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Bioavailability Adjustments in Human Health Risk Assessment for Metals-Contaminated Sites

Submitted by: Australia

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Bioavailability Adjustments in Human Health Risk Assessment for Metals-Contaminated Sites

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State of the Science: Relative Oral Bioavailability of Metals from Soil

- Concepts, definitions, and applications
- Science and Policy
- Lead
- Arsenic
- "Other Metals"
- Examples of application to metals-contaminated sites

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California Gulch Superfund Site — Leadville, Colorado USA

- Highest incorporated town in the U.S.
- Mining, processing, smelting, starting in 1859
- Gold, sliver, lead, zinc
- Numerous source materials -- slag piles, railroad easements, smelter waste, waste rock, tailings

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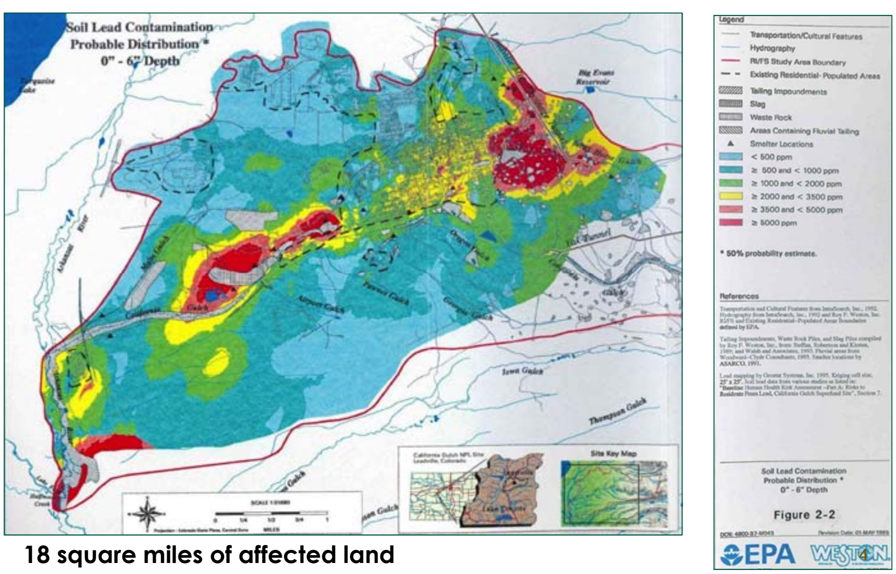
California Gulch Superfund Site, Leadville, Colorado, USA



18 square miles of affected land

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California Gulch Superfund Site—Leadville, Colorado

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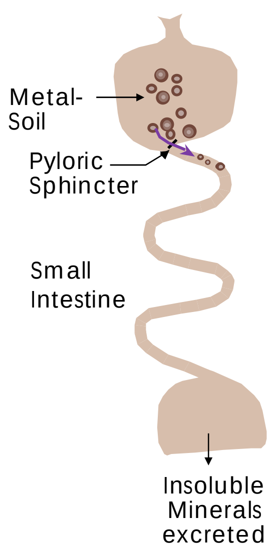
Gastro-Geochemistry of Metals



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

- pH increases to 7

- Soluble metals absorbed into bloodstream
- Metals precipitate/adsorb

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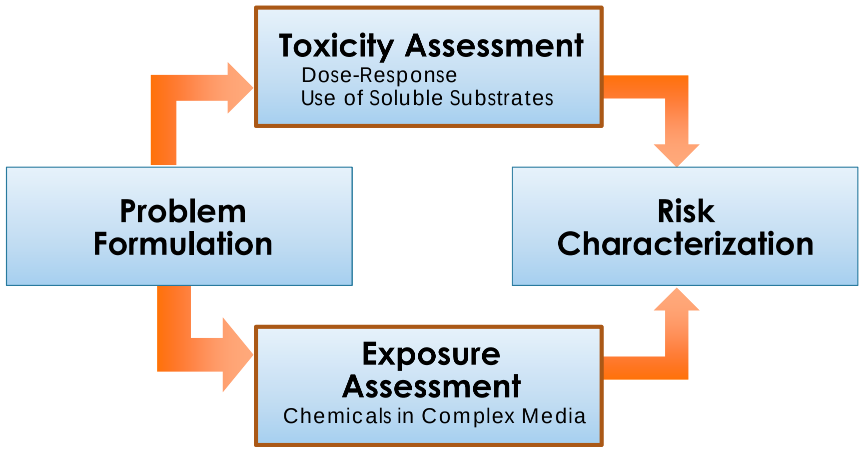
Incorporating Bioavailability Adjustments in Risk Assessment



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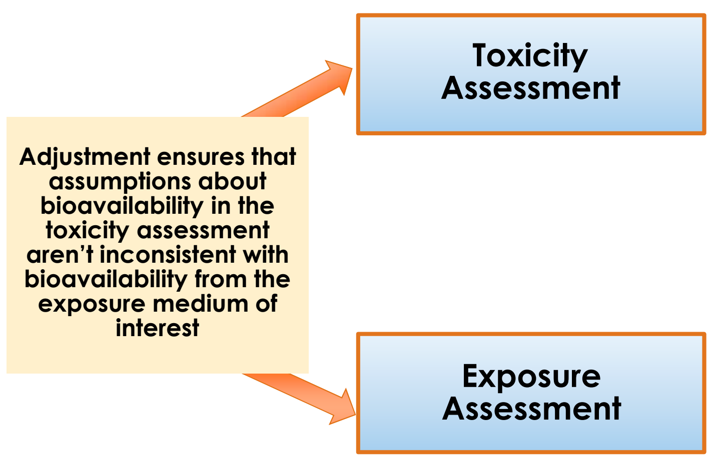
Incorporating Bioavailability Adjustments in Risk Assessment



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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

Defining Terms

- **Absolute bioavailability (ABA)**
- **Fraction of intake reaching the central compartment (i.e., blood)**

$$\text{Absolute Bioavailability} = \frac{\text{Absorbed dose}}{\text{Administered dose}}$$

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Defining Terms

- **Relative oral bioavailability (RBA)**

$$\text{RBA} = \frac{\text{Absorbed from soil}}{\text{Absorption from medium used in toxicity study}}$$

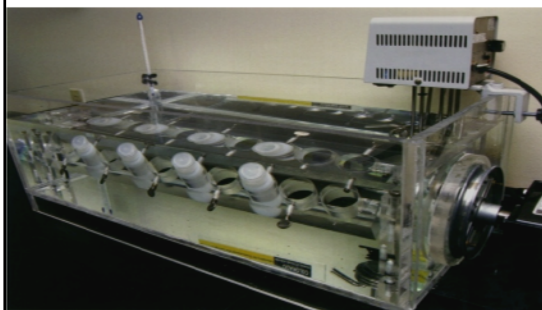
Defining Terms

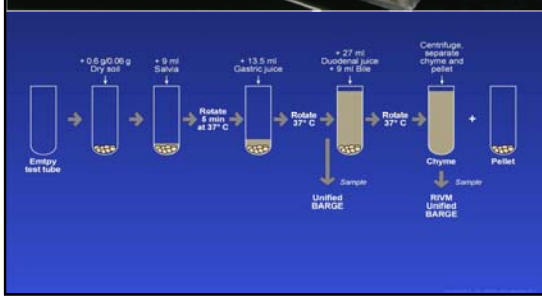
- ***In vitro* bioaccessibility**

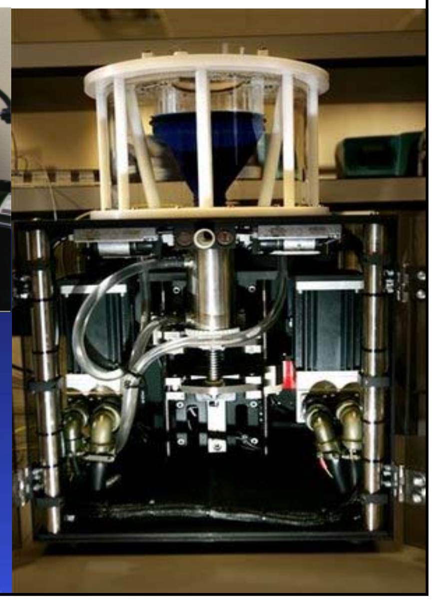
Soluble fraction that may be available for absorption

- **Laboratory tests of solubility**
- **Many methods exist**
- **Assumed to capture rate-limiting component controlling RBA**
- **Various levels of complexity**
- **May or may not be physiologically based**
- **May or may not be validated against animal data**

In vitro Methods for Bioaccessibility Testing

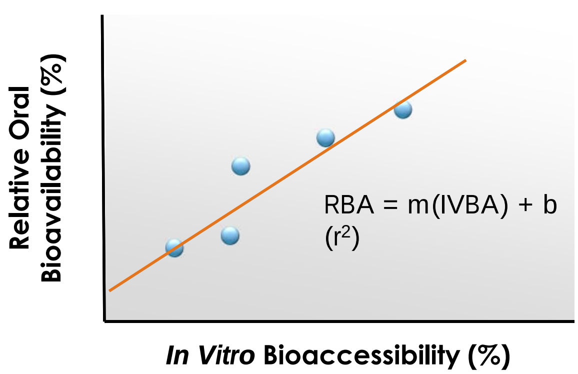






Defining Terms

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



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Incorporating Relative Oral Bioavailability into Human Health Risk Assessment

Can be addressed in **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

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Incorporating Relative Oral Bioavailability into Human Health Risk Assessment

…Or in the **Toxicity Assessment**

- Reference Dose$_{(\text{RBA-adjusted})}$ **=** $\frac{\mathbf{RfD}}{\mathbf{RBA}}$
- Cancer Slope Factor$_{(\text{RBA-adjusted})}$ **= CSF x RBA**

Where:
RfD = Reference Dose (non-cancer endpoints of toxicity)
CSF = Cancer Slope Factor

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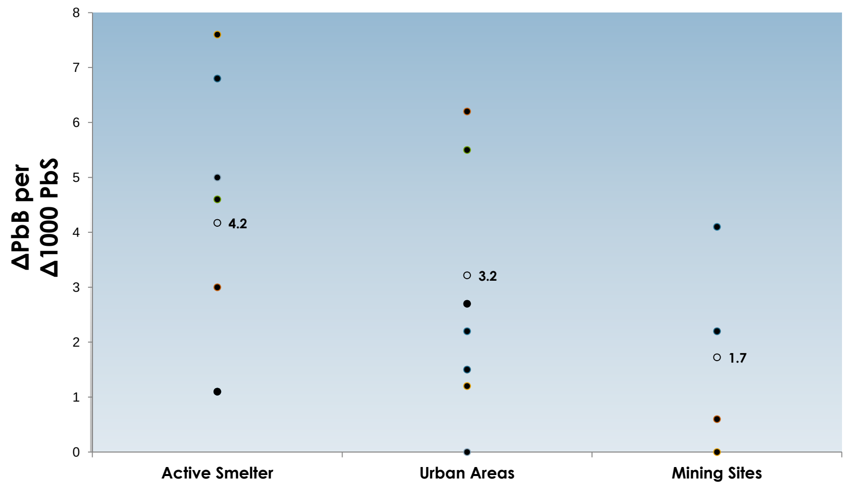
Relation Between Soil Lead and Blood Lead



Data presented in Steele et al., 1990.

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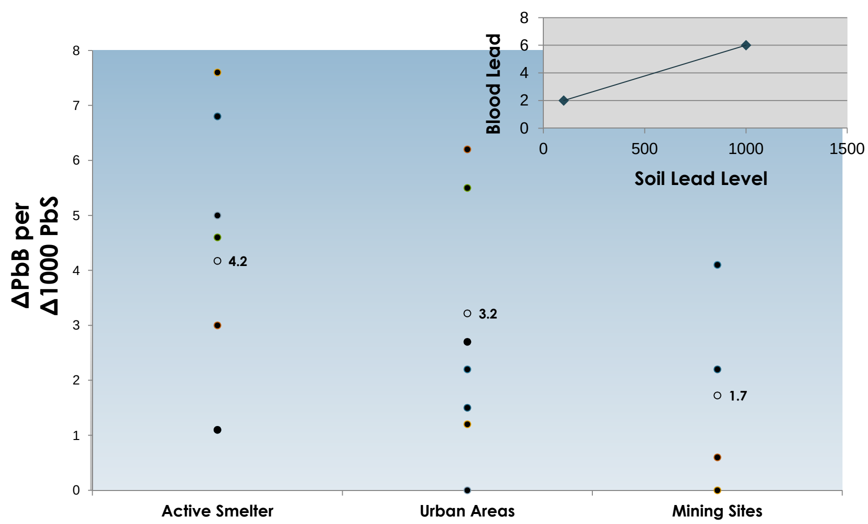
Relation Between Soil Lead and Blood Lead



Data presented in Steele et al., 1990.

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Tools for Assessing RBA of Metals from Soil

- **Animal studies**
  - Gold standard
  - Complex technical issues
  - Expensive
- **Solubility testing**
  - Aqueous solubility
  - *In vitro* bioaccessibility
- **Mineralogy**

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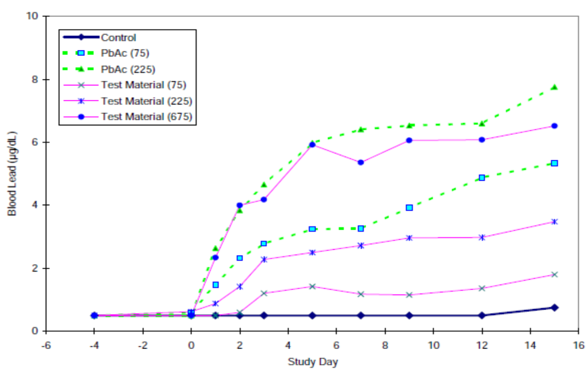
Bioavailability of Lead in Soil: Assessing RBA in Animal Studies



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.

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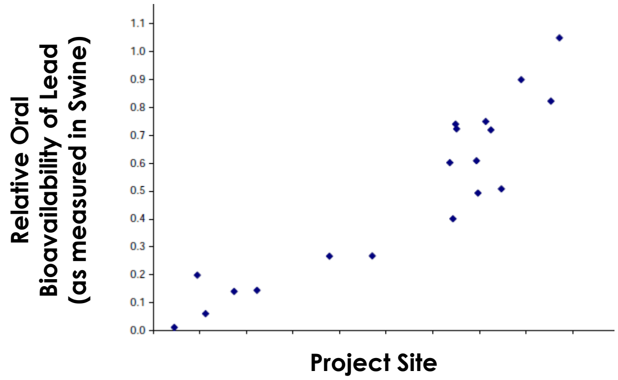
Bioavailability of Lead in Soil: Range of RBAs Observed



- RBA values in animal studies range from 1% to 100%
- Vary based on site-specific characteristics
- Vary based on source-specific characteristics

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

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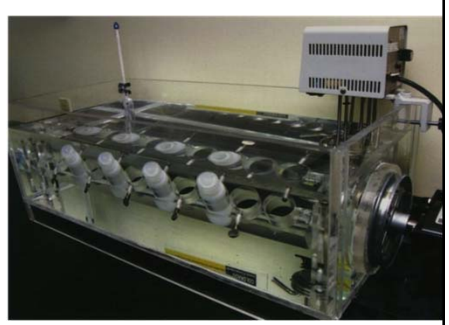
In Vitro Methods to Estimate the RBA of Lead in Soil

- **Evaluation of factors that affect solubility of lead under laboratory conditions**
- **Physiologically-based, then simplified**
  - 0.4 M Glycine
  - pH 1.5
  - 37°C
  - 1 hour
- **19 soils with RBA measured in swine**



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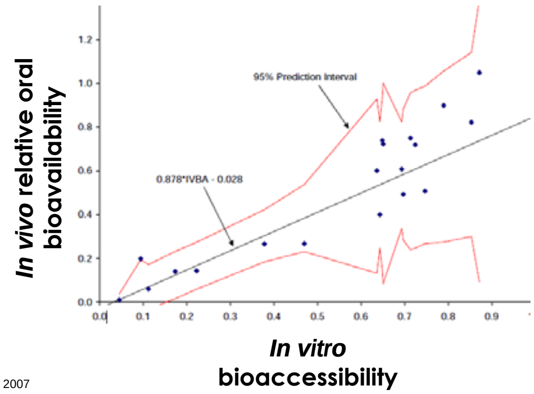
Development of *In Vitro* Methods to Estimate Bioavailability of Lead in Soil

- *In vitro* method "validated" for use in risk assessment
- 19 soils with RBA measured in swine
- RBA = (0.878)IVBA – 0.028 (r^2 = 0.924))



Source: OSWER 9285.7-77 2007

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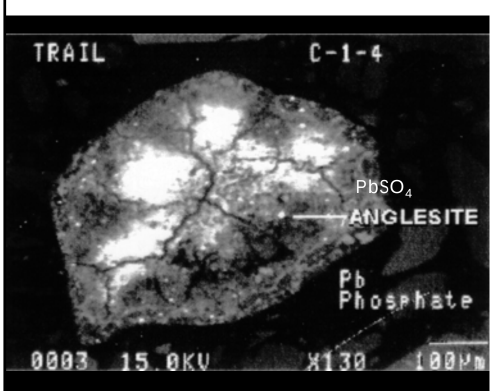
Bioavailability of Lead in Soil: Mineral and Physical Controls on RBA



Electron Micrograph, Electron Microprobe Analysis (EMPA)

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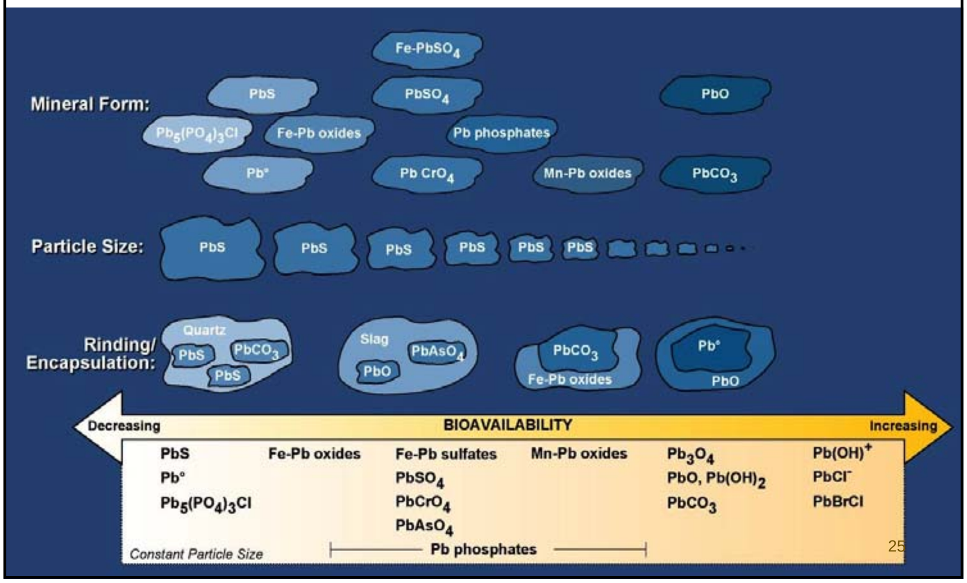
Factors Affecting the Relative Oral Bioavailability of Lead



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Lead RBA: State of the Science for Use in Human Health 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 "validated"**
  – Predictive of RBA as measured in animals
  – Good reproducibility within and across laboratories
- **RBA adjustments widely accepted in risk assessment**

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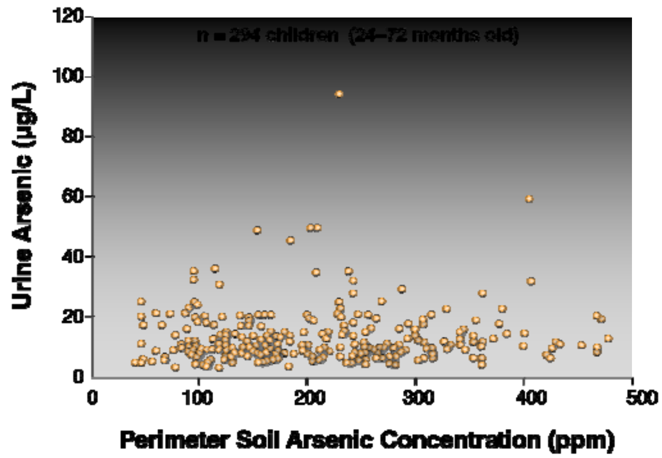
Arsenic Bioavailability

- Anaconda Arsenic Exposure Study (U.S. CDC)



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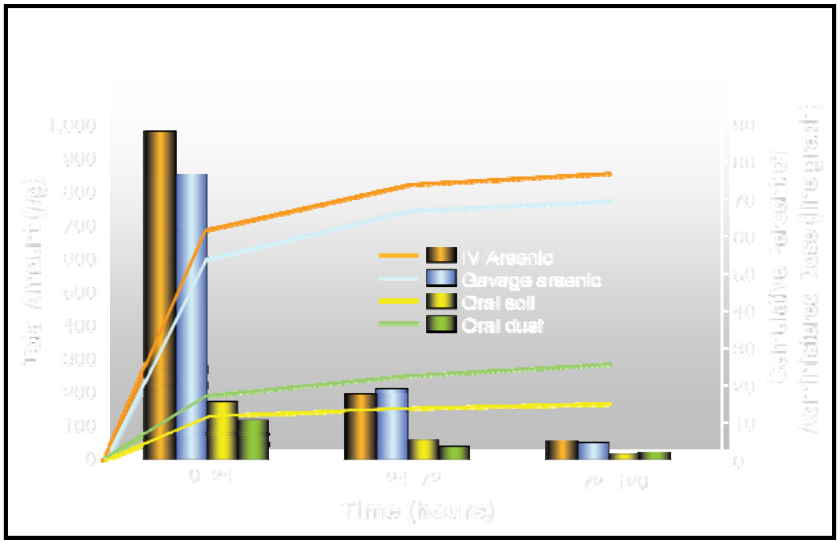
Monkey Bioavailability Study: Arsenic Excretion in Urine



Relative Oral Bioavailability of Arsenic is Well Studied

- **Swine Studies**
  - Casteel et al. 1996–2010
  - Juhasz et al. 2007
  - Basta et al. 2007
  - Rodriguez et al. 1999
  - Denys et al. 2012
- **Primate Studies**
  - Freeman et al. 1995
  - Roberts et al. 2002, 2007
- **Rodent Studies**
  - Bradham et al. 2011, 2012
  - Freeman et al. 1993 (rabbits)

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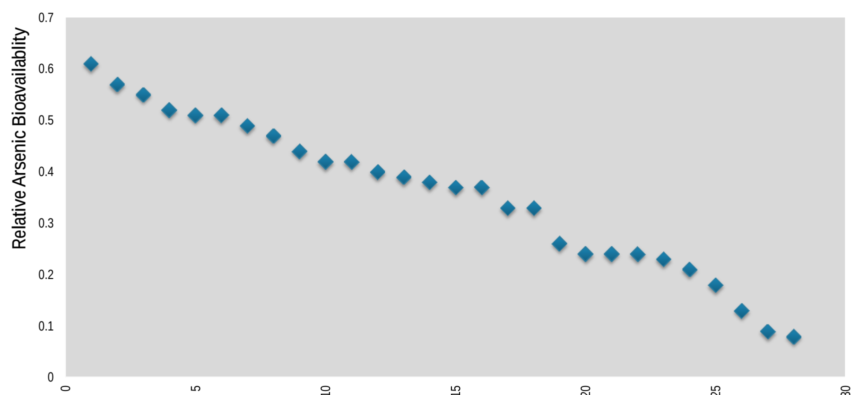
Site-Specific Factors Control Arsenic RBA

Swine Studies



- Across 28 soils studied by EPA, RBA values range from 8% to 61%
- Supported default of 60% RBA (U.S. EPA 2012)
- RBA controlled by site-specific factors

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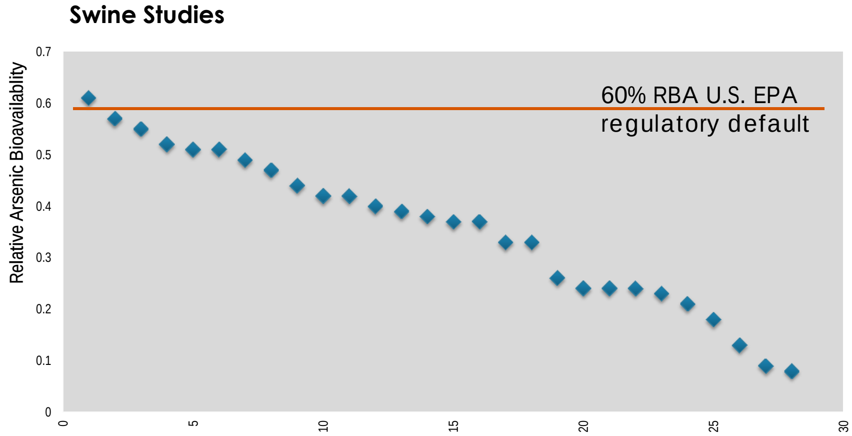
Site-Specific Factors Control Arsenic RBA



- Across 28 soils studied by EPA, RBA values range from 8% to 61%
- Supported default of 60% RBA (U.S. EPA 2012)
- RBA controlled by site-specific factors

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Investigations to Identify Mineralogy

- **Swine Studies**
  - **Casteel et al. 1996–2010 (Published as Brattin et al., 2013)**
  - Juhasz et al. 2007
  - Basta et al. 2007
  - Rodriguez et al. 1999
  - Denys et al. 2012
- **Primate Studies**
  - Freeman et al. 1995
  - **Roberts et al. 2002, 2007**
- **Rodent Studies**
  - **Bradham et al. 2011, 2012**
  - Freeman et al. 1993 (rabbits)

Many studies characterize soil chemistry/mineralogy, But no clear link between mineralogy and bioavailability

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Investigations to Identify *In Vitro* Bioaccessibility Method

- **Swine Studies**
  - **Casteel et al. 1996–2010**
  - **Juhasz et al. 2007**
  - **Basta et al. 2007**
  - Rodriguez et al. 1999
  - **Denys et al. 2012**
  - **Wragg et al. 2011**
- **Primate Studies**
  - Freeman et al. 1995
  - **Roberts et al. 2002, 2007**
- **Rodent Studies**
  - **Bradham et al. 2011, 2012**
  - Freeman et al. 1993 (rabbits)

Many studies evaluated in vitro bioaccessibility of arsenic.
Limited agreement between the different studies

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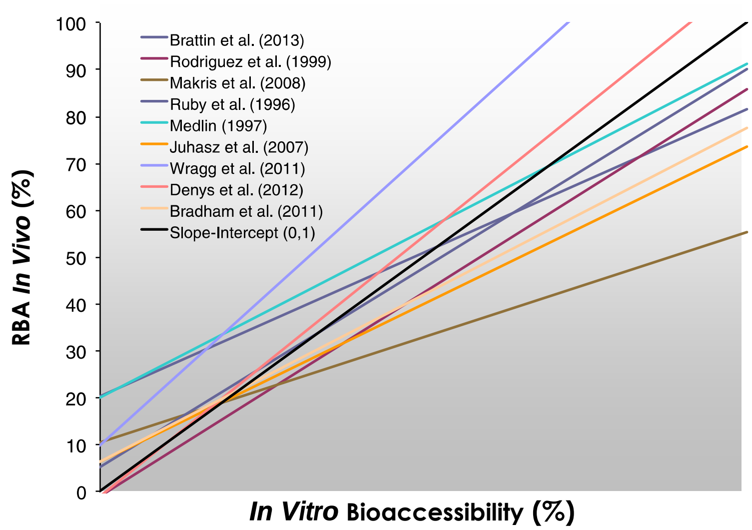
In Vitro Bioaccessibility of Arsenic: Comparison of Methods



Derived from data presented in Brattin et al., 2013

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

- **Clear evidence that site- and source-specific factors control bioavailability**
- **Animal studies used to develop RBA values**
- **Factors controlling bioavailability not fully characterized**
  - Chemical form
  - Particle size
  - Redox
  - Soil Characteristics
- ***In vitro* methods widely investigated**
  - Varying success in predicting RBA as measured in animals
  - Varying level of acceptance by regulatory agencies

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Other Metals

- **Substantial progress on developing methods for assessing RBA of metals in soil and applying results to HHRA**
  - Yields more accurate estimates of potential exposures
  - Primary focus to date has been focused on lead and arsenic
- **Other metals have been subject of investigation**
  - Cadmium, chromium, mercury, nickel
- **Factors to consider**
  - Metal speciation in soil
  - Soil characteristics
  - Emerging studies from animal and in vitro tests

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Other Metals

- Cadmium
  - Several studies in rat, mice, and swine
  - Studies compare absorption from soil versus reference compound
  - Solubility varies greatly with chemical form
  - Absorption of soluble Cd is low
    - 3-8% in humans
  - In vitro bioaccessibility values range from 5-99%
  - Some validation of in vitro studies against animal data
  - Animal and in vitro data have formed basis for RBA values in risk assessment

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Other Metals

- Nickel and Chromium
  - Primarily excreted in urine
  - Urinary excretion potentially viable endpoint
  - Difficult to detect due to background exposures from the diet
    - Dietary exposures greatly exceed contribution from soil

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Other Metals

- **Nickel**
  - **Animal studies and *in vitro* extraction data available**
  - **High variability in bioavailability estimates**
  - **Predictive relation between animal and *in vitro* data not clearly established**
  - **RBAs have been accepted**
    - **11-28% Port Colborne**
    - **30% (dust) 42% (soil) Sudbury**

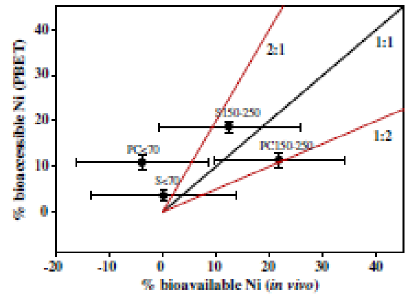
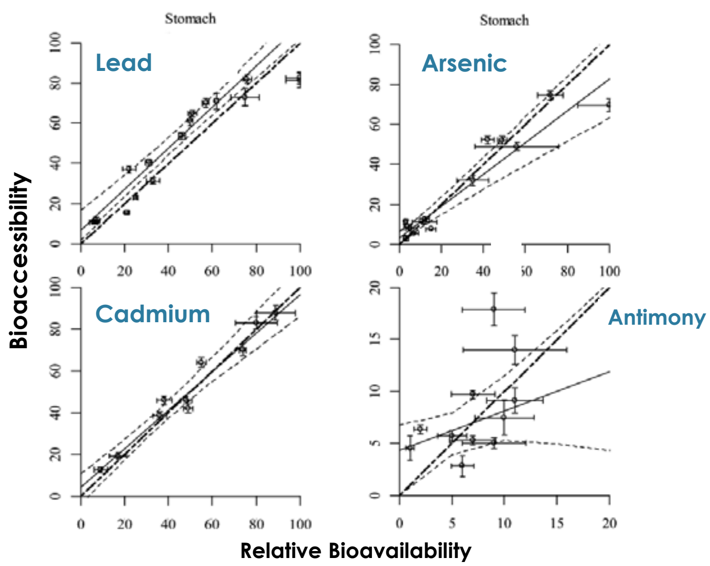


Fig. 2. Correlation between Ni bioaccessibility measured using PBET and Ni bioavailability after 24 h measured in vivo. Each value is the least-square mean ± SEM.

Source: Vasiluk et al. 2011

Other Metals



Source: Denys et al., 2012.

Status of Information Availability: RBA of Metals from Soil for HHRA

Metal	Animal Studies	Regulatory Default RBA	*In Vitro* Studies	Mineralogic Controls
Lead	YES	YES	Fully Validated	Well Characterized
Arsenic	YES	YES	Varying Acceptance	Characterized but Complex
Cadmium	SOME	NO	Limited	Limited
Chromium	Limited	NO	Limited	Limited
Nickel	SOME	NO	Limited	Limited
Mercury	Limited	No	Limited	Limited 41

Meaningful Application of RBA in the Decision Process

- Bartlesville, Oklahoma, USA
- Former zinc smelter site
- Lead, cadmium, arsenic in soils
- Accelerated cleanup
  - U.S. EPA
  - ODEQ

Bartlesville: Critical Studies to Support RBA Adjustment in Remediation Goals

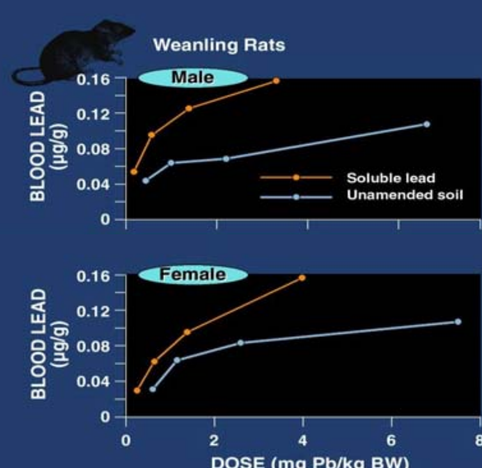
- **Mineralogy/speciation analyses**
  – lead, cadmium, and arsenic
- **Bioavailability study in rats**
  – lead and cadmium
- **In vitro bioaccessibility study**
  – arsenic

Bartlesville: Bioavailability of Lead in Soil

Dosing of lead in soil vs. soluble lead:

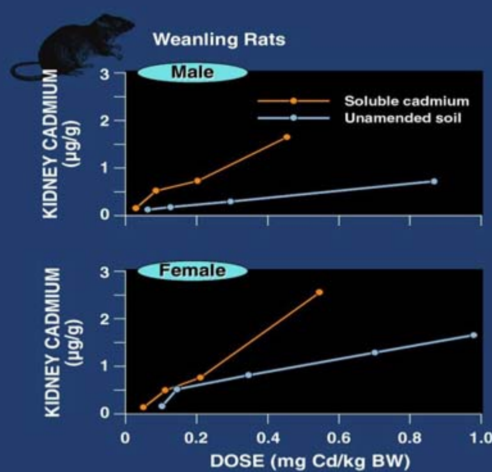
Demonstrated different blood lead profile than soluble forms of lead

Both male and female rats

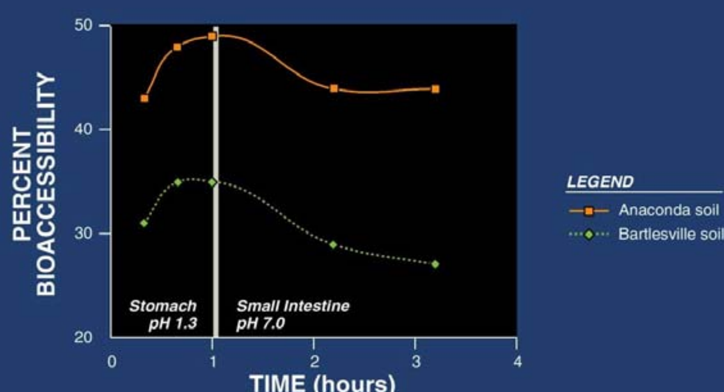


Bartlesville: Bioavailability of Cadmium in Soil

- Dosing of cadmium in soil vs. soluble cadmium:
- Demonstrated different absorption profile than soluble forms
- Kidney measurement endpoint
- Both male and female rats



Arsenic: *In vitro* Bioaccessibility

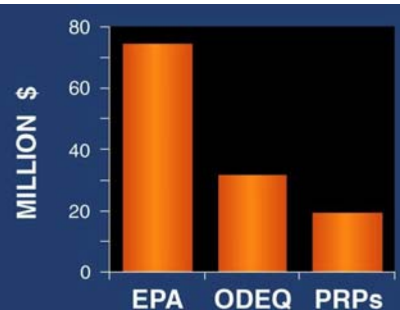


Bartlesville: Relative Bioavailability Impacts on Cleanup Levels

	Default RBA	Relative Oral Bioavailability	Approximate Change in Cleanup Levels
Lead	**0.60**	**0.40**	**<2x**
Cadmium	**1.0**	**0.33**	**3x**
Arsenic	**1.0**	**0.25**	**4x**

Bartlesville: Residential Cleanup Levels vs. Remediation Cost

Bioavailability adjustments resulted in significant impact on cost of remediation



Cleanup Levels (mg/kg)	EPA	ODEQ	PRPs
Lead	500	925	925
Cadmium	30	100	190
Arsenic	20	60	88

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

State of the Science: Relative Oral Bioavailability of Metals from Soil

- The bioavailability of metals from soils can be different than the bioavailability of test material in the critical toxicity study
- RBA is affected by source materials and site/soil characteristics
- Lead and arsenic RBAs are well characterized
- Information is emerging for other metals
- Bioavailability considerations should be addressed in the risk assessment of metals-contaminated sites
  - Result in more accurate estimates of exposure and risk
  - *In vivo* and *in vitro* tools are available to characterize RBA

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Information Sources

International Resources for Information on Bioavailability Assessment for Human Health Risk Assessment	
U.S. EPA	Assessing RBA in Soil at Superfund Sites
U.S. EPA	Standard Operating Procedures for an *in vitro* bioaccessibility assay for lead in soil
UK Environment Agency	Oral Bioaccessibility Testing
The Netherlands RIVM	Bioaccessibility of Contaminants from Ingested Soils in Humans
The Netherlands RIVM	Bioaccessibility and RBA of lead in soils for fasted and fed conditions
Australia EPHC	Assessment of Site Contamination, Guideline on Health Risk Assessment Methodology
Australia NEPC	Technical Report 14: Contaminant Bioavailability and Bioaccessibility
Health Canada	DQRA
Canada Bioaccessibility Research Consortium	http://www.bioavailabilityresearch.ca/
EU Bioaccessibility Research Group Europe	http://www.bgs.ac.uk/barge/

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Full links to these documents are provided in ICMM supporting materials