EPA United States Environmental Protection Agency

Clarifications on Select Topics for the External Peer Review of EPA's Inorganic Arsenic (iAs) IRIS Assessment

Presentation for the Science Advisory Board Inorganic Arsenic Review Panel

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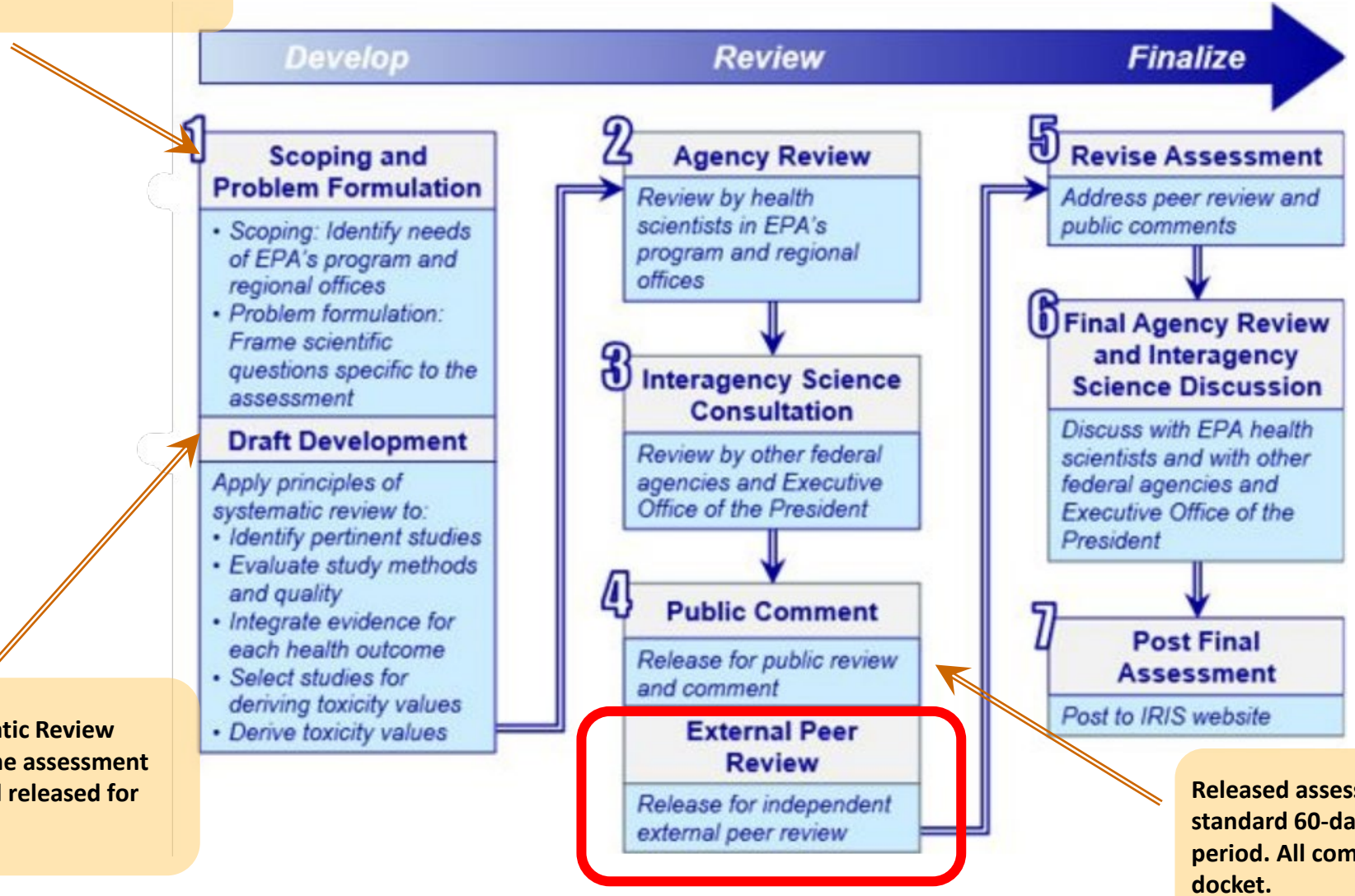
IRIS 7 Step Process

EPA held a public planning and scoping workshop



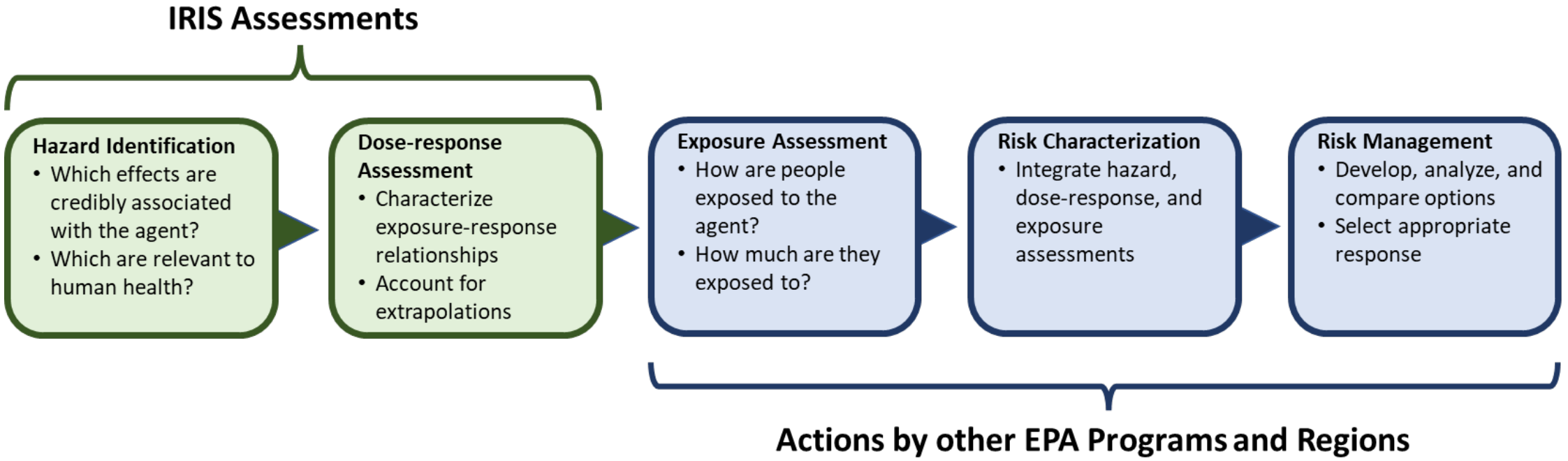
Released Systematic Review Protocols: <u>How</u> the assessment will be conducted released for public comment

Released assessment materials for standard 60-day public comment period. All comments added to docket.

Elements Performed by IRIS

IRIS assessments are systematic reviews of publicly available scientific studies on environmental agents, with 2 goals:

1. Qualitative → the nature of hazardous effects
2. Quantitative → the concentrations associated with effect induction



Public Opportunities during the iAs Assessment Development

- Nov 2012: EPA released Problem Formulation Materials for public comment
- Jan 2013: EPA hosted an iAs workshop to discuss planning and scoping
- Mar-Aug 2013: EPA hosted Arsenic Webinar Series
- June 2014: EPA hosted a public science meeting on preliminary materials (e.g., assessment plan, literature search strategy, literature search results, study evaluations)
- May 2019: EPA released an *Updated Problem Formulation and Systematic Review Protocol for the iAs IRIS Assessment* for public comment
- July 2019: NAS hosted public meeting to evaluate *Updated Problem Formulation and Systematic Review Protocol for the iAs IRIS Assessment*
- Oct 2023: EPA released the draft assessment for public comment
- Dec 2023: EPA released BMD Model Code and BMD Modeling Results for public comment

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Major Elements in Scoping and Problem Formulation

Focus on Human Data for Dose-Response

- NRC (2013) concluded that human data are expected to be the basis for dose-response analyses
- Using human data avoids uncertainty related to species extrapolation and relevance, and it allows for observations in human variability
- Human data are preferred as recommended in guidelines: EPA guidelines, technical, and methodological documents state that human data is preferred over animal data when epidemiologic studies of sufficient quality are available (EPA Cancer Guidelines, external NRC/NASEM reports on iAs)

Mode of Action (MOA) Analyses

- 2019 IRIS iAs Protocol: Considerable efforts were undertaken to conduct MOA analyses to determine whether the available MOA evidence can inform dose-response of health outcomes
  - Approach presented in current draft assessment supported during 2019 NASEM peer review
  - The majority of the committee [10 out of 11 members] agrees that *MOA information will not contribute directly to determining the shape of the dose-response curve based on epidemiological data…"*
- 2023 iAs Draft Appendix A of Updated Problem Formulation and Protocol
  - Analysis of modes of action common to multiple health effects
    - Reactive oxygen species (ROS) generation and oxidative stress responses, As(III) binding to thiol groups and inhibition of key enzymes, As(V) inhibition of oxidative phosphorylation, cell cycling and damage repair impairment, epigenetics, endocrine disruption, cytotoxicity and regenerative proliferation
    - ~5726 studies screened, 191 studies summarized in appendix A
  - Case study using bladder cancer to address feasibility of using MOA and mechanistic data to inform dose-response
    - Introduction of uncertainty due to in vitro studies conducted at high concentrations, assumptions of applicability of in vitro model systems to human response, ability to extrapolate in vitro concentrations to human exposure levels, and difficulty from extrapolating from rodent studies

MOA Approach Adheres to Cancer Guidelines

- The Cancer Guidelines state that MOA analyses are used to "address the question of human relevance of animal tumor responses; to address the differences in anticipated responses among humans…; and as the basis of decisions about the anticipated shape of the dose response relationship.":
  - Human relevance: iAs is a known carcinogen with a large amount of high-quality epidemiological evidence with carcinogenic risk to humans established by multiple organizations (NRC, ATSDR, IARC, WHO.)
  - Human variability: extensive information on risk modifiers is available in numerous epidemiological studies
  - Dose-response: there are abundant epidemiological studies of low-level exposure to inorganic arsenic

Health Effects Evaluation and Conclusions

Non-cancer effects

- Circulatory system (*evidence demonstrates*)
- Diabetes (*evidence demonstrates*)
- Pregnancy and birth outcomes (*evidence indicates*)
- Neurodevelopmental effects (*evidence indicates*)

Well-established cancer effects not re-evaluated*

- Bladder Cancer: *human carcinogen*
- Lung cancer: *human carcinogen*
  - Focus was on dose-response

Other outcomes considered to be out of scope

- Skin cancer, skin lesions, and immune effects (RRB comparison)
- renal cancer, liver cancer, and nonmalignant respiratory (moderate evidence and no benefit-cost need)

* Classification of *human carcinogen* for these cancer effects (NRC, ATSDR, IARC, WHO) was adopted

iAs Dose-Response Methodology

- Dose-response approach described in Allen et al. (2020a,b) and Appendix C

Environment International 142 (2020) 105810

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Systematic dose-response of environmental epidemiologic studies: Dose and response pre-analysis

Bruce Allen[a], Kan Shao[b], Kevin Hobbie[c], William Mendez Jr.[c], Janice S. Lee[d], Ila Cote[d], Ingrid Druwe[d], Jeff Gift[d,1], J. Allen Davis[e,*,1]

Environment International 145 (2020) 106111

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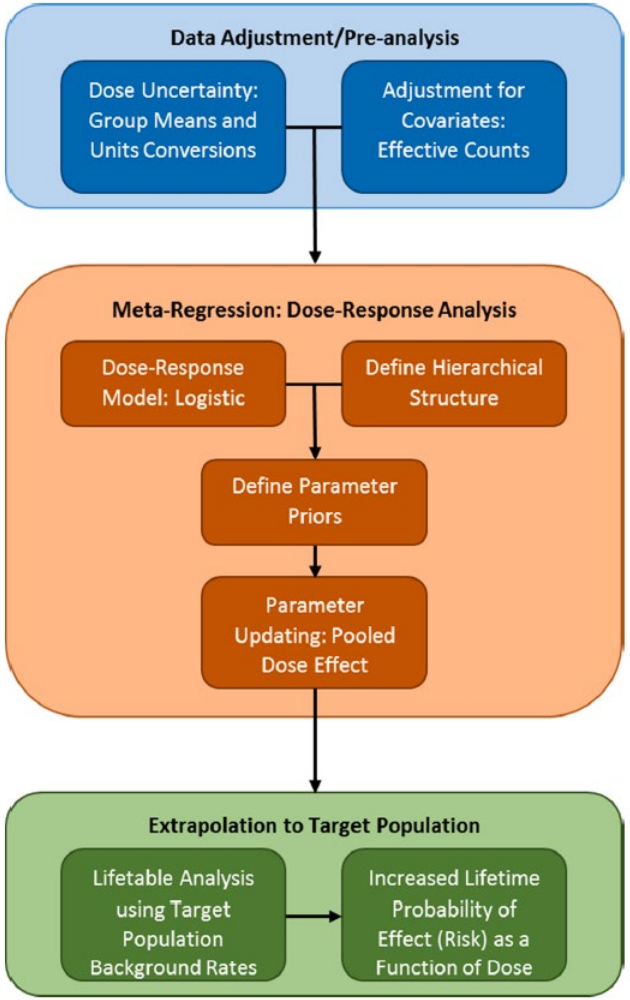
Bayesian hierarchical dose-response meta-analysis of epidemiological studies: Modeling and target population prediction methods

Bruce Allen[a], Kan Shao[b], Kevin Hobbie[c], William Mendez Jr.[c], Janice S. Lee[d], Ila Cote[d], Ingrid Druwe[d], Jeffrey S. Gift[d,1], J. Allen Davis[e,*,1]

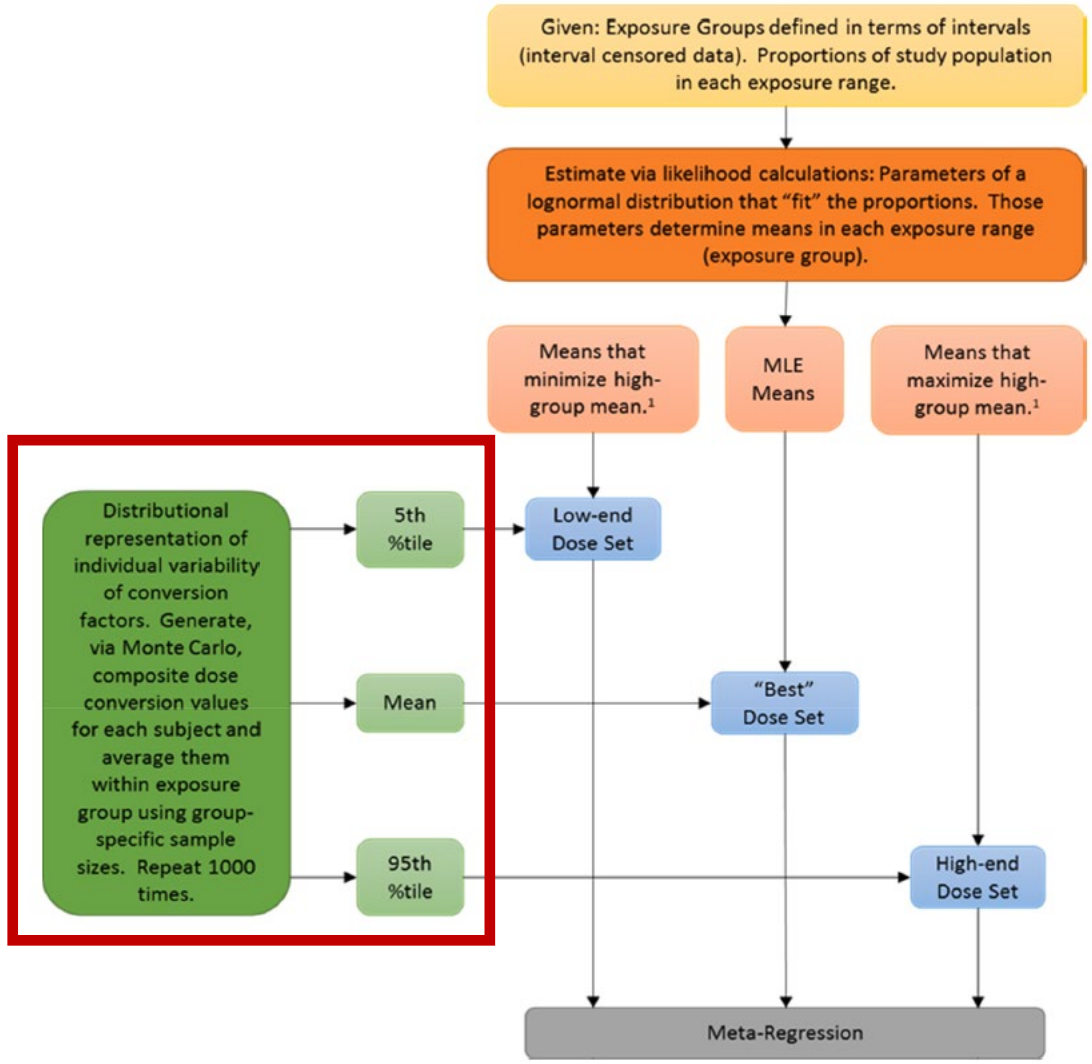


Dose Conversions

- Study-specific exposure metrics were converted into a unified daily intake metric ($^{\mu g}/_{kg-day}$)
- Exposure factors necessary for conversions identified from multiple sources
- For example, for a study reporting cumulative exposure ($^{\mu g}/_{L} \times years$), conversion was carried out as follows:

$$dose = DI + f \times (WCR \times WE) + (1 - f) \times (WCR \times LE)$$

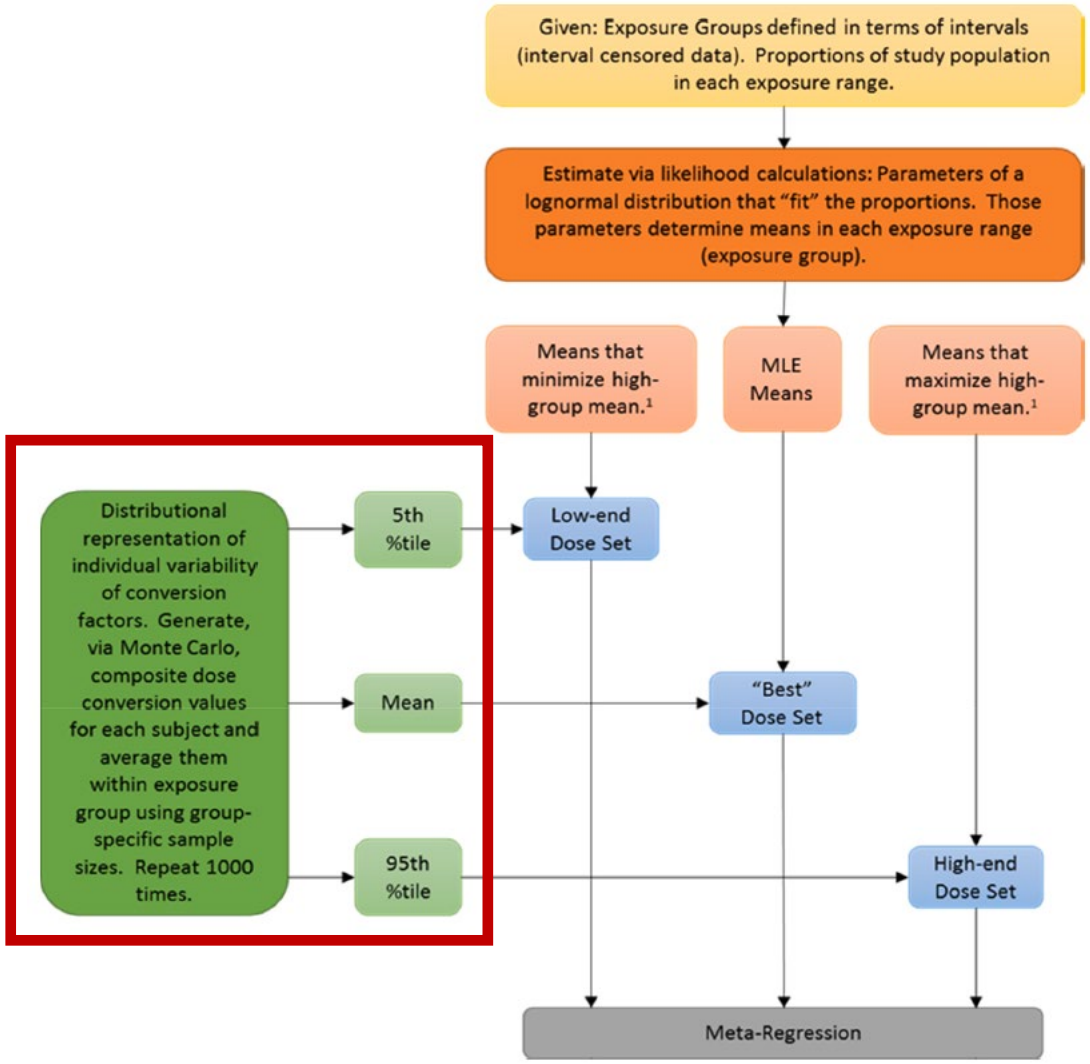
DI = dietary intake (daily µg/kg)
f = fraction of time spent consuming water
WCR = water consumption rate (L/kg)
WE = water concentration (µg/L)
LE = low end water concentration (µg/L)



Charge Question 4b

Dose Conversions

- Probability distributions were inferred for each conversion factor with parameters based on the reported means and standard deviations
- Monte Carlo (MC) analysis was conducted, sampling the assumed distributions N times, where N = study specific dose group size (truncated at N = 1000)
- Individual daily intake values averaged across samples
- This process was repeated 1000 times to generate a MC distribution where 5th percentile, mean, and 95th percentile values were used in subsequent dose-response analysis



Charge Question 4b

Dose Conversions – Urinary Biomarker Studies

- The El-Masri and Kenyon (2008, 2018) PBPK models provides the basis for assuming a 1:1 ratio between ug iAs/kg-day oral intake and µg total As/kg-day urinary excretion
- EPA assumed that urinary levels come from iAs intake, from drinking water consumption that varies across exposure groups and a study-specific estimate of dietary intake that is constant across exposure groups

Dose Conversions – Urinary Biomarker Studies

- EPA assumed that, for a given individual, the following equation and coefficients reported by Forni Ogna et al. (2015) and el Masri and Kenyon (2018) can be used:

$$\mu mol \frac{creatine}{kg - day} = \beta_0 + \beta_1 \times sex + \beta_2 \times BMI + \beta_3 \times age + \beta_4 \times age^2$$

- EPA estimated an oral ug iAs/kg-day dose for each individual in each study dose group using the above equation and study relevant distributions for height, body weight, age, sex and total arsenic urinary excretion
- The average of the simulated population ug iAs/kg-day exposure group estimates were estimated via MC sampling and then used as doses for the primary dose-response analyses

Bayesian Dose-Response Meta-Analysis (DRMA)

- Purpose is to combine data from multiple cohort and case-control studies
- EPA assumes the prospective likelihood is given by a logistic equation, with arsenic intake, X, as the explanatory variable

$$logit\{\Pr(D = 1|X\} = \alpha^* + \beta(X)$$

- Allows estimation of prospective likelihood from case-control studies (which are retrospective by definition) and thus inclusion with cohort studies in a DRMA
- Logistic model flexible enough to represent nonlinear "sigmoidal" dose-response relationships expected at a population level for toxicants with widely differing individual sensitivities (e.g., due to human heterogeneity and/or multiple iAs MOAs) (NRC, 2006, 2009, 2014)
- This type of sigmoidal shape is possible at the population level "even if the dose-response relationship has a clear threshold in a single rodent species or cell line" (NRC, 2014)

Bayesian Dose-Response Meta-Analysis (DRMA)

- Priors for hierarchical Bayesian modeling:
  - Normal distribution for individual studies
  - Gamma for pooled estimate (does not allow negative values, consistent with causal HI determination)
- Output of modeling is a set of study-specific logistic slopes and a pooled estimate of the logistic slope

Lin et al. (2018)	b	0.9097	0.005	0.3925	0.1828	0.6354	0.8945	1.1689	1.7216
	vlambda[1]	0.9019	0.0061	0.5295	0.1868	0.5089	0.8036	1.1805	2.2069
	vlambda[2]	1.4529	0.0098	0.844	0.3011	0.8322	1.3016	1.8961	3.5238
	vlambda[3]	0.6385	0.0044	0.3728	0.1306	0.3657	0.5684	0.8387	1.5605
	OR_RR[1]	1	NaN	0	1	1	1	1	1
	OR_RR[2]	1.2532	0.0015	0.121	1.0454	1.167	1.2429	1.3286	1.5197
	OR_RR[3]	1.7357	0.0052	0.4076	1.1113	1.4433	1.6763	1.9641	2.7027
Pooled β_mean		0.3138	0.0026	0.1956	0.0048	0.1654	0.3056	0.4407	0.7342
β_sigma		0.5804	0.0029	0.2118	0.2886	0.4355	0.5397	0.6831	1.09

Table 4-1. Prior parameter values for meta-regressions

Parameter	Prior distribution
β(i)[a]	Normal (β_mean, β_sigma)
β_mean	Gamma (a = 0.52, b = 1.12)
β_sigma	Half-Cauchy (scale = 5)

[a]β(i) is the dose coefficient for data set i.

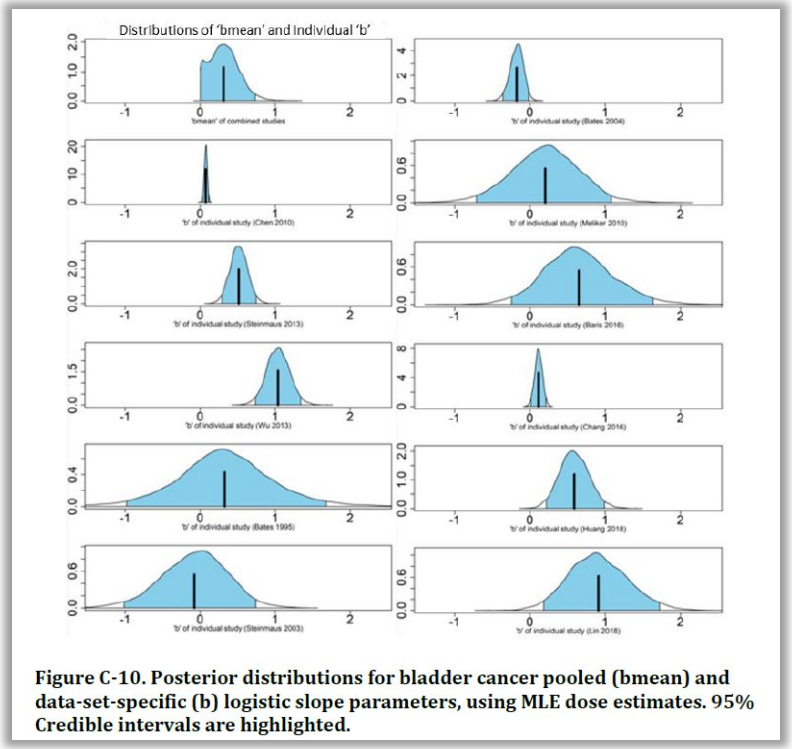


Figure C-10. Posterior distributions for bladder cancer pooled (bmean) and data-set-specific (b) logistic slope parameters, using MLE dose estimates. 95% Credible intervals are highlighted.

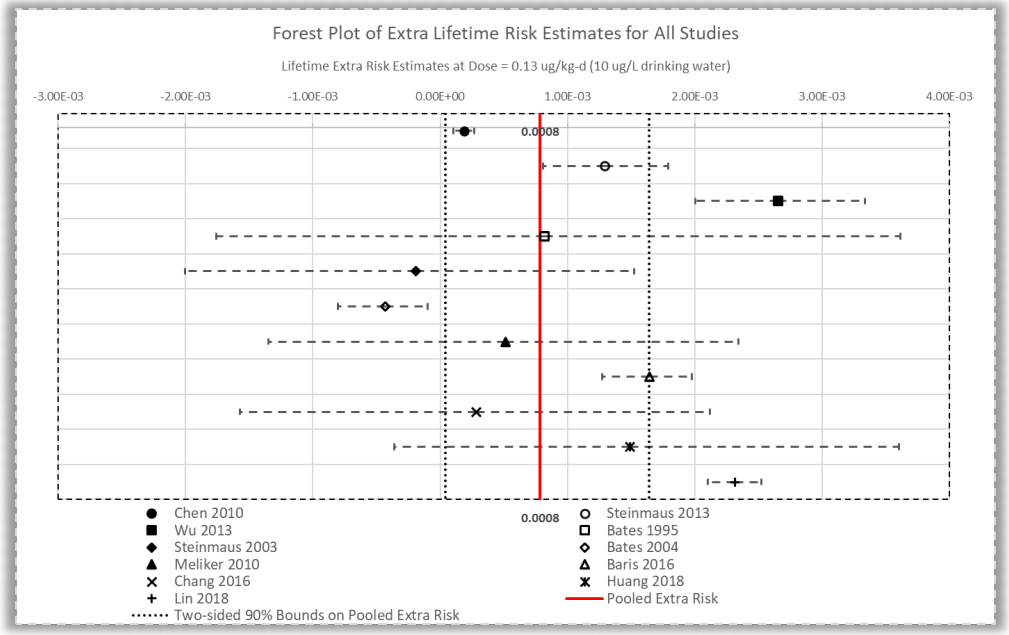
Charge Question 4b

Lifetable Analysis

- Age stratified morbidity and mortality data used to calculate lifetime probability of disease at assumed background dose
- Individual study and pooled logistic slopes then used to estimate lifetime probability of disease over a range of hypothetical doses
- Extra lifetime risk calculated as

$$ER = \frac{P(d) - P(0)}{1 - P(0)}$$

		b			extra risk; d = 0.13 ug/kg-d		
		5th	mean	95th	5th	mean	95th
Chen 2010	1	0.0411746	0.0752772	0.106897	1.02E-04	1.87E-04	2.66E-04
Steinmaus 2013	2	0.3238836	0.5148644	0.70916	8.11E-04	1.30E-03	1.79E-03
Wu 2013	3	0.7902154	1.0393566	1.296354	2.00E-03	2.65E-03	3.33E-03
Bates 1995	4	-0.723699	0.3279311	1.400362	-1.76E-03	8.21E-04	3.61E-03
Steinmaus 2003	5	-0.826559	-0.076506	0.604969	-2.01E-03	-1.89E-04	1.53E-03
Bates 2004	6	-0.327208	-0.175284	-0.04004	-8.05E-04	-4.33E-04	-9.92E-05
Meliker 2010	7	-0.551266	0.2049776	0.920782	-1.35E-03	5.11E-04	2.34E-03
Baris 2016	8	-0.083815	0.6510162	1.454691	-2.07E-04	1.64E-03	3.76E-03
Chang 2016	9	0.0296468	0.1151488	0.19821	7.36E-05	2.87E-04	4.94E-04
Huang 2018	10	0.2789166	0.5908449	0.917179	6.97E-04	1.49E-03	2.33E-03
Lin 2018	11	0.2928053	0.9096531	1.588773	7.32E-04	2.31E-03	4.12E-03
	12				0.00E+00	0.00E+00	0.00E+00
	pooled	0.0160786	0.3137993	0.650794	3.99E-05	7.85E-04	1.64E-03
					*10,000	0.399112	7.852797	16.43872



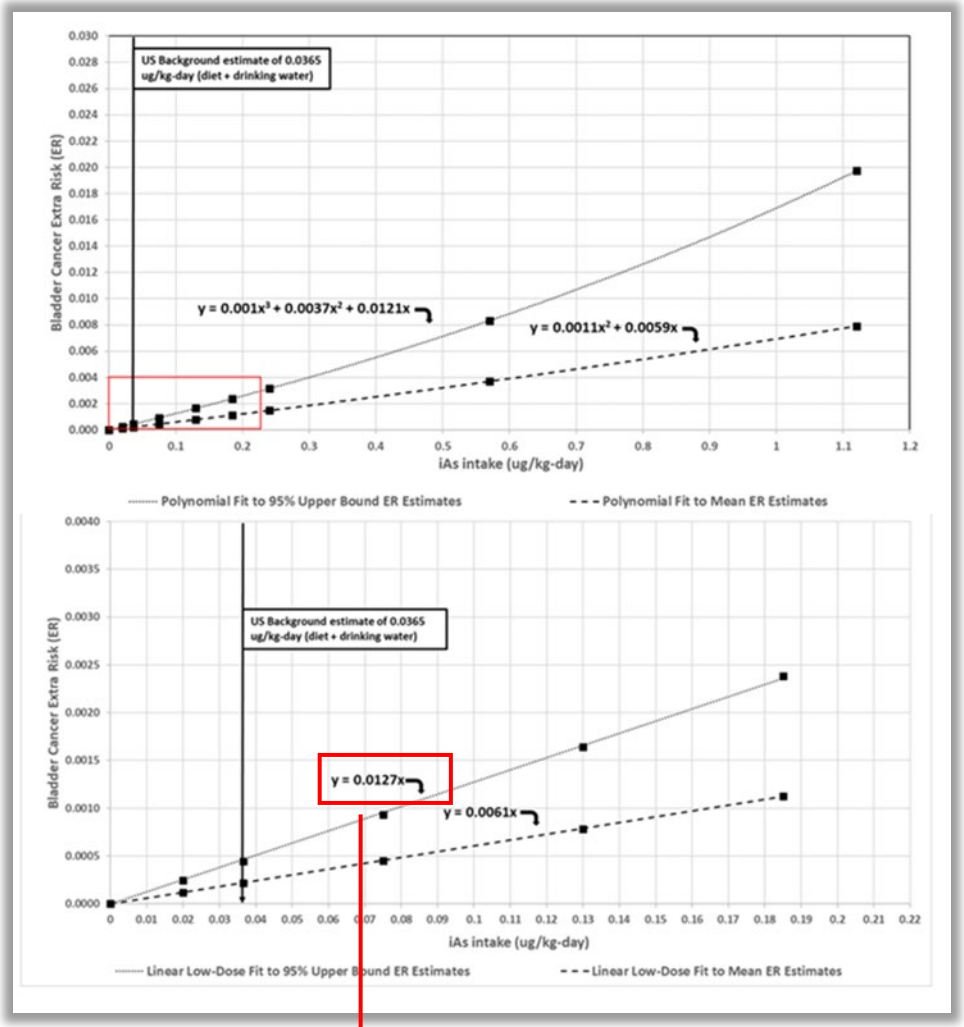
Cancer Dose-Response: Bladder cancer

- *Carcinogenic to Humans*
- Eleven epidemiologic studies in diverse populations used in DRMA

Table 4-3. Pooled meta-regression estimates of extra lifetime bladder cancer incidence risk (per 10,000) at various average daily iAs doses using MLE doses[a, b]

Extra lifetime risk estimates (per 10,000)[a]	Average daily inorganic arsenic dose (µg/kg-day)[b]								
	0	0.02	0.0365[b]	0.075	0.13	0.185	0.24	0.57	1.12
5th percentile	0	0.06	0.11	0.23	0.40	0.57	0.74	1.76	3.47
Mean	0	1.19	2.17	4.49	7.85	11.27	14.75	36.87	79.04
95th percentile	0	2.44	4.48	9.32	16.44	23.81	31.44	83.24	197.26

[a]Extra lifetime risks are presented as mean risk/10,000 with 5%–95% probabilities based on mean, 5% and 95% estimates of dose-response slopes.
[b]Doses used in EPA modeling. U.S. daily background dose is estimated at 0.0365 µg/kg, 0.02 µg/kg from diet, 0.0165 µg/kg from water and 0 µg/kg from air (see Section 4.3.4).



Lifetime Cancer Slope Factor (CSF): 1.27 × 10^{-2} $(\mu g/kg\text{-}d)^{-1}$

Charge Questions 5c,6

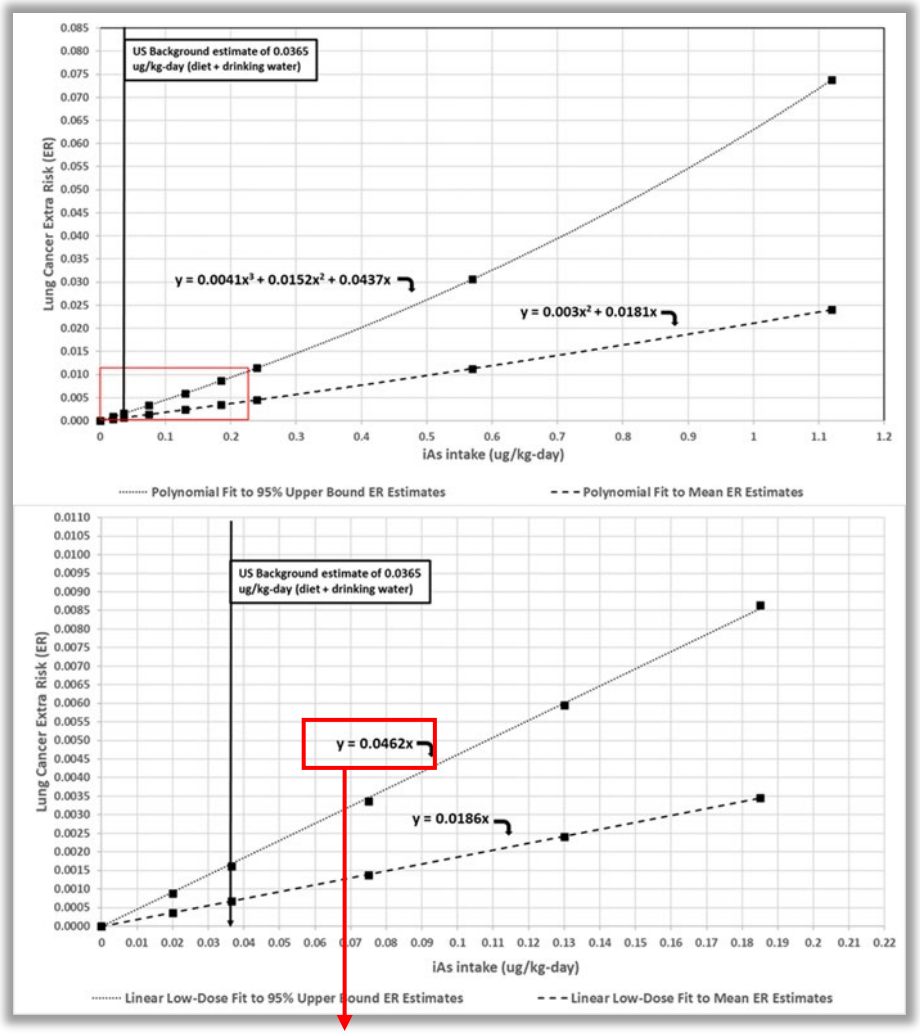
Cancer Dose-Response: Lung cancer

- *Carcinogenic to Humans*
- Eight epidemiologic studies (ten datasets) in diverse populations used in DRMA

Table 4-5. Pooled meta-regression estimates of extra lifetime lung cancer incidence risk (per 10,000) at various average daily iAs doses using MLE doses[a, b]

Extra lifetime risk estimates (per 10,000)[a]	Average daily inorganic arsenic dose (µg/kg-day)[b]								
	0	0.02	0.0365[b]	0.075	0.13	0.185	0.24	0.57	1.12
5th percentile	0	0.16	0.29	0.59	1.03	1.46	1.90	4.52	8.90
Mean	0	3.65	6.67	13.79	24.10	34.57	45.21	112.72	240.40
95th percentile	0	8.80	16.15	33.65	59.49	86.35	114.27	306.17	737.83

[a]Extra lifetime risks are presented as mean risk/10,000 with 5%–95% probabilities based on mean, 5% and 95% estimates of dose-response slopes.
[b]Doses used in EPA modeling. U.S. daily background dose is estimated at 0.0365 µg/kg, 0.02 µg/kg from diet, 0.0165 µg/kg from water and 0 µg/kg from air (see Section 4.3.4).



Lifetime Cancer Slope Factor (CSF): 4.62 × 10^{-2} (µg/kg-d)$^{-1}$

Charge Questions 5d,6

Cancer Dose-Response: Combined CSF

- A combined cancer slope factor was calculated to estimate risk of developing either bladder cancer or lung cancer separately, or both cancers combined
  - Individual tumor slope factors were assumed to be normally distributed
  - Combined CSF equaled the summed central tendency slopes + 1.645 * composite SD

Table ES-1. Toxicity values for cancer outcomes associated with inorganic arsenic exposure

Health Outcome	Hazard Descriptor	Cancer Slope factor (CSF) 1/(µg/kg-day) [a, b]
Bladder cancer	Accepted hazard	1.3E-2
Lung cancer		4.6E-2
Combined cancer risk		5.3E-2[c]

Charge Question 6

Noncancer Dose-Response Analyses

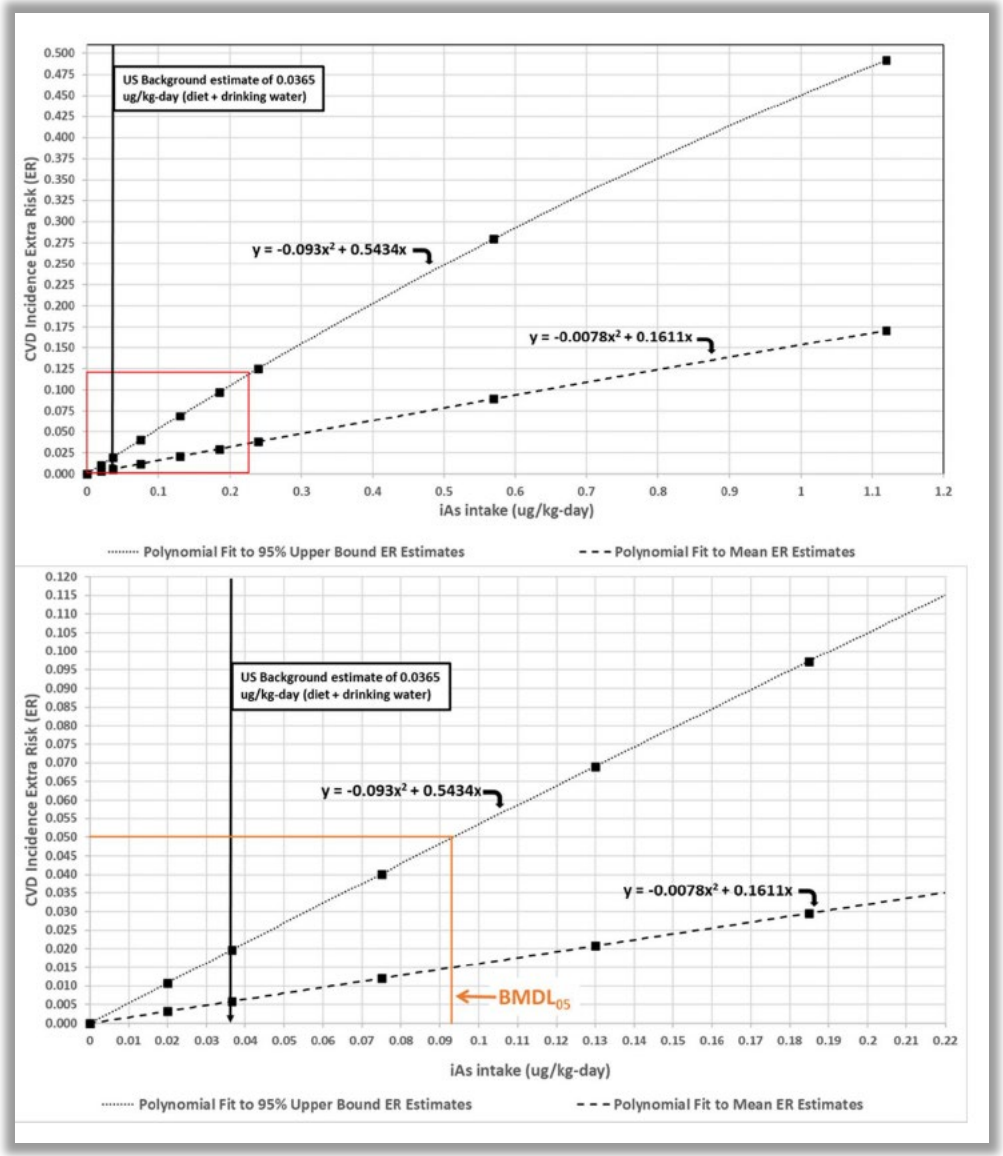
- Diseases of the circulatory system (DCS) modeled using Bayesian DRMA approach:
  - Cardiovascular disease (CVD) incidence: two studies
  - Ischemic heart disease (IHD) incidence: four studies
- Diabetes modeled using Bayesian DRMA approach: four studies
- Pregnancy outcomes (birth weight)
  - Single study: Kile et al. (2016)
- Neurodevelopmental effects not advanced primarily due to non-monotonicity in the exposure-response relationship in critical study (Wasserman et al., (2014)) (see Appendix C.2)

Non-Cancer Dose-Response: DCS

- **Evidence demonstrates** that iAs causes diseases of the circulatory system in humans based on *robust* evidence in humans

Table 4-10. Pooled meta-regression estimates of extra lifetime incidence risk (per 10,000) for DCS outcomes at various average daily iAs doses and estimated U.S. equivalent drinking water exposures above median U.S. doses and exposures using MLE doses [a, b]

Health outcome	Extra lifetime risk (per 10,000)	Average daily inorganic arsenic dose (µg/kg-d)[c]								
		0	0.02	0.0365[c]	0.075	0.13	0.185	0.24	0.57	1.12
CVD incidence	5%	0.00	0.31	0.57	1.18	2.04	2.90	3.77	8.95	17.58
	mean	0.00	32.16	58.65	120.31	208.00	295.24	382.03	892.96	1706.02
	95%	0.00	107.90	196.41	401.18	689.32	972.20	1249.70	2797.36	4918.66
IHD incidence	5%	0.00	0.55	1.00	2.05	3.55	5.05	6.55	15.55	38.39
	mean	0.00	27.34	49.93	102.74	178.41	254.34	330.53	792.25	1687.70
	95%	0.00	70.71	129.24	266.49	464.05	663.18	863.64	2081.04	4539.95
Fatal CVD	5%	0.00	0.11	0.20	0.42	0.72	1.03	1.34	3.17	6.24
	mean	0.00	7.83	14.31	29.50	51.41	73.54	95.89	234.91	485.77
	95%	0.00	22.81	41.82	86.85	152.87	220.89	290.97	756.19	1712.15
Fatal IHD	5%	0.00	0.08	0.15	0.32	0.55	0.78	1.01	2.40	4.72
	mean	0.00	6.59	12.07	24.99	43.76	62.16	82.50	208.70	455.88
	95%	0.00	17.75	32.68	68.51	122.23	173.16	239.15	676.91	1770.18



Lifetime extra risk plots for CVD incidence

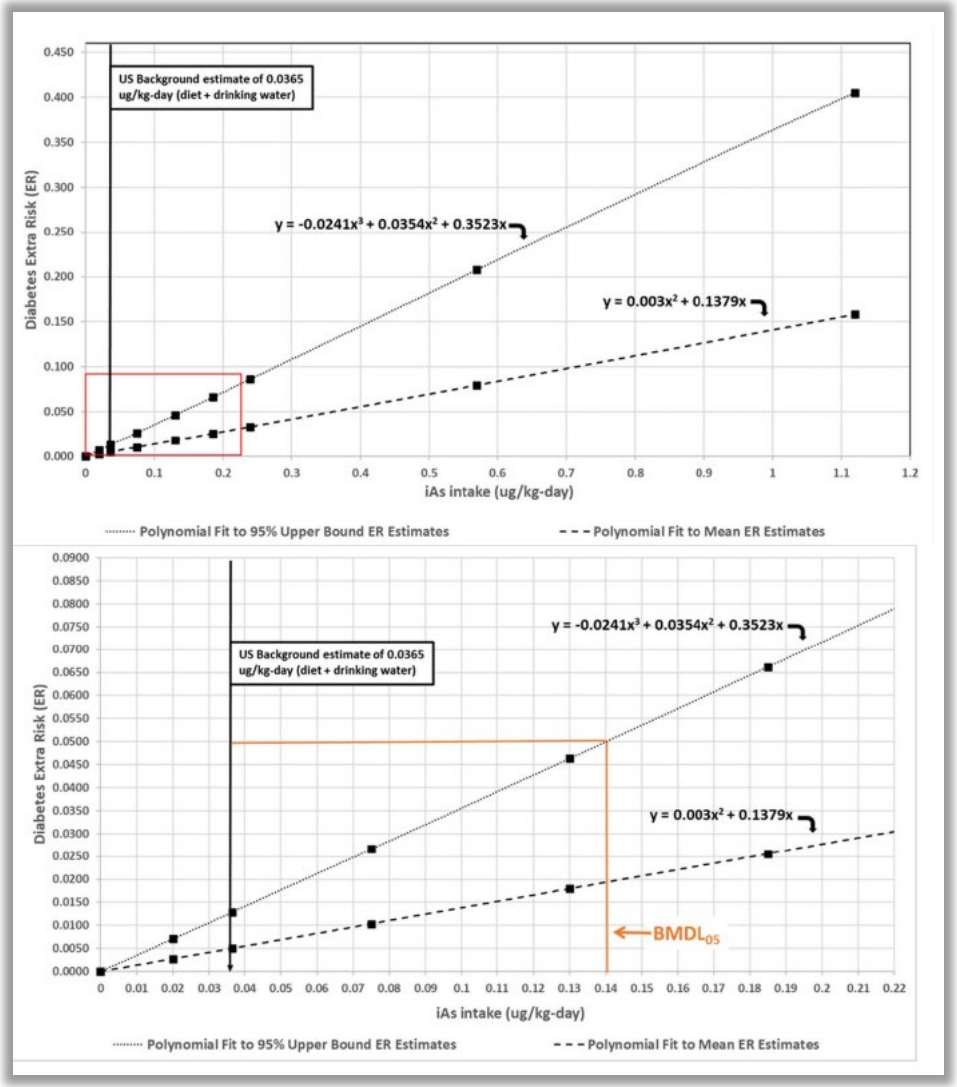
Charge Question 5a

Non-Cancer Dose-Response: Diabetes

- **Evidence demonstrates** that iAs causes diabetes in humans based on *robust* evidence in humans

Table 4-12. Pooled meta-regression estimates of extra lifetime diabetes incidence risk (per 10,000) at various average daily iAs doses and U.S. equivalent drinking water above median U.S. doses and exposures using MLE dose estimates [a, b]

Extra lifetime risk estimates (per 10,000)	Average daily inorganic arsenic dose (µg/kg-d)[c]								
	0	0.02	0.0365	0.075	0.13	0.185	0.24	0.57	1.12
5th percentile	0	1.72	3.14	6.45	11.18	15.91	20.64	49.06	96.51
Mean	0	27.49	50.20	103.30	179.38	255.73	332.34	796.62	1581.96
95th percentile	0	70.62	129.08	266.14	463.45	662.31	862.51	2078.32	4050.39



Lifetime extra risk plots for diabetes

Refence Dose (RfD) Derivations

- Dose-response was harmonized between cancer and non-cancer endpoints were possible
  - Probabilistic risk-at-a-dose values were provided for bladder cancer, lung cancer, DCS endpoints, and diabetes
- Reference doses (RfDs) were additionally provided in the assessment to met the needs of EPA Program and Regional offices
- Definition for the RfD:
  - *An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.*

RfD Derivation: CVD incidence

- Using CVD incidence as an example:
  - Lifetime background rate of disease = 0.70 at an assumed background exposure of 0.0365 µg/kg-day iAs
  - Using logistic slope (β mean) = 0.23, probability of response at zero dose, $P(0)$,was estimated to be 0.698
  - Given an extra risk of 5%, $P(d)$ estimated to be 0.713
  - Odds (i.e., $\frac{p}{1-p}$) at $P(0)$ and $P(d)$ calculated as 2.313 and 2.488 and the ratio as 1.075
  - $BMD = \frac{\ln(1.075)}{0.23} = 0.315$ µg/kg-day iAs
  - BMDL = 0.094 µg/kg-day iAs (calculated as above using 95th lower bound on β mean)

RfD Derivation: Birth Weight

- Kile et al. (2016) provided linear regression coefficient for the association between iAs in drinking water and low birth weight: -19.2 g (95% CI: -24.6,-13.7) per ln(µg/L) iAs in drinking water
- This regression coefficent was re-expressed in terms of per µg/L: -4.3 g (95% CI: -5.5, -3.1) per µg/L iAs in drinking water
- Then, given the average birth weight in the United States and the percentage of those births falling below the clinical definition of low birth weight (2500 g), the BMR was defined as 5% extra risk of falling below that cut-off
- Rearranging linear equation and solving for dose results in a BMD of 21.4 µg/L and a BMDL of 17.3 µg/L

Noncancer Oral Reference Dose

- **DCS and Diabetes**: candidate values based on $BMDL_{05}$s derived from the 95th upper bound on DRMA logistic slopes
- **Pregnancy outcomes (birth weight)**: candidate value based on $BMDL_{05}$ derived from the 95th upper bound on study-reported linear regression coefficient

Table 4-17. Points of departure (PODs) considered for use in deriving candidate RfDs for iAs

Health outcome	Study	Basis for point of departure	Point of departure (µg/kg-day)
CVD incidence	Meta-regression of 2 studies	$BMDL_{05}$	0.094[a]
IHD incidence	Meta-regression of 4 studies	$BMDL_{05}$	0.128[a]
Diabetes	Meta-regression of 4 studies	$BMDL_{05}$	0.127[a]
Birth weight	Kile et al., 2016	$BMDL_{05}$[b]	0.23

[a] $BMDL = \frac{\ln\left(odds\ at\ P(d) / odds\ at\ P(0)\right)}{95^{th} upper\ bound\ on\ mean(\beta\ mean)}$, where P(d) and P(0) are the probabilities associated with 5% and 0% extra risk, respectively, see details and modeling results in Appendix C, Section C.3.

Table 4-19. Candidate RfD values for inorganic arsenic (iAs)

Endpoint	POD (µg/kg-d)	UF_A	UF_H	UF_S	UF_L	UF_D	UF_C	Candidate value (µg/kg-d)
CVD Incidence	0.094	1	3	1	1	1	3	0.031
IHD Incidence	0.128	1	3	1	1	1	3	0.043
Diabetes	0.127	1	3	1	1	1	3	0.042
Birth weight	0.23	1	3	1	1	1	3	0.077

Overall RfD of 0.031 µg/kg-day based on CVD incidence

Charge Questions 8a,c

EPA United States Environmental Protection Agency

Thank you!

To the Scientific Advisory Board Inorganic Arsenic Panel and staff

Questions?

IRIS INTEGRATED RISK INFORMATION SYSTEM

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