Human Health Risk Assessment:
Exposure Assessment - Bioavailability and Amortization

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Preliminary Quantitative Risk Assessment

- Tool to rank sites
  - Standardized approach
- Use maximum concentrations
  - Limited site data
- Assume 100% oral bioavailability

Detailed Quantitative Risk Assessment

- Useful for risk management/remediation
  - Detailed assessment
- Use representative concentrations
  - Sufficient site data
- Site-specific oral bioavailability
- Site-specific exposure duration

Exposure - Incorporating Bioavailability

- Bioavailability can be used in human health risk assessments to get a more realistic estimate of exposure
- More realistic exposure estimates may reduce remediation costs and still ensure protection of human health
- Bioavailability depends on a variety of things, including media and exposure routes:
  - Dermal
  - Inhalation
  - Ingestion

Dermal and Inhalation Bioavailability

- Dermal
  - Relative absorption factors from literature sources are provided in PQRA guidance - updated
- Inhalation
  - not generally considered if the toxicity reference value (TRV) is from inhalation study
  - adjust bioavailability if using oral TRV
  - *in vitro* tests (e.g. lung fluid *in-vitro* assays) to estimate inhalation bioavailability of particle-bound contaminants have been reviewed but are not currently recommended

Oral Bioavailability

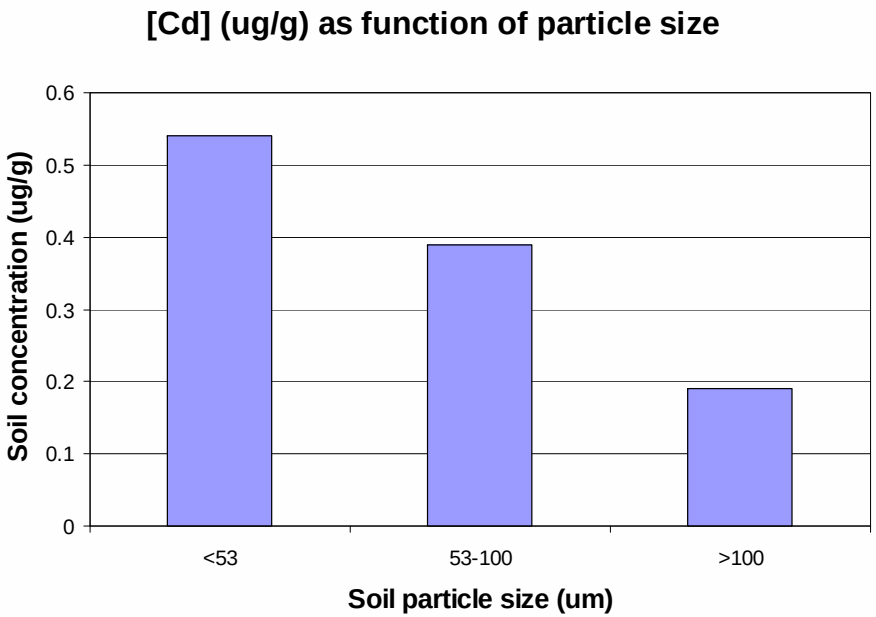
- site-specific *in vivo* or *in vitro* tests are required
- no specific protocols available, consult with HC
- consider range of soil particle sizes *in vitro* (e.g., <65 um, 65-100 um, 100-150 um, 150-250 um). Do concentration and/or bioaccessibility increase with decreasing particle size?
- employ a range of ratios of simulated gastric fluid (mL) to soil mass (g) *in vitro*, ranging from 100:1 to 5,000:1, and up to 10,000:1. Does bioaccessibility increase as ratio increases?
- use statistical analysis of data to confirm that contaminant solubility is not a confounding factor. What is being measured: bioaccessibility or solubility?
- adjust absolute bioaccessibility (directly measured) ***relative*** to the (likely) bioavailability of the contaminant in the key TRV study

Why Site-Specific Bioavailability Data?

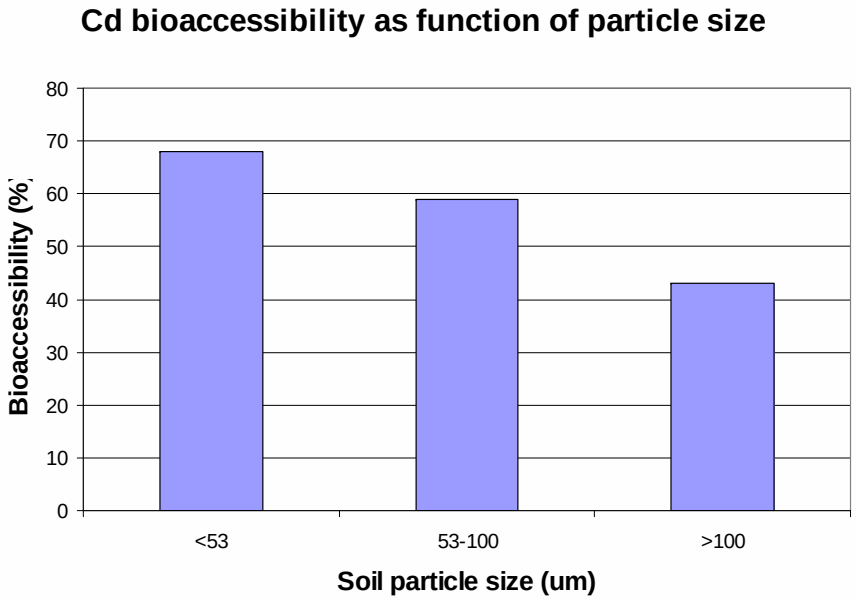
- Various site-specific factors that may affect bioavailability include:
  - metal species
  - soil type (organic carbon content, pH, etc)
  - particle size
  - contaminant concentration
  - route of exposure
  - presence of mixtures

  - And also… receptor characteristics

Concentration/Bioaccessibility vs. Particle Size



Concentration vs. particle size

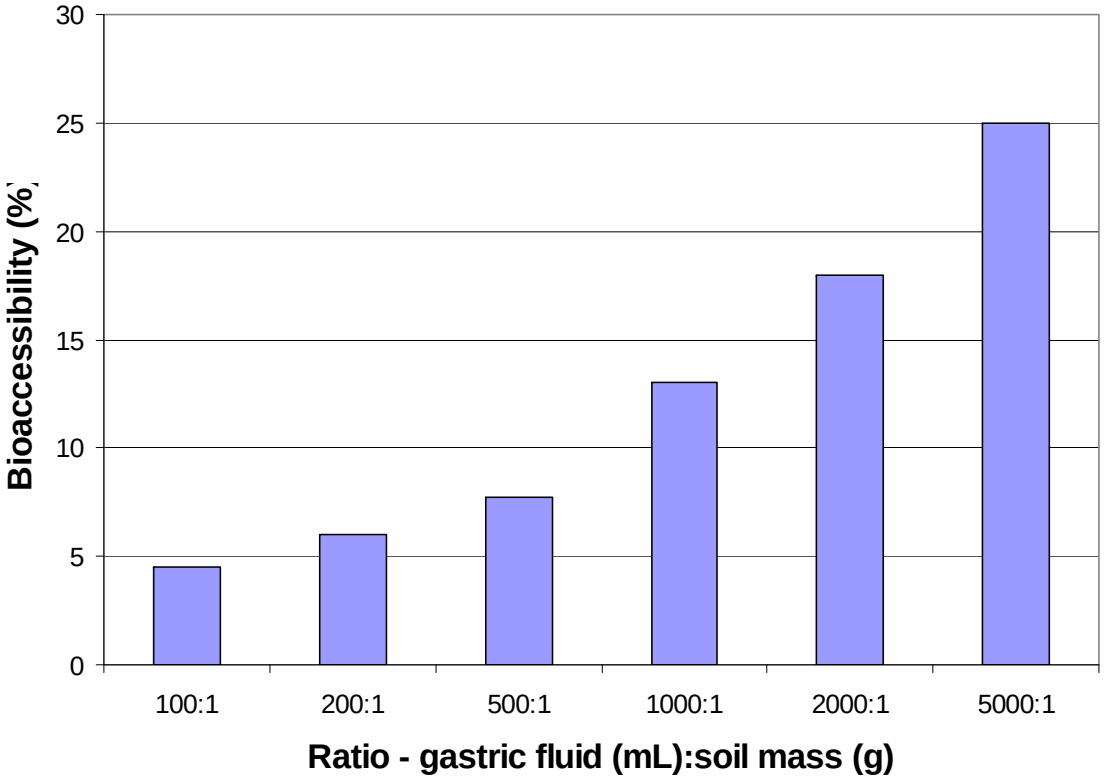


Bioaccessibility vs. particle size

But not always…

Ottawa topsoil
After Rasmussen (2004)

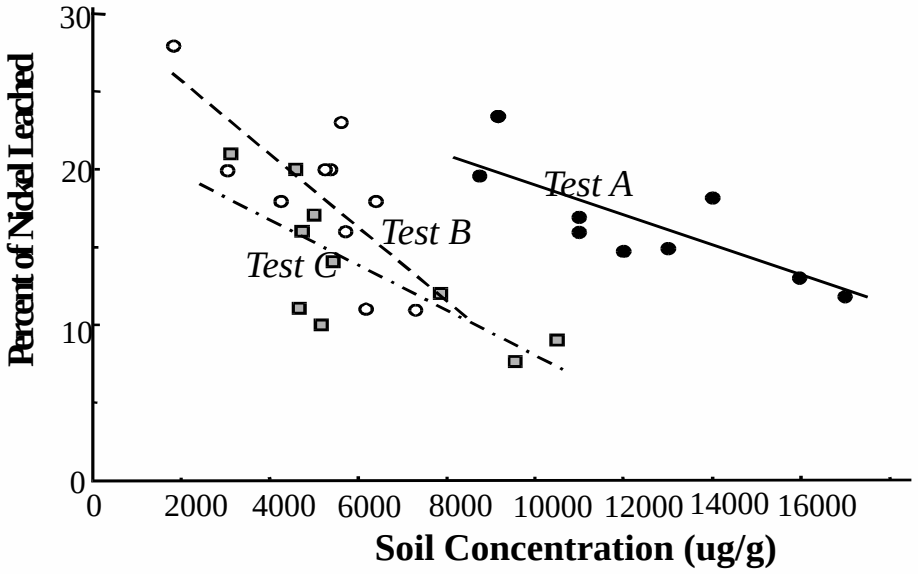
Bioaccessibility of arsenic as function of solvent:soil ratio

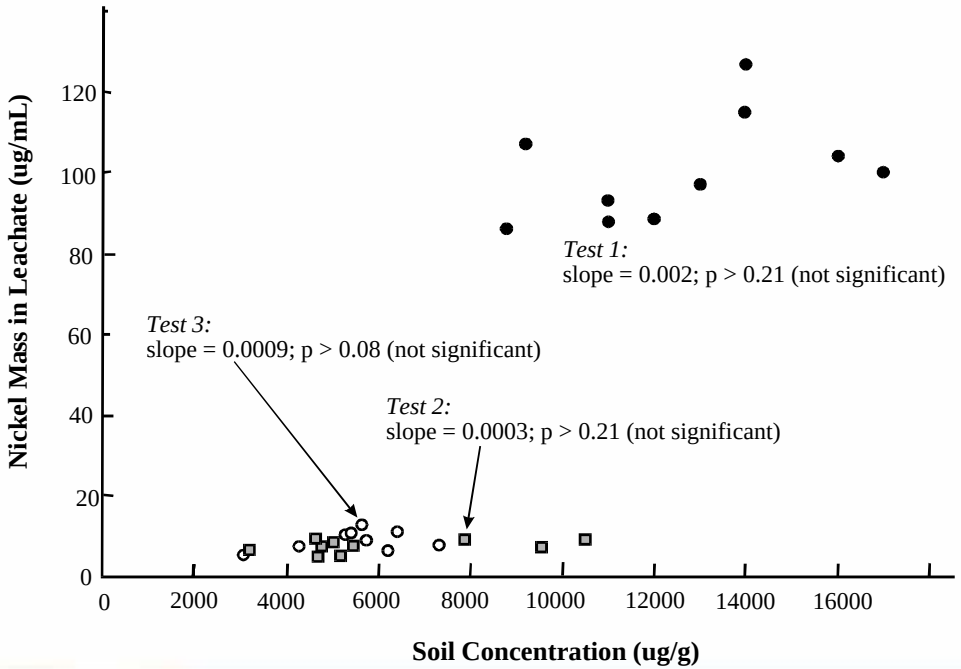


(data from Hamel et al., 1998)

Ratio of gastric fluid volume to ingested soil mass in the human gut ≈ 10,000:1

Assays should measure bioaccessibility, not solubility





(Richardson et al. 2006)

Relative Bioavailability

- Dermal exposure to arsenic-contaminated soil and the TRV is based on oral exposure
- Dermal AF = 4.5% (assumed for the example)
- Water ingestion AF = 74.4% (assumed for the example)
- Relative absorption factor could be calculated for dermal exposure from soil

$$\frac{0.045}{0.744} = 0.060$$

- Dermal relative absorption factor (6%)

Bioaccessibility-Related Projects 2003-05

- Review of bioavailability/bioaccessibility of As, Pb, Cd (JW)
- Critical review of the particle size range(s) that adheres to skin and is most predominantly associated with dermal exposure (Globaltox)
- Literature review to determine the bioavailability of chemicals in key toxicology studies used to establish TRVs (AMEC)
- Preliminary literature review of bioavailability of organics in soil (Meridian)
- Influence of liquid to volume ratio on bioaccessibility (RRU/UMA)
- Bioaccessibility of metals in indoor dust (EHSB, Rasmussen)
- Critical review of lung fluid solubility assays for predicting respiratory bioavailability (UMA/Wilson Scientific)
- Begin investigation of dermal penetration of soil-borne contaminants through viable human skin (EHSB, Rick Moody)

Bioaccessibility-Related Projects 2005-06

- Continue investigation of dermal penetration of soil-borne contaminants through viable human skin (EHSB, Rick Moody)
- Evaluation of best animal model, and study design (Cantox)
- Review of default dermal bioavailability factors for application to PQRA at federal sites (Dillon)
- Research workshop on bioavailability; creation of BARC (CNTC/U Guelph/RMC)
- Publication: Richardson et al. 2006. *Do current standards of practice measure what is relevant to human exposure at contaminated sites? II: Oral bioaccessibility of contaminants in soil. HERA 12(3): 606-616.*

Bioaccessibility-Related Projects 2006-07

- Continue investigation of dermal penetration of soil-borne contaminants through viable human skin (EHSB, Rick Moody)
- Development of HC capacity for *in vivo* swine bioavailability studies; bioavailability and pharmacokinetics of Pb (EHSB, Wayne Bowers)
- Bioaccessibility of lead from soils used in swine study (RRU)
- Bioaccessibility of arsenic from historic gold mine sites in NS (RRU)
- Industry workshop on bioavailability; collaboration on BARC research plan (CNTC/U Guelph/RMC)
- Chapter dedicated to oral bioaccessibility in $DQRA_{Chem}$ guidance

Bioaccessibility-Related Projects 2007-09

- Continue investigation of dermal penetration of soil-borne contaminants through viable human skin (EHSB, Rick Moody)
- *In vivo* swine bioavailability studies of soil from DFO lightstations (EHSB, Wayne Bowers)
- Bioaccessibility of metals from indoor dusts collected in cross-Canada indoor dust survey (EHSB, Pat Rasmussen)
- Canadian bioaccessibility round robin (BARC)
- *In vivo* swine bioavailability studies of soil used in BARC round robin (EHSB, Wayne Bowers)
- *In vitro* bioaccessibility assays of soil samples collected as part of the GSC's planned survey of elemental concentrations in background soil samples collected from across Canada (NRCan, RRU)
- *In vitro* bioaccessibility assays of PAH contaminated soils using SHIME test (Steve Siciliano)

Amortization

- Def'n: the pro-rating (averaging) of less-than-lifetime exposures over estimated life expectancy to derive a lifetime average daily dose

- Is the practice of amortization valid and scientifically defensible?

Short-Term Exposure

- For non-carcinogens, do you amortize a short term exposure over 365 days?
- If so, do you check the TRV to confirm that this is protective?
- What about developmental toxicants?
- Acute and/or subchronic health risks may “drive” the results of the HHRA

Scenarios Where Short-Term Risk Assessment May Be Important

- Sites that are only visited seasonally
  - Example 1: summer camp for 2 weeks
  - Example 2: hunting camp used for 3 months
- Sites where exposure periods are short
  - Example 1: construction work for 1 month
  - Example 2: spill cleanup

What Does the Guidance Say?

- No formal CSD guidance for short-term exposure for HHRA of non-carcinogens
- Some guidance for evaluation of short-term risk:
  - Canadian Cyanide Soil Quality Guideline (Health Canada, 1995)
  - A Protocol for the Derivation of Environmental and Human Health Soil Quality Guidelines (CCME, 2006)
  - US EPA, ATSDR and others

Key Issues for Short Term Exposure

- You can use a short-term TRV, but short-term TRVs may not necessarily be applicable for repeat short-term exposures
- TRV time period should be at least as long as the exposure period
- No generic default adjustment factor for deriving acute or subchronic TRVs from chronic values

Is There a Default Ratio?

ATSDR MRL dataset:

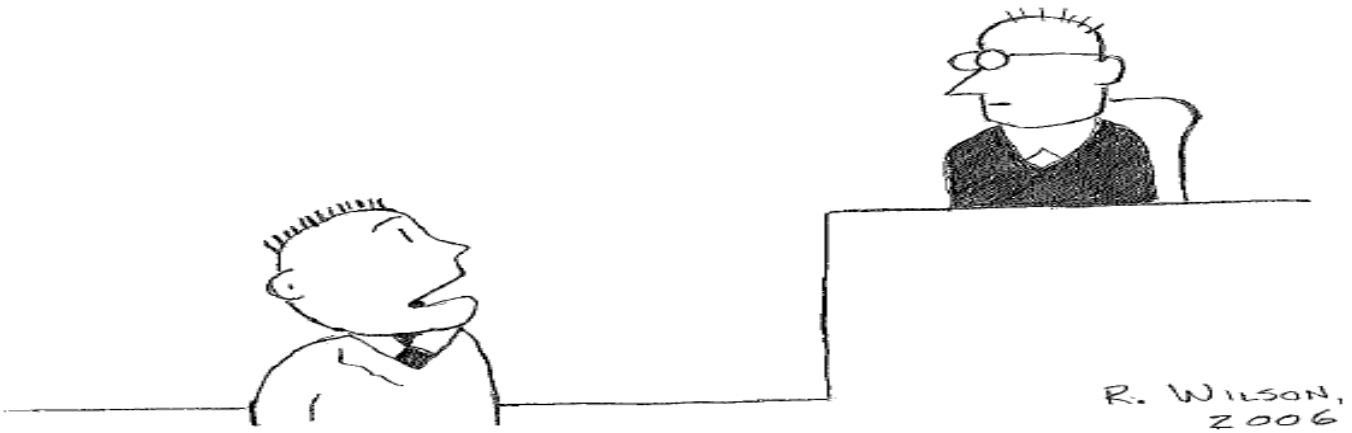
Ratio of Acute to Chronic MRLs		Ratio of Subchronic to Chronic MRLs	
n = 41	Arith mean = 25 But range = 1 to 200	n= 44	Arith mean = 9 But range = 1 to 100

- Not advisable to multiply a chronic TRV by “10” (for example) to estimate a short-term TRV without full consideration of all factors

What is an Appropriate Amortization Period?

- Most exposures for comparison to chronic TDI's should not be amortized over a period greater than one week
  - exceptions include COPCs with TMIs
- Some TDIs are based on developmental endpoints
  - no amortization would be applicable for TRVs with teratogenic endpoints
- Provide rationale on a case-by-case basis
- PQRA update

Reality Check



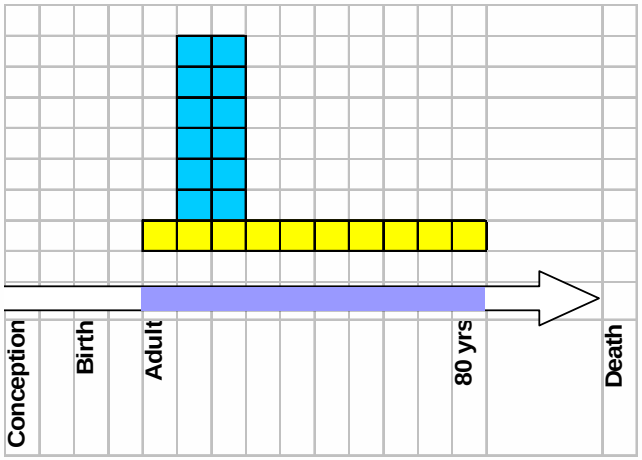
"So you see, your Honour, given that this was the first time that I drank all year, the 12 drinks that I consumed on the night of September 29 were actually equivalent to about 0.033 drinks per day when amortized evenly over the entire year. As a result, I could not have been impaired and the DUI charge should be thrown out."

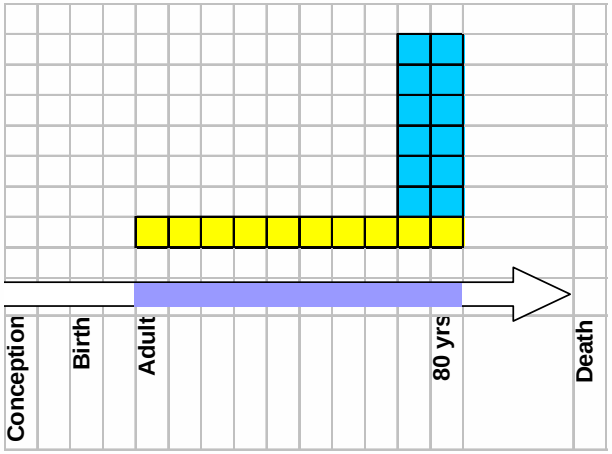
Bottom Line

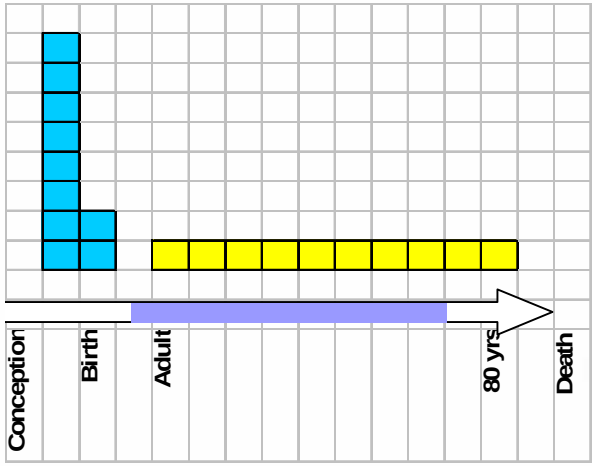
- Amortization of exposure should not underestimate the potential for exceeding threshold effects and mathematical amortization needs to be carefully justified

365 ug/kg/day for 1 day ≠ 1 ug/kg/day for 365 days

What About Carcinogens?







Is timing important?

Are the risks equivalent?

Early life stage and late life stage less-than-lifetime exposures ***DO NOT*** present equivalent risks