PUBLIC STAKEHOLDER WORKSHOP
TO INFORM EPA'S UPCOMING IRIS

TOXICOLOGICAL REVIEW OF INORGANIC ARSENIC

SESSION 3:
DOSE-RESPONSE

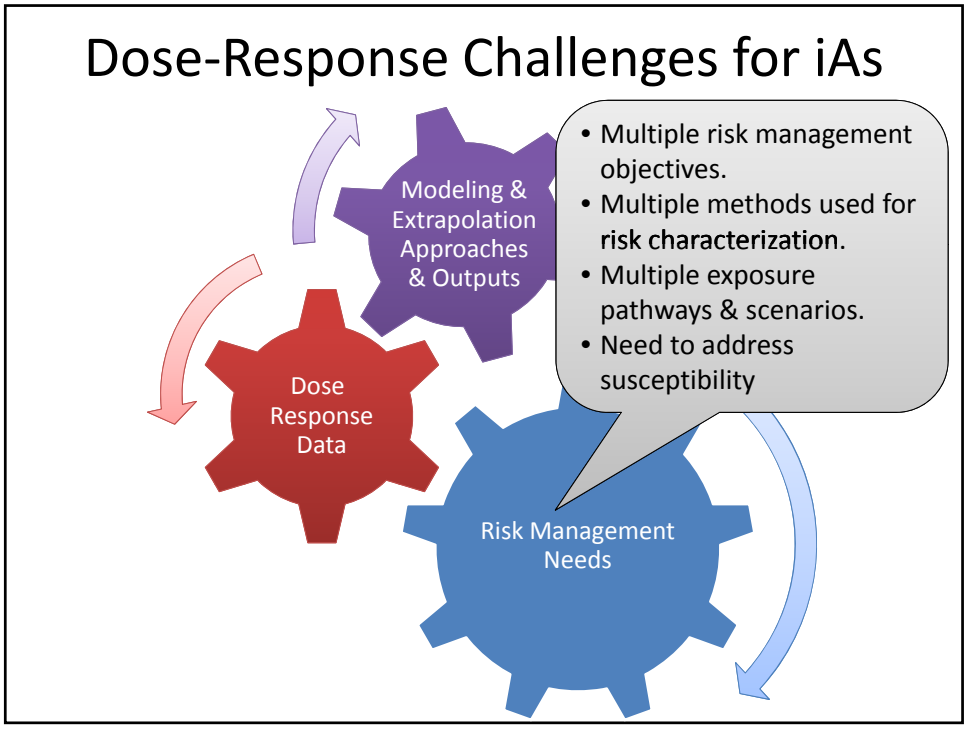
Tuesday, January 8 &
Wednesday, January 9
RTP, North Carolina

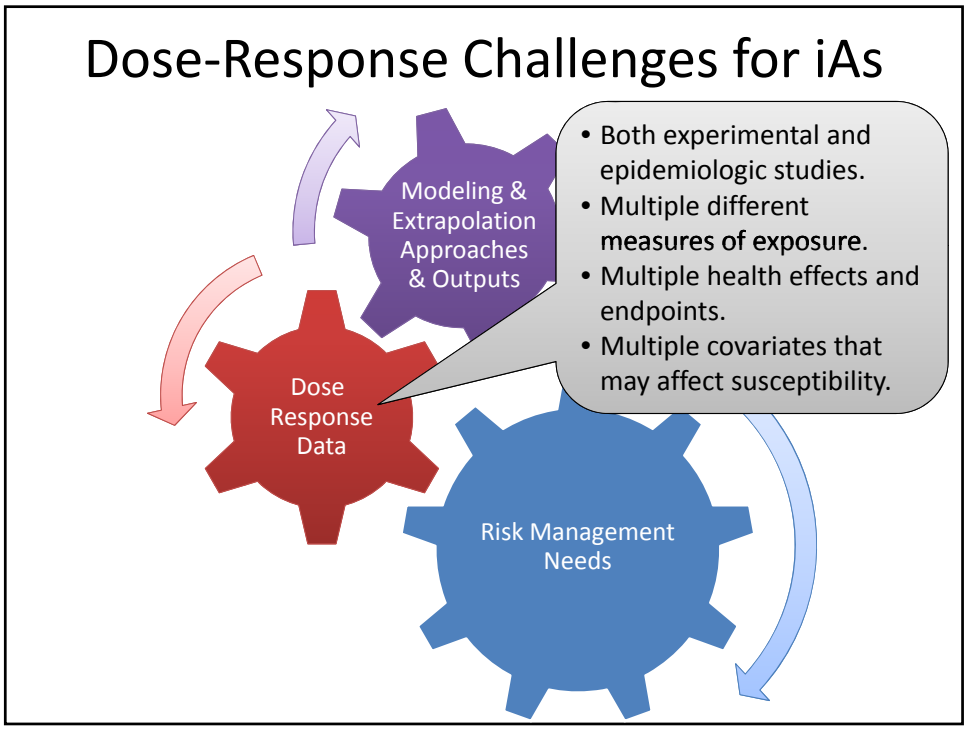
HOSTED BY EPA'S NATIONAL CENTER
FOR ENVIRONMENTAL ASSESSMENT

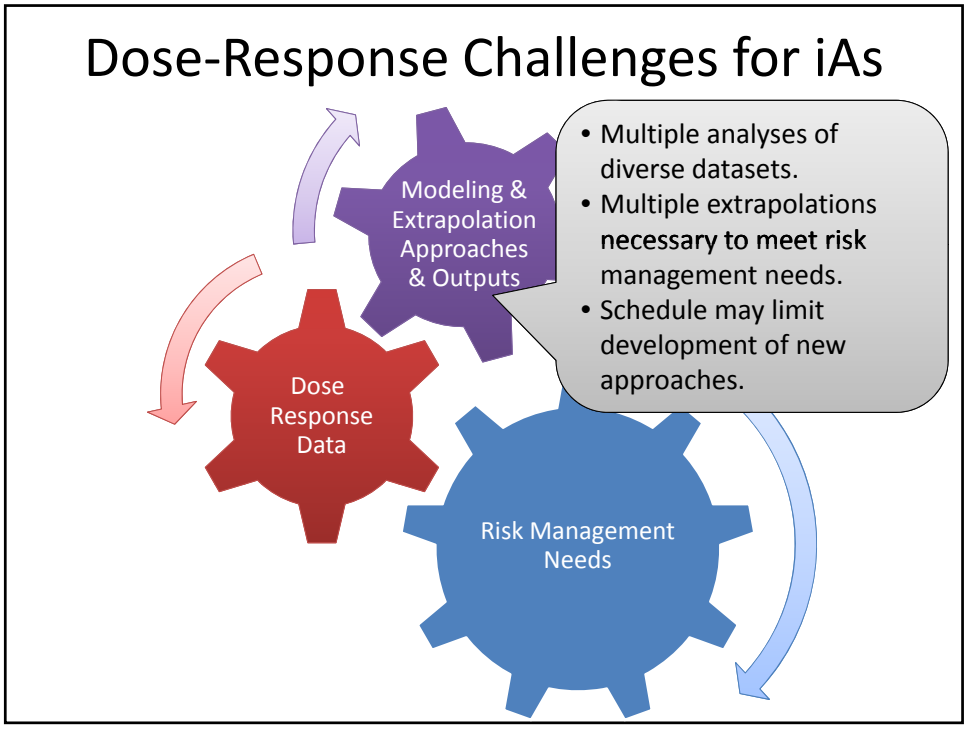
Dose-Response

Weihsueh Chiu

Dose-Response Assessment = Smoothly Meshing Three Components


Dose-Response Challenges for iAs
Modeling & Extrapolation Approaches & Outputs
Dose Response Data
Risk Management Needs
• Multiple risk management objectives.
• Multiple methods used for risk characterization.
• Multiple exposure pathways & scenarios.
• Need to address susceptibility


Dose-Response Challenges for iAs
Modeling & Extrapolation Approaches & Outputs
Dose Response Data
Risk Management Needs
• Both experimental and epidemiologic studies.
• Multiple different measures of exposure.
• Multiple health effects and endpoints.
• Multiple covariates that may affect susceptibility.

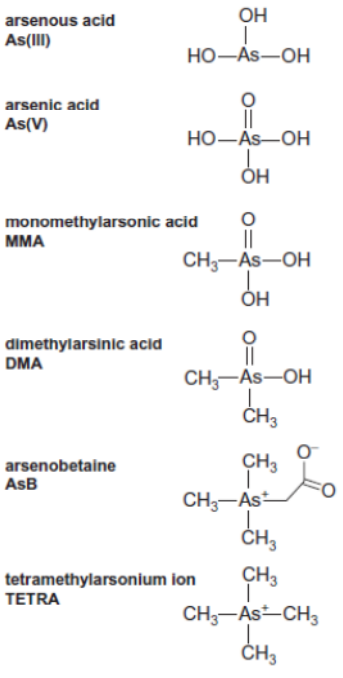

Dose-Response Challenges for iAs
Modeling & Extrapolation Approaches & Outputs
Dose Response Data
Risk Management Needs
• Multiple analyses of diverse datasets.
• Multiple extrapolations necessary to meet risk management needs.
• Schedule may limit development of new approaches.

IS ARSENIC AN APHRODISIAC?

The sociochemistry of an element

William R Cullen

Royal Society of Chemistry

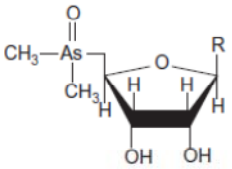


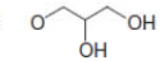
"SIMPLE" ARSENICALS IN THE ENVIRONMENT

Arsenosugars AsS

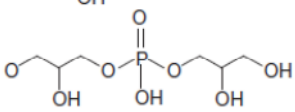
Thioarsenosugars thioAsS

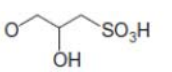
As=S replaces As=O

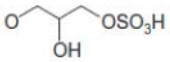


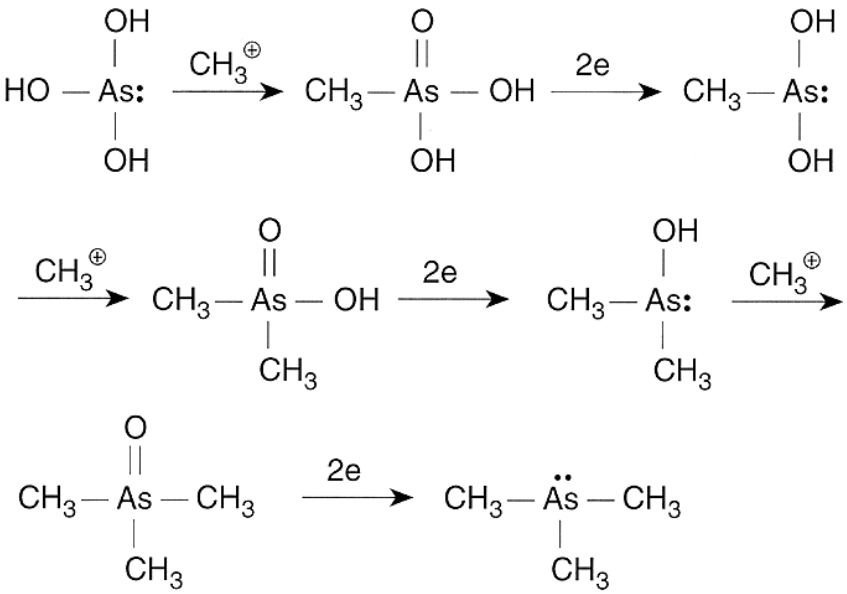
R = 

AsS-OH	thioAsS-OH
AsS-PO4	thioAsS-PO4
AsS-SO3	thioAsS-SO3
AsS-SO4	thioAsS-SO4

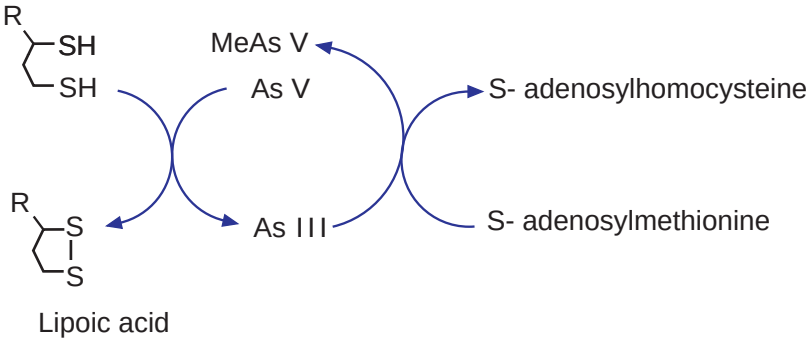




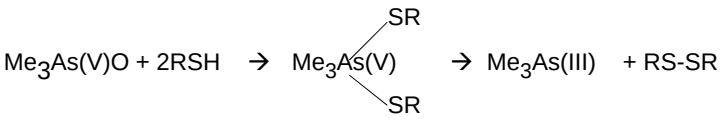




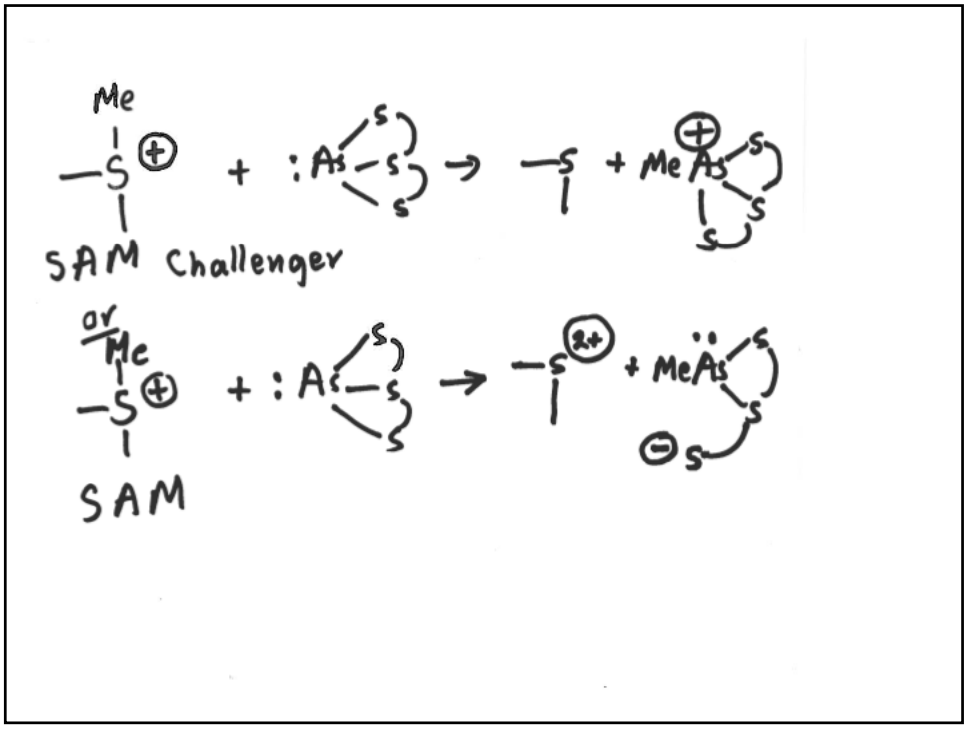
Challenger



Reductive Elimination



Reglinski 1984


Me
SAM
Challenger
or
Me
SAM

Identifying Factors Relevant to Dose Response

3.1 What types of exposure could contribute to the aggregate dose, and in what ways might this impact how an iAs dose-response characterization is used/applied? How can we estimate impact of drinking water exposure alone vs. aggregate exposure on possible effects of iAs exposure?

Lead Discussants: Karen Bradham, Bill Mendez

3.1. What types of exposure could contribute to the aggregate dose, and in what ways might this impact how an iAs dose-response characterization is used/applied? How can we estimate impact of drinking water exposure alone vs. aggregate exposure on possible effects of iAs exposure?

Bill Mendez

Inorganic Arsenic Public Stakeholder Workshop

January 8-9, 2013

What types of exposure could contribute to the aggregate dose…

- Dietary
  - Food contaminated by arsenic from soil/water
- Contaminated Soil/Dust
  - Inhalation
  - Ingestion
- Severity of As contamination varies widely
  - Many natural and man-made sources

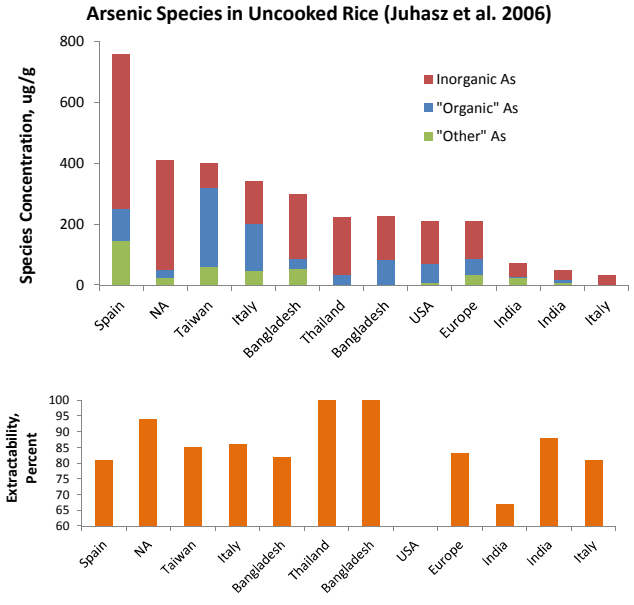
…and in what ways might this impact how an iAs dose-response characterization is used/applied?

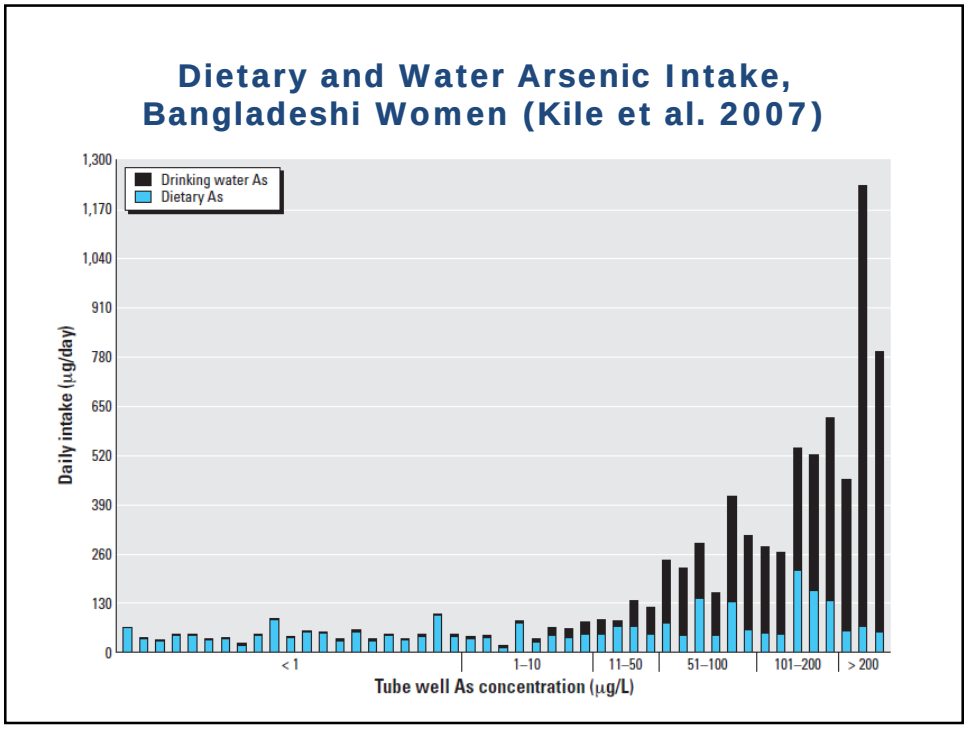
- Adverse effects in epidemiological studies usually reported as function of single exposure medium concentration
- Failure to account for other exposures can:
  - Bias magnitude/form of dose-response
  - Effect statistical significance of relationship
  - Serious problem if "background" dose is a large fraction of dose from primary exposure medium

How can we estimate impact of drinking water exposure alone vs. aggregate exposure on possible effects of iAs exposure?

- Need to account for water and non-water As
  - Estimate As dose from primary medium exposures and exposure factors
  - Add in dose from other media
    - Varies by region, proximity to point sources
  - Consider speciation, bioavailability, absorption
  - Fit dose- (instead of exposure-) response model to estimate risk
- Need to consider As intake of target population (U.S. general public)
- Account for uncertainty through sensitivity analysis, simulation

Speciation / Bioavailability Assessment for Rice




Dietary and Water Arsenic Intake, Bangladeshi Women (Kile et al. 2007)
Drinking water As
Dietary As
Daily intake (μg/day)
1,300
1,170
1,040
910
780
650
520
390
260
130
0
< 1
1–10
11–50
51–100
101–200
> 200
Tube well As concentration (μg/L)

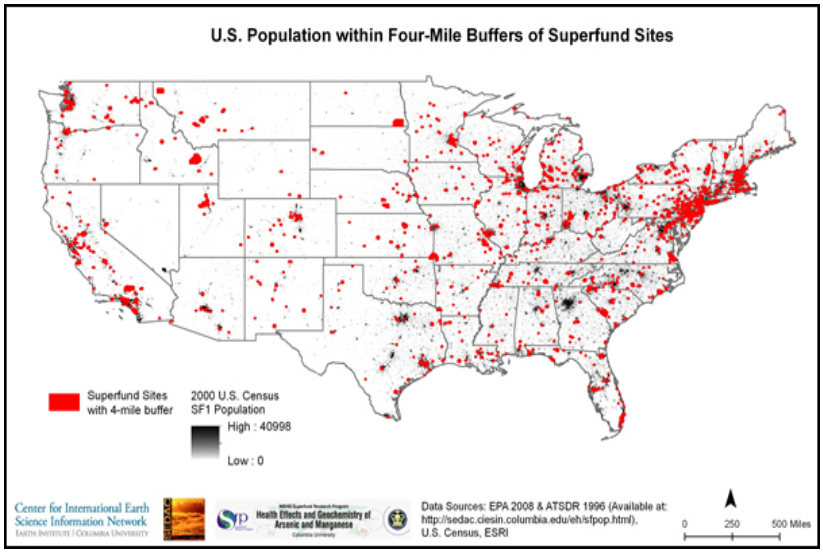
Bioavailability of Inorganic Arsenic

Workshop on the Integrated Risk Information System (IRIS)
Toxicological Review of Inorganic Arsenic

Presented by Dr. Karen Bradham

U.S. Environmental Protection Agency
Office of Research and Development

Potential for exposure to toxicants at contaminated sites



2007 Priority list of hazardous substances

1 ARSENIC
2 LEAD
3 MERCURY
4 VINYL CHLORIDE
5 POLYCHLORINATED BIPHENYLS
6 BENZENE
7 CADMIUM
8 POLYCYCLIC AROMATIC HYDROCARBONS
9 BENZO(A)PYRENE
10 BENZO(B)FLUORANTHENE

FREQUENTLY OCCURRING AT NPL SITES
TOXICITY POTENTIAL FOR HUMAN EXPOSURE

Arsenic exposure at contaminated sites

- Oral ingestion of soil and dust – "risk driver" for human exposure
- Conventional methods or default values – do not adequately address metal bioavailability under site conditions
- Bioavailability of metals in soils and dusts vary depending on the mineralogy and physicochemical properties
- Default assumption for assessing risk from arsenic in soil is that the bioavailability of arsenic in soil is the same as the bioavailability of arsenic dissolved in water
- Recent bioavailability studies conducted in animal models show that the bioavailability of arsenic in soil is typically less than that of highly water soluble forms of arsenic (< 100%)

EPA bioavailability guidance

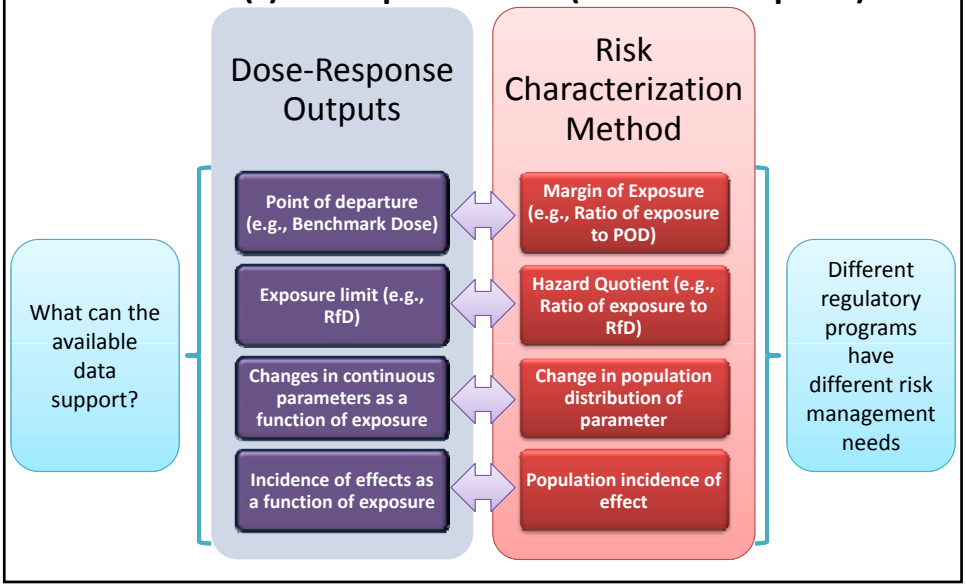
- EPA's Technical Review Workgroup, Bioavailability Committee recently conducted a review of all available in vivo estimates of soil arsenic bioavailability
- 103 studies identified, most studies had values < 60% and studies were performed to support remedial investigations and risk assessments of specific sites
- OSWER Directive 9200.1-113:
  - Based upon evaluation of current data sets of arsenic bioavailability, the upper percentile of the data set results in a default value of 60%
  - The default value for arsenic in soils should only be used if site-specific assessments for arsenic are not feasible
- EPA's Guidance for Evaluating the Bioavailability of Metals in Soils for Use in Human Health Risk Assessment
  http://www.epa.gov/superfund/bioavailability/guidance.htm

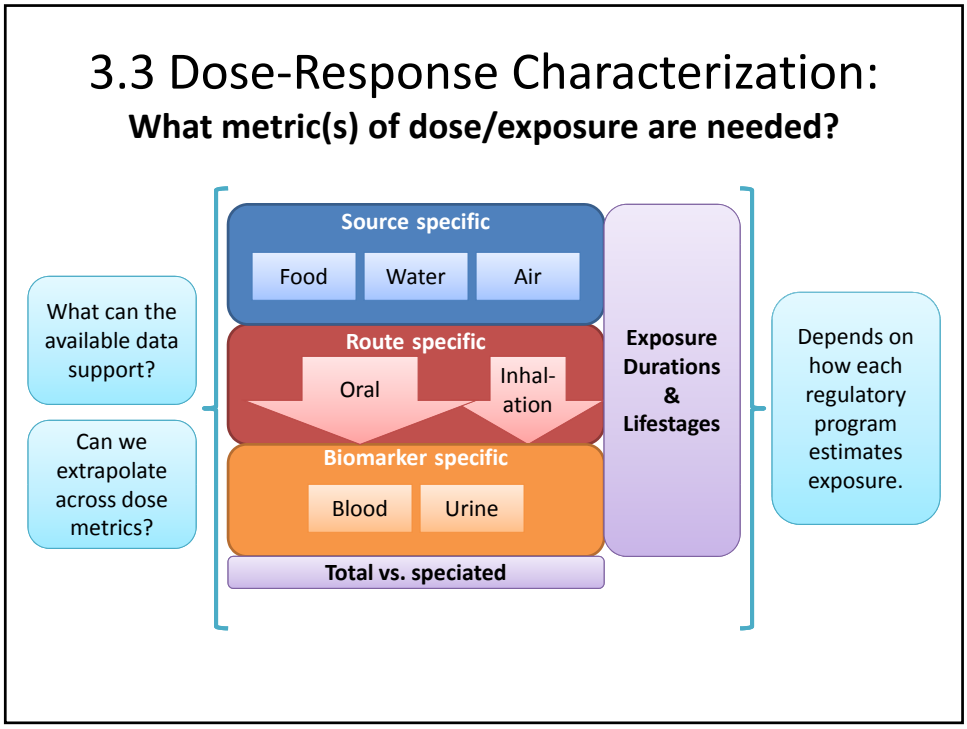
What kinds of dose-response characterization may be needed (e.g., reference value, incremental change in risk with dose, probabilistic risk at dose) for aggregate (e.g., urine, blood) and source-specific (e.g., food, water) dose metrics?

Weihsueh Chiu

3.3 Dose-Response Characterization:

What kind(s) of output needed (for each endpoint)?

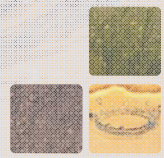



3.3 Dose-Response Characterization:
What metric(s) of dose/exposure are needed?
What can the available data support?
Can we extrapolate across dose metrics?
Source specific
Food
Water
Air
Route specific
Oral
Inhal-ation
Biomarker specific
Blood
Urine
Total vs. speciated
Exposure Durations & Lifestages
Depends on how each regulatory program estimates exposure.

Approaches to Dose-Response Analysis

3.4 What kinds of approaches are available to analyze dose-response data (e.g., statistical models, non-parametric approaches)?

Lead Discussants: Weihsueh Chiu, Jeff Gift



EPA United States Environmental Protection Agency

What kinds of approaches are available to analyze dose–response data (e.g., statistical models, non–parametric approaches)?

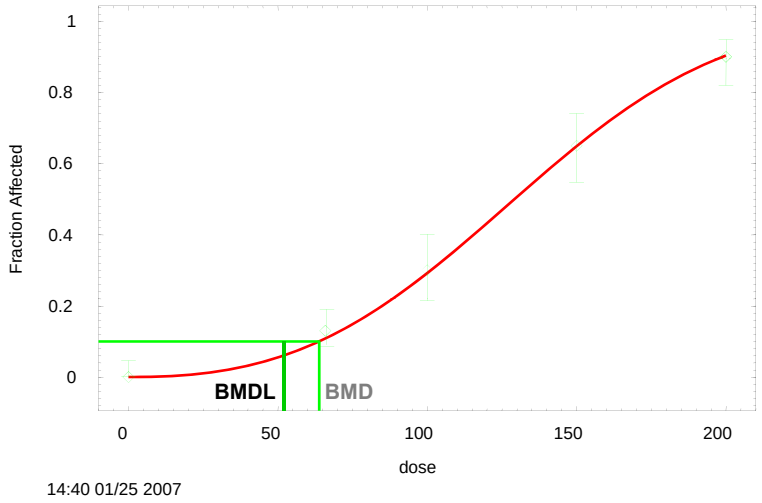
Multitumor Analysis

Jeff Gift

(January 9, 2013)

Benchmark Dose Training California Environmental Protection Agency Training Workshop 128

Analyzing Dose-response Data



Benchmark Dose Training California Environmental Protection Agency Training Workshop 129

Possible Topics

- Beyond BMDL?
- Parametric or semiparametric modeling?
- Probabilistic risk?
- Model uncertainty?
- Other parametric models?
- Other methods for estimating BMDLs for an endpoint
- Multitumor analysis

Benchmark Dose Training California Environmental Protection Agency Training Workshop 130

Multiple Tumor Analysis

- Basing unit risk on one tumor type may underestimate cancer risk of a chemical that induces neoplasia at multiple sites (NRC, 1994).
- **Tumor selection** and derivation of **confidence limits** are key aspects of a multitumor analysis.

Selection of Tumors

- Tumors must be independent of one another.
  - MOA for arsenic related tumor formation not known
  - No reason to assume tumors not formed independently
- Low risk tumors combined with high risk tumors
  - For example, though skin cancer is rarely fatal and less potent than internal tumors, its risk can theoretically be accounted for in a combined risk analysis.

Confidence Limits for Combined Risk

- LED (BMDL) from BEIR IV model is not 95% LB on dose.
- "Normally distributed uncertainties" assumption used to get LB for combined risk has been criticized in peer review.
- Two alternative approaches are used in the EPR draft of the EPA 1,4-Dioxane assessment:
  - Markov Chain Monte Caro (MCMC)/Bayesian computational approach (Kopylev et al., 2009)
  - BMDS multitumor (MS_combo) profile likelihood approach (epa.gov/ncea/bmds)
- These approaches were well received by peer reviewers, but do not account for time/age dependency.

Dose-response modeling results for male rat tumors that inhaled 1,4-dioxane for 2 years

Tumor Type	Multistage Model Degree	Rat Exposure (ppm)		Human Equivalent (mg/m3)		Inhalation Unit Risk $(\mu g/m3)^{-1}$
		BMC10	BMCL10	BMC10	BMCL10	
Nasal squamous cell carcinoma	1	1107	629.9	712.3	405.3	2.5×10^{-7}
Hepatocellular adenoma or carcinoma	1	252.8	182.3	162.7	117.3	8.5×10^{-7}
Renal cell carcinoma	3	1355	1016	872	653.7	1.5×10^{-7}
Peritoneal mesothelioma	1	82.21	64.38	52.89	41.42	2.4×10^{-6}
Mammary gland fibroadenoma	1	1635	703.0	1052	452.4	2.2×10^{-7}
Zymbal gland adenoma	3	1355	1016	872	653.7	1.5×10^{-7}
Subcutis fibroma	1	141.8	81.91	91.21	52.70	1.9×10^{-6}
Bayesian Total Tumor Analysis		39.2	31.4	25.2	20.2	5.0×10^{-6}
BMDS Multitumor (MS_Combo)		40.5	32.3	26.1	20.8	4.8×10^{-6}

Questions

- Should all "confirmed" As-related tumors (lung, bladder, kidney and skin) be included in a multitumor analysis?
- If so, how should lower risk cancers (e.g., skin) be "weighted" relative to the other cancer risks?
- Should a time dependent multitumor modeling approach be developed that can calculate more defensible confidence limits?

Confidence Limits for Combined Risk

- Most recent approach proposed for As:

  "Upper confidence limits on the combined cancer risks can be calculated based in the assumption that the uncertainties in the two CSFs are both normally distributed. If this is the case, the 95% upper bound, U, for the combined cancer potency can be calculated as:

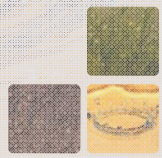
  $$U = (m_1 + m_2) + (u_1 - m_1) + (u_2 - m_2) \quad \textit{(Equation 5-5)}$$

  where mi and ui, i = 1,2, are respectively mean and 95% upper bound cancer potency for the two tumor types."

Approaches to Dose-Response Analysis

3.5 What are factors (e.g., toxicokinetics, bioavailability, water consumption rates, background exposure, susceptibility) that can impact the dose response analysis, and how could these factors be transparently accounted for?

Lead Discussants: William Cullen, Hisham El-Masri



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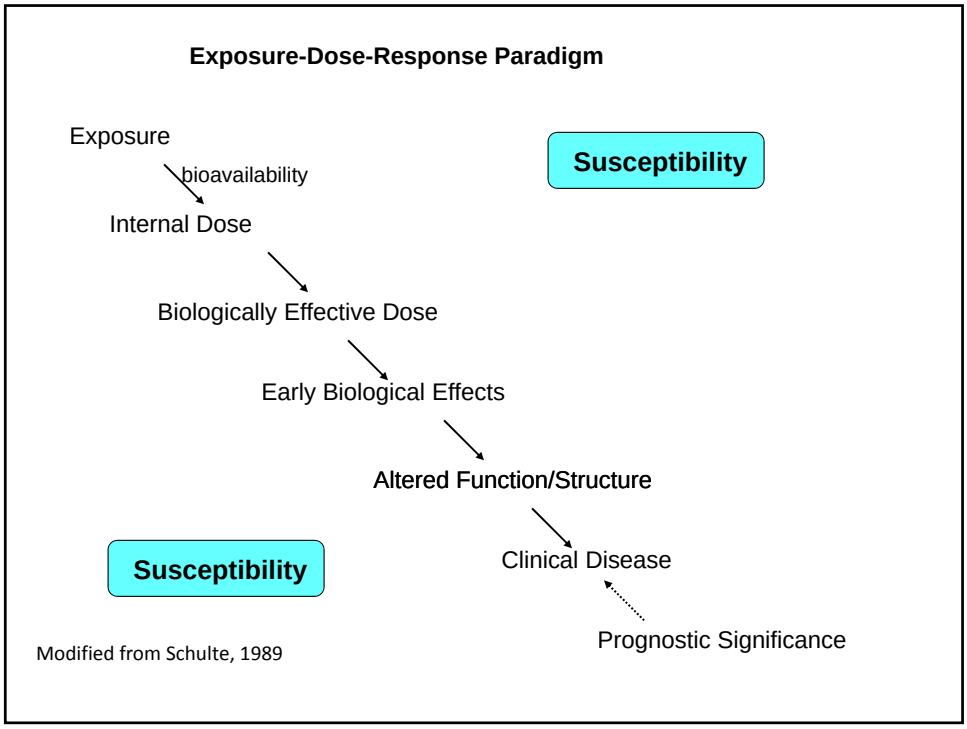
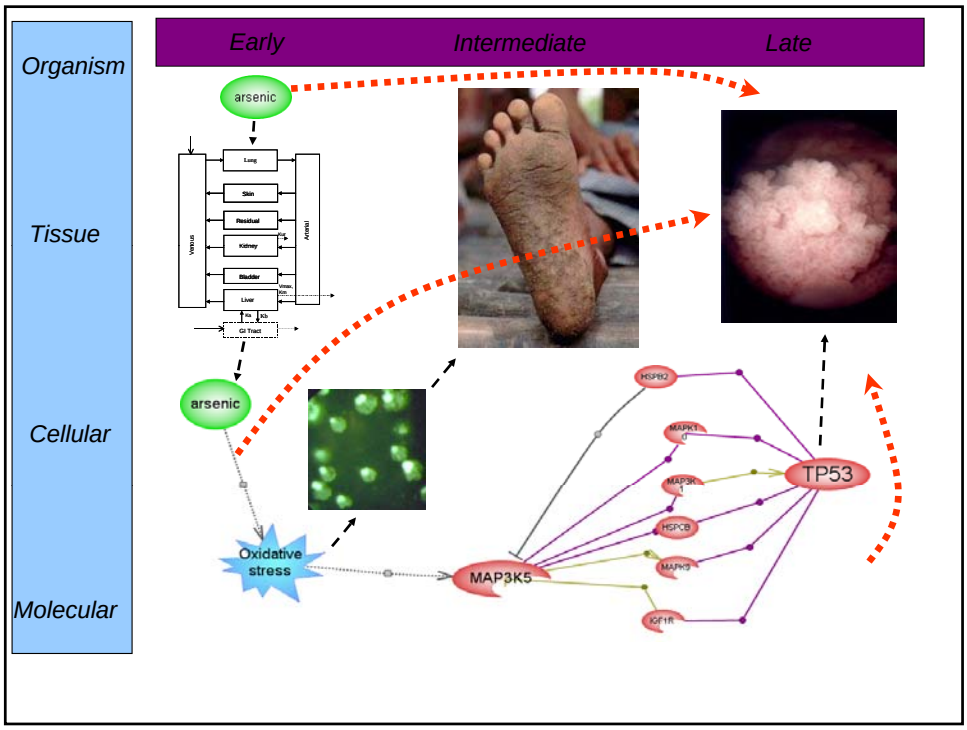
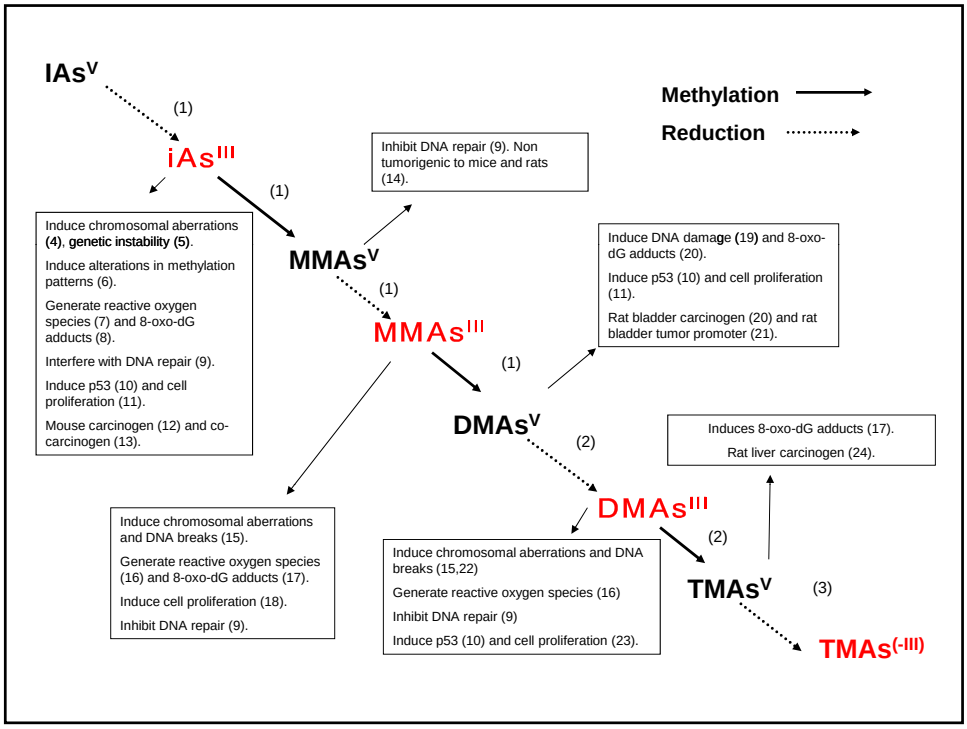
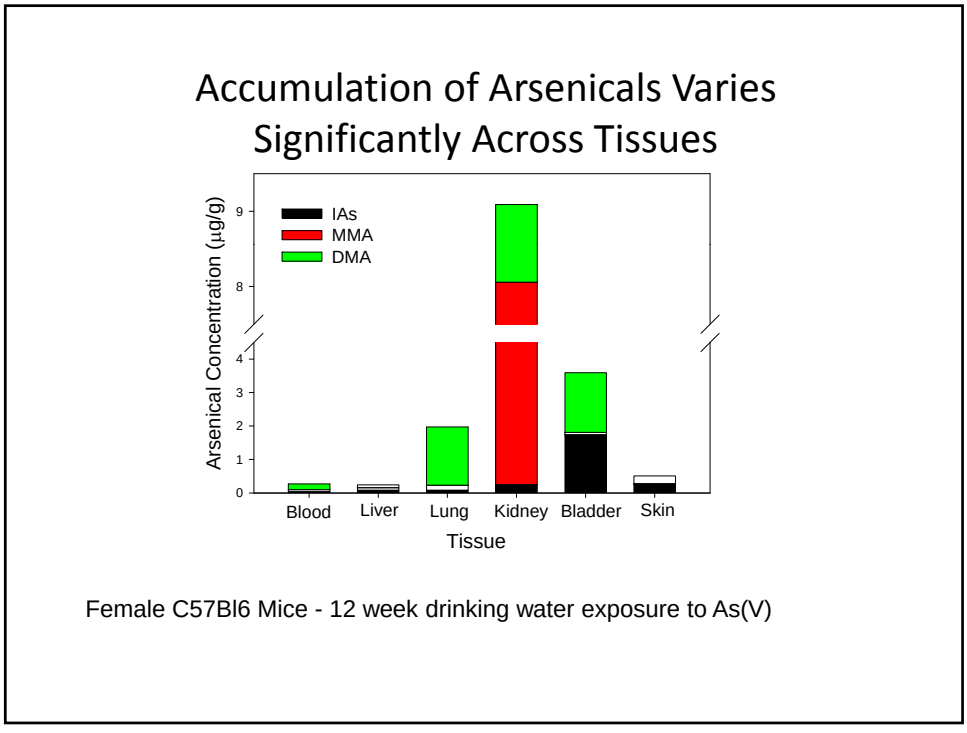
Hisham El-Masri


Exposure-Dose-Response Paradigm
Exposure
bioavailability
Internal Dose
Biologically Effective Dose
Early Biological Effects
Altered Function/Structure
Clinical Disease
Prognostic Significance
Susceptibility
Susceptibility
Modified from Schulte, 1989


Organism
Tissue
Cellular
Molecular
Early
Intermediate
Late
arsenic
arsenic
Oxidative stress
MAP3K5
TP53


IAsV
(1)
iAsIII
(1)
MMAsV
(1)
MMAsIII
(1)
DMAsV
(2)
DMAsIII
(2)
TMAsV
(3)
TMAs(-III)
Methylation
Reduction
Inhibit DNA repair (9). Non tumorigenic to mice and rats (14).
Induce chromosomal aberrations (4), genetic instability (5).
Induce alterations in methylation patterns (6).
Generate reactive oxygen species (7) and 8-oxo-dG adducts (8).
Interfere with DNA repair (9).
Induce p53 (10) and cell proliferation (11).
Mouse carcinogen (12) and co-carcinogen (13).
Induce DNA damage (19) and 8-oxo-dG adducts (20).
Induce p53 (10) and cell proliferation (11).
Rat bladder carcinogen (20) and rat bladder tumor promoter (21).
Induces 8-oxo-dG adducts (17).
Rat liver carcinogen (24).
Induce chromosomal aberrations and DNA breaks (15).
Generate reactive oxygen species (16) and 8-oxo-dG adducts (17).
Induce cell proliferation (18).
Inhibit DNA repair (9).
Induce chromosomal aberrations and DNA breaks (15,22)
Generate reactive oxygen species (16)
Inhibit DNA repair (9)
Induce p53 (10) and cell proliferation (23).


Accumulation of Arsenicals Varies Significantly Across Tissues
IAs
MMA
DMA
Arsenical Concentration (μg/g)
0
1
2
3
4
8
9
Blood
Liver
Lung
Kidney
Bladder
Skin
Tissue
Female C57Bl6 Mice - 12 week drinking water exposure to As(V)

What Makes Arsenic Unique?

- Pancarcinogenic in humans, whereas rodents are much less responsive
- Large cross-species differences in metabolism
- Tissue-specific differences in metabolite accumulation
- Toxicity most likely mediated by metabolism
- Known variations in metabolism due to age and ethnicity in humans
- Polymorphisms identified in AS3MT, the principal As metabolizing enzyme

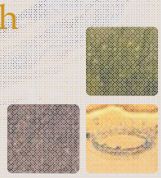
Factors Impact on Dose-Response

- TK
  - Linkage to a hypothesized mode of action to identify key target tissue dosimetry
    - HUMAN VS ANIMAL
- Epidemiological studies (human only)
  - Exposure (speciation of organic vs inorganic As, DMA, MMA..etc.)
    - Is As dose-response a mixture problem?
  - Susceptible populations
  - Can biomarkers (e.g. levels of DMA in urine) be misleading?
    - Need of appropriate target tissue levels (blood levels of affected population at minimum)

Approaches to Dose-Response Analysis

3.6 EPA has traditionally addressed uncertainty in modeling dose-response data by using a statistical lower confidence bound on the benchmark dose. What other approaches are available to address and transparently convey the impact of uncertainty on the dose-response analysis?

Lead Discussants: Bill Mendez, Warner North



3.6

"EPA has traditionally addressed uncertainty in modeling dose-response data by using a statistical lower confidence bound on the benchmark dose (BMD). What other approaches are available to address and transparently convey the impact of uncertainty on the dose-response analysis?"

D. Warner North

Comments for the Arsenic/IRIS Workshop Jan 8-9, 2013

D. Warner North

President and Principal Scientist, NorthWorks, Inc.

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Web: www.northworks.net

3.6:

"EPA has traditionally addressed uncertainty in modeling dose-response data by using a statistical lower confidence bound on the benchmark dose (BMD). What other approaches are available to address and transparently convey the impact of uncertainty on the dose-response analysis?"

Section 1.3 North comments

- Inorganic arsenic is **unusual** as an IRIS entry.
- Not all risk assessments should be done the same way – for IRIS, or in other contexts. (Reference: the NAS "Color" books)
- Focus should be on **health risk at potential low-dose human exposure.**
  - Is the health risk potentially significant?
  - If so, want quantitative estimate(s) and uncertainty disclosure. **Key aspect**: dose-response relationship, built upon evidence from epidemiology, mode of action/toxicology investigations.

Section 1.3 North comments, 2

- For **important** cases/IRIS entries, may want **more** than a review of published papers.
  - Convene a gathering of the **best experts** for discussion and debate. Publish the proceedings.
  - **Frame** the problem first. What is included?
  - Want a **transparent process**, understandable by stakeholders.
  - **Don't preclude evidence**: Assemble it, then evaluate it.

  Reference: *Public Participation in Environmental Assessment and Decision Making*, National Academy Press, 2008, See esp. Chapter 6, "Practice: Integrating Science," particularly page 141 on defaults and guidelines. (Page 141 to be handed out). On web at www.nap.edu/catalogue.php?record_id=12434.

Dose-Response with uncertainty

- **Goal:** Summarize the information available, disclosing uncertainty.
- Consider three levels : (response y, given dose x)
  1. A **range** (e.g., zero to a plausible upper bound)
  2. A **probability distribution** over the range
  3. A **model** that computes a probability distribution based on inputs, permitting **sensitivity analysis** to these inputs.

Section 3.6: D-R with uncertainty

- **Goal:** Summarize the information available, disclosing uncertainty.
- Consider three levels : (response y given dose x)
  1. A **range** (e.g., zero to a plausible upper bound – old pre-BMD, EPA cancer risk number – see page 141 handout)
  2. A **probability distribution** over the range
  3. A **model** that computes a probability distribution based on inputs, permitting **sensitivity analysis** to these inputs.

Section 3.6: D-R with Uncertainty

- **Goal:** Summarize the information available, disclosing uncertainty.
- Consider three levels : (response y given dose x)
  1. A **range** (e.g., zero to a plausible upper bound)
  2. A **probability distribution** over the range
  3. A **model** that computes a probability distribution based on inputs, permitting **sensitivity analysis** to these inputs.

Example for Level 3: (ecological risk, introduced species)

Reference:

D. W. North, "Limitations, definitions, principles, and methods of risk analysis, Rev. sci. tech. Off. Int. Epiz.**14**(4), 913-923, 1995

Available at: http://www.northworks.net/limitations.pdf

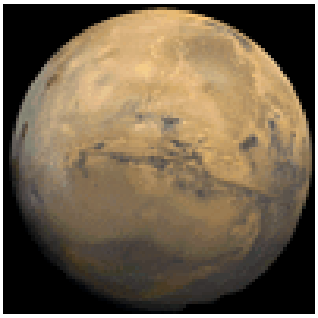
Microbes on Mars

Do we infect Mars with terrestrial microbes by landing a spacecraft on its surface?

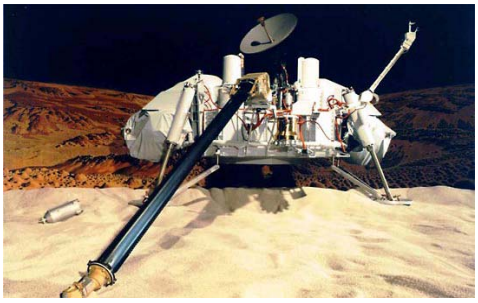
(Decision facing NASA in 1972 for billion-dollar Project Viking Mission, first surface landing)

Planetary Environmental Protection (an example of risk assessment with almost no “data”)

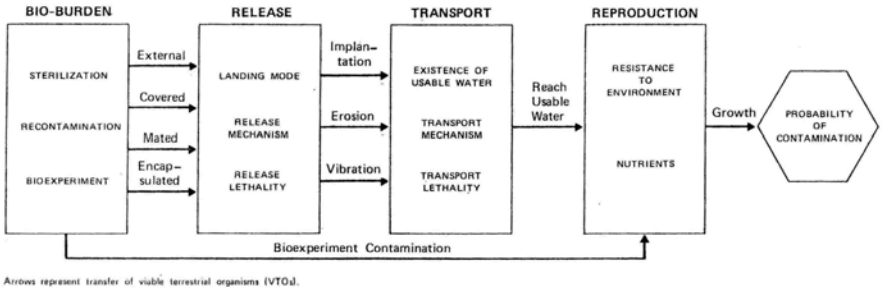
Mars from Viking Orbiter



Viking Lander, 1976



Mission Contamination Model

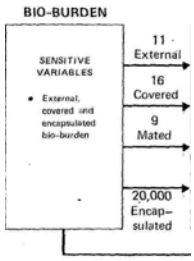


Mission scenarios, fate and transport of microbes on lander

Bio-burden Submodel (Microbes on Spacecraft)

Input Elements:

- Pre-sterilization burden by location
- Sensitivity to sterilization
- Sterilization regime
- Recontamination
- Inflight mortality or proliferation
- Contamination and subsequent amplification in biology experiment: (probability = 10^{-6})



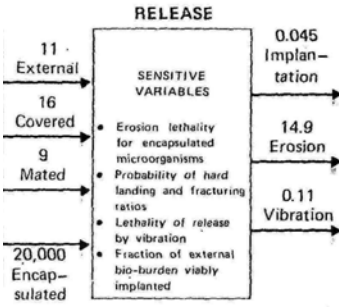
Outputs:

- Bio-burden estimates by Viking Project
- Expected number of **Viable Terrestrial Organisms (VTOs),** by location on spacecraft

Release Submodel (How Does the Spacecraft Land?)

Input Elements:

- Bioburden by location **(from bio-burden submodel)**
- Probability of hard landing
- Fracture ratio for hard landing
- Lethality for release, given location and landing (hard versus nominal)



Outputs:

- **Implantation**: microbes (VTOs) directly deposited in Martian soil, without UV exposure
- **Erosion:** VTOs released through aeolian erosion of spacecraft into Martian atmosphere
- **Vibration:** VTOs fall from spacecraft onto surface of Mars due to mechanical vibration, thermal effects, etc. VTOs require shielding to survive UV exposure.

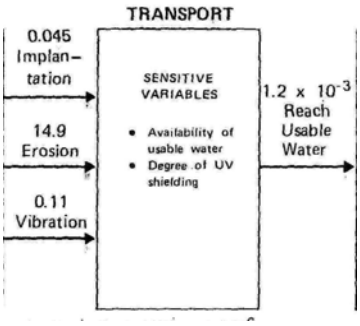
Transport Submodel (How Many Get to "Usable Water"?)

Input Elements:

- Expected number of VTOs released, by mechanism
- Lethality of UV radiation, in normal atmosphere and dust storm (probability that a VTO survives transit)
- Extent of usable water
  - Probability it exists anywhere
  - Portion of surface covered

Output

- Expected number of VTOs that will reach usable water



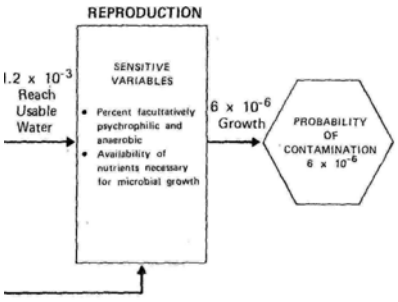
Reproduction Submodel (Can at Least One Do It?)

Input Elements:

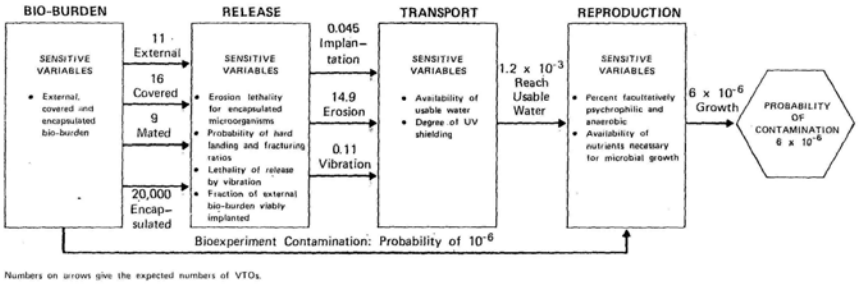
- Fraction of VTOs that are facultatively anaerobic and psychrophilic: (0.05)
- Probability that nutrients needed for reproduction will be present in the water microenvironment (0.10)

Output:

- Expected number of VTOs that reproduce at least once, defined as "contamination"



Mission Contamination Model Results



Mission Contamination Model Marginal Sensitivity Analysis

Probability of Contamination

Contamination Model Variables			**Values**			Units: = 10**-6	
	Extreme	Intermed.		Intermed.	Extreme	**Nominal: 5.9**	
	Low	Low	**NOMINAL**	High	High	**Low**	**High**
Bio-Burden Variables							
1. bio External	2.2	5.5	11	22	55	5	10.7
2. bio Covered	3.2	8	16	32	80	3.1	20.2
3. bio Encapsulated	4,000	10,000	20,000	40,000	100,000	5	10.4
Release Variables							
1. rel Hard Landing Probability	0.0004	0.001	0.002	0.004	0.01	5.2	9.6
3. rel Newly Exposed/Hard, Encaps	0.0001	0.0002	0.001	0.005	0.01	5.4	10.9
4. rel Implanted, Soft	0.0001	0.0002	0.001	0.005	0.01	5.7	8.7
6. rel VTO/Vibration	0.001	0.002	0.01	0.05	0.01	5.4	11.1
9. rel VTO/Erosion, Encaps	0.00001	0.00002	0.0001	0.0005	0.001	5.4	10.9

Mission Contamination Model Marginal Sensitivity Analysis -2

Probability of Contamination

Contamination Model Variables	Values					Units: = 10**-6	
	Extreme	Intermed.		Intermed.	Extreme	Nominal: 5.9	
	Low	Low	**NOMINAL**	High	High	**Low**	**High**
Transport Variables							
1 tra Survive Transit	0.001	0.002	0.01	0.05	0.1	2.2	45.2
2 tra Find Water	0.0005	0.001	0.005	0.025	0.05	1.5	49.9
4 tra Water Deposition	0.00005	0.0001	0.0005	0.0025	0.005	5	15.2
5 tra Stay Lodged	0.1	0.2	0.5	0.8	0.9	5.5	10
Reproduction Variables							
1 rep Psychrophilic, Anaerobic	0.005	0.01	0.05	0.1	0.25	0.6	29.6
2 rep Availability of Nutrients	0.01	0.02	0.1	0.2	0.5	0.6	29.6

Results

- Contamination probability 6 x10^{-6}, well below mission limit of 10^{-4}, insensitive to model assumptions and input data
- Simple explanation for why number is low: UV flux through thin atmosphere kills microbes
- NASA Scientific Advisory Committee (Carl Sagan, Joshua Lederberg, et al.) persuaded of acceptable safety
- Mission flew, Viking Lander successful
- Mid-course correction eliminated, Orbiter life extended to one year

National Academy of Sciences, Viewpoint -1992

"… it is the unanimous opinion of the task group that terrestrial organisms have almost no chance of multiplying on the surface of Mars and in fact have little chance of surviving for long periods of time, especially if they are exposed to wind and to UV radiation."

---- Space Studies Board, National Research Council, *Biological Contamination of Mars,* 1992, page 49: http://www.nap.edu/catalog.php?record_id=12305

Retrospective on this Case Example

- Planetary Quarantine since Viking Landing (1976):
  - Not a major concern, perhaps excepting Mars sample return. (Possibly new observations might change the concern level.)
- Example of Quantitative Risk Analysis built on highly judgmental information
- Accepted by scientific leaders and Agency managers; no public concern or controversy regarding risk assessment

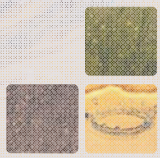
A Key Conceptual Aspect for Levels 2 and 3

- **Probability assessments are summaries of information** and subject to change:
  - "Necessarist" viewpoint; Ref: E. T. Jaynes, *Probability Theory: The Logic of Science*, Cambridge Univ. Press, 2003. (Endorsement in Nassim Taleb, *The Black Swan*, 2007)
  - Usual statistics viewpoint: probabilities are frequencies in data obtained in independent, identical experimental trials.

Extrapolation approaches

3.7 What kinds of extrapolations are needed (e.g., interspecies, exposure route, human variability, low-dose/effect)?

Lead Discussants: Bill Mendez, Warner North



3.7. What kinds of extrapolations (e.g., high-low dose/effect, exposure route, human variability, interspecies) are needed?

Bill Mendez

Inorganic Arsenic Public Stakeholder Workshop

January 8-9, 2013

High to low exposure / dose

- Context: High-quality epidemiological studies are available for many endpoints
- Often address primarily or exclusively high exposures
- Tradition: identify point of departure (POD), extrapolate to low doses (linear, UFs)
- Feasibility of model-based extrapolation
  - Need to account for covariates
  - Uncertainty about model form, confidence bounds, at low exposures
  - Use in vivo, in vitro toxicity, metabolism data to support extrapolation?

exposure route

- Epidemiology available for inhalation and ingestion exposures
- Dosimetry for cross-pathway (ingestion/ inhalation) extrapolation is not well-established
- Portal-of-entry effects can be significant
- Consensus(?) is that cross-pathway estimation of PODs for risk assessment is not advisable

human variability

- Exposure/dose-response
  - Important covariates (diet, smoking, exposure to other stressors) not always available
  - Sensitive developmental windows
  - Hard to generalize relationships between genetic/metabolic variations and risks
- Risk extrapolation to U.S. population
  - Differences in mortality, background disease rates, background As exposures, smoking, etc.

interspecies

- In vivo tests could, in theory, be used to estimate endpoints for risk assessment
  - Derive POD (NOAEL, BMDL) in range of data (curve fitting)
  - Then ??
- BMD models generally do not have a mechanistic basis
- Apply CSAF (based on PBPK modeling) to account for pharmacokinetic differences
- Pharmacodynamic differences are highly species- and endpoint-dependent, and generally not well-characterized
- Use animal tests as back-stop for PODs derived from epidemiology?

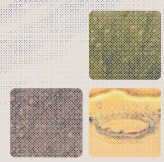
in vitro, "omics" data

- Role of *in vitro* data? (We have lots)
  - Quantitative risk assessment
  - Safety assessment
  - Inform low-dose extrapolation
- Questions
  - How to simulate transport, metabolism
  - Identification of key pathways/events
  - Modeling of complex causal networks over time
  - Assessment of uncertainty

Extrapolation approaches

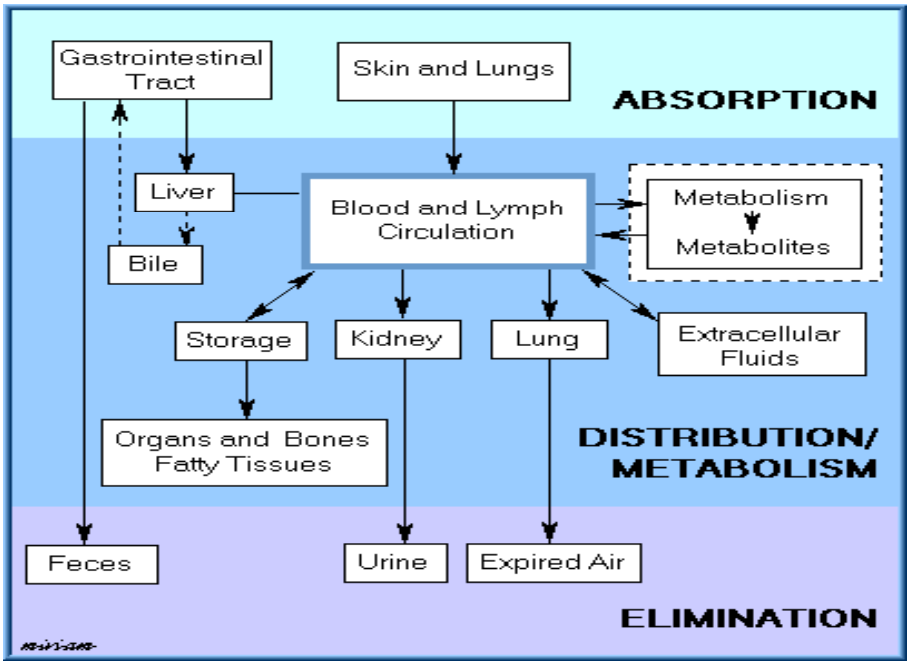
3.8 What approaches are available for such extrapolations (e.g., PBPK modeling, uncertainty factors, probabilistic factors, linear/non-linear dose-response)?

Lead Discussants: Hisham El-Masri, Jeff Gift



What approaches are available for such extrapolations (e.g., PBPK modeling, uncertainty factors, probabilistic factors, linear/non-linear dose-response)?

Hisham El-Masri



PBPK Models: Internal Dosimetry

- Defines the relationship between external concentration and an internal measure of (biologically effective) exposure in both experimental animals and humans

- **Use of PBPK Models can account for:**
  - Interspecies differences in ADME
  - Nonlinear uptake, metabolism, clearance
  - Toxicity associated with products of metabolism rather than parent chemical only
  - Tissue interactions (e.g. GSH depletion, induction of clearance/repair, receptor occupancy)

Previous As PBPK Models

Yu (1999) model:

- Partition coefficients were solely determined using a child poisoning case. This study provided **total** arsenic levels only. There was no information in poisoning study that would help the researchers to determine the partition coefficients for arsenic and its metabolites (MMA and DMA) as was published and referenced in the Yu (1999) publication.
- Yu (1999) stated in their publication that they used the child poisoning study to determine **metabolic parameters such as Vmax and Km**. The child poisoning study did not have any information that can lead to these estimates.
- Yu (1999) model simulations were **not tested** against data.

Previous As PBPK Models

Mann et al. (1996) model:

- The modeling effort for the humans was based on modification of an earlier one that was established for rabbits and hamsters. Both models did not include descriptions of ***current knowledge about metabolism of arsenic*** (such as the inhibition effects of Arsenic and MMA).
- The model calibration relied heavily on **"global" optimization of parameters** such as partition coefficients, first order oral absorption constant, methylation rate constants, oxidation and reduction constants. All of these parameters were optimized using urine data. "Global" optimization would yield a set of unidentifiable parameters.

As Human PBPK Model

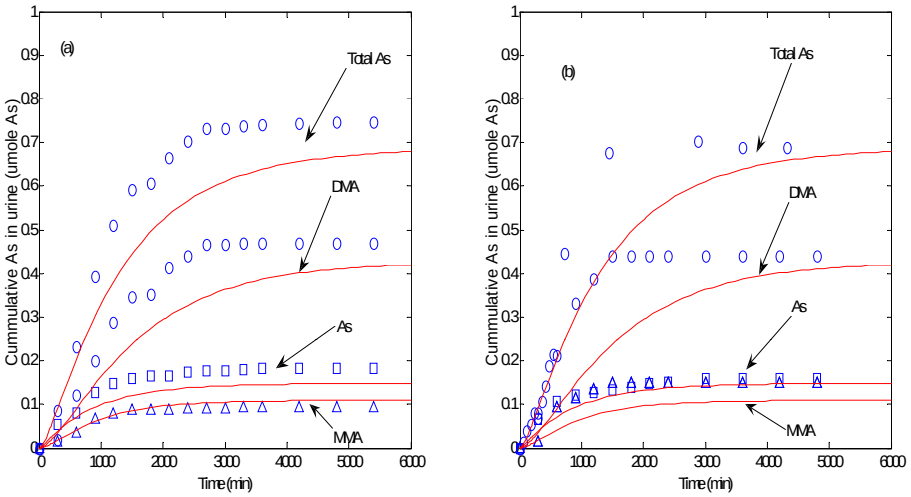
• A physiologically-based pharmacokinetic (PBPK) model was developed to estimate levels of arsenic and its metabolites in human tissues and urine after oral exposure to arsenate (AsV), arsenite (AsIII) or organoarsenical pesticides.

• The overall model consists of interconnected individual PBPK models for Asv, AsIII, monomethylarsenic acid (MMAv), and, dimethylarsenic acid (DMAv).

• Metabolism of inorganic arsenic in liver was described as a series of reduction and oxidative methylation steps incorporating the inhibitory influence of metabolites on methylation.

• Unique aspects of this model development effort are that it addresses parameter sensitivity and identifiably, utilizes human data whenever possible and incorporates new data on arsenic methylation.

Model Evaluation



What approaches are available for such extrapolations (e.g., PBPK modeling, uncertainty factors, probabilistic factors, linear/non-linear dose-response)?

Low Dose Linear/Nonlinear Approaches

Jeff Gift

(January 9, 2013)

EPA 2005 Cancer Guidelines

- Low dose linear – "slope is greater than zero at a dose of zero" (curvature is possible near observed data).
- Low dose nonlinear – "slope is zero at (and perhaps above) a dose of zero."
- "It is the Agency's long-standing science policy position that use of the linear low-dose extrapolation approach provides adequate public health conservatism in the absence of chemical-specific data indicating differential early-life sensitivity or when the mode of action is not mutagenic."

EPA 2005 Cancer Guidelines

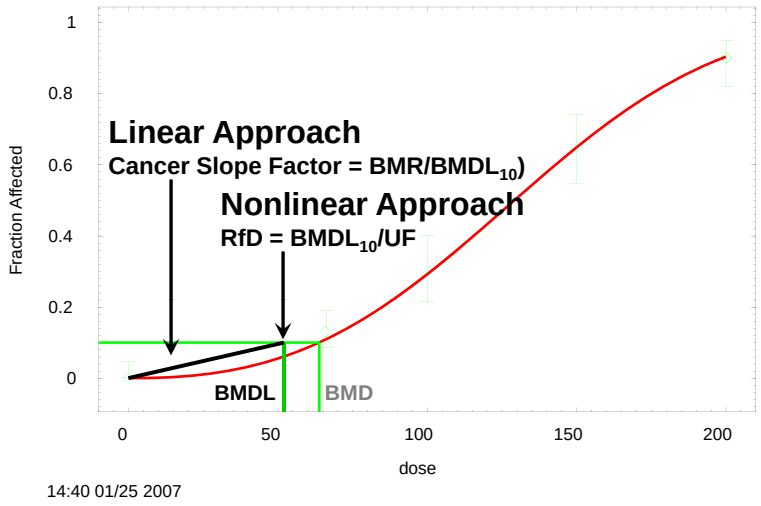
Linear Approach

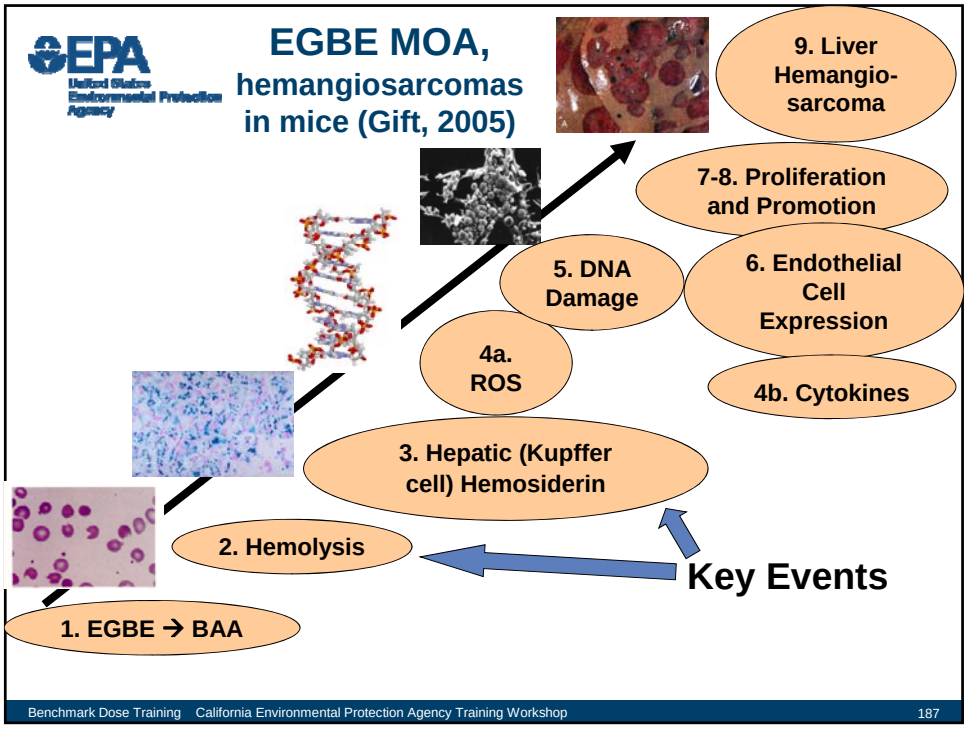
- MOA known, evidence for direct mutagenic activity
- MOA known, background doses of As (or other agents with a common MOA) near levels associated with key precursor events.
- MOA Unknown

Nonlinear Approach

- MOA known, evidence for nonlinearity at low doses (e.g., key precursor events with well defined nonlinear dose-response relationships) and no evidence for mutagenic or other activity consistent with linearity at low doses.

Linear vs NonLinear Approach





Arsenic History

- Following the commendations of NRC (2001), EPA (2010) used the linear approach because of "remaining uncertainties regarding the ultimate carcinogenic metabolites and whether mixtures of toxic metabolites interact at the site(s) of action."
- SAB (2007) concurred, indicating that:
  - As has the potential for a highly complex mode of action.
  - What is known about PK/PD properties of As not sufficient to support a specific nonlinear dose-response relationship.
  - Agreed with NRC (2001) recommendation for linear dose-response analysis of southwestern Taiwan population.

Benchmark Dose Training California Environmental Protection Agency Training Workshop 188

Questions/Considerations

Population Data

- Is population data useful for judging low dose shape given what is know about individual predispositions (e.g., from smoking, diet, genetic variants, bimethylation)?

MOA

- Does MOA evidence exists for nonlinearity of Arsenic cancer dose-responses (e.g., key nonlinear events)?

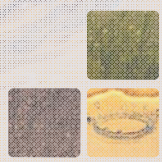
Arsenic's Low Dose Anticancer Activity

- Is arsenic's therapeutic effect on certain cancers (e.g., leukemia) relevant to its ability to initiate the subject (e.g., lung and bladder) cancers at low doses?

Extrapolation approaches

3.9 EPA has traditionally addressed uncertainty via the application of uncertainty factors. What other approaches may be available to address and transparently convey the impact of uncertainty on these extrapolations?

Lead Discussants: Ken Cantor, Weihsueh Chiu



3.9 Uncertainties in Extrapolation

Weihsueh Chiu

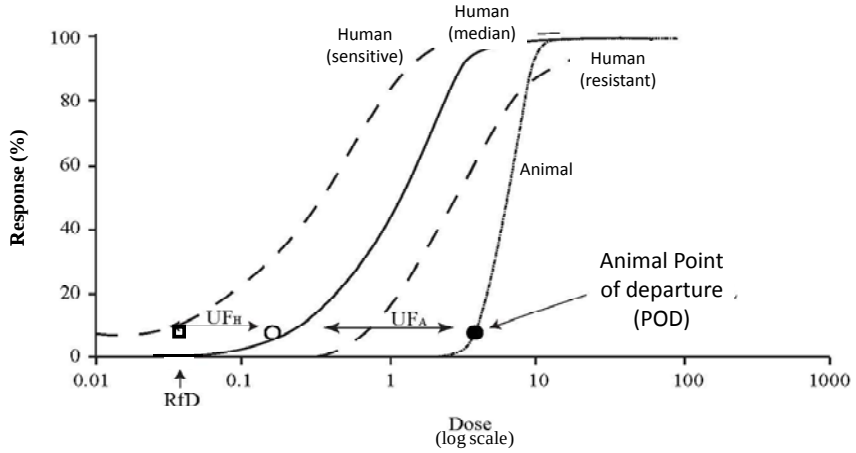
- Each extrapolation has associated uncertainty.
- EPA is moving towards separating out the "adjustment" component from the "uncertainty" component.
- For example, for interspecies extrapolation of oral doses:
  - $BW^{¾}$-scaling is considered a "central estimate" cross-species adjustment.
  - A remaining $10^{½}$-fold "Uncertainty Factor" addresses residual uncertainty.
  - Could also combine these probabilistically based on analyses of multiple chemicals & endpoints.

What options are available for the extrapolations needed for iAs?

- Uncertainties
  - Across dose metrics
  - In variability in susceptibility across population (including lifestages)
  - From precursor markers to disease endpoints
  - Below detectable effect levels
- Data (or lack thereof) to support different approaches
  - Fixed factors
  - Sensitivity analyses
  - Probabilistic factors
  - Other approaches?

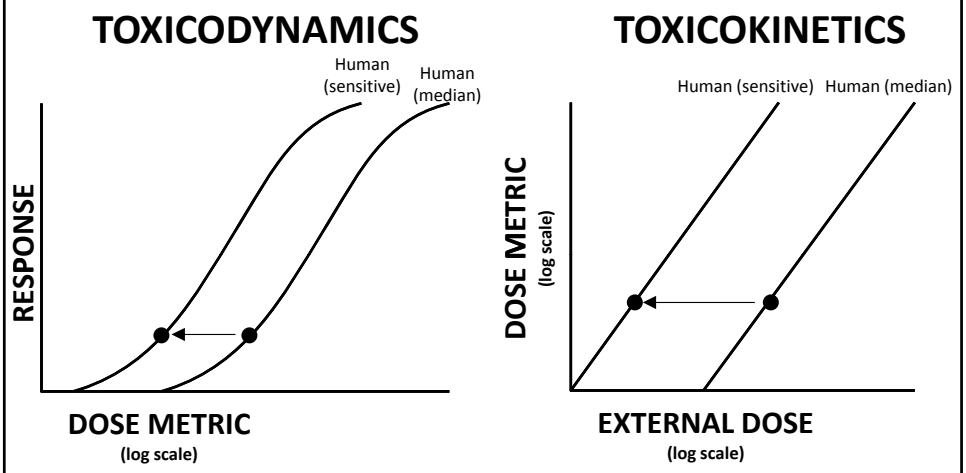
Extrapolations to derive a RfD are performed at a **fixed** level of response

Are there empirical data for iAs to support these extrapolations?



Disaggregating TK & TD requires an internal dose metric

Is such data available for iAs endpoints?



"Low dose extrapolation" is a bit of a misnomer, and is also related to uncertainty

- In the Benchmark Dose approach, we are fixing the response level (usually in the observable range), and estimating the associated dose.
  - In the range of observation, sensitivity to the model form generally less.
- Extrapolation is to lower response levels.
  - As the response level decreases below the observable range, the uncertainty increases dramatically, especially due to the assumed model form.
  - Linear extrapolation from the POD serves to define a bound of the uncertainty range.

Alternative approaches to "low-response extrapolation"

- Both avoid the "linear/non-linear" (false) dichotomy.
- Quantitatively characterize the extrapolation uncertainty
  - Acknowledges multiple dose-response shapes consistent with the data.
  - Should incorporate both parameter and model uncertainty.
- Use a dose-response characterization approach that does not require "low-response extrapolation."
  - Even for cancer, could fix the response at "X% increased risk" and derive an exposure limit that "protects" sensitive individuals from that level of risk.
  - But not useful for addressing some risk management needs (e.g., estimating overall population incidence).
  - For precursor endpoints, may shift debate to (false) dichotomy of "adaptive" versus "adverse."