

Bioavailability – Metals, Organics, and Use at Hazardous Waste Sites

June 18th, 2008 Session 3: "Use of Bioavailability Information at Hazardous Waste Sites"

Mike Beringer, U.S. EPA Region VII toxicologist
U.S. EPA Guidance for Evaluating the Oral Bioavailability of Metals

Mark Maddaloni, U.S. EPA Region II toxicologist
Point – Counterpoint
The FMC Site

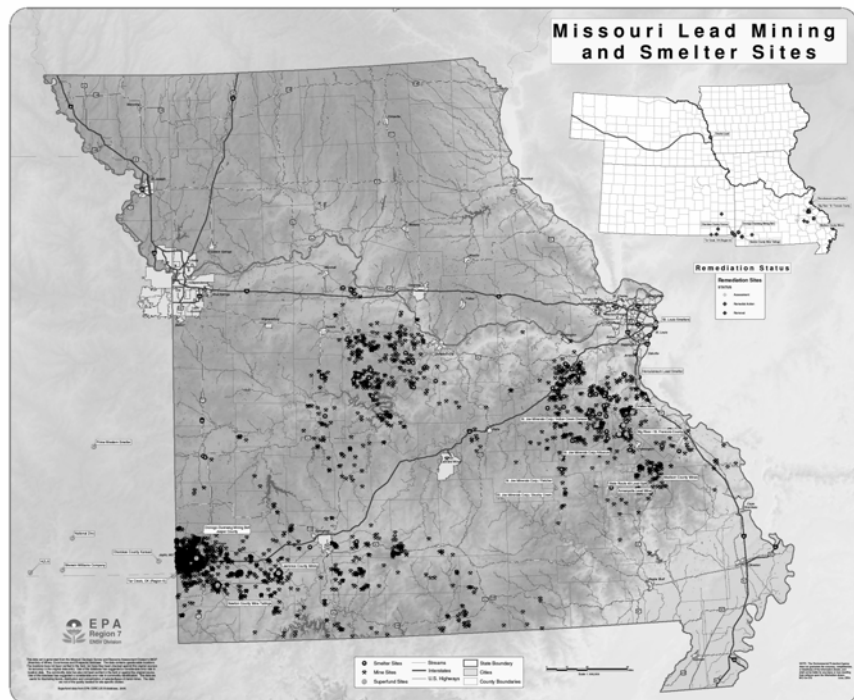


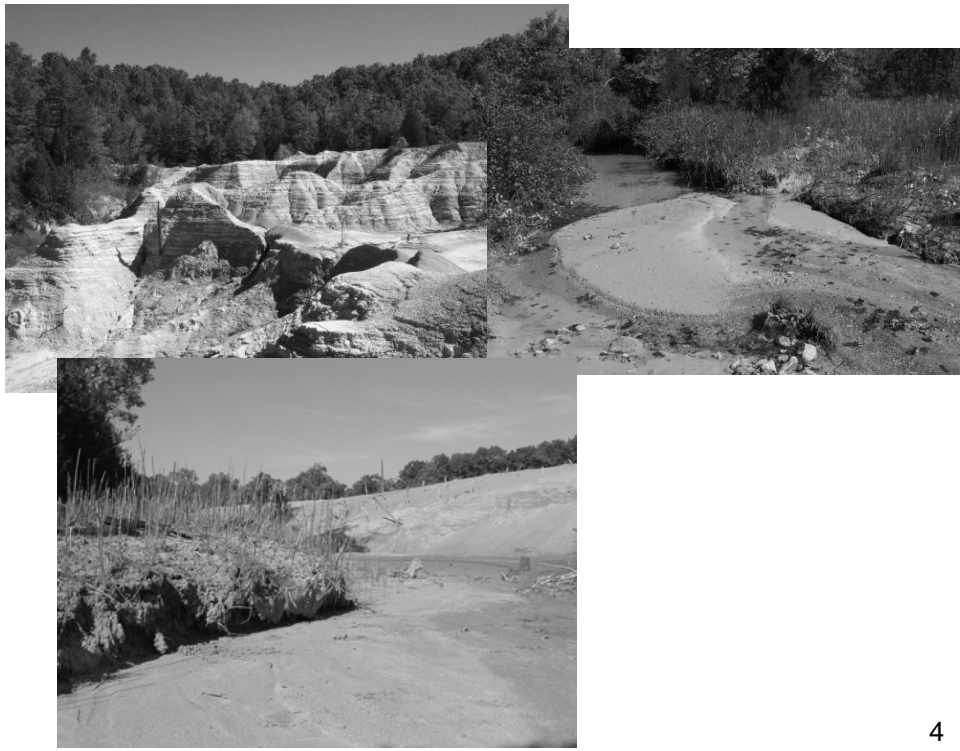


U.S. EPA Guidance for Evaluating the Oral Bioavailability of Metals

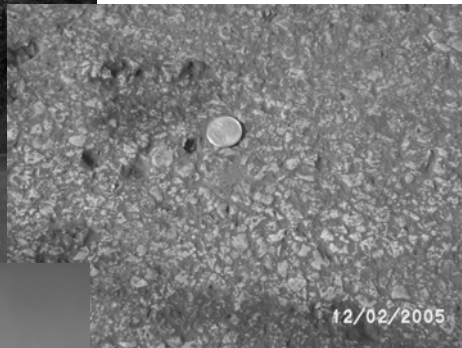
**Superfund Basic Research Program
Risk-e-Learning Seminar
June 18, 2008**

**Mike Beringer
U.S. EPA Region VII**







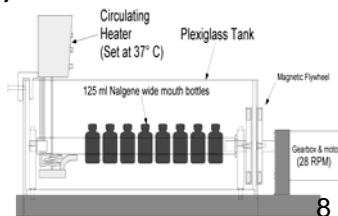






Methods for Assessing Bioavailability in Soil

- **Mineralogical studies**
 - Importance of speciation and particle size
 - $\text{PbCO}_3 > \text{Pb Oxide} > \text{PbS}$
 - Provides supporting bioavailability information
- ***In vivo* methodologies**
 - Blood concentration vs. time (AUC)
 - Quantification of amount present in urine or feces
 - Used for quantitative bioavailability adjustments
- ***In vitro* methodologies**
 - Physiologically-based extraction tests
 - Used for screening purposes and uncertainty analysis



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Need for Additional Bioavailability Guidance

- Default assumption likely overestimates health risks
 - Bioavailability is equal in soil, diet and water
 - Relative bioavailability or RBA is 1.0
 - Lead is the exception where default RBA is 0.60
- Existing guidance supports bioavailability adjustments
 - Does not address when data collection should be pursued
 - Does not address how to evaluate site-specific bioavailability
- Limited use of site-specific bioavailability information
 - Absence of rapid and inexpensive tools
 - Lack of criteria for evaluating alternative test methods

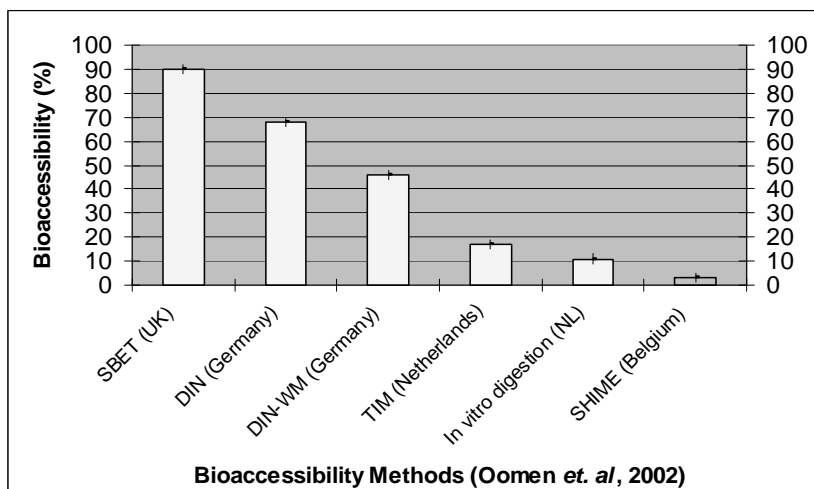
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Bioaccessibility of Lead in Montana SRM 2711



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Bioavailability Guidance Development

- Bioavailability Workshop – April 2003
 - Obtained expert technical opinions on several issues
 - *In vivo* and *in vitro* assessment of bioavailability of soil lead
 - Validation and quality assurance of predictive models
 - Characterization of site bioavailability of metals
- Two Related Bioavailability Documents
 - Bioavailability Guidance Document
 - Lead Technical Support Document
- Internal and External Peer Reviews Conducted
- Released by OSRTI on July 3, 2007

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Guidance for Evaluating the Oral Bioavailability of Metals in Soils for Use in Human Health Risk Assessment

- Limited in scope
- Outlines a decision framework – series of questions
 - Is a validated method available?
 - Does the added value exceed the costs?
- Addresses site-specific documentation
 - Basis for relying on the selected method
 - Data translation
 - Sample collection
- Recommends criteria for evaluating alternative methods

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Recommended Decision Framework for Assessing Oral Bioavailability of Metals

- Step 1: Are risks below a level of concern using default bioavailability values?
- Step 2: Has EPA identified a validated method?
- Step 3: Does the added value exceed the costs?
- Step 4: Document site-specific implementation of the validated method
- Step 5: Collect samples and assess bioavailability
- Step 6: Integrate results into risk characterization

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Validation of Bioavailability Test Methods

- Relying on ICCVAM criteria (Interagency Coordinating Committee for Validation of Alternative Methods)
 - <http://iccvam.niehs.nih.gov/>
- Method validation criteria
 - Demonstrate method is reliable and relevant for its proposed use
- Regulatory acceptance criteria
 - Method fulfills a specific regulatory need
- Regulatory methodologies
 - Must satisfy both sets of criteria
 - Appropriate for making quantitative site-specific adjustments

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Method Validation Criteria (ICCVAM, 1997)

- Scientific and Regulatory Rationale
- Relationship Between Test Method Endpoint and Biological Effect
- Detailed Protocol and Known Limitations
- Within-Test Variability and Reproducibility Among Labs
- Test Method Performance with Representative Agents
- Comparison to Existing Test Method
- Data in Accordance with Good Laboratory Practices (GLP)
- Validity Assessment Data Available for Review
- Independent Scientific Review

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Regulatory Acceptance Criteria (ICCVAM, 1997)

- Independent Scientific Peer Review
- Detailed Protocol with SOPs
- Adequately Predicts Bioavailability and Demonstrates a Linkage
- Representative Chemicals Tested
- Generates Data Useful for Risk Assessment Purposes
- Documentation of Strengths and Limitations
- Robust and Transferable
- Time and Cost Effective
- Can Be Harmonized
- Suitable for International Use
- Reduction of Animal Use

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Estimation of Relative Bioavailability of Lead in Soil and Soil-Like Materials Using *In Vivo* and *In Vitro* Methods (Lead TSD)

- Describes *in vivo* and *in vitro* methodologies
 - Juvenile swine model
 - Relative bioaccessibility leaching procedure
- Characterizes 19 soil and soil-like test materials
 - Mineral phase
 - Particle size distribution
 - Matrix association
 - Clear differences in RBA between materials
 - Data not sufficient for predictions based on mineral content alone
- Evaluates the correlation between both methods

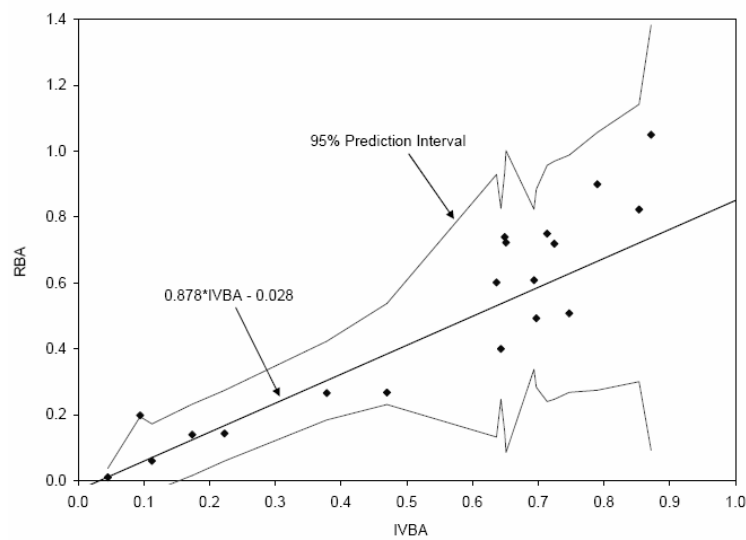
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Lead – Correlation Between *In Vivo* RBA and *In Vitro* Bioaccessibility (IVBA)



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Lead TSD Transmittal Memo

- Evaluated both methods using ICCVAM criteria
 - Broad range of relative bioavailability
 - Variety of mineralogical forms
 - Pairwise comparison shows a good fit ($r^2=0.92$)
- Both methods considered regulatory methodologies
 - Weight-of-evidence determination
 - Method validation and regulatory acceptance criteria achieved
 - Appropriate for use in site-specific risk assessment
- Outlines limitations and considerations for use
 - Quality assurance
 - Sample lead concentration limits
 - Particle size and soil mineralogy
 - Extrapolation to adults
 - Valid for soil samples from mining and milling sites

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Ongoing Activities

- Formation of Bioavailability Committee
 - Information archive
 - Provide technical support to the USEPA Regions
 - Develop additional guidance
 - Review new bioavailability methods
 - <http://www.epa.gov/superfund/health/contaminants/bioavailability/>
- Evaluation of Arsenic
 - Formal consideration of arsenic bioavailability data
 - Develop an upper bound RBA value for arsenic

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Point – Counterpoint The FMC Site

Mark Maddaloni DrPH, DABT
SBRP
June 18, 2008

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Superfund Bioavailability Guidance

Released July, 2007

Limited to evaluating site-specific bioavailability of metals in soils for use in human health risk assessment

Three main features:

- Outlines a decision framework for deciding when to collect and incorporate site-specific bioavailability information
 - Is a validated method available?
 - Does the added value exceed the costs?
- Process for documenting the site-specific implementation of a validated method
- Recommends criteria for evaluating alternative methods

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Middleport Former Arsenic Pesticide Plant

- Production stopped in the 1970s
- Offsite arsenic due to air deposition and runoff
- High proportion of land area former orchardland
- Biomonitoring did not detect exposures
- Oral and dermal bioavailability examined



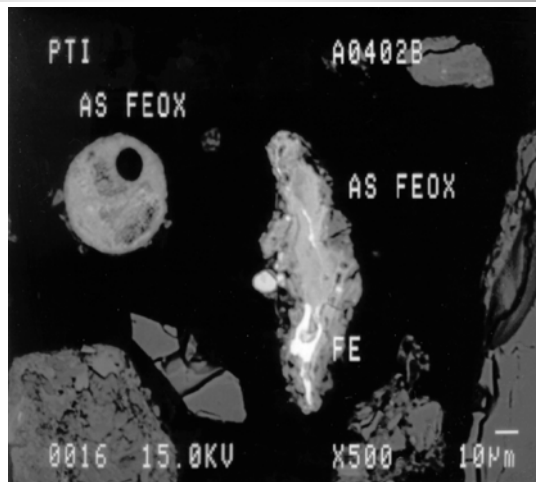
What bioavailability studies have been done with Middleport soils?

- 1995 study showed arsenic bioavailability was only 20 percent compared to arsenic dissolved in water.
- Recent studies directed by Yvette Lowney and Mike Ruby of Exponent (part of SERDP grant).
- Electron microprobe studies have found less soluble mineral forms of arsenic in Middleport soil (Univ. of CO).
- An oral bioavailability study in monkeys has shown reduced arsenic absorption from soil (19-28% relative bioavailability) (Univ. of FL).
- A monkey study of dermal absorption has shown that soil arsenic absorption across skin is negligible (Univ. of CA).



Soil Arsenic Mineralogy Supports Bioavailability Study Results

Most arsenic is associated with iron oxides or arsenic-iron oxides.



Photomicrograph of Arsenic-Iron Oxide Grain



Relative Oral Bioavailability Studies of Arsenic in Cynomolgus Monkeys

- Conducted by Dr. Stephen Roberts at the University of Florida in collaboration with Yvette Lowney
- Results for 14 soils from 12 sites
- Positive and negative reference materials also tested
- Results published in 2007 in *Toxicological Sciences*



Selection of Research Model

- Arsenic
 - Simple pharmacokinetics
 - Rapid elimination
- Use of cynomolgus monkey vs. swine
- Primates phylogenetically closer to humans
- GI physiology — similarities to human
- Evaluated for bioavailability research in the study of pharmaceuticals
 - “Good model for oral bioavailability in humans” (Ikegami, 2003)



Study Design

- Low arsenic diet prior to dosing
 - Dosed with slurry of soil in water Soil dose ≤ 1 g/kg bw
 - Arsenic dose ≤ 1 mg/kg bw
- Collection of urine and feces
- Five animals received each treatment



Study Design – Reference Doses

- Intravenous administration of sodium arsenate (1 mg As/kg bw)
- Oral dosing of sodium arsenate by gavage (3 dose levels)
- Oral dosing of sodium arsenate mixed with soil
- Oral dosing of arsenopyrite (FeAsS) mixed with soil



Relative Bioavailability (RBA) Calculations

- $RBA = (\% \text{ of soil As dose in urine}) - (\text{background})$
- $(\% \text{ of soluble As dose in urine}) - (\text{background})$
- *Corrections made on animal-specific basis



Soil Arsenic Relative Bioavailability

Soil Sample	Relative Bioavailability ^a
WAOS	0.24 ± 0.09
NYOS	0.15 ± 0.08
NYF-5B	0.19 ± 0.05
NYF-8B	0.28 ± 0.10
NYF-13B	0.20 ± 0.10
AsPyrite spike	0.002 ± 0.003
Arsenate spike	0.94 ± 0.05

^a Relative Bioavailability = % Dose in urine (soil) / % Dose in urine (arsenate)
Results expressed as mean ± SD (N=5)

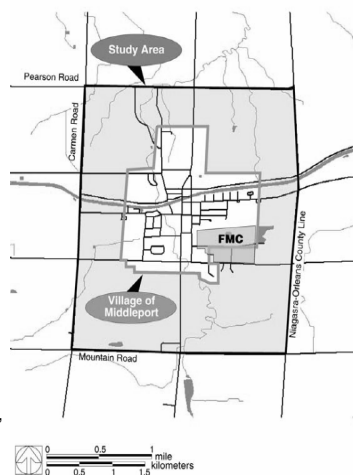


Middleport Environmental Exposure Study - 2003

- Conducted by Exponent independent of FMC
- Review of study design and results overseen by an independent panel of experts*
- Participation was voluntary
- Results have been published in *Env. Health Perspectives*

*Members of the scientific advisory panel:
D. Barr, R. Borschein, F. Frost Jr., D. Gute, P. Kostecki,
H. Pastides, and P. Succop

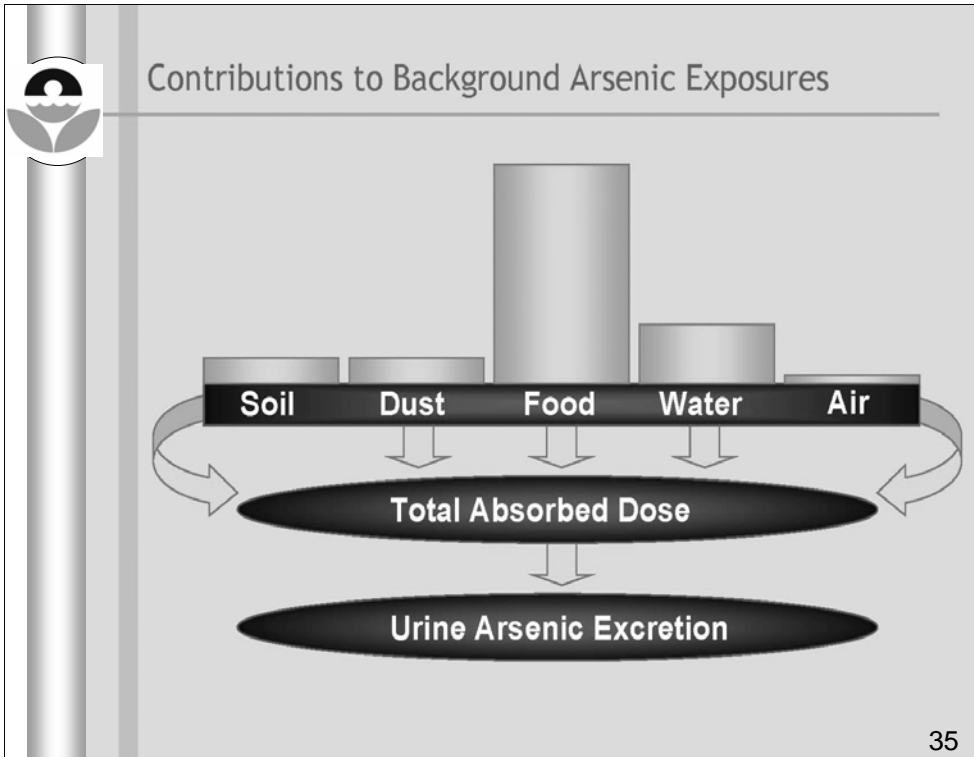
Middleport Study Area





Middleport Environmental Exposure Study Design

- Participants – 439 of 1,930 residents in study area, including 77 of 164 children < 7 years old.
- Collected first morning urine sample on 2 days, analyzed for total and speciated As and for creatinine, plus toenail samples (84).
- Collected soil from yards (84), gardens (23), and play areas (28), plus indoor dust (111) and vegetables (42 gardens).
- Administered questionnaire on demographic, socioeconomic, and behavioral information and housing characteristics.





General Conclusions

- Low level As presence in soils (i.e., <50ppm) is widespread in the U.S.
- In most cases, the amount of As that could be absorbed from soils is small compared to natural sources (i.e., diet)
- There is no measurable difference in exposure and health risk from soil containing 20 or 50 ppm of arsenic



Evaluating the Weight of Evidence

FMC Primate Study generally satisfies ICCVAM Criteria

However....

Concern with derivation of a point-estimate absorption adjustment

Concern with applicability of results across the site

Concern with use of biomonitoring study and background study to “tweak numbers”

Biomonitoring study

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Biomonitoring Study

- A) Snapshot in time
- B) Soil As masked by dietary exposure
- c) Lacks sensitivity for protecting against ELCR

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Site Background

Soil Background Study conducted by FMC to inform site delineation and soil arsenic remediation goal

–Background characterization still under development

Remediation goals should consider background and bioavailability independently unless the case can be made that the bioavailability of arsenic is lower in site soil compared to background

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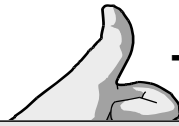
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http://tools.niehs.nih.gov/sbrp/risk_elearning/



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