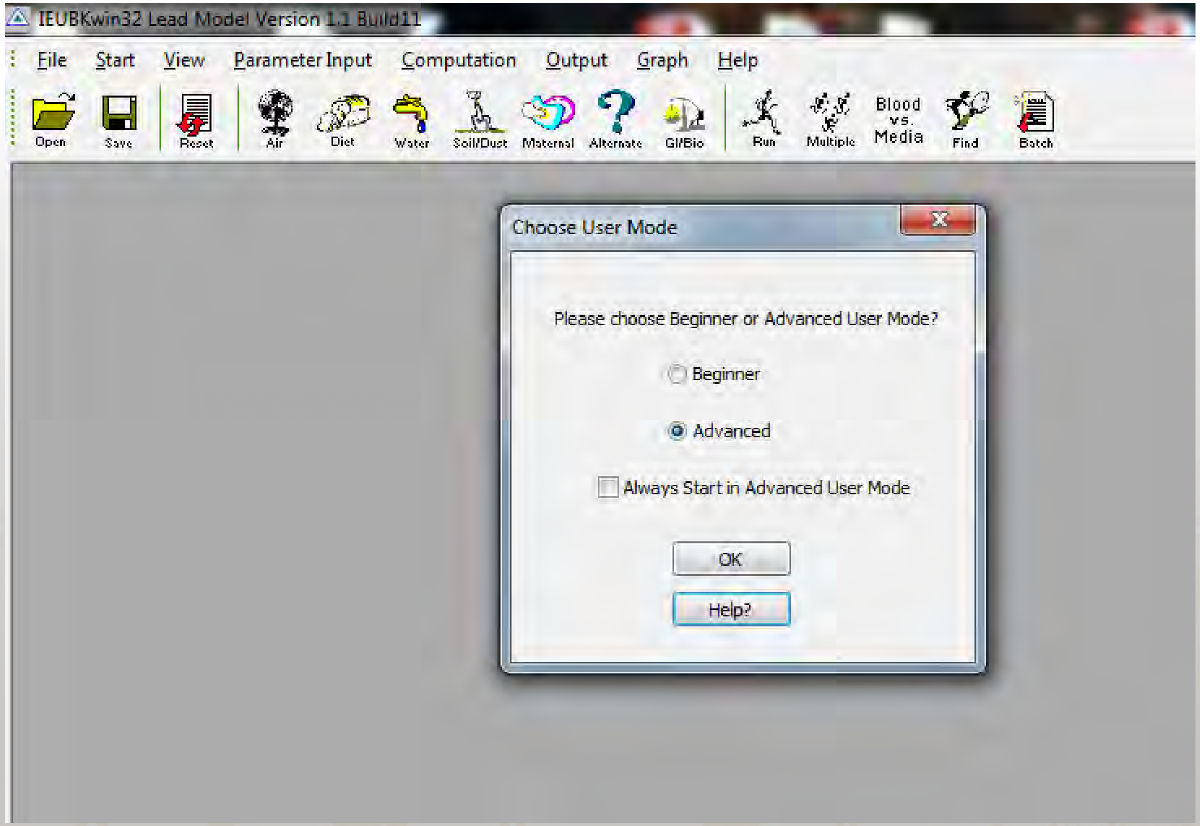
IEUBK Model for Lead Exposure



Sites (or homes) with different types of lead may have different relation between soil concentration and blood lead

Blood Lead Modeling with IEUBK Model

Initial Screen when you open the IEUBK Model (U.S. EPA)

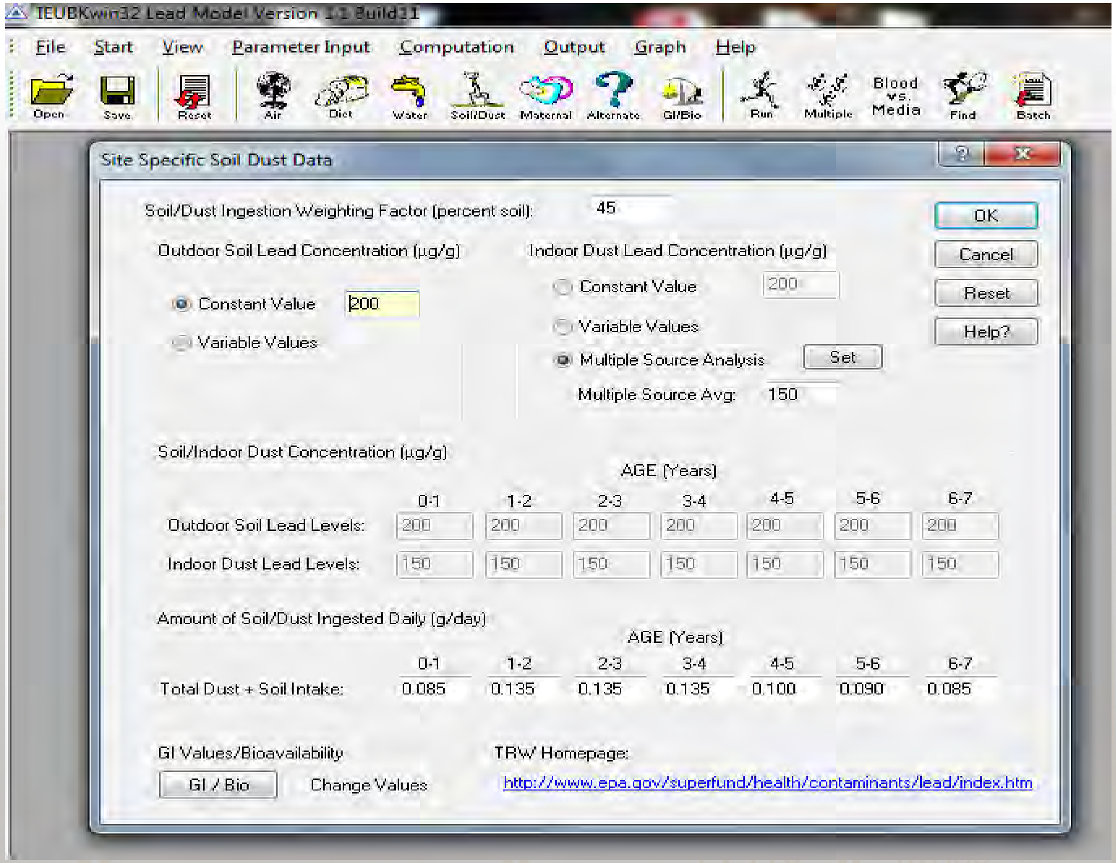


1. **Select "Advanced" mode**

Blood Lead Conc (ug/dL)

Blood Lead Modeling with IEUBK Model

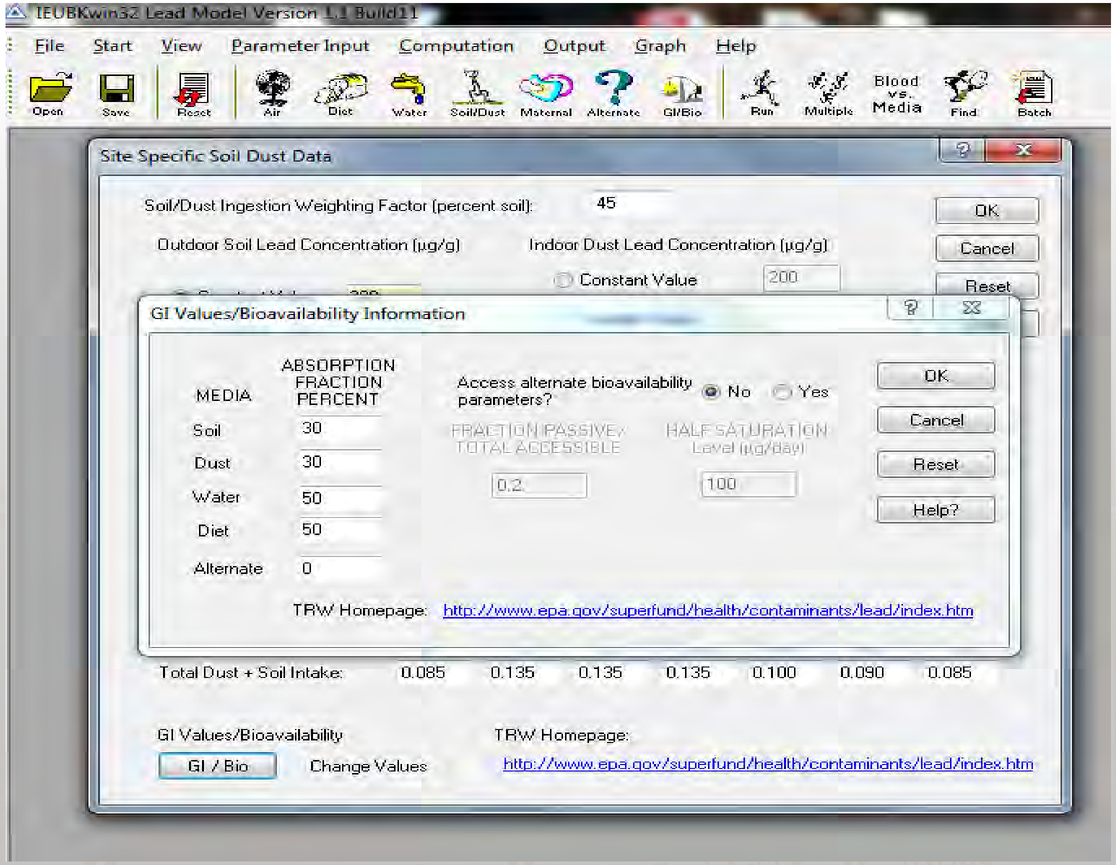
Inputs for Site-Specific Soil/Dust Data



1. Select "Soil/Dust" on menu
2. Select to change values for "GI/Bio"

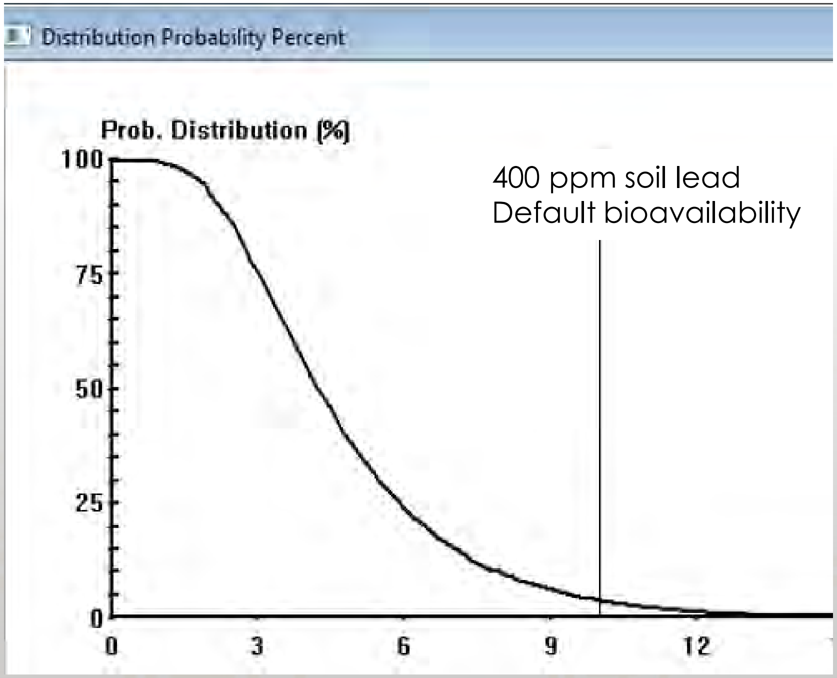
Blood Lead Modeling with IEUBK Model

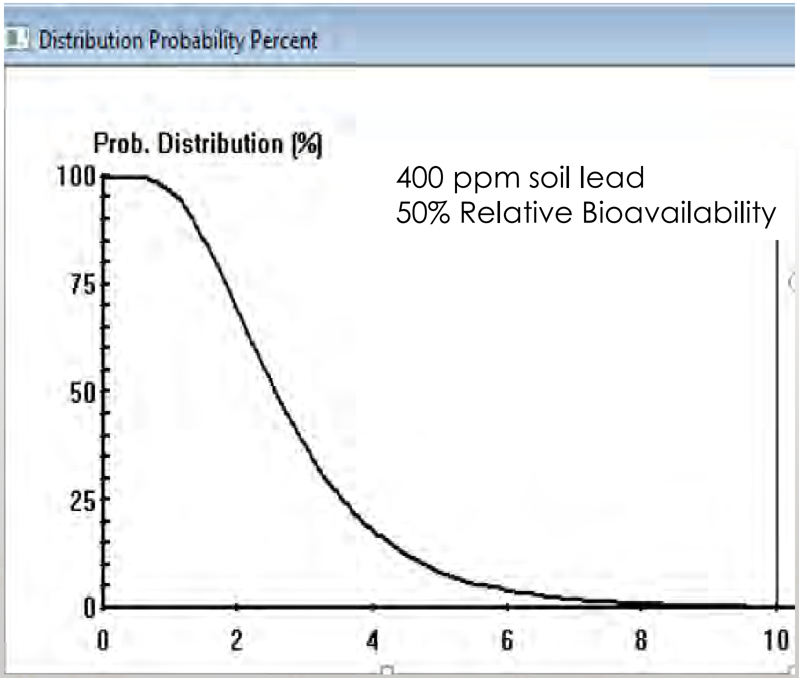
Inputs for Site-Specific Soil/Dust Data



1. Change "Absorption Fraction Percent" to reflect site data

Blood Lead Modeling with IEUBK Model





Impact of 50% RBA:

Equivalent soil concentration, but probability distribution of blood lead levels shifts to the left with lower bioavailability

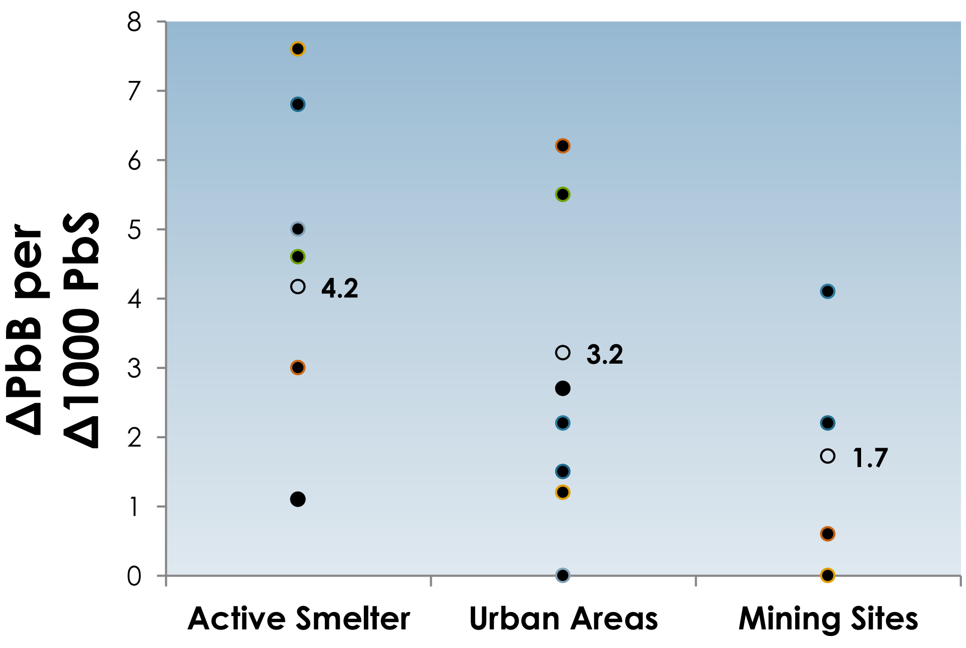
Applying Bioavailability Adjustment in Human Health Risk Assessment

RBA adjustments widely accepted in risk assessment

- **Clear evidence that site- and source-specific factors control bioavailability**
- **Factors controlling bioavailability well characterized**
  - Chemical form
  - Particle size
  - Soil characteristics
- ***In vitro* methods developed and provide inexpensive tool for estimating bioavailability**
  - Predictive of RBA as measured in animals
  - Good reproducibility within and across laboratories
- **Lead and arsenic are well researched**
- **Increased research on other metals**
  - Cadmium, nickel, chromium, mercury

Applying Bioavailability Adjustment in Human Health Risk Assessment

Bioavailability adjustments can improve our understanding of human exposure to metals in soil

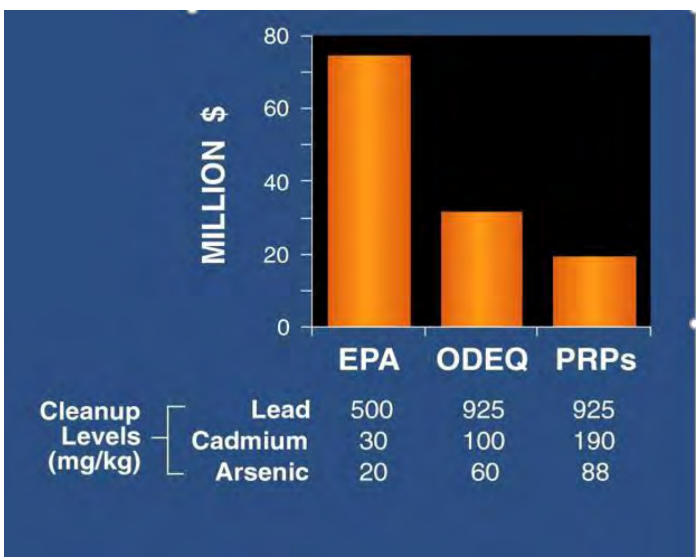


Data presented in Steele et al., 1990.

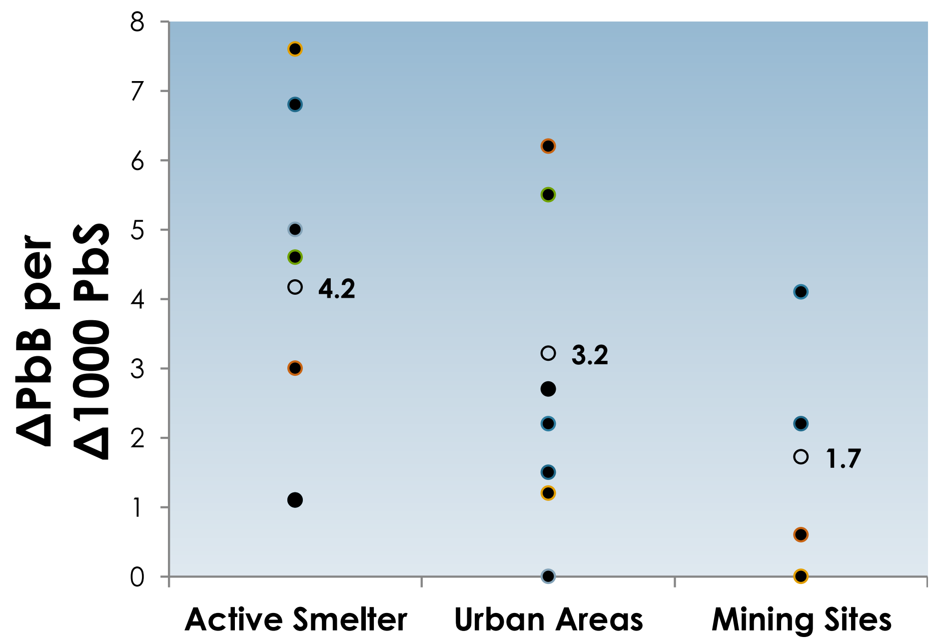
Applying Bioavailability Adjustment in Human Health Risk Assessment

Bioavailability adjustments can improve our understanding of human exposure to metals in soil

…. And can have significant impact on the scope (and costs) of cleanup



EPA PRGs, PRP values in RI report, ODEQ values in ROD 12/94



Data presented in Steele et al., 1990.

Questions?