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IRIS Toxicological Review of Inorganic Arsenic Supplemental Information

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TABLES

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ABBREVIATIONS

AC50	activity concentration at 50%
ADME	absorption, distribution, metabolism, and excretion
AIC	Akaike's information criterion
ALT	alanine aminotransferase
AOP	adverse outcome pathway
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMC	benchmark concentration
BMCL	benchmark concentration lower confidence limit
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
$BW^{3/4}$	body weight scaling to the 3/4 power
CA	chromosomal aberration
CAA	Clean Air Act
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service registry number
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CHO	Chinese hamster ovary (cell line cells)
CI	confidence interval
CL	confidence limit
CNS	central nervous system
COI	conflict of interest
CPAD	Chemical and Pollutant Assessment Division
CPHEA	Center for Public Health and Environmental Assessment
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
ER	extra risk
FDA	Food and Drug Administration
FEV_1	forced expiratory volume of 1 second
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GLP	Good Laboratory Practice
GSH	glutathione
GST	glutathione-*S*-transferase
HAP	hazardous air pollutant
HAWC	Health Assessment Workspace Collaborative
Hb/g-A	animal blood: gas partition coefficient
Hb/g-H	human blood: gas partition coefficient
HBCD	hexabromocyclododecane
HEC	human equivalent concentration
HED	human equivalent dose
HERO	Health and Environmental Research Online
i.p.	intraperitoneal
i.v.	intravenous
IAP	IRIS Assessment Plan
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
LOEL	lowest-observed-effect level
MeSH	Medical Subject Headings
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MOA	mode of action
MTD	maximum tolerated dose
NCI	National Cancer Institute
NMD	normalized mean difference
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
OAR	Office of Air and Radiation
OECD	Organisation for Economic Co-operation and Development
OLEM	Office of Land and Emergency Management
ORD	Office of Research and Development
OSF	oral slope factor
PBPK	physiologically based pharmacokinetic
PECO	populations, exposures, comparators, and outcomes
PK	pharmacokinetic
PND	postnatal day
POD	point of departure
$POD_{[ADJ]}$	duration-adjusted POD
QSAR	quantitative structure-activity relationship

RD	relative deviation
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	regional gas dose ratio
RNA	ribonucleic acid
ROBINS I	Risk of Bias in Nonrandomized Studies of Interventions
SAR	structure-activity relationship
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase, also known as AST
SGPT	serum glutamic pyruvic transaminase, also known as ALT
TK	toxicokinetics
TSCATS	Toxic Substances Control Act Test Submissions
TWA	time-weighted average
UF	uncertainty factor
UF_A	animal-to-human uncertainty factor
UF_D	database deficiencies uncertainty factor
UF_H	human variation uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
WOS	Web of Science

APPENDIX A. SYSTEMATIC REVIEW PROTOCOL FOR THE IRIS INORGANIC ARSENIC ASSESSMENT

In May 2019, the IRIS Program released an Updated Problem Formulation and Systematic Review Protocol for the IRIS Inorganic Arsenic Assessment for a 30-day public comment period. The updated protocol was then discussed with the National Academies of Sciences, Engineering, and Medicine (NASEM) at a public meeting on July 16, 2019. Following this public release, the systematic review protocol was updated taking NASEM recommendations and public comments into consideration, and can be found on the IRIS website at the following location (see the Downloads section: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=343951#tab-3).

APPENDIX B. STUDY EVALUATION: HAZARD EVALUATION

B.1. DRAFT (NTP, 2013) RISK OF BIAS QUESTIONS AND ASSESSMENT-SPECIFIC CLARIFICATIONS EXAMPLE

Table B-1. Risk of bias questions and rating guidelines—epidemiological studies

1. Was administered dose or exposure level adequately randomized?

++ OHAT:
Human Controlled Trial: There is direct evidence that subjects were allocated to any study group including controls using a method with a random component. Acceptable methods of randomization include referring to a random number table, using a computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice, or drawing of lots (Higgins and Green, 2011). Restricted randomization (e.g., blocked randomization) to ensure particular allocation ratios will be considered low risk of bias. Similarly, stratified randomization and minimization approaches that attempt to minimize imbalance between groups on important prognostic factors (e.g., body weight) will be considered acceptable.
Assessment-specific Clarification:
None.

\+ OHAT:
Human Controlled Trial: There is indirect evidence that subjects were allocated to study groups using a method with a random component (i.e., authors state that allocation was random, without description of the method used) **OR** it is deemed that allocation without a clearly random component during the study would not appreciably bias results. For example, approaches such as biased coin or urn randomization, replacement randomization, mixed randomization, and maximal randomization may require consultation with a statistician to determine risk of bias rating (Higgins and Green, 2011).
Assessment-specific Clarification:
None.

– **OHAT:**
Human Controlled Trial: There is indirect evidence that subjects were allocated to study groups using a method with a non-random component **OR** there is insufficient information provided about how subjects were allocated to study groups. Non-random allocation methods may be systematic but have the potential to allow participants or researchers to anticipate the allocation to study groups. Such "quasi-random" methods include alternation, assignment based on date of birth, case record number, or date of presentation to study (Higgins and Green, 2011).
Assessment-specific Clarification:
None.

–– **OHAT:**
Human Controlled Trial: There is direct evidence that subjects were allocated to study groups using a non-random method including judgment of the clinician, preference of the participant, the results of a laboratory test or a series of tests, or availability of the intervention (Higgins and Green, 2011).
Assessment-specific Clarification:
None.

2. Was allocation to study groups adequately concealed?

++ **OHAT:**
Human Controlled Trial: There is direct evidence that at the time of recruitment the research personnel and subjects did not know what study group subjects were allocated to, and it is unlikely that they could have broken the blinding of allocation until after recruitment was complete and irrevocable. Methods used to ensure allocation concealment include central allocation (including telephone, web-based and pharmacy-controlled randomization); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes; or equivalent methods.
Assessment-specific Clarification:
None.

\+ **OHAT:**
Human Controlled Trial: There is indirect evidence that the research personnel and subjects did not know what study group subjects were allocated to **OR** it is deemed that lack of adequate allocation concealment would not appreciably bias results.
Assessment-specific Clarification:
None.

− **OHAT:**
Human Controlled Trial: There is indirect evidence that at the time of recruitment it was possible for the research personnel and subjects to know what study group subjects were allocated to, or it is likely that they could have broken the blinding of allocation before recruitment was complete and irrevocable **OR** there is insufficient information provided about allocation to study groups.
Note: Inadequate methods include using an open random allocation schedule (e.g., a list of random numbers), assignment envelopes used without appropriate safeguards (e.g., if envelopes were unsealed or nonopaque or not sequentially numbered), alternation or rotation; date of birth; case record number; or any other explicitly unconcealed procedure. For example, if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque, and sealed.
Assessment-specific Clarification:
None.

−− **OHAT:**
Human Controlled Trial: There is direct evidence that at the time of recruitment it was possible for the research personnel and subjects to know what study group subjects were allocated to, or it is likely that they could have broken the blinding of allocation before recruitment was complete and irrevocable.
Assessment-specific Clarification:
None.

3. Were the comparison groups appropriate?

++ **OHAT:**

Cohort, Cross-sectional: There is direct evidence that subjects (both exposed and non-exposed) were similar (e.g., recruited from the same eligible population, recruited with the same method of ascertainment using the same inclusion and exclusion criteria, and were of similar age and health status), recruited within the same time frame, and had the similar participation/response rates.

Case-Control: There is direct evidence that cases and controls were similar (e.g., recruited from the same eligible population including being of similar age, gender, ethnicity, and eligibility criteria other than outcome of interest as appropriate), recruited within the same time frame, and controls are described as having no history of the outcome. Note: A study will be considered low risk of bias if baseline characteristics of groups differed, but these differences were considered as potential confounding or stratification variables (see question #4).

Assessment-specific Clarification:

Ecological and Semi-individual: For ecological studies, a table of information or text on potential differences in characteristics that could bias results is provided, and these characteristics are adjusted for as potential confounders. There is direct evidence that subjects (both exposure groups and referent groups) were similar (e.g., of similar geographic region, ethnicity, socioeconomic status, etc.) **OR** baseline characteristics of groups differed but these differences were considered as potential confounding or stratification variables in analyses (see question #4).

Additional Guidance:

Comparison groups selected adequately. Study provides table of subject characteristics by exposure levels and/or by case status. Cross-sectional studies can be considered low risk of bias if a general table of subject characteristics is provided, and analyses are adjusted for confounders.

\+ **OHAT:**

Cohort, Cross-sectional: There is indirect evidence that subjects (both exposed and non-exposed) were similar (e.g., recruited from the same eligible population, recruited with the same method of ascertainment using the same inclusion and exclusion criteria, and were of similar age and health status), recruited within the same time frame, and had the similar participation/response rates **OR** differences between groups would not appreciably bias results.

Case-Control: There is indirect evidence that cases and controls were similar (e.g., recruited from the same eligible population, recruited with the same method of ascertainment using the same inclusion and exclusion criteria, and were of similar age), recruited within the same time frame, and controls are described as having no history of the outcome **OR** differences between cases and controls would not appreciably bias results.

Assessment-specific Clarification:

Ecological and Semi-individual: There is indirect evidence that subjects (both exposure groups and referent groups) were similar (e.g., of similar geographic region, ethnicity, socioeconomic status) **OR** differences between groups would not appreciably bias results.

Additional Guidance:

Recruitment methods stated to be similar, but no table of information or text provided on potential differences in study subjects' characteristics that could bias results, **OR** no breakdown of subject characteristics by exposure group (or by case status) to display potential differences. For ecological studies, groups are stated to be similar, but no table of information or text is provided on potential characteristic differences that could bias results.

- **OHAT:**
  Cohort, Cross-sectional: There is indirect evidence that subjects (both exposed and non-exposed) were not similar, recruited within very different time frames, or had very different participation/response rates **OR** there is insufficient information provided about the comparison group including a different rate of non-response without an explanation.
  Case-Control: There is direct evidence that controls were drawn from a very dissimilar population than cases or recruited within very different time frames **OR** there is insufficient information provided about the appropriateness of controls including rate of response reported for cases only.
  Assessment-specific Clarification:
  Ecological and Semi-individual: There is indirect evidence that subjects (both exposure groups and referent groups) were not similar (e.g., of similar geographic region, ethnicity, socioeconomic status) **OR** there is insufficient information provided about the appropriateness of comparison groups.

- **OHAT:**
  Cohort, Cross-sectional: There is direct evidence that subjects (both exposed and non-exposed) were not similar, recruited within very different time frames, or had very different participation/response rates.
  Case-Control: There is direct evidence that controls were drawn from a very dissimilar population than cases or recruited within very different time frames.
  Assessment-specific Clarification:
  Ecological and Semi-individual: There is direct evidence that subjects (both exposure groups and referent groups) were not similar (e.g., of similar geographic region, ethnicity, socioeconomic status).
  Additional Guidance:
  At least one known difference between the groups was not accounted for (e.g., the study authors acknowledged that the groups were different with respect to a variable that is a potential confounder not considered in the analysis) **OR** recruitment methods were very different (e.g., recruitment completed during different time frames, different criteria were used for recruitment).

4. Did the study design or analysis account for important confounding and modifying variables?

++ **OHAT:**

Human Controlled Trial, Cohort, Cross-sectional, Case Series/Report: There is direct evidence that appropriate adjustments or explicit considerations were made for primary covariates and confounders in the final analyses through the use of statistical models to reduce research-specific bias including standardization, case matching, adjustment in multivariate model, stratification, propensity scoring, or other methods were appropriately justified. Acceptable consideration of appropriate adjustment factors includes cases when the factor is not included in the final adjustment model because the author conducted analyses that indicated it did not need to be included.

Case-Control: There is direct evidence that appropriate adjustments were made for primary covariates and confounders in the final analyses through the use of statistical models to reduce research specific bias including standardization, matching of cases and controls, adjustment in multivariate model, stratification, propensity scoring, or other methods were appropriately justified.

Assessment-specific Clarification:

Ecological and Semi-individual: There is direct evidence that appropriate adjustments or explicit considerations were made for covariates and confounders in the final analyses through the use of statistical models (e.g., standardization, multivariate adjustment). Acceptable consideration of appropriate adjustment factors includes cases when the factor is not included in the final adjustment model because the author conducted analyses that indicated it did not need to be included.

Additional Guidance:

Study adjusted for or addressed important potential confounders. Age, gender, education, and socioeconomic status are potential confounders that need to be addressed and considered in the study design or analyses. In addition, specific important confounders for this assessment depend on the health outcome and include smoking for lung cancer, sun exposure for skin lesions, and alcohol drinking for hepatic outcomes. Other confounders might also be judged important for certain health outcomes. A low risk of bias rating was assigned for this question if potential confounders deemed important were adequately addressed (e.g., distribution of variables was compared between groups, and there was no statistically significant difference).

\+ **OHAT:**

Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/Report: There is indirect evidence that appropriate adjustments were made for most primary covariates and confounders **OR** it is deemed that not considering or only considering a partial list of covariates or confounders in the final analyses would not appreciably bias results.

Assessment-specific Clarification:

Ecological and Semi-individual: There is indirect evidence that appropriate adjustments were made for most covariates and confounders **OR** it is deemed that not considering or only considering a partial list of covariates or confounders in the final analyses would not appreciably bias results.

Additional Guidance:

Study adjusted only for some important potential confounders (e.g., sex and age), but it is likely that other confounders were present and not addressed (i.e., minimal number of confounders addressed).

– **OHAT:**
Human Controlled Trial, Cohort, Cross-sectional, Case Series/Report: There is indirect evidence that the distribution of primary covariates and known confounders differed between the groups and was not appropriately adjusted for in the final analyses **OR** there is insufficient information provided about the distribution of known confounders.
Case-Control: There is indirect evidence that the distribution of primary covariates and known confounders differed between cases and controls and was not investigated further **OR** there is insufficient information provided about the distribution of known confounders in cases and controls.
Assessment-specific Clarification:
Ecological and Semi-individual: There is indirect evidence that the distribution of covariates and known confounders differed between the groups and was not appropriately adjusted for in the final analyses **OR** there is insufficient information provided about the distribution of known confounders.
Additional Guidance:
Design or analysis did not adjust for important potential confounders. Adjustments were made for some potential confounders, but at least one major confounder was not addressed (e.g., no adjustment for smoking when evaluating lung cancer, no adjustment for sun exposure when evaluating skin cancer).

–– **OHAT:**
Human Controlled Trial, Cohort, Cross-sectional, Case Series/Report: There is direct evidence that the distribution of primary covariates and known confounders differed between the groups, confounding was demonstrated, and was not appropriately adjusted for in the final analyses.
Case-Control: There is direct evidence that the distribution of primary covariates and known confounders differed between cases and controls, confounding was demonstrated, but was not appropriately adjusted for in the final analyses.
Assessment-specific Clarification:
Ecological and Semi-individual: Same as OHAT Human Controlled Trial, Cohort, Cross-sectional, and Case Series/report criteria.
Additional Guidance:
None.

5. Did researchers adjust or control for other exposures that are anticipated to bias results?

++ **OHAT:**
Human Controlled Trial: There is direct evidence that other exposures anticipated to bias results were not present or were appropriately adjusted for.
Cohort, Case- Control, Cross-sectional, Case Series/Report: There is direct evidence that other exposures anticipated to bias results were not present or were appropriately adjusted for. For occupational studies or studies of contaminated sites, other chemical exposures known to be associated with those settings were appropriately considered.
Assessment-specific Clarification:
Ecological and Semi-individual: Same as OHAT Human Controlled Trial criteria.
Additional Guidance:
Researchers adjusted for other chemicals or accounted for occupational exposures likely to be associated with the outcome.

\+ **OHAT:**
Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/Report: There is indirect evidence that other co-exposures anticipated to bias results were not present or were appropriately adjusted for **OR** it is deemed that co-exposures present would not appreciably bias results. Note, as discussed above, this includes insufficient information provided on co-exposures in general population studies.
Assessment-specific Clarification:
Ecological and Semi-individual: Same as OHAT criteria.
Additional Guidance:
No evidence that co-exposures were addressed as confounders, but other specific chemicals or occupational exposures were addressed.

− **OHAT:**
Human Controlled Trial: There is indirect evidence that the control group may have received the treatment or there was an unbalanced provision of additional co-exposures, which were not appropriately adjusted for.
Cohort, Cross-sectional, Case Series/Report: There is indirect evidence that there was an unbalanced provision of additional co-exposures across the primary study groups, which were not appropriately adjusted for **OR** there is insufficient information provided about co-exposures in occupational studies or studies of contaminated sites where high exposures to other chemical exposures would have been reasonably anticipated.
Case-Control: There is indirect evidence that there was an unbalanced provision of additional co-exposures across cases and controls, which were not appropriately adjusted for **OR** there is insufficient information provided about co-exposures in occupational studies or studies of contaminated sites where high exposures to other chemical exposures would have been reasonably anticipated.
Assessment-specific Clarification:
Ecological and Semi-individual: There is indirect evidence that there was an unbalanced provision of additional co-exposures, which were not appropriately adjusted for **OR** there is insufficient information provided about co-exposures in studies of contaminated sites where high exposures to other chemical exposures would have been reasonably anticipated.
Additional Guidance:
There is evidence that co-exposures might not have been addressed. Examples include a study population with farmers and/or other types of workers but occupational co-exposures (e.g., to pesticides) not addressed; or a study with known co-exposures, but the relevance of the co-exposure to arsenic effects is unknown, or it is not clear if other compounds were adjusted for in the analyses.

−− **OHAT:**
Human Controlled Trial: There is direct evidence that the control group received the treatment or there was an unbalanced provision of additional co-exposures, which were not appropriately adjusted for.
Cohort, Cross-sectional, Case Series/Report: There is direct evidence that there was an unbalanced provision of additional co-exposures across the primary study groups, which were not appropriately adjusted for.
Case-Control: There is direct evidence that there was an unbalanced provision of additional co-exposures across cases and controls, which were not appropriately adjusted for.
Assessment-specific Clarification:
Ecological and Semi-individual: There is direct evidence that there was an unbalanced provision of additional co-exposures, which were not appropriately adjusted for.
Additional Guidance:
Known differential exposure to other chemical/pollutant also associated with the health outcome of interest occurred with arsenic, and exposure was not addressed by study authors. An example is a study of copper smelter workers where the study authors either (a) list other chemicals likely to be associated with the health outcome that the subjects were exposed to, or (b) provide levels of the other compounds, **AND** there were statistically significant differences related to the arsenic exposure that were not addressed. Such differences might have resulted from differential exposure to another compound or arsenic; thus, it cannot be determined which exposure impacted the results.

6. Were experimental conditions identical across study groups?

NA NA

7. Did researchers adhere to the protocol?

++ **OHAT:**
Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/Report: There is direct evidence that there were no deviations from the protocol (i.e., the study report explicitly provides this level of detail).
Assessment-specific Clarification:
Ecological and Semi-individual: Same as OHAT criteria.
Additional Guidance:
None.

\+ **OHAT:**
Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/Report: There is indirect evidence that there were no deviations from the protocol (i.e., authors did not report any deviations) **OR** deviations from the protocol are described and it is deemed that they would not appreciably bias results.
Assessment-specific Clarification:
Ecological and Semi-individual: Same as OHAT criteria.
Additional Guidance:
Taking into consideration typical reporting practices, it seems unlikely that deviations from the protocol will be explicitly reported in most studies. Thus, unless stated otherwise by the authors (i.e., evidence of deviation is reported), or it is clear from the study report that deviations from the planned approach occurred, assume that no deviations occurred. It is anticipated that this approach will result in a rating of "probably low risk of bias" (+) for most studies. If there are deviations, the rating reflects how the deviations changed direction, magnitude, and/or significance of the results.

− **OHAT:**
Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/report: There is indirect evidence that there were large deviations from the protocol as outlined in the methods or study report.
Assessment-specific Clarification:
Ecological and Semi-individual: Same as OHAT criteria.
Additional Guidance:
None.

−− **OHAT:**
Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/Report: There is direct evidence that there were large deviations from the protocol as outlined in the methods or study report.
Assessment-specific Clarification:
Ecological and Semi-individual: Same as OHAT criteria.
Additional Guidance:
None.

8. Were the research personnel and human subjects blinded to the study group during the study?

++ **OHAT:**
Human Controlled Trial: There is direct evidence that the subjects and research personnel were adequately blinded to study group, and it is unlikely that they could have broken the blinding during the study. Methods used to ensure blinding include central allocation, sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes; or equivalent methods.
Assessment-specific Clarification:
None.

\+ **OHAT:**
Human Controlled Trial: There is indirect evidence that the research personnel and subjects were adequately blinded to study group, and it is unlikely that they could have broken the blinding during the study, **OR** it is deemed that lack of adequate blinding during the study would not appreciably bias results.
Assessment-specific Clarification:
None.

− **OHAT:**
Human Controlled Trial: There is indirect evidence that it was possible for research personnel or subjects to infer the study group, **OR** there is insufficient information provided about blinding of study group. Inadequate methods include using an open random allocation schedule (e.g., a list of random numbers), assignment envelopes used without appropriate safeguards (e.g., if envelopes were unsealed or nonopaque or not sequentially numbered), alternation or rotation; date of birth; case record number; or any other explicitly unconcealed procedure. For example, if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.
Assessment-specific Clarification:
None.

−− **OHAT:**
Human Controlled Trial: There is direct evidence for lack of adequate blinding of the study group including no blinding or incomplete blinding of research personnel and subjects. For some treatments, such as behavioral interventions, allocation to study groups cannot be concealed.
Assessment-specific Clarification:
None.

9. Were outcome data complete without attrition or exclusion from analysis?

++ **OHAT:**

Human Controlled Trial: There is direct evidence that there was no loss of subjects during the study and outcome data were complete **OR** loss of subjects (i.e., incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from a study. Review authors should be confident that the participants included in the analysis are exactly those who were randomized into the trial. Acceptable handling of subject attrition includes: very little missing outcome data [less than 10% in each group (Genaidy et al., 2007)]; reasons for missing subjects unlikely to be related to outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across study groups, with similar reasons for missing data across groups **OR** analyses (such as intention-to-treat analysis) in which missing data have been imputed using appropriate methods (ensuring that the characteristics of subjects lost to follow up or with unavailable records are described in an identical way and are not significantly different from those of the study participants).

NOTE: Participants randomized but subsequently found not to be eligible need not always be considered as having missing outcome data (Higgins and Green, 2011). Cohort: There is direct evidence that loss of subjects (i.e., incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from a study. Acceptable handling of subject attrition includes: very little missing outcome data; reasons for missing subjects unlikely to be related to outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across study groups, with similar reasons for missing data across groups; **OR** missing data have been imputed using appropriate methods, **AND** characteristics of subjects lost to follow up or with unavailable records are described in an identical way and are not significantly different from those of the study participants.

Case-Control, Cross-sectional: There is direct evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.

Assessment-specific Clarification:

Ecological and Semi-individual: There is direct evidence that there was no loss of subjects (e.g., due to moving or migration) or data during the study and outcome data were complete **OR** incomplete outcome data were adequately addressed **AND** characteristics of subjects lost to follow up or with unavailable records are described in an identical way and are not significantly different from those of the study participants.

Additional Guidance:

There are no reported data lost to attrition, and the numbers in the results tables sum to the total number of subjects, **OR** less than 10% of data are missing, **OR** there are some missing outcome data but study report clearly identifies missing data and how it was handled (e.g., loss to follow-up for a cohort study is determined to be minimal if there are some missing data for either the exposure or outcome for certain subjects at a specific time measured and the authors clearly explain what happened to everyone and which results were used in the analyses). For ecological studies specifically, there are no reported data lost to attrition **OR** there are some missing data but study report clearly identifies missing data and how they were handled (e.g., migration in and out of study area and residence location within study area were tracked and accounted for or references provided to verify that population migration within or in/out of study area is not a concern for this population), and characteristics of subjects lost to attrition do not differ significantly from those included in study.

\+ **OHAT:**

Human Controlled Trial: There is indirect evidence that loss of subjects (i.e., incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from a study **OR** it is deemed that the proportion lost to follow-up would not appreciably bias results [less than 20% in each group (Genaidy et al., 2007)]. This would include reports of no statistical differences in characteristics of subjects lost to follow up or with unavailable records from those of the study participants. Generally, the higher the ratio of participants with missing data to participants with events, the greater potential there is for bias. For studies with a long duration of follow-up, some withdrawals for such reasons are inevitable.
Cohort: There is indirect evidence that loss of subjects (i.e., incomplete outcome data) was adequately addressed and reasons were documented when human subjects were removed from a study **OR** it is deemed that the proportion lost to follow-up would not appreciably bias results. This would include reports of no statistical differences in characteristics of subjects lost to follow up or with unavailable records from those of the study participants. Generally, the higher the ratio of participants with missing data to participants with events, the greater potential there is for bias. For studies with a long duration of follow-up, some withdrawals for such reasons are inevitable.
Case-Control, Cross-sectional: There is indirect evidence that exclusion of subjects from analyses was adequately addressed, and reasons were documented when subjects were removed from the study or excluded from analyses.
Assessment-specific Clarification:
Ecological and Semi-individual: There is indirect evidence that there was no loss of subjects (e.g., due to migration during the study) and outcome data were complete **OR** it is deemed that the proportion of subjects lost to follow-up would not appreciably bias results. This would include reports of no statistical differences in characteristics of subjects lost to follow up or with unavailable records of outcomes. For studies with a long duration of follow-up, some withdrawals for such reasons are inevitable.
Additional Guidance:
No direct evidence of loss to follow-up, attrition, or loss of subjects due to migration/moving provided. The tables of results do not include the number of subjects and it is not stated that there was any loss data missing **OR** there appear to be no or very few missing data, **OR** in a cohort study, there is no mention of loss to follow-up.

\- **OHAT:**

Human Controlled Trial: There is indirect evidence that loss of subjects (i.e., incomplete outcome data) was unacceptably large [greater than 20% in each group (Genaidy et al., 2007)] and not adequately addressed **OR** there is insufficient information provided about numbers of subjects lost to follow-up.
Cohort: There is indirect evidence that loss of subjects (i.e., incomplete outcome data) was unacceptably large and not adequately addressed **OR** there is insufficient information provided about numbers of subjects lost to follow-up.
Case-Control, Cross-sectional: There is indirect evidence that exclusion of subjects from analyses was not adequately addressed, **OR** there is insufficient information provided about why subjects were removed from the study or excluded from analyses.
Assessment-specific Clarification:
Ecological and Semi-individual: There is indirect evidence that incomplete outcome data (e.g., due to subject migration or moving) were unacceptably large [greater than 20% in each group (Genaidy et al., 2007)] and not adequately addressed **OR** there is insufficient information provided about missing outcome data.
Additional Guidance:
Missing outcome data with no explanation of why data were missing, and it is unclear from the characteristics table or other information provided in the report why the data might be missing.

−− **OHAT:**

Human Controlled Trial, Cohort: There is direct evidence that loss of subjects (i.e., incomplete outcome data) was unacceptably large and not adequately addressed. Unacceptable handling of subject attrition includes reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across study groups, or potentially inappropriate application of imputation.

Case-Control, Cross-sectional: There is direct evidence that exclusion of subjects from analyses was not adequately addressed. Unacceptable handling of subject exclusion from analyses includes reason for exclusion likely to be related to true outcome, with either imbalance in numbers or reasons for exclusion across study groups.

Assessment-specific Clarification:

Ecological and Semi-individual: There is direct evidence that incomplete outcome data were unacceptably large and not adequately addressed **OR** that characteristics of subjects lost to attrition were significantly different from those included in study.

Additional Guidance:

The missing outcome data are clearly related to exposure (more missing data for exposed compared to unexposed groups), but the study authors do not address why. For ecological studies, there is unacceptable handling of subject migration into and out of study area or subject residence locations within study area.

10. Were the outcome assessors blinded to study group or exposure level?

++ **OHAT:**

Human Controlled Trial: There is direct evidence that the outcome assessors (including study subjects, if outcomes were self-reported) were adequately blinded to the study group, and it is unlikely that they could have broken the blinding prior to reporting outcomes.

Cohort, Cross-sectional, Case Series/Report: There is direct evidence that the outcome assessors (including study subjects, if outcomes were self-reported) were adequately blinded to the exposure level, and it is unlikely that they could have broken the blinding prior to reporting outcomes.

Case-Control: There is direct evidence that the outcome assessors (including study subjects if outcomes were self-reported) were adequately blinded to the exposure level when reporting outcomes.

Assessment-specific Clarification:

Ecological and Semi-individual: Same as OHAT Cohort, Cross-sectional, and Case Series/Report criteria.

Additional Guidance:

The study report states that outcome assessors were blinded to subjects' exposure levels, **OR** in a case-control study, researchers who assigned exposure levels based on drinking water level were blinded to the case/control status of the participant.

\+ **OHAT:**

Human Controlled Trial: There is indirect evidence that the outcome assessors (including study subjects, if outcomes were self-reported) were adequately blinded to the study group, and it is unlikely that they could have broken the blinding prior to reporting outcomes, **OR** it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results, which may vary by outcome (i.e., blinding is especially important for subjective measures).

Cohort, Cross-sectional, Case Series/Report: There is indirect evidence that the outcome assessors were adequately blinded to the exposure level, and it is unlikely that they could have broken the blinding prior to reporting outcomes **OR** it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (including that subjects self-reporting outcomes were likely not aware of reported links between the exposure and outcome lack of blinding is unlikely to bias a particular outcome).

Case-Control: There is direct evidence that the outcome assessors were adequately blinded to the exposure level when reporting outcomes **OR** it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results (including that subjects self-reporting outcomes were likely not aware of reported links between the exposure and outcome, or lack of blinding is unlikely to bias a particular outcome).

Assessment-specific Clarification:

Ecological and Semi-individual: Same as OHAT Human Controlled Trial criteria.

Additional Guidance:

No direct statement that outcome assessors were blind, but it is likely that they were (e.g., pathologists conducting histopathology on the tissue would most likely be blind to the exposure status), **OR** outcomes were assessed using an automated instrument, making it unlikely that the results would be biased since automated instrument would not be biased.

\− **OHAT:**

Human Controlled Trial: There is indirect evidence that it was possible for outcome assessors (including study subjects if outcomes were self-reported) to infer the study group prior to reporting outcomes, **OR** there is insufficient information provided about blinding of outcome assessors.

Cohort, Cross-sectional, Case Series/Report: There is indirect evidence that it was possible for outcome assessors to infer the exposure level prior to reporting outcomes (including that subjects self-reporting outcomes were likely aware of reported links between the exposure and outcome) **OR** there is insufficient information provided about blinding of outcome assessors.

Case-Control: There is indirect evidence that it was possible for outcome assessors to infer the exposure level prior to reporting outcomes (including that subjects self-reporting outcomes were likely aware of reported links between the exposure and outcome) **OR** there is insufficient information provided about blinding of outcome assessors.

Assessment-specific Clarification:

Ecological and Semi-individual: Same as OHAT Case-Control criteria.

Additional Guidance:

Not enough information to determine if outcome assessors were blind to exposure status and possibility exists that they could have knowledge (e.g., it is a cohort and exposure was assessed prior to outcome), **OR** likely that outcome assessors were aware of exposure, but not necessarily level of exposure (e.g., outcome was assessed in subject's home, which is in either the control village or exposed village, but the study report evaluated different exposure levels in village so that when assessing the outcome, assessors would be aware that subjects were exposed or controls but not exact exposure level).

−− **OHAT:**
Human Controlled Trial: There is direct evidence for lack of adequate blinding of outcome assessors (including study subjects if outcomes were self-reported), including no blinding or incomplete blinding.
Cohort, Cross-sectional, Case Series/Report: There is direct evidence that outcome assessors were aware of the exposure level prior to reporting outcomes (including that subjects self-reporting outcomes were aware of reported links between the exposure and outcome).
Case-Control: There is direct evidence that outcome assessors were aware of the exposure level prior to reporting outcomes (including that subjects self-reporting outcomes were aware of reported links between the exposure and outcome).
Assessment-specific Clarification:
Ecological and Semi-individual: Same as OHAT Case-Control criteria.
Additional Guidance:
There is direct evidence that outcome assessor knew exposure status (e.g., same situation as above with outcome assessed in the village, but the report only evaluates exposure as "exposed versus unexposed," with no arsenic levels measured).

11. Were confounding variables assessed consistently across groups using valid and reliable measures?

++ **OHAT:**
Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/Report: There is direct evidence that primary covariates and confounders were assessed using valid and reliable measurements.
Assessment-specific Clarification:
Ecological and Semi-individual: There is direct evidence that group- or individual-level primary covariates and confounders were assessed using valid and reliable measurements.
Additional Guidance:
Methods provide specific details on how confounders were measured (e.g., for body weight, details provided to indicate precision of measurement instrument and, ideally, calibration of instrument). Validated or pretested questionnaires used, and there was low potential for interviewer bias.

\+ **OHAT:**
Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/Report: There is indirect evidence primary covariates and confounders were assessed using valid and reliable measurements **OR** it is deemed that the measures used would not appreciably bias results (i.e., the authors justified the validity of the measures from previously published research).
Assessment-specific Clarification:
Ecological and Semi-individual: There is indirect evidence that group- or individual-level primary covariates and confounders were assessed using valid and reliable measurements **OR** it is deemed that the measures used would not appreciably bias results (i.e., the authors justified the validity of the measures from previously published research).
Additional Guidance:
Self-administered questionnaire, **OR** questionnaire administered by a single interviewer for all subjects (thus eliminating the possibility for interviewer agreement bias), **OR** methods for assessing confounders were mixed (e.g., some methods well conducted and consistent, but others may have been obtained from questionnaires not stated to be validated).

- **OHAT:**
  Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/Report: There is indirect evidence that primary covariates and confounders were assessed using measurements of unknown validity **OR** there is insufficient information provided about the measures used.
  Assessment-specific Clarification:
  Ecological and Semi-individual: There is indirect evidence that group- and individual-level primary covariates and confounders were assessed using measurements of unknown validity **OR** there is insufficient information provided about the measures used.
  Additional Guidance:
  Not enough details were provided on how the confounders were assessed. Questionnaire used and administered by several interviewers with no details on validity/reliability of the questionnaire or on consistency between the interviewers.

- **OHAT:**
  Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/Report: There is direct evidence that primary covariates and confounders were assessed using nonvalid measurements.
  Assessment-specific Clarification:
  Ecological and Semi-individual: There is direct evidence that group- or individual-level primary covariates and confounders were not assessed using valid and reliable measures.
  Additional Guidance:
  There is direct evidence of selective recall by disease status.

12. Can we be confident in the exposure characterization?

++ **OHAT:**

Human Controlled Trial: There is direct or indirect evidence that the test material is confirmed as ≥99% pure (or impurities have been characterized and not considered to be of serious concern), and that the concentration, stability, and homogeneity of stock material and formulation have been verified as appropriate (Note: ≥99% purity value is considered achievable based on current advertised purity from Sigma-Aldrich); **AND FOR INTERNAL DOSIMETRY STUDIES** there is direct evidence that most data points for the aglycone, conjugated and/or total BPA are *above* the level of quantitation (LOQ) for the assay; **AND** the study utilized spiked samples to confirm assay performance and the stability of BPA and conjugated BPA in biological samples was appropriately addressed; **AND** studies took measures to assess potential BPA contamination that might have occurred during sample collection and analysis, including method blanks. Note: Use of method blanks is necessary to identify potential sources of contamination in blood and urine but cannot rule out all possible sources of contamination (Ye et al., 2012). The risk of contamination for blood-based measurements is likely higher than for urinary measurements in part because sterile plastic blood collection containers can increase the number of sources of contamination and because of higher levels of protein and lipid levels in blood versus urine. Preferred practices include (1) measurement of aglycone AND conjugated or total BPA for blood measurements, and (2) use of isotopically labeled BPA dosing material (e.g., deuterated) to avoid issues of contamination, although we will not "downgrade" if a study did not follow these preferred practices.

Cohort, Case-Control, Cross-sectional, Case Series/Report: There is direct evidence that most data points for the aglycone, conjugated and/or total BPA are *above* the level of quantitation (LOQ) for the assay; **AND** the study utilized spiked samples to confirm assay performance and the stability of BPA and conjugated BPA in biological samples was appropriately addressed; **AND** studies took measures to assess potential BPA contamination that might have occurred during sample collection and analysis including method blanks. Note: Use of method blanks is necessary to identify potential sources of contamination in blood and urine but cannot rule out all possible sources of contamination (Ye et al., 2012). The risk of contamination for blood-based measurements is likely higher than for urinary measurements in part because sterile plastic blood collection containers can increase the number of sources of contamination and because of higher levels of protein and lipid levels in blood versus urine. Preferred practices include (1) measurement of aglycone AND conjugated or total BPA for blood measurements, and (2) inclusion of multiple measurements of BPA because a single sample from an individual does not appear to be strong predictor of a subject's exposure category. Mahalingaiah et al. (2008) analyzed samples from at least six repeat urinary BPA measurements from eight subjects. The sensitivity, specificity, and positive predictive value of a single urine sample to predict the highest BPA tertile were 0.64, 0.76, and 0.63, respectively. The positive predictive value increased to 0.85 when two samples were used to predict those individuals in the highest BPA tertile. Use of a single measurement in large sample size studies such as NHANES is less of an issue because the number of participants offsets potential concern for differential exposure misclassification. We will not downgrade if a study did not follow these preferred practices.

Assessment-specific Clarification:

Ecological and Semi-individual: This rating is not applicable. Only studies with individual-level exposure characterization can earn this rating. If individual-level exposure data are provided, the study is not an ecological study, and should be re-classified and rated according to other study-type ROB criteria.

Additional Guidance:

Single spot urine samples are reported for a large number of subjects (over 1,000), **OR** multiple (repeated) spot urine samples were reported. Individual-level drinking water levels (e.g., obtained from household tap or household well, but not village-level well) with methods well described, including reporting of levels of detection (LODs). Toenail and hair samples were cleaned, **AND** the recovery rate of the method or use of internal standards is reported. More than one arsenic exposure assessment (more than one matrix, and/or more than one measurement) and at least one of them is excellent (e.g., the large HEALS cohort and spot urine spot samples, in addition to village-level water arsenic measurements) and a correlation reported between the different measurements.

+ **OHAT:**

Human Controlled Trial: There is direct or indirect evidence that purity was ≥98%, (or impurities have been characterized and not considered to be of serious concern, i.e., purity was independently confirmed by lab, purity is reported in paper or obtained through author query, or purity not reported but the source is listed and the supplier of the chemical provides documentation of the purity of the chemical; **AND FOR INTERNAL DOSIMETRY STUDIES** there is indirect evidence that most data points for the aglycone, conjugated and/or total BPA are *above* the level of quantitation (LOQ) for the assay, i.e., the central estimate (median, mean, geometric mean) is *above* the LOQ but results for individual data values are not presented or the presentation of variance estimates does not permit assessment of whether most data points are likely *above* the LOQ; **AND** the study utilized spiked samples to confirm assay performance and the stability of BPA and conjugated BPA in biological samples was appropriately addressed; **AND** studies took measures to assess potential BPA contamination that might have occurred during sample collection and analysis including method blanks.

Cohort, Case-Control, Cross-sectional, Case Series/Report: There is indirect evidence that most data points for the aglycone, conjugated and/or total BPA are *above* the level of quantitation (LOQ) for the assay, i.e., the central estimate (median, mean, geometric mean) is *above* the LOQ but results for individual data values are not presented or the presentation of variance estimates do not permit assessment of whether most data points are likely *above* the LOQ; **AND** the study utilized spiked samples to confirm assay performance and the stability of BPA and conjugated BPA in biological samples has been appropriately addressed; **AND** studies took measures to assess potential BPA contamination that might have occurred during sample collection and analysis including method blanks; **OR** use of questionnaire items where results of biomonitoring studies support the use of the questionnaire item(s) as an indicator of relative level of exposure; **OR** job description for occupational studies where levels in the work environment or results of biomonitoring studies support the use of job description as an indicator of relative level of exposure.

Assessment-specific Clarification:

Ecological and Semi-individual: There is direct or indirect evidence that the exposure to the chemical of concern was adequately characterized by appropriate measures and methods (e.g., adequate monitoring over time of multiple sources per exposure group, cumulative exposures based on historical changes in measured exposures, exposure measures taken for a moderate proportion of population).

Additional Guidance:

Single spot urine samples with a moderate number of subjects (i.e., hundreds or more). Adequate measurements and methods, but LODs are not provided. Exposure based on occupational title but supported by some arsenic monitoring (air, urine, or other biomarker). For ecological studies, drinking water levels were obtained from the smallest groups available (e.g., household or village level) with methods well described and monitoring over time to estimate cumulative exposure based on changes in arsenic concentrations, including reporting of LODs and residential durations.

- **OHAT:**
  Human Controlled Trial: Neither the source or purity of the chemical was reported in the study and information on purity could not be obtained through author query/vendor documentation; **AND FOR INTERNAL DOSIMETRY STUDIES** there is direct or indirect evidence that most data points for the aglycone, conjugated and/or total BPA are above the level of quantitation (LOQ) for the assay **BUT** no steps were taken to assess potential BPA contamination that might have occurred during sample collection and analysis; **OR** there is indirect or direct evidence that most individual data points for the aglycone, conjugated and/or total BPA are below the level of quantitation (LOQ) for the assay; **OR** method to measure BPA used ELISA, which is less accepted as providing quantitatively accurate values and because of potential uncharacterized antibody cross-reactivity with conjugates and endogenous components of sample matrices (Chapin et al., 2008; Vandenberg et al., 2007)
  Cohort, Case-Control, Cross-sectional, Case Series/Report: There is direct or indirect evidence that most data points for the aglycone, conjugated and/or total BPA are above the level of quantitation (LOQ) for the assay **BUT** no steps were taken to assess potential BPA contamination that might have occurred during sample collection and analysis; **OR** there is indirect or direct evidence that most individual data points for the aglycone, conjugated and/or total BPA are below the level of quantitation (LOQ) for the assay; **OR** method to measure BPA used ELISA, which leads to concern because of uncharacterized antibody cross-reactivity with conjugates and endogenous components of sample matrices (Chapin et al., 2008; Vandenberg et al., 2007); **OR** use of questionnaire items that are not supported by results of biomonitoring studies; **OR** job description for occupational studies that are not supported by information on levels in the work environment or results of biomonitoring studies
  Assessment-specific Clarification:
  Ecological and Semi-individual: There is indirect evidence that the chemical in question was not adequately characterized by appropriate measures and methods (e.g., no historical monitoring, isolated or remote-time samples taken to be representative of large areas, no cumulative exposures estimated).
  Additional Guidance:
  Exposure based on single spot urine sample for a limited number of subjects (less than 100), **OR** exposure based on occupational title with no arsenic monitoring, **OR** cumulative arsenic levels based on self-reported duration/resident history and group well-water measurements.

- **OHAT:**
  Human Controlled Trial: There is indirect or direct evidence that purity was <98%; **AND FOR INTERNAL DOSIMETRY STUDIES** there is direct evidence of uncontrolled contamination.
  Cohort, Case-Control, Cross-sectional, Case Series/Report: There is direct evidence of uncontrolled contamination; **OR** not reporting of methods used to assess exposure and this information could not be obtained through author query; **OR** self-report exposure.
  Assessment-specific Clarification:
  Ecological and Semi-individual: There is direct evidence that the chemical in question was not adequately characterized by appropriate measures and methods (e.g., no historical monitoring, isolated or remote-time samples taken to be representative of large areas, no cumulative exposures estimated), **OR** there is direct evidence of uncontrolled contamination, **OR** methods used to assess exposure not reported, **OR** self-reported exposure.
  Additional Guidance:
  No measured arsenic concentrations. Exposure assessed based on presence/absence of skin lesions **OR** self-reported duration of drinking water or living in a certain area **OR** lifetime cumulative arsenic exposure determined using self-reported information on residential history and drinking-water daily consumption rates, and village-level median arsenic concentration in drinking water.

13. Can we be confident in the outcome assessment?

++ **OHAT:**

Human Controlled Trial, Cohort: There is direct evidence that the outcome was assessed using well-established methods, the "gold standard" or with validity and reliability >0.70 (Genaidy et al., 2007) and subjects had been followed for the same length of time in all study groups. Acceptable assessment methods will depend on the outcome, but examples of such methods may include: objectively measured with diagnostic methods, measured by trained interviewers, obtained from registries (Shamliyan et al., 2010).
Case-Control: There is direct evidence that the outcome was assessed in cases using well-established methods (the gold standard) and subjects had been followed for the same length of time in all study groups.
Cross-sectional, Case Series/Report: There is direct evidence that the outcome was assessed using well-established methods (the gold standard).

Assessment-specific Clarification:

Ecological and Semi-individual: There is direct evidence that the outcome was assessed using well-established methods, the "gold standard" (e.g., individual-level outcome data were assessed, as in the case of semi-individual ecological studies) and subjects have been followed for the same length of time in all study groups. Acceptable assessment methods will depend on the outcome, but examples of such methods may include: objectively measured with diagnostic methods, measured by trained interviewers, obtained from reliable registries or records.

Additional Guidance:

Cancer cases are histologically confirmed, **OR** data obtained from nationwide registry are accepted as valid and complete (e.g., Taiwan), **OR** outcome diagnosed by physician, **OR** outcome obtained from medical record data or validated with such data (if self-reported).

\+ **OHAT:**

Human Controlled Trial, Cohort: There is indirect evidence that the outcome was assessed using acceptable methods [i.e., deemed valid and reliable but not the gold standard or with validity and reliability ≥0.40 (Genaidy et al., 2007)] and subjects had been followed for the same length of time in all study groups **OR** it is deemed that the outcome assessment methods used would not appreciably bias results. Acceptable, but not ideal assessment methods will depend on the outcome, but examples of such methods may include proxy reporting of outcomes and mining of data collected for other purposes.
Case-Control: There is indirect evidence that the outcome was assessed in cases (i.e., case definition) using acceptable methods and subjects had been followed for the same length of time in all study groups **OR** it is deemed that the outcome assessment methods used would not appreciably bias results.
Cross-sectional, Case Series/Report: There is indirect evidence that the outcome was assessed using acceptable methods OR it is deemed that the outcome assessment methods used would not appreciably bias results.

Assessment-specific Clarification:

Ecological and Semi-individual: There is indirect evidence that the outcome was assessed using acceptable methods (i.e., deemed valid and reliable but not the gold standard) and subjects had been followed for the same length of time in all study groups **OR** it is deemed that the outcome assessment methods used would not appreciably bias results **OR** group-level outcomes were assessed using well-established methods. Acceptable, but not ideal assessment methods will depend on the outcome, but examples of such methods may include proxy reporting of outcomes and mining of data collected for other purposes.

Additional Guidance:

Death certificates are used, but there is no statement that they were coded by certified nosologist, **OR** information on the accuracy/validity/completeness of the death certificates is missing, **OR** incident cancer cases are not stated to be histologically confirmed, but the study was conducted in a hospital setting (e.g., hospital-based case-control study).

– **OHAT:**
Human Controlled Trial, Cohort: There is indirect evidence that the outcome assessment method is an insensitive instrument, the authors did not validate the methods used, or the length of follow up differed by study group **OR** there is insufficient information provided about validation of outcome assessment method.
Case-Control: There is indirect evidence that the outcome was assessed in cases using an insensitive instrument or was not adequately validated **OR** there is insufficient information provided about how cases were identified.
Cross-sectional, Case Series/Report: There is indirect evidence that the outcome assessment method is an insensitive instrument or was not adequately validated **OR** there is insufficient information provided about validation of outcome assessment method.
Assessment-specific Clarification:
Ecological and Semi-individual: There is indirect evidence that the authors did not validate the methods used, or the length of follow up differed by study group **OR** there is insufficient information provided about validation of outcome assessment method.
Additional Guidance:
Outcome is self-reported (e.g., "ever been diagnosed by a physician") and not verified by medical records or other means. There is insufficient information on quality of self-report or validation of answers. Outcome is assessed by nurses and there is no information on assessor agreement.

–– **OHAT:**
Human Controlled Trial, Cohort: There is direct evidence that the outcome assessment method is an insensitive instrument, or the length of follow up differed by study group.
Case-Control: There is direct evidence that the outcome was assessed in cases using an insensitive instrument.
Cross-sectional, Case Series/Report: There is direct evidence that the outcome assessment method is an insensitive instrument.
Assessment-specific Clarification:
Ecological and Semi-individual: There is direct evidence that the authors did not validate the methods used, or the length of follow up differed by study group.
Additional Guidance:
Self-reported outcome when question is not worded "as diagnosed by a physician" and cannot be verified.

14. Were all measured outcomes reported?

++ **OHAT:**
Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/Report: There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported. This would include outcomes reported with sufficient detail to be included in meta-analysis or fully tabulated during data extraction.
Assessment-specific Clarification:
Ecological and Semi-individual: Same as OHAT criteria.
Additional Guidance:
None.

\+ **OHAT:**
Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/Report: There is indirect evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported **OR** analyses that had not been planned at the outset of the study (i.e., retrospective unplanned subgroup analyses) are clearly indicated as such and it is deemed that the omitted analyses were not appropriate and selective reporting would not appreciably bias results. This would include outcomes reported with insufficient detail such as only reporting that results were statistically significant (or not).
Assessment-specific Clarification:
Ecological and Semi-individual: Same as OHAT criteria.
Additional Guidance:
All outcomes outlined in abstract, introduction, and methods are reported.

– **OHAT:**
Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/Report: There is indirect evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported **OR** there is insufficient information provided about selective outcome reporting.
Assessment-specific Clarification:
Ecological and Semi-individual: Same as OHAT criteria.
Additional Guidance:
An outcome mentioned in a part of the study report is obviously missing from the results.

–– **OHAT:**
Human Controlled Trial, Cohort, Case-Control, Cross-sectional, Case Series/Report: There is direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have not been reported. In addition to not reporting outcomes, this would include reporting outcomes based on composite score without individual outcome components or outcomes reported using measurements, analysis methods or subsets of the data (e.g., subscales) that were not pre-specified or reporting outcomes not pre-specified (unless clear justification for their reporting is provided, such as an unexpected effect).
Assessment-specific Clarification:
Ecological and Semi-individual: Same as OHAT criteria.
Additional Guidance:
None.

15. Were there no other potential threats to internal validity (e.g., statistical methods were appropriate)?

OHAT: On a project specific basis, additional questions for other potential threats to internal validity can be added and applied to study designs as appropriate.

++ **Assessment-specific Clarification:**
Statistical analyses were appropriate and no other threats to internal validity were identified. Study authors might acknowledge limitations, but these are not expected to affect the study's internal validity.

\+ **Assessment-specific Clarification:**
There are study limitations likely to bias the results toward or away from the null, but adequate sample size was available in each cell ($n \geq 5$), **OR** sample size is small and acknowledged as a potential limitation by study authors, but significant results were still observed.

– **Assessment-specific Clarification:**
There are study limitations likely to bias results towards or away from the null, **OR** analyses were conducted on a small number of subjects ($n < 5$ in any given cell) and no statistically significant results were observed.

–– **Assessment-specific Clarification:**
None.

B.2. AUTHOR-PROVIDED DATA

As part of the screening (see assessment Section 4.3) and meta-regression (see assessment Section 4.3) analyses study selection process, authors were contacted for additional data whenever the study met minimal requirements for inclusion in the analysis but not all data needed for the exposure-response analysis was available. The data supplied by the authors is documented in this Appendix section.

B.2.1. Author-Provided Data for Screening Analyses

Table B-2. Data provided for Argos et al. (2007)

Study	Parameter	Cases	Non-cases	Notes
Argos et al. (2007)	**Well water arsenic concentration (µg/L)**			
Skin Lesions (Owns Land)	<7	18	839	Cases and Non-Cases provided by author
Hero ID: 627505	7–38	20	772	
	39–90	46	807	
	91–177	38	774	
	>177	51	664	
Argos et al. (2007)	**Well water arsenic concentration (µg/L)**	**Cases**	**Non-cases**	**Notes**
Skin Lesions (Does not own land)	<7	39	1,309	Cases and Non-Cases provided by author
Hero ID: 627505	7–38	76	1,503	
	39–90	91	1,398	
	91–177	114	1,442	
	>177	188	1,577	
Argos et al. (2007)	**Urinary As concentration (µg/g-creatinine)**	**Cases**	**Non-cases**	**Notes**
Skin Lesions (Owns land)	≤35	38	1,018	Cases and Non-Cases provided by author
Hero ID: 627505	36–66	50	1,156	
	67–114	48	1,072	
	115–204	90	1,089	
	>204	82	1,021	

Study	Parameter	Cases	Non-cases	Notes
Argos et al. (2007)	Urinary As concentration (µg/g-creatinine)	Cases	Non-cases	Notes
Skin Lesions (Does not own land)	≤35	36	1,101	Cases and Non-Cases provided by author
Hero ID: 627505	36–66	49	1,050	
	67–114	70	1,079	
	115–204	78	1,039	
	>204	125	1,149	
Argos et al. (2007)	Cumulative As exposure (mg)	Cases	Non-cases	Notes
Skin Lesions (Owns land)	≤62	34	1,208	Cases and Non-Cases provided by author
Hero ID: 627505	62–224	37	933	
	225–583	54	1,096	
	584–1,490	74	1,023	
	>1,490	110	1,049	
Argos et al. (2007)	Cumulative As exposure (mg)	Cases	Non-cases	Notes
Skin Lesions (Does not own land)	≤62	27	1,169	Cases and Non-Cases provided by author
Hero ID: 627505	62–224	35	940	
	225–583	65	1,070	
	584–1,490	84	1,136	
	>1,490	148	1,095	

Table B-3. Data provided for Aschengrau et al. (1989)

Aschengrau et al. (1989)	Drinking water As exposure (µg/L)	Cases	Non-cases	Notes
Spontaneous abortion/miscarriage	Not detected	128	701	Cases and non-cases provided by author
Hero ID: 1032517	0.8–1.3	151	668	
	1.4–1.9	7	22	

Table B-4. Data provided for Chen et al. (2011)

Chen et al. (2011)	Drinking water As concentration by mean (µg/L)	Total N	Notes
Hero ID: 1015960	3.7	2,982	Total N per exposure level provided by author
	35.9	2,943	
	102.5	2,886	
	265.7	2,935	
Chen et al. (2011)	**Urinary Arsenic Concentration by mean (µg/g creatinine)**	**Total N**	**Notes**
Hero ID: 1015960	68.5	2,793	Total N per exposure level provided by author
	150.6	2,829	
	264.9	2,805	
	641.5	2,797	

Table B-5. Data provided for D'Ippoliti et al. (2015)

D'Ippoliti et al. (2015)	Average As during first yr of residence (µg/L)	Total N	Notes
Males	<10	21,997	Total N per exposure level provided by author
Hero ID: 3005297	10–20	20,533	
	>20	26,228	
D'Ippoliti et al. (2015)	**Average As during first yr of residence (µg/L)**	**Total N**	**Notes**
Females	<10	22,347	Total N per exposure level provided by author
Hero ID: 3005297	10–20	20,946	
	>20	26,749	
D'Ippoliti et al. (2015)	**Cumulative As Dose (mg)**	**Total N**	**Notes**
Males	<204.9	26,944	Total N per exposure level and unit provided by author
Hero ID: 3005297	204.9–804.0	44,537	
	>804	21,636	
D'Ippoliti et al. (2015)	**Cumulative As Dose (mg)**	**Total N**	**Notes**
Females	<204.9	26,459	Total N per exposure level and unit provided by author
Hero ID: 3005297	204.9–804.0	44,702	
	>804	23,175	

Table B-6. Data provided for Gilbert-Diamond et al. (2013)

Gilbert-Diamond et al. (2013)	Total urinary arsenic (µg/L)	Cases	Controls	Notes
Hero ID: 1797805	<3.36	165	141	Cases and controls provided by author
	3.36–<5.31	145	161	
	≥5.31	137	168	
Gilbert-Diamond et al. (2013)	**Inorganic urinary As (µg/L)**	**Cases**	**Controls**	**Notes**
Hero ID: 1797805	<0.23	156	153	Cases and controls provided by author
	0.23–<0.45	149	153	
	≥0.45	142	164	

Table B-7. Data provided for James et al. (2015)

James et al. (2015)	As TWA exposure (µg/L-yr)	Mean As TWA exposure (µg/L-yr)	Cases	Non-cases	Notes
coronary heart disease	1–20	7.31	58	370	Means and cases provided by author and non-cases calculated against total n presented in paper
Hero ID: 2822189	20–30	25.1	18	68	
	30–45	36.6	16	17	
	45–88	50.2	4	4	

Table B-8. Data provided for Moon et al. (2013)

Moon et al. (2013)	Urinary As concentration (µg/g-creatinine)	Mean urinary As concentration (µg/g-creatinine)	Cases	Non-cases	Notes
coronary heart disease incidence	<5.8	4.10	202	694	Means and non-cases provided by author
Hero ID: 2064267	5.8–9.7	7.60	206	687	
	9.8–15.7	12.5	197	695	
	>15.7	26.3	241	653	

Moon et al. (2013)	**Urinary As concentration (µg/g-creatinine)**	**Mean Urinary As concentration (µg/g-creatinine)**	**Cases**	**Non-cases**	**Notes**
coronary heart disease mortality	<5.8	4.10	68	828	Means and non-cases provided by author
Hero ID: 2064267	5.8–9.7	7.60	67	826	
	9.8–15.7	12.5	87	805	
	>15.7	26.3	119	775	
Moon et al. (2013)	**Urinary As concentration (µg/g-creatinine)**	**Mean Urinary As concentration (µg/g-creatinine)**	**Cases**	**Non-cases**	**Notes**
cardiovascular disease incidence	<5.8	4.10	265	631	Means and non-cases provided by author
Hero ID: 2064267	5.8–9.7	7.60	297	596	
	9.8–15.7	12.5	291	601	
	>15.7	26.3	331	563	
Moon et al. (2013)	**Urinary As concentration (µg/g-creatinine)**	**Mean Urinary As concentration (µg/g-creatinine)**	**Cases**	**Non-cases**	**Notes**
cardiovascular disease mortality	<5.8	4.10	68	828	Means and non-cases provided by author
Hero ID: 2064267	5.8–9.7	7.60	67	826	
	9.8–15.7	12.5	87	805	
	>15.7	26.3	119	775	
Moon et al. (2013)	**Urinary As concentration (µg/g-creatinine)**	**Mean Urinary As concentration (µg/g-creatinine)**	**Cases**	**Non-cases**	**Notes**
stroke incidence	<5.8	4.10	55	841	Means and non-cases provided by author
Hero ID: 2064267	5.8–9.7	7.60	75	818	
	9.8–15.7	12.5	62	830	
	>15.7	26.3	72	822	
Moon et al. (2013)	**Urinary As concentration (µg/g-creatinine)**	**Mean Urinary As concentration (µg/g-creatinine)**	**Cases**	**Non-cases**	**Notes**
stroke mortality	<5.8	4.10	6	890	Means and non-cases provided by author
Hero ID: 2064267	5.8–9.7	7.60	17	876	
	9.8–15.7	12.5	13	879	
	>15.7	26.3	18	876	

Table B-9. Data provided for Sohel et al. (2009)

Sohel et al. (2009)	Average historic arsenic exposure (µg/L)	Mean historic arsenic exposure (µg/L)	Notes
Hero ID: 710822	<10	1.40	Means provided by author
	10–49	31.1	
	50–149	97.0	
	150–299	209	
	≥300	403	

Table B-10. Data provided for Tseng et al. (2003)

Tseng et al. (2003)	Total urinary arsenic (µg/L)	Cases	Non-cases	Notes
Hero ID: 628705	0	4	73	Cases and non-cases provided by author
	0.1–14.9	15	123	
	≥15	35	110	

Table B-11. Data provided for Wade et al. (2009)

Wade et al. (2009)	Drinking water As concentration (µg/L)	Mean drinking water As concentration (µg/L)	Notes
Hero ID: 628466	0–5	1.61	Means provided by author
	5.1–20	12.0	
	20.1–100	38.9	
	100.1–300	168	
	>300	421	

Table B-12. Data provided for Wade et al. (2015)

Wade et al. (2015)	Water As concentration (µg/L)	Mean water As concentration (µg/L)	Notes
Hero ID: 2854656	<10	3.02	Means provided by author
	10–39	20.9	
	≥40	78.8	

Table B-13. Data provided for Wasserman et al. (2004)

Wasserman et al. (2004)	Drinking water As concentration (µg/L)	Total N	Full IQ score mean	SE	Notes
Hero ID: 180230	0.1–5.5	50	76.56	2.87	Total N per exposure level and Full IQ score mean (SE) provided by author
	5.6–50.0	50	71.81	2.89	
	50.1–176	50	68.80	2.99	
	177–790	51	65.25	2.89	
Wasserman et al. (2004)	**Drinking water As concentration (µg/L)**	**Total N**	**Performance IQ score mean**	**SE**	**Notes**
Hero ID: 180230	0.1–5.5	50	59.51	2.44	Total N per exposure level and Performance IQ score mean (SE) provided by author
	5.6–50.0	50	54.41	2.46	
	50.1–176	50	52.23	2.55	
	177–790	51	49.77	2.46	
Wasserman et al. (2004)	**Drinking water As concentration (µg/L)**	**Total N**	**Verbal IQ score mean**	**SE**	**Notes**
Hero ID: 180230	0.1–5.5	50	17.05	0.74	Total N per exposure level and Verbal IQ score mean (SE) provided by author
	5.6–50.0	50	17.40	0.75	
	50.1–176	50	16.56	0.78	
	177–790	51	15.47	0.75	

Table B-14. Data provided for Wu et al. (2012)

Wu et al. (2012)	**Well water As (µg/L)**	**MMP-9 mean (ng/mL)**	**SD**	**Notes**
Hero ID: 1070384	0.10–2.00	105.90	59.30	MMP-9 mean (SD) provided by author
	2.01–23.13	101.20	78.70	
	23.14–73.46	104.10	62.20	
	73.47–500.62	107.00	70.10	
Wu et al. (2012)	**Well water As (µg/L)**	**MPO (ng/mL)**	**SD**	**Notes**
Hero ID: 1070384	0.10–2.00	21.00	16.30	MPO mean (SD) provided by author
	2.01–23.13	20.30	14.10	
	23.14–73.46	20.20	14.70	
	73.47–500.62	20.30	14.00	
Wu et al. (2012)	**Well water As (µg/L)**	**sE-selectin (ng/mL)**	**SD**	**Notes**
Hero ID: 1070384	0.10–2.00	35.30	14.60	sE-selectin mean (SD) provided by author
	2.01–23.13	36.30	17.00	
	23.14–73.46	34.80	14.30	
	73.47–500.62	35.70	17.10	
Wu et al. (2012)	**Well water As (µg/L)**	**PAI-1 (ng/mL)**	**SD**	**Notes**
Hero ID: 1070384	0.10–2.00	72.60	14.60	PAI-1 mean (SD) provided by author
	2.01–23.13	70.90	17.00	
	23.14–73.46	68.80	14.30	
	73.47–500.62	81.70	17.10	
Wu et al. (2012)	**Well water As (µg/L)**	**sICAM-1 (ng/mL)**	**SD**	**Notes**
Hero ID: 1070384	0.10–2.00	160.70	145.00	sICAM-1 mean (SD) provided by author
	2.01–23.13	134.30	125.50	
	23.14–73.46	136.00	94.60	
	73.47–500.62	156.30	125.00	

Wu et al. (2012)	**Well water As (µg/L)**	**sVCAM-1 (ng/mL)**	**SD**	**Notes**
Hero ID: 1070384	0.10–2.00	1,001.70	325.10	sVCAM-1 mean (SD) provided by author
	2.01–23.13	1,054.70	331.20	
	23.14–73.46	1,109.50	312.40	
	73.47–500.62	1,117.90	344.10	
Wu et al. (2012)	**Urinary As (µg/g creatinine)**	**MMP-9 mean (ng/mL)**	**SD**	**Notes**
Hero ID: 1070384	12.05–88.21	116.00	74.30	MMP-9 mean (SD) provided by author
	88.22–141.69	99.50	63.30	
	141.7–275.63	97.40	63.00	
	275.64–1,869.57	105.00	65.90	
Wu et al. (2012)	**Urinary As (µg/g creatinine)**	**MPO (ng/mL)**	**SD**	**Notes**
Hero ID: 1070384	12.05–88.21	22.60	16.90	MPO mean (SD) provided by author
	88.22–141.69	18.90	12.10	
	141.7–275.63	20.50	15.40	
	275.64–1,869.57	19.80	14.10	
Wu et al. (2012)	**Urinary As (µg/g creatinine)**	**sE-selectin (ng/mL)**	**SD**	**Notes**
Hero ID: 1070384	12.05–88.21	37.40	16.30	sE-selectin mean (SD) provided by author
	88.22–141.69	35.00	15.10	
	141.7–275.63	33.70	14.60	
	275.64–1,869.57	35.50	16.40	
Wu et al. (2012)	**Urinary As (µg/g creatinine)**	**PAI-1 (ng/mL)**	**SD**	**Notes**
Hero ID: 1070384	12.05–88.21	74.10	34.70	PAI-1 mean (SD) provided by author
	88.22–141.69	71.30	39.50	
	141.7–275.63	68.20	31.90	
	275.64–1,869.57	80.70	48.00	

Wu et al. (2012)	**Urinary As (µg/g creatinine)**	**sICAM-1 (ng/mL)**	**SD**	**Notes**
Hero ID: 1070384	12.05–88.21	149.60	139.70	sICAM-1 mean (SD) provided by author
	88.22–141.69	142.20	114.50	
	141.7–275.63	154.00	144.70	
	275.64–1,869.57	147.20	92.30	
Wu et al. (2012)	**Urinary As (µg/g creatinine)**	**sVCAM-1 (ng/mL)**	**SD**	**Notes**
Hero ID: 1070384	12.05–88.21	1,010.90	320.90	sVCAM-1 mean (SD) provided by author
	88.22–141.69	1,053.50	345.90	
	141.7–275.63	1,120.80	331.60	
	275.64–1,869.57	1,126.60	314.70	

B.2.2. Additional Author-Provided Data

The authors of (Wasserman et al., 2014; 2004) provided raw data for their studies which included individual data on exposures, outcomes, and covariates. The authors of Moon et al. (2017) provided data in supplemental materials that they had obtained from authors for the purposes of their meta-analysis. The author-provided data from these supplemental tables that were used in this assessment are summarized below in Table B-15.

Table B-15. Author-provided data obtained from Moon et al. (2017) meta-analysis

Data set (exposure units)	Exposure ranges	Means	Health outcome	Person years	Notes
Chen et al. (2011) (µg/g creatinine)	6.6–105.9	68.5	Fatal CVD	18,818	Means provided to Moon et al. (2017) by author
			Fatal IHD	18,818	
	105.9–199	150.6	Fatal CVD	18,335	
			Fatal IHD	18,335	
	199–351.8	264.9	Fatal CVD	18,161	
			Fatal IHD	18,161	
	351.8–1,100	641.5	Fatal CVD	18,501	
			Fatal IHD	18,501	
Chen et al. (2013) (µg/L)	0.1–25	7.20	CVD Inc.	2,823	
			IHD Inc.	2,823	

Data set (exposure units)	Exposure ranges	Means	Health outcome	Person years	Notes
	25.1–107	59.90	CVD Inc.	2,718	Means and person-yrs provided to Moon et al. (2017) by author
			IHD Inc.	2,718	
	108–864	222.80	CVD Inc.	2,770	
			IHD Inc.	2,770	
D'Ippoliti et al. (2015) (µg/L)	6.5 ± 2.8	6.5 ± 2.8	Fatal CVD	771,860	Means and SDs and adjusted RRs for combined males and female responses were provided to Moon et al. (2017) by authors
			Fatal IHD	771,860	
	13.7 ± 2.6	13.7 ± 2.6	Fatal CVD	713,276	
			Fatal IHD	713,276	
	34.5 ± 19.7	34.5 ± 19.7	Fatal CVD	904,129	
			Fatal IHD	904,129	
James et al. (2015) (µg/L)	1–20	7.31	IHD Inc.	4,806	Means provided to Moon et al. (2017) by author
	20–30	25.1	IHD Inc.	1,335	
	30–45	36.6	IHD Inc.	534	
	45–88	50.2	IHD Inc.	98	
Moon et al. (2013) (µg/g creatinine) 12,146 – for CVD and IHD incidence 13,616 – for CVD and IHD fatality	0–5.8	4.1	CVD Inc.	12,146	Means and person-yrs provided to Moon et al. (2017) by author
			IHD Inc.		
			Fatal CVD	13,616	
			Fatal IHD		
	5.8–9.7	7.6	CVD Inc.	11,701	
			IHD Inc.		
			Fatal CVD	13,430	
			Fatal IHD		
	9.7–15.7	12.5	CVD Inc.	11,305	
			IHD Inc.		
			Fatal CVD	12,720	
			Fatal IHD		
	>15.7	26.3	CVD Inc.	10,586	
			IHD Inc.		
			Fatal CVD	12,033	
			Fatal IHD		

Data set (exposure units)	Exposure ranges	Means	Health outcome	Person years	Notes
Sohel et al. (2009) (µg/d)	0–10	1.40	Fatal CVD	114,068	Person-yrs and means provided to Moon et al. (2017) by author
	10–49	31.06	Fatal CVD	139,233	
	50–149	97.04	Fatal CVD	365,496	
	150–299	208.61	Fatal CVD	241,930	
	300–500	402.55	Fatal CVD	78,786	
Wade et al. (2009) (µg/L)	0–5	1.61	Fatal CVD	14,636	Person-yrs and means provided to Moon et al. (2017) by author
			Fatal IHD		
	5–20	11.98	Fatal CVD	9,047	
			Fatal IHD		
	20–100	38.86	Fatal CVD	21,367	
			Fatal IHD		
	100–300	168.22	Fatal CVD	3,313	
			Fatal IHD		
	300–500	421.18	Fatal CVD	249	
			Fatal IHD		
Wade et al. (2015) (µg/L) Case-control	0–10	3.02	IHD Inc.	–	Means provided to Moon et al. (2017) by author
	10–39	20.87	IHD Inc.	–	
	40–208	78.75	IHD Inc.	–	

B.3. 2022 LITERATUE SEARCH UPDATE AND SURVEY OF DCS AND DIABETES

Literature searches and updates were completed between 2012 and 2019. Following prioritization of the 6 select outcomes, another literature search was conducted in 2022 (see Figure B-1). A screening and survey of the newly identified studies was conducted to determine if the new studies on DCS and diabetes will impact conclusions in the draft assessment. To further screen studies for dose-response utility, additional consideration was given to study type and key confounding factors, such as smoking, that are important to the dose-response approach. Sixty-seven DCS and diabetes studies were identified, and a literature survey was conducted based on title/abstract screening (see Table B.16). The characterization of newly identified studies focused on EPA's judgment of whether the studies would have a material impact on the conclusions (i.e., identified hazards or toxicity values) in the external review draft. [Note: For pregnancy and birth outcomes and neurodevelopmental effects, studies identified in the 2022 update underwent risk of bias evaluation to determine if new studies would change the hazard conclusion and/or impact

dose-response analyses. Studies from the recent literature search update are included in the synthesis sections for pregnancy and birth outcomes and neurodevelopmental effects.]

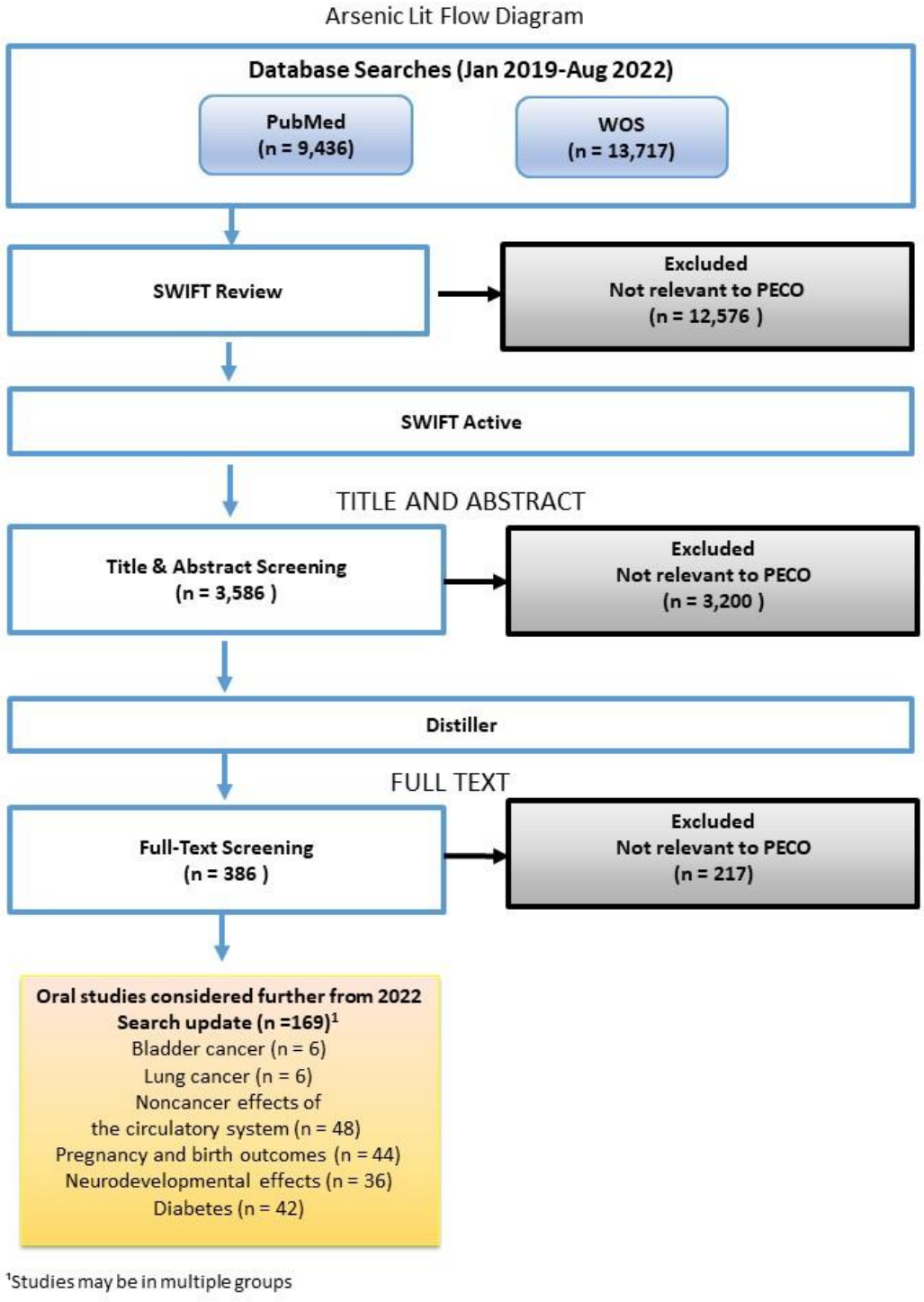


Figure B-1. Literature search and screening flow diagram for inorganic arsenic (August 2022 search update).

Table B-16. Literature survey of DCS and diabetes studies identified from 2022 literature search update

Reference (HERO ID)	Health outcome	Summary of study findings	EPA characterization for hazard identification	Included in meta-regression (rationale)
Bulka et al. (2019)	DCS, Diabetes	Association observed for urinary iAs/Hg pattern due to elevated prevalence of high blood pressure, low HDL, and high triglycerides among those with greater exposures	Based on title/abstract screening for newly identified studies identified in the most recent literature search update, EPA has determined that these new studies will not have a material impact on the hazard conclusions for DCS and diabetes in the external review draft.	No (cross-sectional study)
Kupsco et al. (2019)	DCS	Blood arsenic associated with lower leptin in children 4–6 yo		No (blood biomarker study)
Wen et al. (2019)	DCS	Plasma arsenic associated with increased risk of ischemic stroke		No (blood biomarker study)
Wang et al. (2020a)	DCS	Study investigated association between metals in blood and hypertension; arsenic measured but not mentioned in results		No (cross-sectional study)
Medina-Estevez et al. (2020)	DCS	Study investigated association between metals in blood and stroke; arsenic not mentioned in results		No (blood biomarker study)
Zhong et al. (2019)	DCS	Urinary arsenic associated with increased incidence of hypertension		No (hypertension study)
Wang et al. (2020e)	DCS	Blood arsenic associated with increased prevalence of preeclampsia		No (blood biomarker study)

Reference (HERO ID)	Health outcome	Summary of study findings	EPA characterization for hazard identification	Included in meta-regression (rationale)
Howe et al. (2021)	DCS	Child blood pressure study, urinary arsenic measured but not mentioned in results		No (did not adjust for creatinine)
Velmurugan et al. (2020)	DCS, Diabetes	Total organophosphate level and arsenic accumulation in serum showed association with diabetes and atherosclerosis		No (cross-sectional study)
Karakulak et al. (2021)	DCS	Blood arsenic associated with diastolic dysfunction		No (cross-sectional study)
Torres-Arellano et al. (2020)	DCS	Associations between plasma BNP and urinary arsenic exposure		No (cross-sectional study)
Sobel et al. (2020)	DCS	Rice intake and urinary arsenic was not associated with subclinical CVD markers in a multiethnic US population		No (rice intake study)
Xu et al. (2020)	DCS	CVD risks increased with iAs exposure from rice at exposures above 0.3 µg/person/day		No (ecological study)
Suchy-Dicey et al. (2020)	DCS	Significant associations between urinary arsenic and higher burden of white matter hyperintensity (WMH)		No (not a meta-regression endpoint – vascular brain injury or cerebral atrophy)

Reference (HERO ID)	Health outcome	Summary of study findings	EPA characterization for hazard identification	Included in meta-regression (rationale)
Pichler et al. (2019)	DCS	Urinary arsenic associated with an increase in LV wall thickness and LV hypertrophy in young American Indians		No (not a meta-regression endpoint – cardiac geometry and left ventricular function)
Karakis et al. (2021)	DCS, Pregnancy, Neuro	Behavioral outcomes associated with urinary arsenic in children		No (did not adjust for creatinine)
Scannell Bryan et al. (2019)	DCS	Urinary arsenic associated with high blood pressure		No (blood pressure study)
Al-Forkan et al. (2021)	DCS	Urinary arsenic associated with SNPs		No (cross-sectional study)
Kaufman et al. (2021)	DCS	Association of urinary arsenic exposure biomarkers with blood pressure, and possible non-linear effects on incident hypertension		No (cross-sectional study)
Xu and Polya (2021)	DCS	Association of arsenic in rice and hypertension		No (cross-sectional study)
Ghaedrahmat et al. (2021)	DCS, Diabetes	Association of urinary arsenic and high fasting blood sugars		No (not a meta-regression endpoint – metabolic syndrome)

Reference (HERO ID)	Health outcome	Summary of study findings	EPA characterization for hazard identification	Included in meta-regression (rationale)
Zhang et al. (2022c)	DCS	No difference in arsenic serum between hypertensive and control groups		No (cross-sectional study)
Nigra et al. (2021)	DCS	Urinary iAs exposure at low-to moderate-levels is consistent with increased heart disease mortality		No (not a meta-regression endpoint – mortality from heart disease [all diseases of the heart])
Grau-Perez et al. (2022)	DCS	Urinary arsenic associated with atherosclerosis risk factors		No (cross-sectional study)
Xu et al. (2022)	DCS	Urinary arsenic associated with diabetes		No (cross-sectional study)
Skalny et al. (2021)	DCS	Hair arsenic associated with CHD in normal weight and obese		No (hair biomarker study)
Wang et al. (2021b)	DCS	Urinary arsenic exposure associated with changes in blood pressure during pregnancy		No (not a meta-regression endpoint – blood pressure)
Yen et al. (2022)	DCS	Study looked at metals and stroke; arsenic in serum and urine measured but not discussed in results		No (cross-sectional study)
Nasab et al. (2022)	DCS, Diabetes	Urinary arsenic associated with with FBS and lipid profile (TC, TG, LDL, HDL)		No (cross-sectional study)

Reference (HERO ID)	Health outcome	Summary of study findings	EPA characterization for hazard identification	Included in meta-regression (rationale)
Wang et al. (2021a)	DCS	Urinary arsenic associated with changes in blood pressure in midlife women		No (not a meta-regression endpoint – blood pressure)
Zhang et al. (2022a)	DCS	Arsenic in blood measured in hypertension study but not mentioned in results		No (cross-sectional study)
Andrews et al. (2022)	DCS	Arsenic exposures during pregnancy were consistently associated with increased average maternal systolic and diastolic BP.		No (not a meta-regression endpoint – blood pressure)
Cheng et al. (2021)	DCS	ADIPOQ/rs266729 and FABP2/rs1799883 polymorphisms affect susceptibility to essential hypertension in individuals exposed to high levels of arsenic		No (not a meta-regression endpoint - hypertension)
da Silva Nunes et al. (2022)	DCS, Diabetes	Negative association between urinary arsenic and VAI, triglycerides, and VLDL cholesterol; Urinary arsenic negatively associated with systolic blood pressure		No (cross-sectional study)
Tang et al. (2022)	DCS	Urinary As associated with diastolic blood pressure in non-hispanic Asians; urinary As associated with increased systolic BP in other groups		No (cross-sectional study)

Reference (HERO ID)	Health outcome	Summary of study findings	EPA characterization for hazard identification	Included in meta-regression (rationale)
Liu et al. (2022c)	DCS	Null association between urinary As and coronary heart disease		No (ORs not reported by dose group)
Liu et al. (2022a)	DCS	Blood arsenic associated with preeclampsia		No (cross-sectional study)
Farzan et al. (2022)	DCS	Well water As concentrations associated with endothelial dysfunction as measured by reactive hyperemia index		No (cross-sectional study)
Xua et al. (2021)	DCS	Conflicting associations between drinking water As concentrations and hypertension, and low and high density lipoprotein		No (cross-sectional study)
Liu et al. (2022b)	DCS	Generally null associations between urinary As and measures of hypertension in children		No (not a study type applicable to meta-regression)
Kuo et al. (2022)	DCS	Urinary As associated with increased cardiovascular mortality		No (numeric dose groups not reported)
Paul et al. (2019)	Diabetes	As drinking water concentration associated with prevalence of hyperglycemia, impaired glucose tolerance, and diabetes		No (cross-sectional study)

Reference (HERO ID)	Health outcome	Summary of study findings	EPA characterization for hazard identification	Included in meta-regression (rationale)
Eick et al. (2019)	Diabetes	As drinking water exposure associated with increased risk of diabetes in low SES, but not high SES, populations		No (high exposure population)
Wang et al. (2020b)	Diabetes	Urinary As levels associated with increased risk of gestational diabetes		No (gestational diabetes study)
Saba et al. (2020)	Diabetes	Urinary As associated with non-statistically significant increase in diabetes		No (did not adjust for creatinine)
Hendryx et al. (2019)	Diabetes	As from air and water emissions statistically significantly associated with increased risk of diabetes		No (not a drinking water study)
Rehman et al. (2019)	Diabetes	Urinary As concentration associated with random blood glucose and HBA1c		No (iAs risk values not reported)
Wang et al. (2020c)	Diabetes	Blood As concentration statistically significantly associated with diabetes		No (numeric dose groups not reported)
Wang et al. (2020d)	Diabetes	Urinary As concentration associated with slightly faster rate of HOMA-beta decline (homeostatic model assessment of insulin resistance)		No (numeric dose groups not reported)
Wang et al. (2019)	Diabetes	Blood As associated with increased risk of gestational diabetes		No (gestational diabetes study)

Reference (HERO ID)	Health outcome	Summary of study findings	EPA characterization for hazard identification	Included in meta-regression (rationale)
Dai et al. (2020)	Diabetes	Blood As (exposure from coal burning) associated with significantly increased risk of diabetes		No (blood biomarker study)
Zhang et al. (2020)	Diabetes	Urinary DMA levels associated with increased risk of diabetes		No (cross-sectional study)
Arab YarMohammadi et al. (2021)	Diabetes	Cases of type 2 diabetes had four times higher urinary As levels compared to controls		No (cross-sectional study)
Lucio et al. (2020)	Diabetes	Urinary total As and As metabolites positively correlated with hemoglobin A1c		No (iAs risk values not reported)
Yang et al. (2019)	Diabetes	Null association between toenail As and diabetes, fasting glucose, insulin, or homeostatic model assessment of insulin resistance		No (toenail biomarker study)
Tinkelman et al. (2020)	Diabetes	Urinary maternal As associated with increased diabetes		No (numeric dose groups not reported)
Chen et al. (2021)	Diabetes	Null association between urinary As and gestational diabetes, however women with gestational diabetes has impaired methylation capacity		No, gestational diabetes study
Zhang et al. (2022b)	Diabetes	Null association between blood and urinary As and diabetes and fasting glucose		No (cross-sectional study)

Reference (HERO ID)	Health outcome	Summary of study findings	EPA characterization for hazard identification	Included in meta-regression (rationale)
Jia et al. (2021)	Diabetes	Null association between maternal hair As and gestational diabetes		No (hair biomarker study, gestational diabetes study)
Weiss et al. (2022)	Diabetes	Urinary As associated with lower HOMA-beta and HOMA-IR and lower HOMA-S		No (cross-sectional study)
Wang et al. (2022)	Diabetes	Urinary As provided positive weight to environmental risk score for metabolic syndrome		No (gestational diabetes study)
Wu et al. (2021)	Diabetes	Null association between total urinary As and prediabetes, diabetes, or HbA1c		No (numeric dose groups not reported)
Rangel-Moreno et al. (2022)	Diabetes	Positive association with urinary arsenic and diabetes		No (non-monotonic dose response)
Fan et al. (2022)	Diabetes	Increased risk of diabetes with increasing urinary As concentration		No (numeric dose groups not reported)
Zhou et al. (2022)	Diabetes	Evidence of increased insulin resistance with increasing urinary As concentration		No (cross-sectional study)
Yang et al. (2022)	Diabetes	Null association with As and risk of diabetes		No (cross-sectional study)

Reference (HERO ID)	Health outcome	Summary of study findings	EPA characterization for hazard identification	Included in meta-regression (rationale)
Li et al. (2021)	Diabetes	Rice consumption associated with lower urinary MMA and increased insulin resistance, especially in obese individuals		No (cross-sectional study)

APPENDIX C. STUDY SELECTION, MODELING METHODS, AND RESULTS FOR DOSE-RESPONSE

C.1. RISK-AT-A-DOSE BAYESIAN META-REGRESSION DOSE-RESPONSE

C.1.1. Meta-Regression Modeling Methods

The Bayesian meta-regression modeling methods described by (Allen et al., 2020b; 2020a) were used in this assessment. This section summarizes those methods, adding additional details (e.g., for sensitivity analyses) relevant to the specific needs of this assessment. Access to all support files used in the application of these methods is available from the inorganic arsenic HERO project page.

Treatment of Dose Uncertainty

The treatment of dose estimation and conversion to a common set of units has been handled as summarized in Figure C-1.

Figure C-1. Dose uncertainty flow chart in relation to MLE, low-end, and high-end dose sets and risk estimates.

[1]High group means minimized or maximized subject to constraint that −2*(LL–MLL) < 2.706 (a 95% bound on the high-group mean). LL is the log-likelihood for the lognormal distribution for the candidate parameter vector; MLL is the maximum log-likelihood. When a published study reports the mean or median values for each group, those values are used directly as the group-specific dose values, with no lognormal fitting.

[2]The terminology "low-end," "high-end," and MLE estimates are used to avoid confusing the values with credible (or confidence) interval bounds having a specific numerical value (e.g., 95%). Combining the log-likelihood bounds for group-specific means, with percentiles from the Monte Carlo analysis, and with percentiles of the β_mean distributions does not allow determination that the bounding estimates have any identifiable associated "confidence level." They do, however produce reasonable semi-quantitative limits on how uncertain the resulting estimates are.

Estimating representative values for exposure groups

When the published reports of a study present results categorized by exposure group, and those groups are defined in terms of ranges of exposure without providing mean or median values for each group,[1] EPA had to estimate those means to serve as the "representative" values for the exposure groups. In essence, EPA treated the data as if the observations within a group had the same (mean) value estimated for that group. The procedure for doing that is described here.

Suppose that a study has G exposure groups defined as $(c_0, c_1), (c_1, c_2), \ldots, (c_{G-1}, c_G)$; c_0 may equal 0 and c_G may equal ∞. Let τ, with elements τ_g, be the vector of observed proportions of individuals in groups g = 1, …, G. As discussed below, for a case-control study, only the control counts were used to define the τ values; otherwise, all individuals were used to define τ.

EPA assumes that individual exposures follow a lognormal distribution with parameters μ and σ (respectively, the mean and standard deviation of natural logarithms of exposure); the same assumption was made by Moon et al. (2017) in their analysis of arsenic risks. EPA estimates these parameters by maximum likelihood (ML), maximizing the following log-likelihood expression appropriate for the censored data:

$$log - likelihood \; = \; N \cdot \sum_{g=1}^{G} \tau_g \cdot ln(\varphi(ln(c_g) \mid \mu, \sigma) \; - \; \varphi(ln(c_{g-1}) \mid \mu, \sigma)) \qquad \text{Eq. 1}$$

where N is the total number of observations under consideration and $\varphi(x \mid \mu, \sigma)$ is the cumulative distribution function for the Normal distribution with mean μ and standard deviation σ. Let μ' and σ' be the ML estimates (MLEs) given τ and the values of c_g (g = 0, …, G). A simple likelihood maximization routine, implemented with an Excel spreadsheet (see Supplemental Material), was used to estimate μ' and σ'.

Given μ' and σ', the mean within a given exposure interval (c_g, c_{g+1}) is given by:

$$mean(g) = e^{\left(\mu\prime + \frac{\sigma\prime^2}{2}\right)} \times \frac{\theta(U_1(g) - \sigma\prime) - \theta(U_0(g) - \sigma\prime)}{\theta(U_1(g)) - \theta(U_0(g))}, \qquad \text{Eq. 2}$$

where $U_1(g) = \frac{(ln(c_{g+1}) - \mu\prime)}{\sigma\prime}$, $U_0(g) = \frac{(ln(c_g) - \mu\prime)}{\sigma\prime}$, and $\theta()$ is the cumulative distribution function for the standard normal distribution (Söderlind, 2013).

In addition to the maximum likelihood estimate of an exposure for each dose group, EPA has computed what are referred to as "low-end" and "high-end" exposure estimates. Those estimates were based on profile likelihood bounds for the mean exposure for individuals in the high-exposure group. First, EPA computed the maximized log-likelihood (MLL) (the log-likelihood associated with MLEs of the parameters μ and σ). Then the mean value for the high group was maximized by modifying μ and σ subject to the constraint that:

[1]If means or medians were reported for the groups, EPA used either of those values as the representative values for those groups. Moreover, EPA did not consider uncertainty associated with estimating mean values for each group, as discussed later in this subsection.

$$-2 \times (LL - MLL) \leq 2.706 \quad \text{Eq. 3}$$

where LL is the log-likelihood associated with the modified μ and σ. This is a chi-squared-based (1 degree of freedom) 95% confidence upper bound on the high-group mean. The same procedure was followed to determine a 95% confidence lower bound on the high group mean by minimizing the mean value for the high group under the same constraint (Eq 2).

Note that we are only specifically maximizing (or minimizing) the mean for the highest exposure group. In some instances, this may result in a change in the estimated mean for other groups (primarily the lowest exposure group) when the modified μ and σ are input into Eq 1. EPA has opted for this procedure for two primary reasons. First, the highest exposure group is almost always the one that is most uncertain, often presented as an open-ended interval. The mean for that group is not easily nor consistently estimated by techniques that can be applied to the other exposure groups (e.g., by taking the midpoint of the interval). Second, the dose and response observations for the highest exposure group often have a large impact on dose-response model estimation. Especially for the slope parameters in a model, the positioning of the highest dose-response pair can be very influential. Thus, our procedure focuses on that influential observation and derives bounds specifically tailored to determine the full range of possible values for exposure consistent with the data (and our assumption of lognormality of exposures over the studied population) for that observation.

Units conversion uncertainties

Estimation of a common dose metric (as opposed to exposure metric[2]) for all studies is imperative to account for the effect of dose on the estimated response. However, epidemiologic studies often use different, but related, exposure- or dose-metrics such as exposure concentration, cumulative exposure, and even biomarkers of exposure such as internal tissue concentrations or urinary concentrations of the chemical of interest. In this specific case-report, if the data presented in all the published studies had been in the units of interest (daily average μg/kg), no conversion would be necessary, and dose-response meta-analysis (DRMA) could be performed with the study-reported data. However, that was not the case for the studies under consideration here, nor would it be in general practice. Furthermore, epidemiological risk assessments do not always include results from regression analysis, the type of data that directly accounts for inter-individual variability. Considering a recent call from the NAS to better account for uncertainty in the dose-response approach, EPA views this as a major shortcoming.

[2]In this document, the term "exposure" represents contact between an agent and a target at an exposure surface; the term "dose" represents the amount of agent that crosses an exposure surface, whether the surface is an absorption barrier or not (e.g., absorption barriers such as the lining of the stomach or lungs versus conceptual surfaces over the nose or open mouth). (Zartarian et al. (2005) official ISEA glossary; J Expo Anal Environ Epidemiol 2005; 15:1–5).

To address these issues, the proposed DRMA includes a dose conversion step that converts disparate exposure or dose metrics into a common dose metric while accounting for uncertainty. The dose conversion is performed at the dose group level. A common dose metric is calculated for each dose group from a set of conversion factors. Conversion factors are typically approximated by population-level sample means in the inorganic arsenic (iAs) literature; dose-group-level data is not often available. However, using population-level means for a group-level analysis ignores sampling variability that would likely exist between group-level means. It also ignores the fact that groups with more observations have less uncertain mean estimates than those with fewer observations. Neglecting to account for these sources of variation impacts the final common dose metric estimate by biasing our estimate away from the null. Accordingly, we include a Monte Carlo (MC) sampling step in our dose conversion process to explicitly consider exposure group sample sizes in the mean estimates of conversion factors.

Our approach allows for the use of multiple exposure metrics to characterize iAs exposure and answers the NAS call to address uncertainty. This approach is designed to accommodate the unique features of the iAs literature (e.g., many studies with large variation in exposure metrics and with results reported as exposure ranges with associated adjusted RRs or ORs with confidence intervals) and is not necessarily intended to be generalized to other approaches. It is worth noting that if group-level summary statistics are in fact reported, EPA recommends proceeding with the dose conversion without the MC sampling step.

Dose-Conversion Method Overview

The first step in our dose conversion approach is to identify the factors required to convert to μg/kg. As an example, consider a study that reported cumulative drinking water exposures, in (μg iAs/L drinking water) × years. The conversion from cumulative exposures to average daily dose (μg/kg) was carried out as follows:

$$dose = DI + f \times (WCR \times WE) + (1 - f) \times (WCR \times LE) \quad \text{Eq.4}$$

where the terms in that expression are DI = dietary intake (average daily μg/kg); f = fraction of time (over lifetime up through the study) spent consuming well water (unitless); WCR = water consumption rate (L/kg); WE = well water concentration (μg/L); and LE = low-end water concentration (μg/L). The variable f was calculated as the ratio of the assumed average duration of well exposure (ADWE), generally the reported duration of drinking well water (RDWE; yr), to the average age at diagnosis (AAD; yr). It was assumed that when drinking non-well water, the subjects consumed water with the low-end water concentration. The parameter WE was derived separately for each group by dividing the reported cumulative exposure (μg/L-yr) for that group by the RDWE: $WE = \frac{CE}{RDWE}$. The values used in Eq 4, above, ideally would come from study-specific data reported in the study of interest but could also be drawn from other suitable sources (e.g., from other studies reporting on the same study population or from national authoritative sources).

Next, probability distributions are inferred for each conversion factor with parameters based on the factor's reported means and standard deviations. The distribution assumed for the individual conversion factors is either based on sources from the scientific literature or assumptions given the nature of the conversion factor (e.g., using a lognormal distribution for non-negative data). For instance, lognormal distributions were assumed for DI, WCR, RDWE, and LE, whereas a beta distribution was used for the f variable. These distributions represent individual or population-level variability in each factor and were based on knowledge of the population from which the study participants were drawn (e.g., exposure factors handbook values or study-specific data). Independence between the conversion factors is assumed.

We then conduct an MC analysis, sampling from the assumed distributions for the exposures within a group and for each exposure factor. For a given study, the respective distributions for the conversion factors are sampled N times, where N is the number of individuals in a dose group, and computed N daily intake values (representing the N individuals in the group). In situations where N>1,000, the analysis is truncated at 1,000 to ease computational burden, as distributions of mean values with this many random values can be expected to be narrow. EPA averaged across the resulting N individual daily intake values to generate a final, average daily intake value for each dose group. This process was repeated 1000 times to derive a MC distribution of average daily intake values. The overall median as well as the 5th and 95th percentiles of the sample means were calculated from the MC simulation results to characterize the MLE, low-end, and high-end dose values. The entire procedure is implemented using the Excel add-in, YASAIw v2.0. When necessary, reported summary statistics were converted to the appropriate scale or value to be used as distribution parameters either via YASAI or by hand. For full details of the analysis, see the published manuscript "Systematic Dose-Response of Environmental Epidemiology Studies: Dose and Response Pre-Analysis" (https://www.sciencedirect.com/science/article/pii/S0160412020317657).

Other items to note include the fact that dietary exposure is included in all the conversions. Thus, our dose estimates represent total iAs intake from all oral routes, not necessarily just exposure from drinking water. Our approach explicitly considers the sample sizes in each exposure group; by averaging over the number of individuals in each group, it is automatically considered that groups with more observations will be less uncertain (about the mean group-specific conversions) than groups with fewer observations.

Finally, note that each study, possibly reporting different exposure summaries, is handled differently depending on the reported units. For example, consider a study that used daily arsenic exposure (in units of μg/day) as the dose metric rather than cumulative exposure in units of (μg iAs/L drinking water) years. Thus, the conversion to average daily μg/kg (dose) was carried out as follows:

$$dose = DI + f \times \left(\frac{WE}{BW}\right) + (1 - f) \times (WCR \times LE) \qquad \text{Eq.5}$$

where the terms in that expression are as above with the addition of BW = body weight (kg). The variable f was estimated as described above, but in the case of a daily exposure study, the parameter WE was derived separately for each group by dividing the reported daily exposure (µg/day) for that group by a BW value.

All dose conversions were computed via Excel, using the MC simulation add-in Yasai (www.yasai.rutgers.edu). While other software programs or languages (i.e., R or Python) are more powerful in some regards and could be used to implement the dose-conversions, Excel was chosen for its ubiquity of use and because Excel workbooks are useful for organizing the analyses for presentation.

Details on Dose Conversion Method Development, Including Sensitivity Analyses

This section contains a discussion and sensitivity analyses which address the following key issues: Distributional assumptions for conversion factors; Sensitivity to reported conversion factor sample means.

Random sampling of exposure metrics

In addition to assuming that all conversion factors follow a probability distribution, the dose conversion methodology also involves random sampling from the distribution of exposure metric values. Our approach utilizes a restricted lognormal distribution where the limits of sampling correspond to the minimum and maximum of each dose metric range and that samples proportionately to the number of individuals observed in each dose range. EPA implemented this approach using inverse probability sampling.

Although including sampling from the exposure metric distribution for the dose conversion method is conceptually more robust than relying on a single dose metric estimate, it does not result in a large difference in the ultimate daily intake estimated via Monte Carlo sampling. This difference is illustrated by comparing dose metric estimates calculated via the sampling approach to dose metric estimates calculated using single point exposure estimates calculated via maximum likelihood estimation (MLE) for the Meliker et al. (2010) and Chen et al. (2010b) study (see Table C-1). Results show that when considering the low dose group, the final "Most Likely (Mean)" daily intake changed 0.0% when comparing the MLE approach to the sampling methodology for the Meliker et al. (2010) study (see "LOGNORMAL" vs. "ORIGINAL" results, Main tab, *Meliker2010_CE5-Ln_ugperday-08-08-22.xlsx* , Supplemental Material, bladder cancer intake uncertainty folder, EPA HERO database). The magnitude of difference is larger when comparing the high dose group for "Low (5th percentile)" and "High (95th percentile) estimates of daily intake: 13.5% (from 0.334 to 0.379) and −23% (from 0.723 to 0.556), for the low and high estimates, respectively. This is consistent with the fact that daily intake estimates reflect sampling in the tails of the distribution (with the larger difference in the high (95th percentile) intake value explained by the right skewedness of the lognormal distribution). The effect on final intake values is of a smaller magnitude in the Chen et al. (2010b) study, with the low dose "Most Likely (Mean)" changing 0.0%

and the high dose group differences being <10% consistent with the larger sample size in that study (see "LOGNORMAL" vs. "ORIGINAL" results, Main tab, *Chen_2010_NE_Taiwan_bladder-08-10-22.xlsx* , Supplemental Material, bladder cancer intake uncertainty folder, EPA HERO database).

Table C-1. Fixed dose metrics versus sampled (random) dose metrics

Dose ranges	Most likely (Mean)		Low (5th percentile)		High (95th percentile)	
	Fixed[a]	Random[b]	Fixed[a]	Random[b]	Fixed[a]	Random[b]
Meliker et al. (2010)						
0–10	0.103	0.103 (0.0%)	0.097	0.096 (−0.6%)	0.110	0.110 (0.8%)
10–100	0.145	0.139 (−4.1%)	0.136	0.130 (−3.9%)	0.154	0.148 (−4.3%)
100–1,000	0.455	0.454 (−0.3%)	0.334	0.379 (13.5%)	0.723	0.556 (−23.1%)
Chen et al. (2010b)						
0–400	0.830	0.830 (0.0%)	0.810	0.810 (0.0%)	0.851	0.853 (0.1%)
400–1,000	1.106	1.108 (0.1%)	1.078	1.080 (0.2%)	1.136	1.135 (−0.1%)
1,000–5,000	2.042	2.039 (−0.1%)	1.956	1.971 (0.8%)	2.120	2.109 (−0.5%)
5,000–10,000	4.65	4.64 (−0.2%)	4.40	4.40 (0.0%)	4.91	4.89 (−0.4%)
10,000–100,0000	21.60	21.72 (0.6%)	18.20	19.65 (8.0%)	26.15	24.02 (−8.1%)

[a]Fixed = original.
[b]Random = MC sampling.

Distributional assumptions for conversion factors

The dose-conversion approach assumes that conversion factors can be described via probability distributions. Details and justifications for all conversion factors used in the EPA meta-regression analyses are documented in the "conversion actor validation spreadsheet" available from a link within the EPA inorganic arsenic HERO project database. This section provides a summary of the choice of distributions used for the individual conversion factors. As Table C-2 summarizes, distributional assumptions stem from the literature where possible, and otherwise, were chosen so as to reflect the most appropriate distribution given the type of data.

The distributions of body weight, low exposure concentration, U.S. water consumption rate (WCR) and dietary intake, can all be justified in the literature. Distributions for the conversion

factors, f-value, WCR outside the U.S. and reported duration of well-exposure (RDWE), were not available in the literature and so were chosen based on the data types and expert judgement. The f-value is bounded between 0 and 1 and has a "most-likely value", namely the quotient of average values of age and duration of exposure. The f-value is defined as the ratio between average age at diagnosis and the reported duration of well exposure. Hence, EPA used the PERT-beta distribution, which is appropriate for bounded data with known "most-likely" value. Since WCR and RDWE are always greater than or equal to zero, and range from zero to infinity (theoretically), EPA chose a lognormal distribution as representative, since it is restricted to non-negative values (see Table C-2 below). For U.S. studies like Meliker et al. (2010) that did not provide an indication of study-specific WCR, a two-step approach was used to derive a WCR that accounts for the (1) zero direct or indirect water consumption reported for 35% of the U.S. population and (2) "consumer-only" direct and indirect water consumption mean of 16.6 mL/kg-day and SE of 0.3 mL/kg-day SE reported for 65% of the sampled U.S. population (15,219) in Table 3-21 of the EPA Exposure Factors Handbook (U.S. EPA, 2019).

Table C-2. Conversion factor probability distributions

Conversion factor	Distribution	Rationale and citation
Body weight	Lognormal	The lognormal distribution is reported to fit the percentiles for weight for men and women as a function of age (from 6 mo to 74 yr (Burmaster and Crouch, 1997; Brainard and Burmaster, 1992).
Low exposure concentration	Lognormal	The lognormal distribution is reported to provide best fit to drinking water concentrations; EPA assumed this is true for low exposure drinking concentrations as well (Xue et al., 2010)[a].
Dietary intake	Limited Normal	The technical manual for SHEDS-Dietary model that Xue et al. (2010) used to estimate dietary intake indicates that a normal distribution was used for consumption. The MCMC simulation limited dietary contribution to between 0 and 1000 µg/kg-d.
f-Value (ratio of assumed avg. duration of well exposure to average age at diagnosis)	PERT-Beta	The PERT-Beta distribution is appropriate for bounded data with known "most likely value" (YASAI-W User Manual). The f-value is bounded by the interval 0–1 given it is a ratio of the duration of well exposure to average age at diagnosis, with a "most likely value" being the ratio of the average values for both of those variables.
Water consumption rate	Lognormal	The lognormal distribution appropriately represents nonnegative data, such as the water consumption rate. To reflect the data reported in U.S. EPA (2019), the MCMC WCR distribution for U.S. studies (lacking study-specific information) simulate a lognormal distribution with a mean of 16.6 µg/kg-d and SD of 37 (0.3 SE × √15,219), adjusting values to zero with a 35% probability.
Reported duration of well exposure	Lognormal	The lognormal distribution appropriately represents nonnegative data, such as reported duration of well exposure.

[a]This additionally provides justification for choosing a lognormal distribution for all dose metrics (see Topic #1, above) as all dose metrics are ultimately derived from drinking water concentrations.

EPA also considered restricted normal and uniform distributions but found no substantial difference between the resulting daily dose estimates and those from an analysis using lognormal distributions for WCR and RDWE (see Table C-3). For example, for the Meliker et al. (2010) study, when assuming a lognormal distribution for both WCR and RDWE, the MLE low dose daily intake estimate is 0.103 µg/kg-day; changing the assumption to either a restricted normal or uniform distribution for both variables only changes the final daily intake MLE value 6% (0.109 µg/kg-day) and 3% (0.106 µg/kg-day), respectively. The magnitude of difference is similar for other MLE, low (5th percentile) and high (95th percentile) dose estimates for Meliker et al. (2010) and Chen et al. (2010b), particularly low- to mid-exposure levels. Hence, EPA concludes that our results are robust to the choice lognormal, restricted normal and uniform distributions, and makes the conceptually appropriate and computationally efficient assumption that WCR and RDWE follow a lognormal distribution.

Table C-3. MLE, low and high MCMC dose estimates for three different WCR and RDWE distribution assumptions[a]

Exposure ranges (µg/L)	Most likely (MLE; µg/kg-d)			Low (5th percentile µg/kg-d)			High (95th percentile µg/kg-d)		
	Log-normal	Normal	Uniform	Log-normal	Normal	Uniform	Log-normal	Normal	Uniform
Meliker et al. (2010)									
0–10	0.103	0.109	0.106	0.101	0.100	0.099	0.110	0.116	0.112
10–100	0.145	0.145	0.152	0.136	0.124	0.142	0.154	0.154	0.162
100–1,000	0.455	0.450	0.457	0.333	0.266	0.336	0.723	0.729	0.706
Chen et al. (2010b)									
0–400	0.830	0.835	0.771	0.810	0.804	0.753	0.851	0.897	0.788
400–1,000	1.106	1.275	0.928	1.078	1.013	0.908	1.136	1.325	0.949
1,000–500	2.042	2.463	1.460	1.956	1.800	1.418	2.120	2.753	1.503
5,000–10,000	4.646	13.561	2.942	4.402	3.551	2.820	4.912	6.973	3.072
10,000–100,0000	21.595	22.264	12.685	18.196	15.074	10.634	26.152	37.053	15.284

[a]Dose estimates obtained from "NORMAL", "UNIFORM" and "LOGNORMAL" results, Main tab, Meliker2010_CE5-Ln_ugperday-08-08-22.xlsx and Chen_2010_NE_Taiwan_bladder-08-10-22.xlsx, Supplemental Material, bladder cancer "Intake Uncertainty…" folder, EPA HERO database).

Sensitivity to reported conversion factor sample means

To define the assumed distributions of the conversion factors, mean and standard deviations identified in the literature are used. While these mean and standard deviation values are from reliable sources (i.e., peer-reviewed articles, authoritative exposure factor documents, etc.), it is possible that error is introduced into the final daily intake values if the reported means do not accurately reflect the true population mean. A sensitivity analysis was conducted to address this.

For two representative studies, Meliker et al. (2010) and Chen et al. (2010b), EPA added/subtracted 5% and 10% to each conversion factor mean. Five and ten percent were chosen to simulate varying amounts of measurement error. The altered means were then used as centrality parameters to define the conversion factor sampling distributions, which were used to carry out the sampling approach to get estimates of the most likely, low and high lifetime daily dose. Finally, EPA compared these estimates to those from an analysis with the default, unchanged means in order to evaluate the robustness of the lifetime daily dose estimates to variation in the conversion factor means (see Table C-4).

Consistent, but small, generally <10%, changes in each estimate were found for the analyses with 5% and 10% added/subtracted. Table C-4 summarizes the results from the analysis with 5% and 10% added/subtracted (for details, see "LOGN" results, Main tab, *Meliker2010_CE5-Ln_ugperday-08-08-22.xlsx* and *Chen_2010_NE_Taiwan_bladder-08-10-22.xlsx* , Supplemental Material, bladder cancer intake uncertainty folder, EPA HERO database). Therefore, EPA concludes that the analysis is tolerably insensitive to changes in the mean values of the exposure factors used to inform the distributions of the conversion factors.

Table C-4. Sensitivity of MC sampling to variation in conversion factor means; dose estimates and percent change

Dose range	Most likely (Mean; µg/kg-d)					Low (5th percentile; µg/kg-d)					High (95th percentile; µg/kg-d)				
	0%	−5%	5%	−10%	10%	0%	−5%	5%	−10%	10%	0%	−5%	5%	−10%	10%
Meliker et al. (2010)															
0–10	0.103	0.102	0.105	0.101	0.107	0.097	0.095	0.098	0.094	0.100	0.110	0.108	0.112	0.108	0.114
		−1.1%	1.8%	−2.0%	3.7%		−1.6%	1.1%	−2.9%	3.5%		−1.1%	1.9%	−1.8%	3.7%
10–100	0.145	0.141	0.148	0.138	0.153	0.136	0.133	0.139	0.129	0.143	0.154	0.150	0.159	0.147	0.162
		−2.6%	2.4%	−4.9%	5.8%		−2.3%	2.9%	−5.0%	5.6%		−3.1%	2.6%	−4.7%	5.2%
100–1,000	0.455	0.422	0.474	0.393	0.497	0.334	0.315	0.345	0.294	0.362	0.723	0.659	0.752	0.610	0.746
		−7.4%	4.0%	−13.7%	9.1%		−5.6%	3.4%	−11.9%	8.4%		−8.9%	4.0%	−15.7%	3.2%
Chen et al. (2010b)															
0–400	0.830	0.796	0.865	0.764	0.899	0.810	0.776	0.845	0.743	0.878		0.819	0.888	0.787	0.920
		−4.1%	4.2%	−8.0%	8.3%		−4.3%	4.3%	−8.3%	8.4%		−3.8%	4.2%	−7.6%	8.1%
400–1,000	1.106	1.068	1.148	1.026	1.190	1.078	1.039	1.122	0.996	1.163		1.097	1.122	1.056	1.218
		−3.5%	3.8%	−7.3%	7.5%		−3.6%	4.1%	−7.5%	7.9%		−3.5%	3.8%	−7.0%	7.2%
1,000–5,000	2.042	1.976	2.105	1.915	2.172	1.956	1.893	2.031	1.832	2.091		2.058	2.031	1.998	2.252
		−3.2%	3.1%	−6.2%	6.4%		−3.2%	3.8%	−6.4%	6.9%		−2.9%	3.1%	−5.7%	6.2%
5,000–10,000	4.65	4.52	4.77	4.39	4.91	4.40	4.26	4.51	4.11	4.67		4.81	4.51	4.67	5.17
		−2.8%	2.7%	−5.5%	5.6%		−3.2%	2.5%	−6.7%	6.0%		−2.2%	2.6%	−4.9%	5.1%
10,000–1,000,000	21.60	21.21	22.29	20.65	22.85	18.20	17.48	18.65	17.12	19.06		25.87	18.65	25.46	27.45
		−1.8%	3.2%	−4.4%	5.8%		−3.9%	2.5%	−5.9%	4.7%		−1.1%	2.7%	−2.7%	5.0%

The most likely low and high lifetime daily dose was estimated for both Meliker et al. (2010) and Chen et al. (2010b) using analyses with no change (0%), 5% and 10% subtracted from, and 5% and 10% added to each conversion factor mean. Since BW has an inverse effect, the opposite was applied.
Units = µg/kg-day; values in parentheses represent magnitude of percent change between original values and ±5% or ±10% values.

Adjusting for Covariates

Computation of Effective Counts for Bayesian Meta-Regression Analyses

For both cohort and case-control studies, published manuscripts almost always report adjusted relative risks (RR's) or odds ratios (OR's), respectively. The adjusted results attempt to factor out the effects of other, possibly confounding, variables, in order to estimate the effect specifically associated with the exposure of interest, in this case arsenic exposure.

The Bayesian approach that EPA has adopted for the dose-response analysis Allen et al. (2020b) is based on likelihoods of observing a particular number of cases. For example, the number of observed cases in a cohort study is commonly modeled as coming from a Poisson distribution.

To deal with this requirement, adjusted counts of cases and controls (or cases and expected numbers) are computed which will be referred to as "effective count(s)" to avoid confusion with other adjustments that may be part of the analysis. The derivation of effective counts had one very specific goal: to construct a set of counts that reflects only the effect of arsenic. It attempts to construct a data set that would be as if all groups under consideration differed only with respect to arsenic dose but were uniform with respect to the other variables for which RR's or OR's were adjusted. As will be shown below, this involves adjusting so as to mimic data that might have been collected had all covariates (other than dose) in all groups been the same as those observed in the referent group. In the context of a case-control study, for example, the effective counts could be viewed as a single 2xG table (G = number of dose groups) of the effective counts of cases and controls which could be considered to represent what data one would have gotten from sets of individuals who were homogeneous with respect to other covariates. Therefore, "effective counts" are the data that would have resulted in the adjusted OR or RR values had confounding not occurred in the study population.

Calculation of effective counts has been the focus of multiple papers: Greenland and Longnecker (1992) reported on a method that retained original sample sizes but obtained the adjusted relative risks, Hamling et al. (2008) used a method that allowed sample sizes to change but resulted in the adjusted RRs and the standard error of the logRR, and Orsini et al. (2012) provided corrected equations for the variance of the logRR and concluded that either adjustment improved estimation (compared to using unadjusted counts). Both Greenland and Longnecker (1992) and Orsini et al. (2012) make clear that "relative risk" includes the metrics of OR, hazard ratio, etc., and so the methods can be applied to case-control studies, incidence rate studies, or cumulative incidence studies (see Rothman and Greenland (1998), for definitions of these study types, which are discussed further below). The definition of the variance terms for logRR varies across these study types, but they are all amenable to effective count calculations.

The term "effective count" refers to the fact that when making the adjustments to OR and RR, the impact of the other variables is removed. But the estimation of the associations between confounders and dose, and between confounders and the endpoint, "uses up" some of the degrees

of freedom associated with the initial sample size. In essence, the approximation of the "otherwise homogeneous set of individuals" mentioned above results in a smaller sample size for evaluating just the arsenic effect. The magnitude of that effect depends (among other things) on how strongly the set of confounders for which RR's or OR's have been adjusted are associated with the arsenic dose and with the endpoint of interest Rothman and Greenland (1998).

In practice, one typically has two sources of information from published literature from which effective counts can be estimated. The first source consists of the values of the adjusted RR's or OR's themselves. The derived counts should result in the values of the adjusted ratios reported when one computes a "simple" ratio from the effective counts. The second source of information is obtained from estimates of the standard errors (or confidence limits) reported for the RR's or OR's (or for log (RR) or log(OR)). Examples will illustrate the procedure for effective count computation.

Incidence Rate Cohort Study

This approach was implemented for cohort studies where observed numbers of cases and expected numbers of cases were presented (or derivable) and the study used an internal referent group for defining the relative risks. Consider the data shown in Table C-5, for the Chen et al. (2010b) dataset. The first group is the internal referent group (adjusted RR = 1 by definition).

Table C-5. Summarized data; cumulative incidence cohort study; Chen et al. (2010b)

Reported number of cases	Adjusted RR	95% LCL on adjusted RR	95% UCL on adjusted RR
6	1		
3	1.11	0.27	4.54
12	2.33	0.86	6.36
5	3.77	1.13	12.6
11	7.49	2.7	20.8

Chen et al. (2010b) reported RRs based on person-years of follow-up through Cox proportional hazard methods, i.e., the study is an incidence *rate* (not incidence proportion or cumulative incidence) study (see first paragraph, p. 105 of Chen et al. (2010b)). Orsini et al. (2012) give the standard deviation of the logRR(i) values from such a study as:

$$SE\big(logRR(i)\big) = \sqrt{\frac{1}{Cases(0)} + \frac{1}{Cases(i)}} \qquad \text{Eq. 6}$$

Here Cases(i) refers to the number of cases in group i, with the referent group being group 0. The number of cases in the referent group will be fixed; reasons for that decision are discussed at

the end of this section. Then it is easy to solve for Cases(i) in Eq 6 and then compute the expected[3] number as $\frac{Cases(i)}{adjusted\ RR}$[4]. Derivation of a value for SE (logRR(i)) is based on the reported confidence limits for the logRR(i) values, as follows. The standard procedure for estimating a 95% upper confidence bound for RR's is this (Rothman and Greenland, 1998):

$$95\%\ upper\ confidence\ limit = e^{(\log(RR)+1.96\times SE(\log(RR))} \quad \text{Eq. 7}$$

So that, by using the referent group and next group from the Chen et al. (2010b) study (see Table C-5),

$$4.54 = e^{(\log(RR_1)+1.96\times SE(\log(RR_1))} = e^{(\log(1.11)+1.96\times SE(\log(RR))}$$

so

$$SE(\log(RR_1)) = \frac{\log 4.54 - \log 1.11}{1.96}$$

from which Eq. 6 gives the effective count for Cases (1), which equals 2.84. In practice (and for results shown in Table C-6, for example), the results of using the upper bound and lower bound for the confidence interval are averaged to reduce the effect of round-off error in reported values. This is equivalent to equating the width of the confidence interval to 2 × 1.96 × SE (on the log scale). EPA computed the SE values for the two sides separately (and then averaged) as that facilitates the identification of errors or typographical mistakes in the reported values. The two SE estimates should be essentially the same, to the number of digits reported; if not, there may be an issue with the values reported. The expected effective count is given by:

$$Expected\ effective(1) = \frac{Cases(1)}{Adjusted\ RR} = \frac{2.84}{1.11} = 2.56 \quad \text{Eq. 8}$$

since, even with effective counts, RR = number of cases divided by expected number. The same procedure is followed for all the other dose groups. The results obtained for this example are displayed in Table C-6. Computation of RR using the effective cases and expected effective counts results in RR's and confidence bounds that match those reported as "adjusted" values in Chen et al. (2010b), as was expected.

In this particular case, the effective counts for the cases are very similar to the raw counts. Adjustment for the other covariates had little effect on effective counts in this instance.

[3]"Expected" here refers to what the expected number in group i would be if it had the same exposure as the reference group, but with its own specific confounder profile.
[4]Adjusted RR here refers to the adjusted relative risk value reported in the included studies.

Table C-6. Effective data derived for incidence rate cohort study; Chen et al. (2010b)

Effective cases	Effective expected number	RR	95% LCL on RR	95% UCL on RR
6.00	6	1		
2.84	2.56	1.11	0.27	4.54
10.65	4.57	2.33	0.86	6.36
4.72	1.25	3.77	1.13	12.6
9.56	1.28	7.49	2.7	20.8

Cumulative Incidence Cohort Study

For some analyses (e.g., for the cardiovascular disease analysis), the type of cohort study dealt with is called a cumulative incidence study (Rothman and Greenland, 1998). In that case, the RR's are ratios of the proportions of subjects getting bladder cancer; the data might be presented as in Table C-7.[5] EPA used this approach when the modeling required proportions of individuals affected (i.e., where binomial likelihoods were required), as with the categorical regression (CatReg) modeling reported for DCS endpoints.

Table C-7. Example cumulative incidence cohort study results

Cases(i)	Sample size (N(i))	Unadjusted		Adjusted	
		RR	SE(log(RR))	RR	SE(log(RR))
6	2,534	1		1	
3	1,120	1.13	0.71	1.11	0.72
12	2,078	2.44	0.50	2.33	0.51
5	524	4.03	0.60	3.77	0.62
11	632	7.35	0.51	7.49	0.52

The unadjusted RRs are simply equal to

$$(\text{Cases}(i)/N(i)) \,/\, (\text{Cases}(0)/N(0)) \qquad \text{Eq. 9}$$

where i indicates the group number and, again, group 0 corresponds to the referent group. The equation for SE(log(RR)) is

[5]These are actually the same data from Table C-6, but instead of presenting expected numbers, the sample sizes for the groups are shown, so as to illustrate the type of adjustment for cumulative incidence studies.

$$SE(\log(RR(i))) = \sqrt{[1/Cases(i) - 1/N(i) + 1/Cases(0) - 1/N(0)]}. \quad \text{Eq. 10}$$

Together, Eq-9 and Eq-10 define 2*n equations for 2*(n+1) unknowns.[6] Two additional equations are required to specify the system. Extending our approach to the incidence rate studies discussed above, Cases (0) will be fixed to be the same as reported in the data (e.g., 6 for the data in Table C-7). In addition, the value of N(0) (the sample size in the referent group, 2,534 for Table C-7) will also be fixed. The rationale for that choice is discussed at the end of this appendix.

The algebra that yields estimates for Cases(i) and N(i) is relatively straight-forward. The calculations are automated in a spreadsheet provided in the Supplemental Material. For the example in Table C-7, the resulting effective counts are shown in Table C-8. As desired the RR's and the confidence limits computed using the effective counts in Table C-8 match the corresponding "adjusted" values in Table C-7.[7]

Table C-8. Effective counts for example cumulative incidence cohort study

Adjusted cases	Adjusted N	RR	95% LCL on RR	95% UCL on RR
6.00	2,534	1		
2.83	1,077.83	1.11	0.27	4.54
10.55	1,912.40	2.33	0.86	6.36
4.67	523.29	3.77	1.13	12.6
9.35	527.47	7.49	2.7	20.8

Case-Control Studies

Consider the data in Table C-9, obtained from a published report of case-control study of arsenic and bladder cancer (Meliker et al., 2010).

[6]"Unknowns" in the sense that the effective counts that we desire are unknown to us and will result in values for Cases(i) and N(i) for i = 0, …, n. N = N(0) + … + N(n).

[7]Coincidently, the effective cases in Table C-7 and Table C-8 are very similar. That is the case because the effective count calculation in those two instances were based on the same data (just treated differently, according to the assumption about whether they are incidence rate or cumulative incidence data).

Table C-9. Reported case-control study results; Meliker et al. (2010)

Cases	Controls	Raw OR	Adjusted OR	95% LCL on adjusted OR	95% UCL on adjusted OR
189	252	1	1		
162	234	0.92	0.83	0.62	1.11
43	48	1.19	1.01	0.62	1.64

Here, we want to replace the case numbers with effective counts (call them a_0 to a_2, for the three groups with 0 corresponding to the referent group as usual). Moreover, we want to replace the control numbers with effective counts (call them b_0 to b_2, for the three groups). As in the case of the cumulative incidence studies, there are 2n equations and 2(n+1) parameters to be estimated. Think of the data table being populated with variable names as follows (see Table C-10).

Table C-10. Basis for obtaining effective counts; case-control study; Meliker et al. (2010)

Cases	Controls	Adjusted OR	95% LCL on adjusted OR	95% UCL on adjusted OR
a0	b0	1		
a1	b1	0.83 (OR1)	0.62	1.11
a2	b2	1.01 (OR2)	0.62	1.64

By the definition of odds ratios, and of standard errors for log(OR), we know that we want, in this example,

$$OR_1 = \frac{b_0 \times a_1}{a_0 \times b_1} = 0.83$$

$$OR_2 = \frac{b_0 \times a_2}{a_0 \times b_2} = 1.01$$

Furthermore, the basis for the confidence limits (Rothman and Greenland, 1998) is in the following equations:

$$SE(\log(OR_1)) = \sqrt{\frac{1}{a_0} + \frac{1}{b_0} + \frac{1}{a_1} + \frac{1}{b_1}} = 0.14$$

$$SE(\log(OR_2)) = \sqrt{\frac{1}{a_0} + \frac{1}{b_0} + \frac{1}{a_2} + \frac{1}{b_2}} = 0.23$$

SEs are calculated from the confidence limits bounds, with the calculation based on the upper bound averaged with the corresponding calculation based on the lower bound, as was described for the cohort studies (Eq 6 but with "OR" replacing "RR"). There are four equations for six unknowns (a0, ...,a2, b0, ...,b2), so two additional constraints must be specified. The first constraint is that a0 will be set to be equal to the observed number of cases in the referent group (189 in this example). The second constraint relates to the number of controls in the referent group, as a proportion of the total number of controls in the 3 groups. Specifically, b0 … b2 is specified to satisfy the equation:

$$\frac{b_0}{(b_0+b_1+b_2)} = r_0. \qquad \text{Eq. 11}$$

The resulting system of equations requires a relatively simple numerical solution.

In this example:

$$a_0 = 189$$

$$r_0 = \frac{252}{(252 + 234 + 48)} = 0.472$$

Table C-11 shows the resulting 3 × 2 table of effective counts that results from the procedure defined above. As desired, using the effective counts for computation results in the ORs and confidence limits shown in that table, and those values match the corresponding values in Table C–9.

Table C-11. Effective count results; case-control study; Meliker et al. (2010)

Cases	Controls	OR	95% LCL on OR	95% UCL on OR
189.00	210.37	1		
145.13	194.62	0.83	0.62	1.11
37.01	40.79	1.01	0.62	1.64

The effect on the counts is a function of the difference between the raw and adjusted OR and SE(log(OR)) values. In this case, using the original counts (i.e., ignoring adjustments for covariables, Table C-9) the two standard errors (on the log scale) were

SE(log(OR1)) = sqrt[1/189 + 1/252 + 1/162 + 1/234] = 0.14

SE(log(OR2)) = sqrt[1/189 + 1/252 + 1/43 + 1/48] = 0.23.

These values are quite similar to the SE values derived from the reported adjusted OR confidence limits (0.15 and 0.25, respectively), reflecting little loss of precision associated with adjusting for other variables.

Rationale for Constraints

Note that the methods EPA have used to derive effective counts differs from those proposed by either Greenland and Longnecker (1992) or Hamling et al. (2008). Our methods result in confidence limits that match those reported for adjusted values; the method of Greenland and Longnecker (1992) does not. Moreover, EPA uses different constraints than used by Hamling et al. (2008). The reasons for the different constraints are as follows. They relate to the observation in the introduction to this appendix section that pointed out that the adjustments are made so as to derive effective data that might have been collected had the covariate levels remained the same as in the referent group, for all groups. Thus, the original referent group characteristics are preserved to the extent possible. The Bayesian analysis perspective also influenced our choices.

For the incidence rate cohort studies, our adjustments preserve the original count of cases in the referent group, while still adjusting the counts in the other dose groups. That choice has been made based on the methodological decision to treat the referent group separate from the other cohort study groups. EPA derived priors for the Poisson expected value in the referent group using that group's observations. That group was then *not* included in the likelihood contributions during subsequent parameter updating (so that those data were not "counted twice"). However, since priors were derived based on the observed count in the referent group, effective counts were derived so as to preserve the original number of cases in that group.

For the cumulative incidence studies, the characteristics of the referent group now include the group sample size as well as the number of cases. It was a natural extension of the option used with incidence rate studies to fix both the referent group cases and sample size.

For the case-control studies, calculation of the log-likelihood contributions for the Bayesian analysis requires an approximation to the distribution of dose in the population (see Table C-19). That approximation depends on the proportions of controls across the various dose groups. Those proportions are not something that is affected by covariate adjustment. Therefore, EPA desired that the method used for effective counts in case-control studies retained as much of the discretized control group distribution as possible. It turns out that it was only possible (with a few rare exceptions) to fix the proportion of controls in the referent group.[8] Thus, while retaining the fixed value of the referent group number of cases, EPA added the constraint that the proportion of controls in the referent group (relative to the total number of controls over all dose groups) be

[8]EPA could have fixed the proportion for control in any group, but the focus on the referent group makes sense given the fact that it is the only group for which its expected value is independent of those in the other groups. As discussed in Table C-19.

constant at the observed value.[9] That latter constraint is one of those that was applied by Hamling et al. (2008).

The adjustments of counts for both case-control and cohort studies, and of expected values for incidence rate cohort studies, have been automated in an Excel spreadsheet (see Supplementary Material).

Bayesian Meta-Regression Methods

Case-Control Studies: The modeling of case-control studies in a Bayesian context has been discussed by several authors (see Mukherjee et al. (2005) for a review of several situations and approaches). As described here, EPA has followed Gustafson et al. (2002) for the initial development of the approach used for this analysis.

It is assumed that the prospective likelihood is given by a logistic equation applied to a vector of p explanatory variables $X = (X_1, \ldots, X_p)$:

$$logit\{\Pr(D = 1|X)\} = \alpha^* + \beta^T s(X) \qquad \text{Eq. 12}$$

where, by "prospective likelihood" means $Pr(D = 1 \mid X)$, the probability of having the disease $(D =)$ as opposed to not having the disease $(D = 0)$, conditional on the values of the explanatory variables, X. Here, $s(X) = (s_1(X), \ldots, s_p(X))$ represents a possible transformation of the explanatory variables. Both $\alpha^* (\in \mathbb{R})$ and β $(\in \mathbb{R}^p)$ are parameters to be estimated. In the application of this method to iAs, EPA is interested in a single explanatory variable, X (a measure of arsenic dose) and we will not, for the time-being, be considering a transformation of that variable. So, $p = 1$ and $s_1(X) = X$, so we will simply replace *s(X)* with *X* in Eq 12 and refer to *X* as "dose."

For a case control study, what is observed relates to the retrospective likelihood. That is, there is a sample (of size n_1) of cases and then observe their doses, and similarly for the sample of controls (of size n_0). Those observations correspond to the retrospective likelihoods $f(X \mid D = 1)$ and $f(X \mid D = 0)$, respectively.

Gustafson et al. (2002) have shown that, using Bayes theorem, the logistic form of the prospective likelihood of interest implies that

$$\ln \frac{f(x|D=1)}{f(x|D=0)} = \alpha + \beta x \qquad \text{Eq. 13}$$

where $\alpha = \alpha^* - logit\{Pr(D = 1)\}$.[10] Using Eq 12, and assuming some density, $h(X)$, for the dose distribution, it can be shown that

[9]Informal observation for the studies considered in the bladder cancer meta-regression suggested that fixing the number of cases and proportion of controls in the referent group did a pretty good job of matching the other control proportions.

[10]Note that this implies that the prospective "intercept," α^*, cannot be estimated without knowledge of the disease prevalence $Pr(D = 1)$.

$$f(x|D) = e^{[D\{\alpha+\beta x\}]}h(x) \quad \text{Eq. 14}$$

This is the retrospective likelihood that needs to be modeled for case-control data. Note that

$$f(x|D=0) = h(x) \quad \text{Eq. 15a}$$

$$f(x|D=1) = e^{[\alpha+\beta x]}h(x) \quad \text{Eq. 15b}$$

and note that, since $f(x|D=1)$ must itself be a density (must integrate to 1 over its support), this implies a constraint on the value of α. In fact, Gustafson et al. (2002) consider α to be a function of the other two "parameters," $\alpha = \alpha(\beta, h)$. They show that α is the solution to

$$E_h\left[e^{[\alpha+\beta X]}\right] = 1 \quad \text{Eq. 16}$$

where E_h is the expectation with respect to X having density $h(X)$. Therefore, the likelihoods needed for the Bayesian analyses depend on an unknown density h (as well as a parameter β). A decision regarding what to do about *h(X)* is needed in order to proceed.

One could define $h(X)$ to be some relatively simple parametric form, such as a lognormal distribution. Given that assumption, and the observed proportions of the cases and controls falling within defined dose intervals, a mean and a variance for an underlying lognormal distribution could be estimated. This is similar to the assumption that was used to derive group-specific mean values described in Section C.1.1.1.

One issue with such an approach is that there may be model misspecification with respect to the density of *X*. Furthermore, the solution for α using Eq. 16, even assuming a single lognormal distribution for dose in the cohort, entails evaluating the integral

$$\int_0^\infty \frac{e^{\beta x}}{\sigma\sqrt{2\pi}} e^{\frac{-(\ln(x)-\mu)^2}{2\sigma^2}} dx \quad \text{Eq. 17}$$

which has no analytical solution.[11] Numerical evaluation of α during an MCMC run is not tractable since that would require a numerical optimization within each step of the MCMC process.

Muller and Roeder (1997) implemented an approach to approximating $h(X)$ through the use of more flexible models. They proposed defining $h(X)$ as a mixture of normal distributions. That procedure is more complicated, and it does not remove entirely the possibility of misspecification. In an attempt to reduce the complexity (and the somewhat arbitrary choice of the number of distributions to include in the mixture, which must balance the relative merits of flexibility with those of tractability), EPA has adopted an approach based on that presented in Gustafson et al. (2002), which approximates $h(X)$ with a discrete distribution.

[11]The parameters μ and σ^2 are the log-scale mean and variance, respectively, for the assumed lognormal distribution defining h(X).

This approach is particularly appealing in the context of analyses based on published reports for which the individual doses are not presented, i.e., where the observations are grouped into exposure-based intervals, but no information is available about how the exposures are distributed within or across those intervals. Suppose there are m dose intervals $(c_0, c_1), (c_1, c_2), \ldots, (c_{m-1}, c_m)$; c_0 may equal 0 and c_m may equal ∞. Let λ_i be the (unknown) true proportion of the doses in the ith interval. We let λ be the m-dimensional simplex (a vector whose elements, λ_i, sum to 1) (see Stan Development Team (2017), page 555) representing those proportions, and approximate $h(X)$ by λ.

In that case, since every observation in interval i is assigned the same dose value, x_i, Eq. 14 becomes

$$f(x_i|D) = e^{[D\{\alpha+\beta x_i\}]}\lambda_i \qquad \text{Eq. 18}$$

and Eq. 16 becomes

$$\sum_{i=1}^{m} e^{[\alpha+\beta x_i]}\,\lambda_i = 1 \qquad \text{Eq. 19}$$

(the integral over $h(X)$ is replaced by the summation over the discrete probabilities). Eq. 19 is easily solvable for α:

$$\alpha = -\ln\left(\sum_{i=1}^{m} \lambda_i e^{[\beta x_i]}\right) \qquad \text{Eq. 20}$$

Therefore, the complicated numerical solution for α is avoided and the problem becomes tractable in an MCMC context, i.e., the likelihood contribution for each observation (Eq 18), can be computed as a function of the values of β and λ. Note that since *h(X)* represents the density of doses given no disease (D = 0), as per Eq 15a, one would use the dose information from controls as the basis for λ estimation (though, of course, Eq. 18 defines the likelihood contribution for both cases and controls).

At this point, there are two options for defining λ for the Bayesian analyses. The first option, and the one adopted in these analyses, would be to assign a prior for λ and proceed with the MCMC-based updating of λ and the other parameters. Gustafson et al. (2002) have suggested a Dirichlet prior for λ:

$$\frac{1}{B(a)}\prod_i \lambda_i^{a_i-1} \qquad \text{Eq. 21}$$

where $B(a)$ is the multivariate Beta function. In particular, the "flat Dirichlet" distribution, for which $a_i = 1\ (all\ i)$, gives equal prior density to all values of λ and in that sense is uninformative with respect to λ.

Note that this option can yield λ_i estimates that are not consistent with any simple parametric density, and in particular not consistent with the lognormal distribution which might be used to characterize the distribution of dose values in the study population (see Section C.1.1.1). In

that sense it is more flexible with respect to "fitting" the dose distribution that underlies the observed (interval-censored) data. On the other hand, because this option is separate from a characterization of the underlying distribution of doses in the study population, it is uninformative with respect to estimation of the values of x_i that go into the likelihood computations (Eq 18).

Cohort Studies: Given the logistic model basis for the case-control studies and the likelihoods derived therefrom, there are certain constraints imposed on the modeling framework for cohort studies, if one wants to include both types of studies in a meta-analysis. The following discussion describes the development of the corresponding dose-response modeling and likelihood contributions for cohort studies (specifically, in this example, for cumulative incidence studies; see Rothman and Greenland (1998) and Orsini et al. (2012)). The logistic form entails that

$$\Pr(D = 1|X) = \frac{1}{1+e^{(-\alpha^* - \beta X)}} \quad \text{Eq. 22}$$

Let

$$\theta = \Pr(D = 1|X = x_1) = \frac{1}{1+e^{(-\alpha^* - \beta x_1)}} \quad \text{Eq. 23}$$

where x_1 is the dose for the referent group in the study under consideration. Continuing the notation introduced above, with dose intervals (c_{i-1}, c_i) $(i = 1, \ldots, m)$ defining the grouping of the data, x_1 is the dose assigned to the group corresponding to (c_0, c_1). θ is an unknown; it must be estimated. Or, in the Bayesian context, it is a parameter for which a prior is assigned (see below). That prior will be updated through the MCMC method.

For any other group defined by the categorization of the results, say for the *ith* group defined by (c_{i-1}, c_i), having n_i subjects and a dose associated with it of x_i, the expected value for number of cases would be

$$\mu_i = n_i \times \frac{1}{1+e^{(-\alpha^* - \beta x_i)}} = n_i \times \theta \times \frac{1+e^{(-\alpha^* - \beta x_1)}}{1+e^{(-\alpha^* - \beta x_i)}} \quad \text{Eq. 24}$$

by the definition of θ (Eq 23). Now note that for group i, $\mu_i = n_i \times \theta$, the number of subjects in the group times the probability of response, is the expected number of cases for the *ith* group, as is typically computed for a cohort study (i.e., with no dose-response modeling, but including adjustments for covariables) had the probability of response for the referent group been θ.

Equation 24 completely defines the format to be used for the analysis of cohort studies where the expected number of cases associated with a dose group are given, or can be derived, and that expected number is based on the referent group probability of response, θ.[12]

In a published report for an internally standardized cohort study, one with a referent group that has a relative risk of 1, by definition, the expected numbers for all the groups appear to be based on the observed number in the referent group. For example, that is why the reported

[12]Equivalently, it is based on the referent group expected number, which equals n_1*θ.

expected value for the referent group is always equal to the observed number in that group (because that is the MLE for the expected number). In actuality, however, it is the expected number in the referent group that determines the expected number reported for the other groups. This has the consequence that the reported expected values in a publication need to be treated not as constants, but as derived variables.

This has been handled in the current analyses by separating out the referent group from the other dose groups. A prior for μ_1' was defined independent of the other dose groups (see below) and μ_1' is included as a parameter in the model. Then the Bayesian analysis used only the *remaining* dose groups to update the model parameters, including μ_1'.

However, there are two issues that we must deal with in order to complete the development of the extension to cohort studies.

First, the relationship between the reported expected number for the referent group and the reported expected number in any other group is not a simple relationship like that given for case-control studies (Eq 24). For case-control studies, the expected number for another group, given an estimate of the expected number in the referent group, was simply proportional to the latter. That is not necessarily the case for the cohort study, where the expected value depends not only on the referent group expected value but also on differences in the patterns of person-years of follow-up. If the individual follow-up data were available, that relationship could be defined explicitly. But it is often the case that individual data are not available for a number of reasons, and methods must be developed that recognize this common limitation.

Published, internally standardized cohort studies use the observed number in the referent group, O_1, to compute all the expected values in the other groups. Those presented (or derivable) expected values, we will call RE_i ("Reported Expected" value for group $i > 1$). So, the simplifying assumption is that the expected values for a non-referent group will be defined by

$$\mu_i' = RE_i \times \frac{\mu_1'}{O_1} \qquad \text{Eq. 25}$$

This borrows from the case-control situation, the proportionality for expected numbers in relation to the observed number of cases in the referent group. That assumption may be appropriate when μ_1 is close to O_1. The prior for μ_1' is lognormal, centered on O_1 (see below); this will tend to push μ_1 toward O_1, further supporting the proportionality assumption.

Second, unlike θ (which can be derived from α^* and β parameter estimates, Eq 23), μ_1' for a cohort study is not expressed in terms of the model parameters. So, for every internal-referent cohort study, we are adding a parameter to the meta-analysis model. On the other hand, as shown here, the parameter α^* can be derived from proposed μ_1' and β values, if we have one other piece of information from the cohort study: the person-years of observation for the referent group, PY_1.

That is the case because

$$\mu_1' = PY_1 \times \frac{1}{1+e^{(-\alpha^*-\beta x_1)}} \qquad \text{Eq. 26}$$

so that

$$\alpha^* = -\ln\left(\frac{PY_1}{\mu_1'} - 1\right) - \beta x_1 \quad \text{Eq. 27}$$

Putting together Equations 23 and 24, the equation for μ_i becomes

$$\mu_i = RE_i \times \frac{\mu_1'}{O_1} \times \frac{1+e^{(-\alpha^*-\beta x_1)}}{1+e^{(-\alpha^*-\beta x_i)}} \quad \text{Eq. 28}$$

with α* computed via Eq 27.

The prior for μ_1' is defined as follows. Given O_1, and assuming that the observations are Poisson distributed with a mean equal to μ_1', we derived the MLE and 95% upper confidence bound for μ_1'. The 95% confidence bound is computed based on profile likelihood methods (Cole et al., 2014). Then, a lognormal distribution was defined such that the median of that distribution is equal to the MLE value and the 95_{th} percentile of that distribution was equal to the 95% upper confidence bound. That lognormal distribution was the prior used in the Bayesian analysis.

Implementation: Given the above development, the implementation of the Bayesian meta-analysis was completed using RStan (version 2.9), a package in R that calls and executes code written in the Stan language (Stan Development Team, 2017). This section highlights the implementation of the methods described above for case-control and cohort studies.

The primary steps in the RStan model consist of the following:

1) Reading in the study data (R code); defining variables for Stan ("Data" section of Stan code);
2) Defining parameters β and λ, for case-controls studies; or β and μ_1', for cohort studies ("Parameters" section of Stan code);
3) Setting priors for β and λ or μ_1' ("Model" section of Stan code);
4) Calculating the parameter α or α* ("Model" section of Stan code);
5) Defining the log-likelihood contributions for each dose group ("Model" section of Stan code).

With respect to the final step, the log-likelihood contributions are explicitly defined as follows. Recall from the discussion of case-control studies above, that Eq 18 shows the likelihood contribution for a single case (D = 1) or control (D = 0). Taking the log of Eq 18, the log-likelihood contribution for an observation that is a case in group i (i = 1, …, m) is $\alpha + \beta x_i + \ln(\lambda_i)$; for a control observation, the contribution is $\ln(\lambda_i)$. Therefore, for dose group i the total contribution is

$$cases[i] \times \{\alpha + \beta x_i + \ln(\lambda_i)\} + controls[i] \times \ln(\lambda_i) \quad \text{Eq. 29}$$

where $cases[i]$ and $controls[i]$ are the number of cases and controls, respectively, in group *i*. That total contribution is what is used in the Stan "Model" section. Note that this formulation will work even if $cases[i]$ and $controls[i]$ are not integers (which may occur when effective counts are computed to adjust for possible confounders).

Similarly, for a cohort-study, non-referent dose-group, i, with $dose = x_i$,[13] where the number of cases is assumed to arise from a Poisson distribution, with mean, μ_i, given by Eq 18, the log-likelihood for such a group is

$$ll_i = -\mu_i + O_i \times \ln(\mu_i) \quad \text{Eq. 30}$$

Estimation of Lifetime Extra Risk in U.S. (Lifetable Analysis Methods)

This development follows a typical lifetable type of analysis (Crump and Allen, 2011; Rothman and Greenland, 1998) but includes consideration of the background exposure in the target population. Spreadsheets that were developed to implement the approach are provided in Excel files that are included in the Supplemental Material available from the EPA HERO database. In general, the probability of disease occurrence (incidence or mortality) between ages t_1 and t_2 (given survival to age t_1) may be expressed as:

$$p(DP, t_1, t_2) = \int_{t_1}^{t_2} haz(t, DP(t))S(t, DP(t))dt \quad \text{Eq.31}$$

where $S(t, DP(t))$ is the probability of survival to age t given survival to age t_1 and $haz(t, DP(t))$ is the instantaneous hazard of disease occurrence at age *t*, both as functions of *DP* which is the pattern of age-specific exposures. At the background exposure level, this integral can be approximated by a sum:

$$p(\text{b}) = \sum_{i=1}^{n} p(i)S(i) \quad \text{Eq. 32}$$

where the age interval $[t_1, t_2]$ has been divided into n subintervals with the *ith* subinterval having width $\Delta(i), i = 1, \ldots, n$. The parameter $p(i)$, representing the probability of disease occurrence in the ith age interval, is calculated as:

$$p(i) = qc(i)\Delta(i) \quad \text{Eq. 33}$$

and $S(i)$, representing the probability of surviving to the beginning of the ith age interval given survival to age x_1, is calculated as $S(0) = 1$ and:

$$S(i) = \prod_{j=1}^{i-1} e^{[-q_a(j)\Delta(j)]} = e^{\left[-\sum_{j=1}^{i-1} qa(j)\Delta(j)\right]}, i > 1 \quad \text{Eq.34}$$

[13]The referent group was not used as part of the observations used for the Bayesian updating, because it was used to define the prior for μ_1'.

where $qc(j)$ and $qa(j)$ are, respectively, the endpoint-specific rate of occurrence and all-cause death rates for the *jth* age interval obtained from standard rate tables.

If the subintervals correspond to individual years, Eqs. 32 and 34 take on the simplified forms:

$$p(\mathrm{b}) = \sum_{i=x_1}^{x_2} qc(i)S(i) \qquad \text{Eq. 35}$$

and

$$S(i) = \prod_{j=x_1}^{i-1} e^{[-qa(j)]} = e^{\left[-\sum_{j=x_1}^{i-1} qa(j)\right]} \qquad \text{Eq. 36}$$

Once the background rates qc and qa are selected and setting $t_1 = 0$ and $t_2 = 85$, these equations completely determine $p(\mathrm{b})$, the lifetime probability of response at the background level of exposure.[14] These same formulae are used to calculate the probability of response, $p(DP)$, from a particular exposure pattern, DP, by replacing the rates qc and qa by the appropriate modification that accounts for the model-predicted effect of exposure on these rates. The appropriate modifications depend upon the form of the dose-response model estimated from the epidemiological data, and the assumed exposure pattern. If the dose-response model predicts relative risk as a function of some exposure metric, then $qc(i)$ is replaced by $qc(i)R(i)$, and $qa(i)$ is replaced by $\mathrm{qa}(i) - qc(i) + R(i)qc(i) = qa(i) + qc(i)[R(i) - 1]$, where $R(i)$ is the relative risk predicted by the dose-response model, for age *i*, associated with exposure pattern *DP*. The latter replacement involves subtracting from the total death rate the background rate from the disease of interest and adding back this contribution adjusted by the effect of exposure.

By setting *DP* to zero, one can estimate *p(0)*, the lifetime probability of response in the absence of exposure. Once *p(0)* has been calculated, the extra risk above zero dose from exposure pattern *DP* is computed as:

$$\frac{p(DP) - p(0)}{1 - p(0)} \qquad \text{Eq. 37}$$

For the health outcomes evaluated in this assessment, EPA assumes that $p(\mathrm{b})$ is associated with a median U.S. background iAs dose of 0.0365 µg/kg-day, consisting of a 0.02 µg/kg-day contribution from diet (Xue et al., 2010), a 0.0165 µg/kg-day contribution from drinking water, and no contribution from inhalation exposures. The estimated drinking water contribution assumes a median background drinking water level of 1.5 µg/L (Mendez et al., 2017) and a water consumption rate of 0.011 L/kg-day U.S. EPA (2019), Table 3-1, "All Ages"). According to the available physiologically based pharmacokinetic model for arsenic (El-Masri and Kenyon, 2008), this 0.0365 µg/kg-day inorganic arsenic dose is equivalent to a total urinary arsenic level of approximately 2 µg/L, which is within the 1–5 µg/L background range estimated by the NRC (2013).

[14]For computational purposes, 85 years was used to define the upper limit for lifetime risk calculations.

The benefit of those assumptions is that $p(\mathrm{b})$ in the above equations does not represent 0 total iAs intake, but rather 0 "extra" iAs intake. It is possible therefore to consider the impact of both positive changes (additional sources of iAs above background) and negative changes (reduction in the background associated with, for example, clean-up of background sources) on lifetime cancer risks. This is analogous to the treatment of the studies that were analyzed in the meta-analysis: the effect was assessed relative to their specific referent intake (or dose) values. And, in fact, the expressions in the form of Eq 34 were used (with the pooled estimate of the dose-response β parameter) along with a referent intake set equal to 0.0365 μg/kg-day, and α^* derived from the lifetables for the U.S. population.

Sensitivity Analysis of Possible Non-monotonic Dose-Response Relationships

Introduction

The primary meta-analyses take advantage of the fact that a logistic model form is suitable for modeling both cohort and case control studies. Moreover, they assume a particular relationship of the form

$$logit\{\Pr(D = 1|d)\} = \alpha^* + \beta * d \qquad \text{Eq. 35}$$

where $\Pr(D = 1|d)$ is the (prospective) probability of response (D, disease state equals 1) at dose d, and α and β are parameters that are estimated. In the context of the meta-analyses, a separate and independent α value was assumed for each study. The parameter β was hierarchical; study specific β values were distributed normally around a mean (or "pooled") β parameter value. One salient feature of such a model is that it describes a monotonic increase in probability of response as dose increases, for all positive doses. An example of such behavior for that model is shown here:

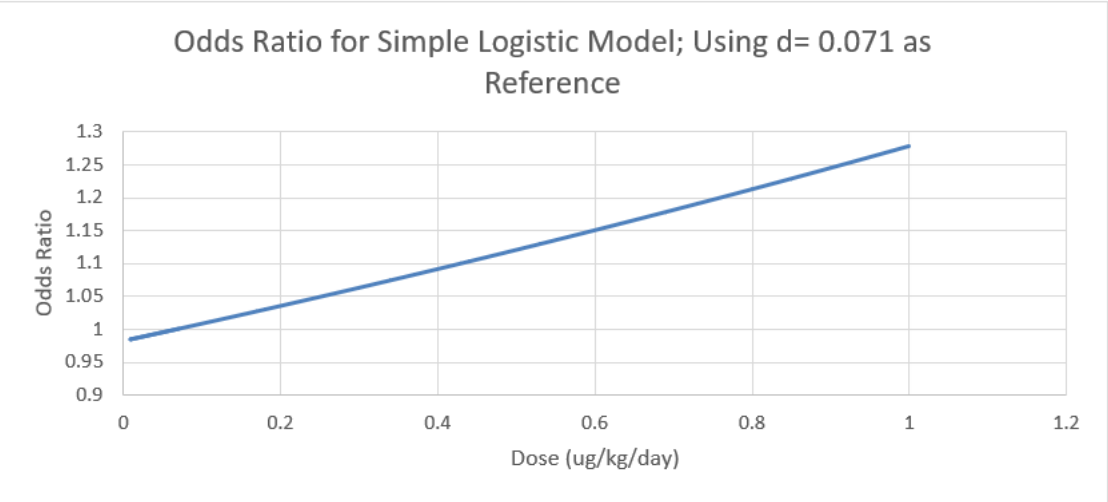


Figure C-2. Odds ratio for simple logistic model using d = 0.071 as reference. [15]

It has been suggested that inorganic arsenic and other ubiquitous elements might have a non-monotonic, hormetic effect on the probability of response for some endpoints, in particular for some cancer endpoints (Calabrese and Agathokleous, 2021). The sensitivity analysis reported here seeks to address that question by using some *potentially* non-monotonic relationships in place of the simple linear relationship on the right-hand-side of Eq 35.

The goals of this analysis are as follows:

- First, determine if non-monotonic functions fit the data any better than the simple, monotonic, logistic relationship given above.
- Second, if they do fit better, determine if they entail an actual non-monotonic relationship, in the range of doses of interest.
- Third, regardless of the relative merits of the non-monotonic relationships, determine the effect on the risk estimates of interest. In this case, those risk estimates are expressed in terms of extra lifetime risk of the endpoint in question at several doses selected because of possible regulatory interest or importance. In all instances, the extra risk estimates are expressed in relation to the average inorganic arsenic in the U.S. (here assumed to be 0.071 μg/kg-day).

A Bayesian hierarchical modeling approach has been adopted to complete the sensitivity analysis. Details of that methodology are described below.

[15]This analysis was done using a prior estimate of the U.S. background dose. As described in the main assessment and previous section, the current U.S. background dose estimate is 0.0365 μg/kg-day.

Classes of non-monotonic models under consideration

This sensitivity analysis addresses the possibility of non-monotonicity by fitting specific models that allow for, but do not necessarily result in, curve shapes that lead to a reduction in risk at low doses (from some non-zero risk at 0 dose) followed by an increase in risk at some somewhat higher doses. The particular forms investigated fall into two categories: fractional polynomial models and "double Hill" models.

Fractional polynomials have been proposed (Bagnardi et al., 2004) as a flexible set of equations that can assume a variety of shapes, including non-monotonic shapes. In the context of the current logistic regression, they are defined as follows:

$$logit\{\Pr(D = 1|d)\} = \alpha^* + b_1 d^{p_1} + b_2 d^{p_2} \quad \text{Eq. 36}$$

with the following provisions:

- p_1 and p_2 are selected from the set {−2, −1, −0.5, 0, 0.5, 1, 2, 3}
- if $p_i = 0$, then $d^{p_i} = ln(d)$
- if $p_1 = p_2 = p$, then the equation becomes $logit\{\Pr(D = 1|d)\} = \alpha^* + b_1 d^p + b_2 d^p ln(d)$.[16]

An example of the non-monotonicity induced by a fractional polynomial model is displayed here:

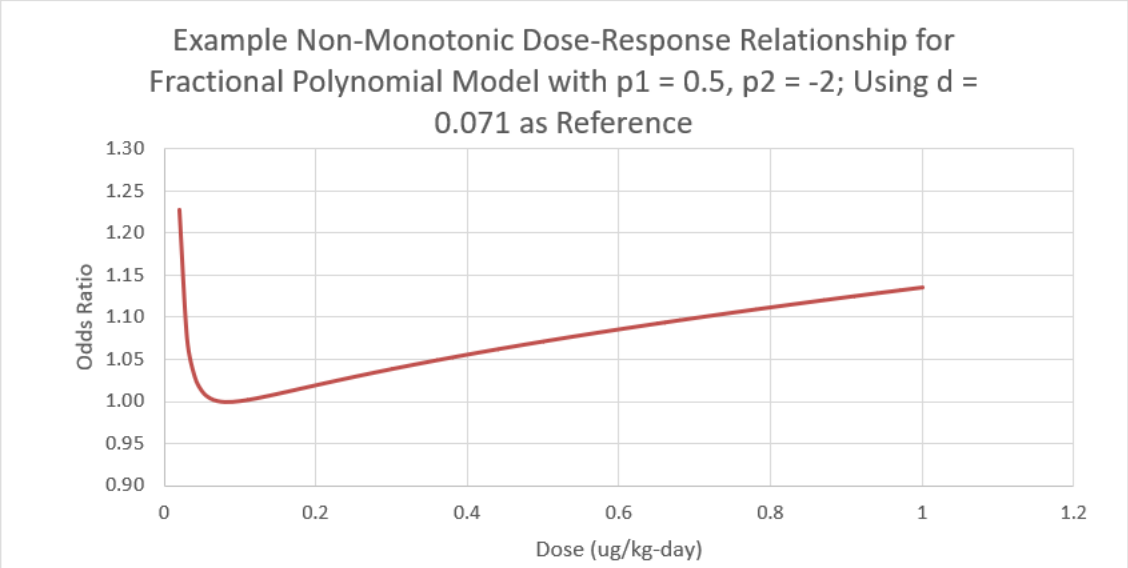


Figure C-3. Example non-monotonic dose-response relationship for fractional polynomial model.

[16]This does not include the model having $p_1 = p_2 = 0$.

The double Hill models are, as the name suggests, a combination of two Hill models and thus have the form.

$$logit\{\Pr(D = 1|d)\} = \alpha^* + v_1 * d^{p_1}/(k_1^{p_1} + d^{p_1}) + v_2 * d^{p_2}/(k_2^{p_2} + d^{p_2}). \quad \text{Eq. 37}$$

When v_1 is positive and v_2 is negative, this *can* (but does not necessarily) lead to non-monotonicity. All of the double Hill modeling reported here is restricted to that particular combination (v_1 positive and v_2 negative), for the pooled values of those parameters (see below for specifics about the hierarchical structure of the modeling). In the current sensitivity analysis, four such models have been investigated by restricting values of p_1 and p_2 to be 1 or 2 (so that there are 4 distinct combinations).

An example of the non-monotonicity induced by the double Hill model is displayed here:

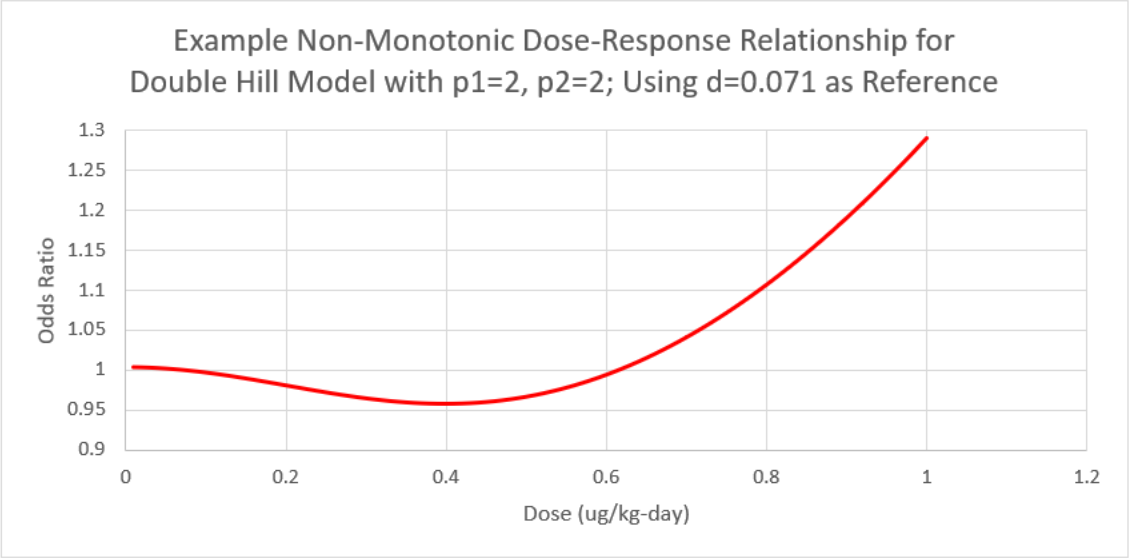


Figure C-4. Example non-monotonic dose-response relationship for double Hill model.

Details and issues related to defining the non-monotonic models

The fractional polynomial models have the potential to lead to curve shapes that approach infinite odds ratios for very small doses, i.e., for doses approaching zero, when a nonzero reference dose is used. The reference dose considered here (as it was for the simple linear logistic model) was set to 0.071 µg/kg-day. Given that possible behavior, which is considered to be biologically unreasonable, measures had to be taken to mitigate the possibility of very large odds ratios for dose values less than but relatively "close to" that reference dose value. The approach taken for the fractional polynomial models was to define a parameter, called ln_OR_low, the log of the odds ratio at a low dose, which constrained its value to be reasonable, a priori. Specifically, the low dose used to define ln_OR_low was set to 0.00071µg/kg, 100 times less than the reference dose of

0.071 μg/kg-day. In a sense, this choice reflects the fact that we want to rely on the model predictions down to a certain relatively low dose value, a value in this case defined in terms of the target population of interest for this risk assessment (that being the US population) and that in order to rely on them, we want to ensure that the model predictions there are "reasonable." Our definition of reasonable is that ln(OR) (using the US background of 0.071μg/kg as the reference) is close to 0 (OR close to 1) down to 0.071/100. Thus, the prior for ln_OR_low has been defined to be Normal (0, 0.5). This entails that, a priori, we think the OR at 0.00071 μg/kg is highly likely (i.e., with about 95% probability) to be between exp(−1) = 0.37 and exp(1) = 2.7. As long as we restrict attention (extrapolation) to doses greater than 0.00071 μg/kg, the model results should not "blow up."

The other constraint imposed on the fractional polynomial models was that, at and above some (undefined) dose level, the ORs should be increasing as dose increases. Given the various forms that the fractional polynomial models can take (see Eq 36 above), this entailed identifying the parameter, *b1* or *b2*, that dominated in the high dose region and setting a prior for that parameter to ensure such monotone increasing behavior at some dose level. Note that that prior assumption implied nothing (in general) about the direction of the slope of the risk curve at all doses, in particular at low doses. Depending on the model form and values of the parameters in it, this prior specification may be compatible and consistent with U-shaped or J-shaped curves, as long as those curves do increase at and above some (again, unknown) dose level.

To that end, the 35 fractional polynomial models that we considered have been subdivided into 6 subsets defined as follows:

Set A: p1 > p2. Subsets: Aneg: p1 < 0; Apos: p1 > 0

Here is a schematic defining the particular combinations of p1 and p2 that are in each of the A subsets:

Set A	$p_1 > p_2$		p_2					
			−2	**−1**	**−0.5**	**0.5**	**1**	**2**
	p_1	**−1**	Aneg					
		−0.5	Aneg	Aneg				
		0.5	Apos	Apos	Apos			
		1	Apos	Apos	Apos	Apos		
		2	Apos	Apos	Apos	Apos	Apos	
		3	Apos	Apos	Apos	Apos	Apos	Apos

Set B: p2 = 0. Subsets: Bneg: p1 < 0; Bpos: p1 > 0

Here is a schematic defining the particular combinations of p1 and p2 that are in each of the B subsets:

Set B	p_2=0	p_1 =	**−2**	**−1**	**−0.5**	**0.5**	**1**	**2**	**3**
			Bneg	Bneg	Bneg	Bpos	Bpos	Bpos	Bpos

Set C: p1 = p2 = p. Subsets: Cneg: $p < 0$; Cpos: $p > 0$

Here is a schematic defining the particular combinations of p1 and p2 that are in each of the C subsets:

Set C	$p_1 = p_2$ =	**−2**	**−1**	**−0.5**	**0.5**	**1**	**2**	**3**
		Cneg	Cneg	Cneg	Cpos	Cpos	Cpos	Cpos

Each subset of the fractional polynomial model group has its own pair of R and Stan programs to implement it. Table C-12 defines how the priors were defined for each of those subsets. Again, those priors guaranteed a curve that eventually would yield increasing risk as dose increased.

Table C-12. Listing of fractional polynomial model runs

Subset:	Hierarchical parameter	Prior for other parameter	Notes
			One parameter hierarchical, the other constrained to give increasing dose-response at high doses
Aneg	b_2[nstudies] ~ N(f_a(ln_OR_low, b_1), bsigma)	b_1 ~ negative half-Normal(0, 10)	(# models = 3)
Apos	b_2[nstudies] ~ N(f_a(ln_OR_low, b_1), bsigma)	b_1 ~ positive half-Normal(0, 10)	(# models = 18)
Bneg	b_1[nstudies] ~ N(f_{bn}(ln_OR_low, b_2), bsigma)	b_2 ~ positive half-Normal(0, 10)	(# models = 3)
Bpos	b_2[nstudies] ~ N(f_{bp}(ln_OR_low, b_1), bsigma)	b_1 ~ positive half-Normal(0, 10)	(# models = 4)
Cneg	b_1[nstudies] ~ N(f_{cn}(ln_OR_low, b_2), bsigma)	b_2 ~ negative half-Normal(0, 10)	(# models = 3)
Cpos	b_1[nstudies] ~ N(f_{cp}(ln_OR_low, b_2), bsigma)	b_2 ~ positive half-Normal(0, 10)	(# models = 4)

f_a(ln_OR_low, b_1) = (ln_OR_low - b_1*pow(0.071,p_1)*(−1.0 + pow(0.01, p_1)))/(pow(0.00071,p_2) - pow(0.071, p_2)).
f_{bn}(ln_OR_low, b_2) = (ln_OR_low - b_2*log(0.01))/(pow(0.071,p_1)*(−1.0 + pow(0.01, p_1))).
f_{bp}(ln_OR_low, b_1) = (b_1*pow(0.071,p_1)*(−1.0 + pow(0.01, p_1)) - ln_OR_low) / log(100).
f_{cn}(ln_OR_low, b_2) = (ln_OR_low - b_2*(pow(0.00071,p_1)*log(0.00071) - pow(0.071, p_1)*log(0.071)))/(pow(0.00071,p_1) - pow(0.071, p_1)).
f_{cp}(ln_OR_low, b_2) = (ln_OR_low - b_2*(pow(0.00071,p_1)*log(0.00071) - pow(0.071, p_1)*log(0.071)))/(pow(0.00071,p_1) - pow(0.071, p_1)).
In all cases: prior for bsigma is positive half-Cauchy(0,20); prior for ln_OR_low is N(0, 0.5).

For the case of the double Hill models, there is no fear of risks increasing towards infinity as dose decreases towards zero. That is because the value of the two Hill functions is always equal to 0 when dose = 0, regardless of the values of the parameters v_i, k_i, and p_i (i = 1,2; see Eq 37). For this reason,[17] the parameterization of the double Hill models was based on the "natural" parameters v_i, and k_i (the power parameters were fixed within each run to be either 1 or 2). The priors for the two ki parameters were the same, half-Cauchy (0, 300) restricted to positive values. The prior for v_1 was half-Cauchy (0,20), restricted to be positive; for v_2 it was half-Cauchy(0,20) but restricted to be negative. As discussed earlier, the combination of a positive v_1 and a negative v_2 is the only way to achieve a nonmonotonic curve shape, although even that combination does not force nonmonotonicity.

For the double Hill models, we did not constrain v_1 to be greater (in absolute magnitude) than v_2, it was possible (and the implementations did result in) curves that would result in ORs less than 1 for some high doses. As these tendencies were all for doses much greater than those of interest for regulatory purposes (i.e., for doses orders of magnitude greater than current and possible revised iAs standards), we still present results for those models and consider their implications for sensitivity analysis.

Moreover, partly in order to compensate for the high-dose behavior just described, the double Hill models included a hierarchical structure for both v_1 and v_2. The study-specific v_1 and v_2 values varied around the pooled v_1 and v_2 values (the means of the study-specific distribution) according to a normal distribution with a standard deviation that had a prior distribution that was half-Cauchy (0,5), restricted to positive values. Note that even though the pooled v1 was constrained to be positive and the pooled v_2 was constrained to be negative, the study-specific values were not so constrained. So, while the overall (pooled) behavior ascribed by the double Hill model would have a positive term and a negative term (allowing for nonmonotonicity), that need not be the case for any individual study. This is analogous to the treatment of the b parameters (dose coefficients) in the simple linear logistic model, i.e., the pooled b parameter was constrained to be positive (because the a priori evidence suggested that arsenic does increase bladder cancer risks rather than decrease them), but the study-specific values for the coefficient were allowed to be positive or negative.

For the bladder cancer meta-analysis data set under consideration, which has 12 studies, there were 16 nominal parameters for the fractional polynomial models. Because the double Hill models were hierarchical with respect to two parameters, the nominal number of parameters was nearly doubled, to 31. Both counts include a parameter defining the mean of the Poisson random variable for the expected number in the reference group of the sole cohort study in the data set Chen et al. (2010b). For comparison, the simple linear logistic model had 15 nominal parameters: a single mean dose coefficient, the 12 study-specific coefficients, and a standard deviation defining

[17]And also because of difficulties getting the double Hill models to converge when additional constraints were imposed via prior specifications.

the variability of those hierarchical coefficients around the mean value, as well as the Poisson mean for the expected number in the cohort study reference group. The number of parameters in the models is important for model comparison and selection.

The MCMC simulations were run using RStan (version 2.21.0) running under R (version 4.0.2). Convergence was checked by monitoring the reported Rhat values (values less than 1.01 for each parameter) and effective sample sizes. Instances of divergent iterations were noted but the frequencies of divergences were less than 0.1% (a rule of thumb adopted for accepting the results, based on guidance supplied by Stan developers)[18] unless otherwise noted. For each variation of the fractional polynomial models, 20,000 post-warm-up draws were obtained (5,000 in each of 4 chains). For the 4 double Hill models, 200,000 post-warm-up draws were obtained (50,000 from each of 4 chains).

Results

The Bayesian analysis used for these investigations is a likelihood-based approach. In particular, it is based on the posterior likelihoods associated with the range of parameter values, given the data and the prior likelihood of those parameters.

One perspective for model selection (or model averaging) would focus on the maximum posterior likelihood that can be obtained across all parameter values. Such a view is analogous to a maximum likelihood perspective for frequentist analyses—a model that provides a greater maximum (posterior) likelihood is preferred over a model that can only achieve a maximum that is less than the first model. In the present analyses, we have characterized that maximum in two ways. First, we have computed the maximum log-posterior (labeled "lp__" in Stan and referred to as "lp" here) from among the parameter samples obtained in the MCMC draws. Second, we have estimated the density of lp using a kernel estimation technique, and reported the maximum estimated by that procedure. The following plot shows the relationship between those two metrics over the suite of models under investigation.

[18] Betancourt (2018). https://arxiv.org/pdf/1701.02434.pdf.

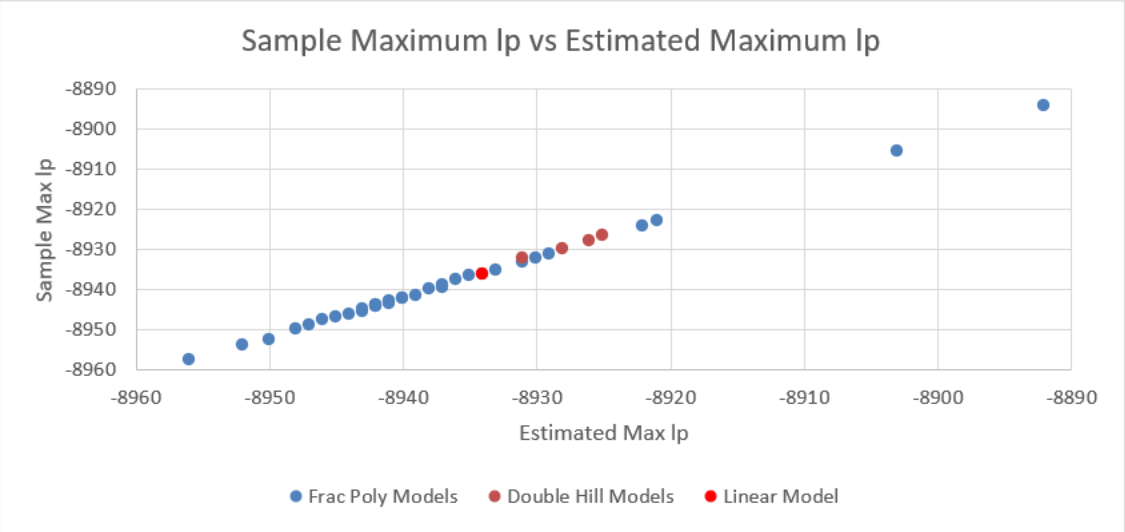


Figure C-5. Sample maximum lp vs. estimated maximum lp.

Note that these two metrics are co-linear; they are obviously closely related, and either would give the same ranking of the models. We focus therefore on the sample maximum lp.

Another perspective on model comparison is to focus on the average fit, over the range of parameter values represented in the posterior sample. Such a metric recognizes that the Bayesian approach does not concentrate on the maximum likelihood, but rather on the variability of the values that are most consistent with the observations; it is a distributional approach and therefore does not focus merely on the single best parameter set. Given that perspective, it is more natural to focus on a value that better represents that distribution. We have chosen the sample mean lp for that representation. The following plot shows the relationship between the sample maximum and the sample mean lp:

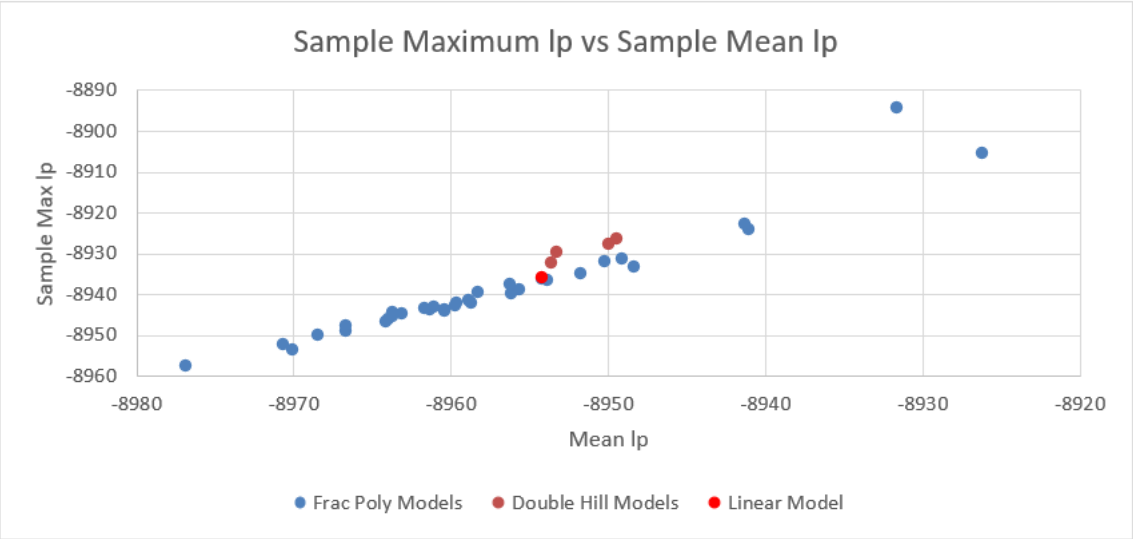


Figure C-6. Sample maximum lp vs. sample mean lp.

The relationship here is not as linear as that between the estimates of the maximum lp. In fact, depending on the choice of metric, one of two fractional polynomial models could be identified as best.

Table C-13 gives the values for all three metrics under consideration, and it highlights those two fractional polynomial models (color coded to associate the model with the basis for selecting it). In fact, if one were to weight the fractional polynomial models on the basis of the maximum or mean lp values, then one or the other of these two models would receive more than 99.5% of the weight—i.e., the other fractional polynomial models would contribute essentially nothing to estimates of quantities of interest.[19]

[19]That is true if the weights were based on standard BIC/2 type weights.

Table C-13. Table of models with results relevant to model selection

Class	Subset[a]	Specification		No. of parameters	Estimated max lp (Kernel Density)	Max sample lp	Mean sample lp
		p1	p2				
Fractional Polynomial	Set A ($p1 > p2; neither = 0$)	–1	–2	16	–8937	–8939.5	–8958.2
		–0.5	–2	16	–8921	–8922.8	–8941.3
		–0.5	–1	16	–8934	–8936.2	–8954.2
		0.5	–2	16	–8892	–8894.3	–8931.6
		0.5	–1	16	–8929	–8931.3	–8949.1
		0.5	–0.5	16	–8938	–8939.8	–8956.1
		1	–2	16	–8922	–8924.1	–8941
		1	–1	16	–8935	–8936.7	–8953.8
		1	–0.5	16	–8942	–8944.2	–8960.4
		1	0.5	16	–8942	–8943.8	–8960.4
		2	–2	16	–8936	–8937.6	–8956.2
		2	–1	16	–8945	–8946.8	–8964.1
		2	–0.5	16	–8947	–8949.0	–8966.6
		2	0.5	16	–8942	–8944.4	–8963.7
		2	1	16	–8941	–8943.3	–8961
		3	–2	16	–8948	–8950.0	–8968.4
		3	–1	16	–8952	–8953.8	–8970
		3	–0.5	16	–8950	–8952.5	–8970.6
		3	0.5	16	–8946	–8947.7	–8966.6
		3	1	16	–8944	–8946.3	–8963.9
		3	2	16	–8943	–8945.5	–8963.7
	Set B ($p2 = 0$)	–2	0	16	–8903	–8905.8	–8926.2
		–1	0	16	–8930	–8932.2	–8950.2
		–0.5	0	16	–8937	–8939.4	–8956
		0.5	0	16	–8931	–8933.3	–8948.3
		1	0	16	–8933	–8935.1	–8951.7
		2	0	16	–8937	–8939.0	–8955.6
		3	0	16	–8939	–8941.6	–8958.8
	Set C ($(p1 = p2)$	–2	–2	16	–8956	–8957.6	–8976.8
		–1	–1	16	–8942	–8943.9	–8961.3

Class	Subset[a]	Specification		No. of parameters	Estimated max lp (Kernel Density)	Max sample lp	Mean sample lp
		p1	p2				
		−0.5	−0.5	16	−8941	−8942.8	−8959.7
		0.5	0.5	16	−8940	−8942.2	−8959.6
		1	1	16	−8940	−8942.4	−8958.7
		2	2	16	−8941	−8943.6	−8961.6
		3	3	16	−8943	−8944.9	−8963.1
Double Hill		1	1	31	−8925	−8926.5	−8949.4
		1	2	31	−8926	−8927.9	−8949.9
		2	1	31	−8928	−8929.8	−8953.2
		2	2	31	−8931	−8932.3	−8953.6

[a]Fractional polynomial sets are characterized as follows. Set A models do not include any ln(d) terms, just two terms having d^{p1} and d^{p2}. Set B includes one ln(d) term, and one terms of the form d^{p1}. Set C models include a term of the form d^{p1} and a term of the form dp1*ln(d).

Interestingly, the two highlighted models have a d−2 term that is a significant contributor only at low doses (increasing risk at doses less than 1 with greatest impact as dose decreases toward zero) and a term that is concave down (becomes less steep as dose increases, i.e., sqrt(d) and ln(d)) so that the change in risk with increasing dose flattens out to some degree at higher doses. The graphs of the associated odds ratios are shown in the following plots, using mean values of the posterior distributions of the relevant parameters for those plots.

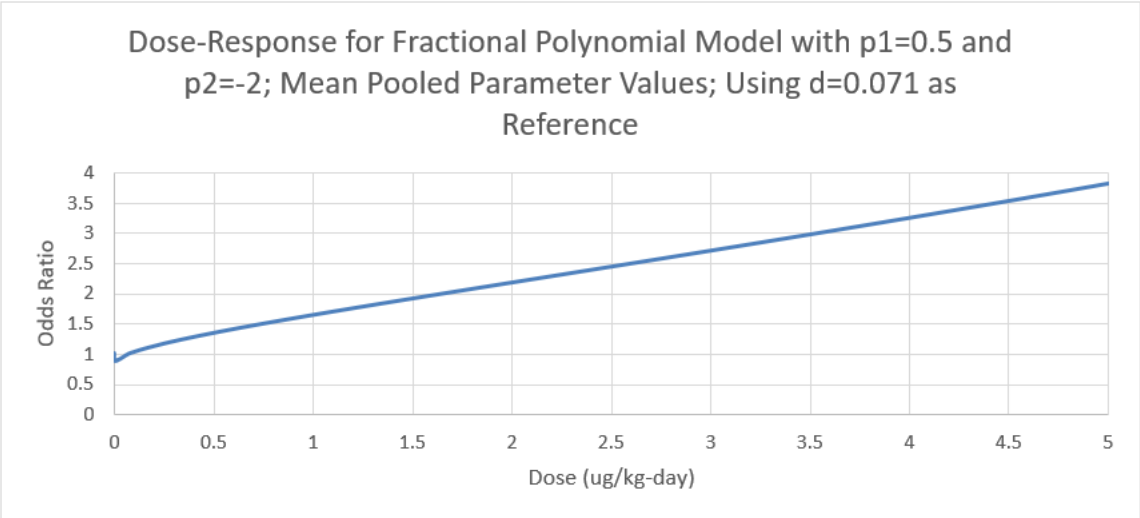


Figure C-7. Dose-response for fractional polynomial model with p1 = 0.5 and p2 = 2.

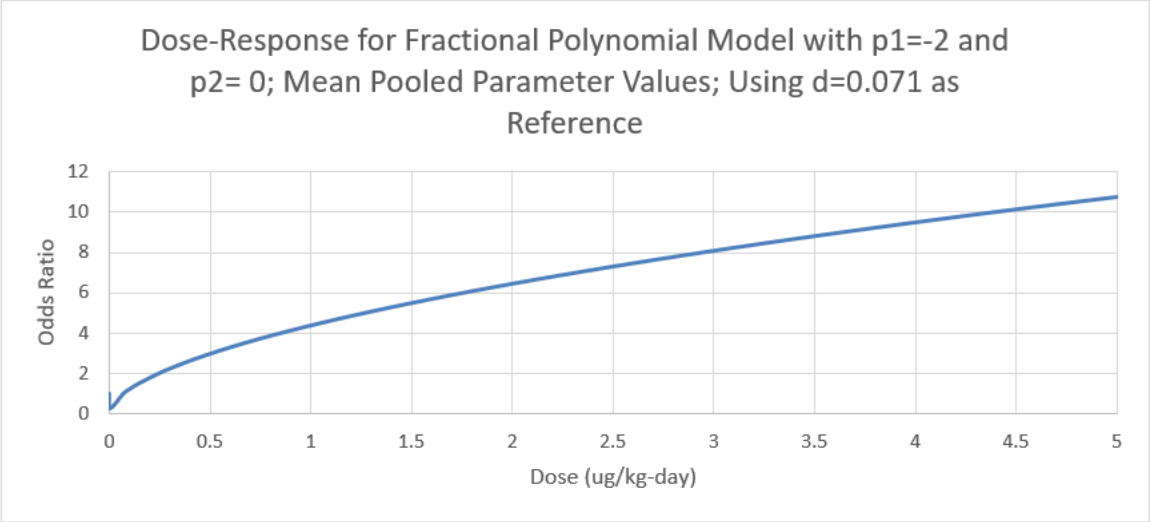


Figure C-8. Dose-response for fractional polynomial model with p1 = −2 and p2 = 0.

The only non-monotonicity evident occurs at doses lower than the reference dose of 0.071 µg/kg-day, the background iAs exposure for the target U.S. population. In other words, these best fractional polynomial models predict no deceases in risk associated with increasing dose for any levels of exposure at or above the current background exposure level.

In the above discussion, we have focused solely on the fractional polynomial model results. The reason for that is because the double Hill models are not competitive with the fractional polynomial models when number of parameters are factored into the consideration. Note from the figures above that the lp values of the double Hill models are in the middle of the range of the fractional polynomial models. But when one considers that the double Hill models have (nominally) 15 additional parameters, it is evident that the added complexity of the double Hill models is not warranted. From a Bayesian Information Criterion (BIC) perspective, whether applied to the maximum or the mean lp values, the double Hill models would be ruled out of consideration.

More generally, if one were to use a BIC approach to identify models that would be preferred over the simple linear logistic model, none of the double Hill models would be preferred. Of the fractional polynomial models, the following versions would be preferred[20]:

[20]The BIC is defined as -2*LL + k*ln(n), where LL is the is the log-likelihood of interest (here we are considering the posterior log-likelihood, either the maximum, which would be the "traditional" approach, or the mean). k is the number of parameters and n is the sample size. For the data set under consideration, n = 47; ln(n) = 3.85. Thus, for a fractional polynomial model (with k = 16) to have a lower BIC than the linear model (with k = 15), the LL would have to be 1.925 (=3.85/2) greater than that of the linear model (lower BIC is better).

Table C-14. Fractional polynomial models referred by BIC to linear model

Specification	
p1	p2
−0.5	−2
0.5	−2
0.5	−1
1	−2
−2	0
−1	0
0.5	0
1	0

The shading in Table C-14 identifies again the two models that are clearly superior to all the others. The listing in Table C-14 is based on mean lp; if maximum lp were considered then the last model version (1 0) would not be considered to be preferred to the linear model.

For that subset of fractional polynomial models, Table C-15 presents the predicted extra lifetime risks at a series of doses selected as being potentially relevant to regulatory decision making. The order of the fractional polynomial models is from greatest mean lp to least mean lp.

Table C-15. Mean lifetime extra risk at various doses, using 0.071 µg/kg-day as the reference

Model	Doses (µg/kg-d)							
	0.0071	**0.05**	**0.12**	**0.19**	**0.26**	**0.33**	**0.75**	**1.45**
Linear	−0.00032	−0.00011	0.00025	0.00061	0.00097	0.0013	0.0037	0.0083
−2, 0	−0.014	−0.0034	0.0065	0.014	0.020	0.026	0.051	0.080
0.5, −2	−0.0022	−0.00055	0.0011	0.0023	0.0034	0.0045	0.00961	0.017
1, −2	−0.00017	−0.000056	0.00013	0.00032	0.00051	0.00070	0.0019	0.0040
−0.5, −2	−0.019	−0.0098	0.026	0.061	0.091	0.12	0.21	0.28
0.5, 0	−0.0024	−0.00056	0.0010	0.0022	0.0032	0.0041	0.0082	0.014
0.5, −1	−0.0018	−0.00050	0.00097	0.0021	0.0031	0.0040	0.0087	0.015
−1, 0	−0.013	−0.0033	0.0064	0.014	0.020	0.026	0.053	0.084
1, 0	−0.0034	−0.00062	0.0010	0.0020	0.0028	0.0035	0.0061	0.0091

For all the models listed in Table C-15, the extra lifetime risk increases monotonically as dose increases. There is no evidence of non-monotonicity within the range of doses displayed,

which includes a dose 10 times less than the estimated average background exposure in the U.S. and extends up to roughly 20 times that exposure level.

For the two fractional polynomial models that were clearly superior to the others with respect to model fit, the extra risks for doses greater than the average background dose are uniformly greater than the corresponding risk estimates from the linear model. The difference is reduced at the high end of the displayed dose range. This reflects the steeper dose-response shape for models that have ln(d) and sqrt(d) terms which, as noted above will be steeper in the lower dose range and then less steep at higher doses. In contrast, the linear model will have the same slope throughout the entire dose range.

C.1.2. Supportive Material (Input Files, Supportive Analyses, and Results)

Bladder Cancer

Bladder cancer study and dataset selection

Table C-16. Data sets selected for bladder cancer Bayesian dose-response meta-regression

Study	Study design	Location	Exposure/ dose metric	Estimate of iAs exposure group mean µg/kg-d intake range (Estimate of mean U.S. equivalent µg/L drinking water range)[a]	Health Outcome/ Endpoint	Description	Limitations
Baris et al. (2016)	Case-control	United States (New England)	Average daily As intake (µg/d)	0.1–0.44 (7–38)	Histologically confirmed carcinoma of the urinary bladder (Including carcinoma in situ)	Very large case-control study (1213 cases, 1418 controls) of U.S. population exposed to low arsenic concentrations in drinking water. Substantial details on residential and occupational histories, and demographic and personal information. Lifetime residential and water consumption histories used to estimate daily and cumulative intake and control for key covariates	Potential for exposure misclassification exists due to very low iAs concentrations and multiple methods employed (i.e., a mix of measurements, models, and predictions based on the use of public water supplies and "deep or dug" private wells).
Bates et al. (1995)	Case-control	United States (Utah)	Cumulative As intake (water)	0.11–0.14 (8.2–11)	Histologically confirmed bladder cancer	Moderate size case-control study (117 cases, 266 controls) of U.S. population exposed to low-moderate arsenic concentrations in drinking water. Lifetime residential and water consumption histories	Exposure estimates were based on As measurements from municipal water supplies, which were assumed to be representative of

Study	Study design	Location	Exposure/ dose metric	Estimate of iAs exposure group mean µg/kg-d intake range (Estimate of mean U.S. equivalent µg/L drinking water range)[a]	Health Outcome/ Endpoint	Description	Limitations
						were used to derive cumulative intake estimates; separate analyses were conducted for smokers	individual exposures and stable over time.
Bates et al. (2004)	Case-control	Argentina	Drinking water As conc.	0.56–8.2 (49–744)	Transitional bladder-cell cancer cases identified by pathologists and urologists in the study area	Moderate size case-control study (114 matched case-control pairs) over a wide exposure range; current and past water concentrations measured, the analysis controlled for major covariates, drinking water consumption, and duration of well use; examined risks versus exposure "time windows"	There were relatively few cases and controls in the higher water concentration strata; exposure estimates depend on relative contributions from well/spring versus public water supplies, for which As concentrations were very different
Chang et al. (2016)	Case-control	Midwest Taiwan	Urinary As excretion	1.1–5.3 (98–480)	Urothelial carcinomas identified by urologists and pathologically confirmed	Moderate size case-control study (205 cases, 406 controls) recruited from China Medical University Hospital, Taichung, Taiwan, between June 2011 and December 2013. Urinary As dose metric; estimated As intakes near typical U.S. values; multiple studies have addressed effects of nutrition, methylation profiles, genetic variants on As-associated bladder cancer risks in subsets of the same cohort. Trend tests	Hospital-based referent population somewhat dissimilar with regard to several covariates from exposed groups; lack of data on historical exposures. Nutritional status of the cohort is not specified, but they are not likely to be malnourished like the SE Taiwan "endemic" area

Study	Study design	Location	Exposure/ dose metric	Estimate of iAs exposure group mean µg/kg-d intake range (Estimate of mean U.S. equivalent µg/L drinking water range)[a]	Health Outcome/ Endpoint	Description	Limitations
						suggest iAs poses a moderate UC risk ($0.05 < p < 0.1$) relative to risk of UC from increased urinary levels of cadmium, chromium, nickel and lead ($p < 0.05$).	
Chen et al. (2010b)	Prosp. Cohort	NE Taiwan	Cumulative As exposure (water)	0.83–18.2 (74–1,653)	Urinary cancers identified in Taiwan national cancer Registry; includes ICD-9 defined bladder (code 188), kidney (Code 189.0), and others (code 189.1–189.9)	Very large cohort study (6888 subjects with exposure measurements), individual well As levels measured for 85% of subjects. Broad exposure range, well-documented case ascertainment, good follow-up (12 yrs), controlled for major covariates. Follow-up study subsequently conducted on the same cohort (Yang et al., 2013).	Relatively small numbers of cases in some exposure strata
Huang et al. (2018)	Case-control	NE Taiwan	Urinary As excretion	0.21–1.81 (17–163)	Urothelial Carcinoma; histological confirmation from National Taiwan University Hospital Department of Urology	Large case-control study (216 cases, 813 controls) in well-studied cohort (National Taiwan University Hospital and the Taipei Municipal Wan Fang Hospital); recruited September 2007 to October 2011. Urinary As dose metric; estimated As intakes near typical U.S. values; multiple studies have addressed effects of nutrition, methylation profiles, genetic	Hospital-based referent population somewhat dissimilar with regard to several covariates from exposed groups; lack of data on historical exposures. Nutritional status of the cohort is not specified, but they are not likely to be malnourished like the SE Taiwan "endemic" area. Ors were adjusted for

Study	Study design	Location	Exposure/ dose metric	Estimate of iAs exposure group mean µg/kg-d intake range (Estimate of mean U.S. equivalent µg/L drinking water range)[a]	Health Outcome/ Endpoint	Description	Limitations
						variants on As-associated bladder cancer risks in subsets of the same cohort. Trend tests suggest urinary As association with increases in UC, BC and upper tract urothelial carcinoma (UTUC) ($p < 0.05$).	hypertension and diabetes, which is not considered appropriate since they are not independent factors (i.e., iAs can cause these effects).
Lin et al. (2018)	Case-control	NE Taiwan	Urinary As excretion	0.22–1.82 (18–164)	Bladder cancer; histological confirmation from National Taiwan University Hospital Department of Urology	Large case-control study (216 cases, 648 controls) in well-studied cohort (National Taiwan University Hospital and the Taipei Municipal Wan Fang Hospital); recruited from September 2007 to October 2011. Urinary As dose metric; estimated As intakes near typical U.S. values; multiple studies have addressed effects of nutrition, methylation profiles, genetic variants on As-associated bladder cancer risks in subsets of the same cohort. Trend tests suggest ($p < 0.05$) urinary As association with increases BC, with greatest increase in subset of subjects with high-risk haplotypes.	Hospital-based referent population somewhat dissimilar with regard to several covariates from exposed groups; lack of data on historical exposures. Nutritional status of the cohort is not specified, but they are not likely to be malnourished like the SE Taiwan "endemic" area

Study	Study design	Location	Exposure/ dose metric	Estimate of iAs exposure group mean µg/kg-d intake range (Estimate of mean U.S. equivalent µg/L drinking water range)[a]	Health Outcome/ Endpoint	Description	Limitations
Meliker et al. (2010)	Case-control	United States (Michigan)	Daily As intake (water)	0.1–0.46 (7.3–40)	Bladder cancer cases identified by the Michigan Cancer Surveillance Program (the state cancer registry)	Large (411 cases, 566 controls) study of U.S. population exposed to mostly low levels or arsenic in water. Lifetime residential, water use, and occupational/lifestyle histories were used to calculate average daily As intake, and control for covariates. Separate analyses for smokers, non-smokers	Reliance on geostatistical model for exposure estimates; narrow exposure range, particularly for public systems; possible case selection bias (~25% of eligible cases participated)
Steinmaus et al. (2003)	Case-control	United States (CA, NV)	Cumulative As intake (water)	0.1–0.46 (7–40)	Bladder cancer cases identified in Nevada Cancer Registry and the Cancer Registry of Central California	Moderate size (181 cases, 328 controls) study of U.S. population exposed to low-moderate levels of As in drinking water. Lifetime residential and water consumption profiles, along with a large database of As levels in public and private water sources, were used to estimate lifetime intake. Controlled for important covariates	Small numbers/proportions of controls, cases in higher exposure strata; unclear if effects of changing water As levels were adequately addressed
Steinmaus et al. (2013)	Case-control	N. Chile	Lifetime avg. daily As intake (water)	1.26–10.7 (113–971)	Histologically (98%) or radiologically/ clinically (2%) confirmed cases of bladder cancer	Large case-control study (232 cases, 640 controls), well-documented historical water As exposures, good resolution in low-moderate exposure range. Residential and water use histories are used to	Relied on municipal water As measurements for exposure estimates, but unique characteristics of study area (lack of alternative sources), suggest this is

Study	Study design	Location	Exposure/ dose metric	Estimate of iAs exposure group mean µg/kg-d intake range (Estimate of mean U.S. equivalent µg/L drinking water range)[a]	Health Outcome/ Endpoint	Description	Limitations
						estimate As intakes. The subject cohort has been the subject of a number of studies of As-related cancer and covariate interactions	not a major source of uncertainty
Wu et al. (2013)	Case-control	NE Taiwan	Urinary As excretion	0.42–1.8 (36–162)	Urothelial Carcinomas diagnosed by Taipei Medical University Hospital Department of Urology	Large case-control) study (300 cases, 594 controls) in well-studied cohort (National Taiwan University Hospital, Taipei Medical University Hospital and Taipei Municipal Wan Fang Hospital); recruited between September 2002 and May 2009 from. Urinary As dose metric; estimated As intakes near typical U.S. values; multiple studies have addressed effects of nutrition, methylation profiles, genetic variants on As-associated bladder cancer risks in subsets of the same cohort.	Hospital-based referent population somewhat dissimilar with regard to several covariates from exposed groups; lack of data on historical exposures. Nutritional status of the cohort is not specified, but they are not likely to be malnourished like the SE Taiwan "endemic" area

[a]The µg/kg-d ranges were obtained from MLE estimates reported in Table C-19; water concentrations were estimated assuming median U.S. dietary background of 0.02 µg/kg-d (Xue et al., 2010) and mean U.S. water consumption rate of 0.011 L/kg-d (U.S. EPA, 2019), Table 3-1, "All Ages").

Comparison of studies selected for EPA meta-regression and studies used in earlier meta-analyses

EPA found considerable overlap between the studies included in the current meta-regression and those identified in earlier meta-analyses (see Table C-17). Of the 11 studies chosen by EPA, a core group of 5 studies were chosen for all (Baris et al., 2016; Meliker et al., 2010; Bates et al., 2004) or for all but 1 (Steinmaus et al., 2013; Chen et al., 2010b) of the meta-analyses published after them. Studies selected for the earlier meta-analysis that were not used in the EPA meta-regression analysis tended to be either (1) superseded by later analyses of the same cohorts, or (2) based on a dose metric that EPA decided not to be sufficiently reliable (toenail arsenic.) EPA judged that outcome measures for several of the other studies were not amenable to meta-regression or that exposure measurements were too uncertain and the range of exposures too narrow.

Table C-17. Study selection for EPA bladder cancer meta-regression compared to earlier meta-analyses

Study	EPA meta-regression analysis	Chu and Crawford-Brown (2006)	Begum et al. (2012)	Tsuji et al. (2014)	Saint-Jacques et al. (2014)	Lynch et al. (2017)	Shao et al. (2021)
Baris et al. (2016)	✓					✓	✓
Bates et al. (1995)	✓	✓	✓	✓			
Bates et al. (2004)	✓	✓	✓	✓	✓	✓	✓
Chang et al. (2016)	✓						
Chen et al. (2010b)	✓			✓	✓	✓	✓
Chiou et al. (1995)		✓	✓			✓	
Chiou et al. (2001)		✓	✓		✓		
Huang et al. (2008)					✓	✓	
Huang et al. (2018)	✓						
Karagas et al. (2004)[a]			✓	✓			✓
Kurttio et al. (1999)		✓	✓	✓	✓	✓	✓
Lewis et al. (1999)				✓			
Lin et al. (2018)	✓						
Meliker et al. (2010)	✓		✓	✓	✓	✓	✓
Michaud et al. (2004)[a]			✓	✓			
Moore et al. (2003)		✓	✓				
Mostafa and Cherry (2015)						✓	✓
Steinmaus et al. (2003)	✓	✓	✓	✓			
Steinmaus et al. (2013)	✓				✓	✓	✓
Wang et al. (2009)						✓	
Wu et al. (2013)	✓						

[a]Toenail iAs study.

Chiou et al. (1995) and Huang et al. (2008) were included in Lynch et al. (2017), Chu and Crawford-Brown (2006) and Saint-Jacques et al. (2014) meta-analyses; EPA chose not to use data from these studies because they were based in the southwest Taiwan "endemic" area. Exposure levels were generally quite high, and the incidence of Blackfoot Disease and potential poor nutrition in the study subjects led EPA not to include data from this region.

Kurttio et al. (1999) was included in five previous meta-regressions. While this study provides some evidence supporting exposure-response for bladder cancer at low water concentrations particularly among smokers, the range of exposures was extremely narrow (exposure groups were <0.1, 0.1–0.5, and > 0.5 µg/L). EPA judged that exposure uncertainties were likely large compared to the within-stratum variation, and the potential for exposure group misclassification was too high to warrant inclusion in its meta-analysis.

Chiou et al. (2001) was used by both Chu and Crawford-Brown (2006) and by Begum et al. (2012) in their meta-analyses. EPA did not include outcome data from this study (although exposure statistics were used), because a later study (Chen et al., 2010b) reported urinary cancer risks in this cohorts after a longer follow-up period.

Moore et al. (2003) was also used as a source of data in the two older meta-analyses. EPA did not select data from this study because only raw counts and relative risks not adjusted for covariates were provided. Thus, there was no way to calculate adjusted counts for the meta-regression.

Karagas et al. (2004) and/or Michaud et al. (2004) were used as data sources by Begum et al. (2012), Tsuji et al. (2014) and Shao et al. (2021). EPA's rationale for not selecting these studies was that the reported dose-metric (toenail arsenic concentrations) could not reliably be converted to equivalent arsenic intake. While limited data concerning empirical relationships between toenail arsenic and water arsenic are available, there is no generally accepted approach for estimating arsenic intake from toenail levels (EPA's PBPK model does not include a toenail compartment.)

Data from Lewis et al. (1999) was selected for meta-analysis by Tsuji et al. (2014). EPA chose not to include this study because it was judged that exposure uncertainty was unacceptable large, and the study reported SMRs for bladder cancer in three exposure groups on the basis of only three deaths in males and two deaths in females.

Data from Mostafa and Cherry (2015) was selected for meta-analysis by Lynch et al. (2017) and Shao et al. (2021). EPA chose not to include this study because it was judged that exposure uncertainty was unacceptably large. The authors associated responses with mean well concentrations within Bangladesh regions called "thana." The 9,870 subjects of the study came from 360 thana. For each individual of a thana, exposure to arsenic in drinking water was estimated as the mean arsenic concentration of multiple wells (1–16) within the thana in which the patient lived at the time of biopsy.

As noted above, several of these studies were relatively "close calls" and might have been included if data from studies that EPA considered superior were not available. In particular, if

additional data become available that better support the estimation of chronic arsenic intake from toenail arsenic measurements, the studies by Karagas et al. (2004) and Michaud et al. (2004) might be logical choices for addition to the meta-regression.

Finally, due in part to the availability of EPA's iAs PBPK model (El-Masri et al., 2018a, b), EPA included four recent urine biomarker studies (Huang et al., 2018; Lin et al., 2018; Chang et al., 2016; Wu et al., 2013) that were not included in any of the previous meta-analysis. These studies were not available at the time most of these authors began their literature reviews and were explicitly excluded from the Saint-Jacques et al. (2014), Lynch et al. (2017) and Shao et al. (2021) meta-analyses.

While there are differences in the modeling approaches used by EPA and earlier meta-analyses, differing results can be attributed largely to study and data selection. For instance, while the Lynch et al. (2017) approach differed from EPA's approach with respect to the exposure metric modeled and the lifetime adjustment method used, when the Lynch et al. (2017) dataset was evaluated by both approaches, the bladder cancer extra risk predictions were nearly identical, with the EPA approach predicting a linear slope of 0.0009 (μg/kg-day)$^{-1}$ and the Lynch et al. (2017) approach predicting a linear slope of 0.008 (μg/kg-day)$^{-1}$ (see Figure C-9).

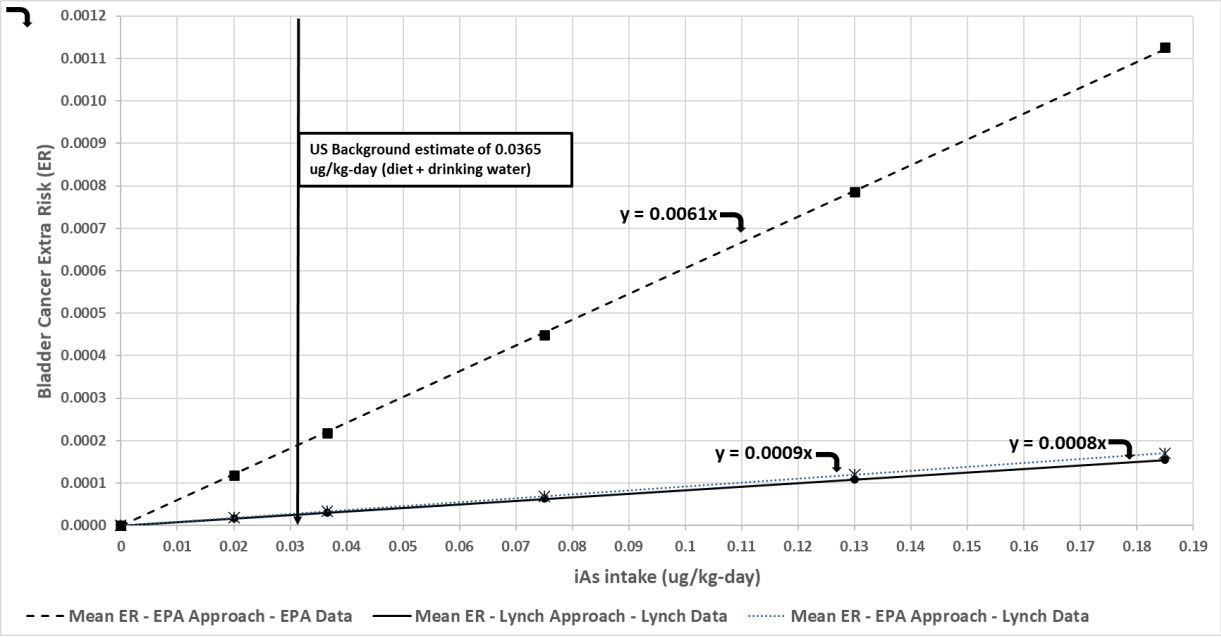


Figure C-9. Relationship between dose (μg/kg-day) and mean extra risk (ER) predicted by EPA approach using EPA data, EPA approach using Lynch et al. (2017) data and Lynch approach using Lynch et al. (2017) data.

Study differences are also at least partially explanatory with respect to differences between the current EPA Bayesian meta-regression results for bladder cancer and the results reported in Shao et al. (2021). The study authors in Shao et al. (2021) preferentially used drinking water studies (or in the case of the Karagas et al. (2004) study, a toenail iAs study with doses converted

into drinking water concentrations). The specific dose metrics also play a part in differences between analyses, with Shao et al. (2021) modeling study results presented for µg/L and EPA instead choosing, in some cases, dose-metrics judged to be more suitable for accurately describing the dose response. An example of this is seen for the Baris et al. (2016) study: EPA used the unlagged cumulative dose metric whereas Shao et al. (2021) used the unlagged drinking water dose metric. Unless a population is limited in its source of fluids (e.g., populations that rely almost exclusively on a single well-water source), it is extremely important to survey individuals as to their consumption habits to approximate their actual iAs dose from the water source of interest. Baris et al. (2016) made a particular point of this, noting that "The contrast in our findings for cumulative arsenic intake and average arsenic concentration underscores the importance of incorporating water intake when estimating an individual's total arsenic exposure in low to moderately exposed populations such as that in northern New England." Shao et al. (2021) also completely ignores the role that dietary exposure has in iAs-induced disease. Differences in dietary exposure to iAs is reasonably assumed across divergent study populations, and thus not taking this into account ignores an important, and differential, source of exposure. EPA's dose-conversions explicitly takes population-specific dietary exposures into account when calculating the daily intake dose-metric.

In addition to study selection and the dose-metrics modeled, the specific methodology employed by Shao et al. (2021) also directly results in the observed differences between their results and EPA results. In brief, Shao et al. (2021) base their analysis on model fits using a Hill model, based on a claim that the Hill model has the greatest flexibility to model different shapes of dose-responses. The authors also state that the Hill model "may plausibly describe underlying biological processes" but are silent on the biological processes that the model ostensibly describes. Importantly, the Hill model has questionable features for use in cancer risk assessment. In particular, the Hill model formula implies that any upward curvature that may be indicated at high doses, is necessarily also present at low doses. In particular, a Hill model fit showing any high dose upward curvature precludes the presence of any linearity of response at low dose. On the contrary, models that allow a degree of low dose linearity—even in the presence of differing patterns of high-dose response—have long been used in developing health protective cancer risk assessments.

Shao et al. (2021) also defend an application of a partially hierarchical Hill model such that, among the 4 model parameters, would only allow for population differences for the "a" (response as zero exposure) and "b" (sensitivity of individuals to iAs exposure) parameters. They state that these parameters "are the most important factors of variability in populations at low exposures" and that parameters "c" (dose at half-maximal response) and "g" (threshold parameter) are "more affected by data points in [the] high exposure range." The paper states that use of partially hierarchical model "will avoid introducing unnecessary uncertainty." However, the characterization of the "c" and "g" parameters as important at high, but not low dose is not appropriate. The "c" parameter is the dose at half-maximal response and essentially defines the point of transition between low and high dose data. Then, the "g" parameter defines the steepness of the dose

response, which in the Hill model applies to both high and low dose response. Arguably, fully addressing "c" and "g" parameters is the most needed feature in this modeling as these models determine the claimed threshold behavior of modeling in this paper. Omission of these parameters in hierarchical modeling implies that all populations are expected to have the same "threshold," which ignores population-specific characteristic such as genetic polymorphisms, dietary exposure, and other risk factors that impact disease risk due to iAs exposure. Lastly, having the "a" parameter be hierarchical is somewhat confusing as, by definition RR equals 1 at the reference dose, so all populations should have the same response at their respective background exposure level.

While the authors do implement a fully hierarchical model for some calculations, insufficient information is given to judge these modeling results. The main paper reports the BMDL-BMDU confidence interval for partially hierarchical modeling results, but the supplemental material on the fully hierarchical model omits this information. Therefore, the claim that the partially hierarchical model "will avoid introducing unnecessary uncertainty" is unverifiable in that the confidence intervals between the two model approaches cannot be compared. This is potentially quite impactful as Shao et al. (2021) report that the BMD for bladder cancer from the fully hierarchical model (16.46 µg/L) is approximately 3 times lower than the BMD from the partially hierarchical model (52.35 µg/L). And, indeed, their BMD value for the fully hierarchical model seems entirely inconsistent with fitted partially hierarchal model and confidence limits shown in Figure 2 of the paper, where a very specific "jump" in both the MLE and confidence limits are shown near the estimated BMD value. An earlier paper (Shao et al., 2017) had concluded that a partially hierarchical model is sufficient in most cases and provide a set of simulations in which partially hierarchical and fully hierarchical models produced similar results in some relatively data rich situations. However, the simulations in Shao et al. (2021) indicate that this is not the case for the iAs bladder cancer studies given the factor of 3 difference between the BMD values estimated by the partially and fully hierarchical models.

EPA also questions the choice of some of the model parameters in the partially hierarchical model. First, the prior on the "g" parameter (threshold) is Uniform (0,50), meaning a uniform distribution where all values between 0 and 50 are equally likely. At first glance, this prior sounds "diffuse" or "uninformative" and implies that the data themselves will influence the modeling results. However, this prior actually provides a very heavy weighting towards dose-response curves that are highly threshold in nature (even step-like). In fact, approximately 96% of the prior weight on this parameter is on "g" values >2 which would imply steeply upward curving or threshold-like behavior. It is not desirable—especially for a health protective assessment—to place the dominant prior weight on threshold-like responses. There also seems to be an internal disagreement in the paper between the prior on the "c" parameter listed in Fig 1, Uniform (0,10), and the results of the modeling that show the half-maximal response dose at approximately 50 µg/L for bladder cancer and lung cancer and BMR = 1 relative deviation. Given a Uniform (0,10) prior, values for "c" close to 50 µg/L would never be possible.

Bladder cancer study-specific dose conversions

The study-specific dose conversions and confidence interval estimations were derived in Excel workbooks with the Yasai add-in for Monte Carlo simulations (http://www.yasai.rutgers.edu/). Each study required a potentially different set of assumptions for the dose conversions. The study-specific conversion assumptions and results are provided in the Excel files, which are included in the health outcome-specific intake uncertainty folders of Supplemental Material available from the EPA HERO database The following tables summarize the input equations and assumptions used in the Monte Carlo analyses (see Table C-18) and the MLE, low and high exposure and µg/kg-day dose estimates, as well as other input data (see Table C-19) for each of the studies used in EPA's bladder cancer meta-regression analyses.

Table C-18. Equations and assumptions for estimating µg/kg-day doses from bladder cancer studies[a]

Citation (country)	ADWE (yrs)	AAD (yrs)	LE, SD (µg/L)	WCR, SD (mL/kg-d)	BW, SD (kg)	DI, SD	H, SD (cm)	RD, SD (yrs)	AGE, SD (yrs)	Exposure or dose metric	Equation
Baris et al. (2016) (USA)	65	65	2.5,3.3	0 for 35%; 16.6, 37 for 65%	68,10	0.05, 0.09	–	–	–	µg/d, DD	dose = DI + f*(CE/(AGE*365)/BW) + (1–f)*(LE*WCR)
Bates et al. (1995) (USA)	34.4	66	2.5,3.3	0 for 35%; 16.6, 37 for 65%	68, 10	0.05, 0.09	–	–	–	mg, CE	dose = DI + f*(CE/(AGE*365)/BW) + (1–f)*(LE*WCR)
Bates et al. (2004) (Argentina)	25.6	68.9	5,3.3	33, 15.7	–	0.1, 0.3	–	–	–	µg/L, WE	dose = DI + f*(CE/(AGE*365)/BW) + (1–f)*(LE*WCR)
Chang et al. (2016)	–	–	–	–	64.6, 6.4	–	164, 4.86	–	65.9, 10.52	µg total As/g creat.	Dose[b] = (µg total As/g creat. × g creat./d)/BW
Chen et al. (2010b) (NE Taiwan)	42	65	5, 15	34.5, 23.2	–	0.65, 3.33	–	42, 15	–	µg/L-yrs, CE	dose = DI + f*(CE/(AGE*365)/BW) + (1–f)*(LE*WCR)
Huang et al. (2018)	–	–	–	–	64.6, 9.4	–	164, 4.86	–	60.8, 0.48	µg total As/g creat.	Dose[b] = (µg total As/g creat. × g creat./d)/BW

Citation (country)	ADWE (yrs)	AAD (yrs)	LE, SD (µg/L)	WCR, SD (mL/kg-d)	BW, SD (kg)	DI, SD	H, SD (cm)	RD, SD (yrs)	AGE, SD (yrs)	Exposure or dose metric	Equation
Lin et al. (2018)	–	–	–	–	64.6, 6.4	–	164, 4.86	–	60.8, 0.55	µg total As/g creat.	Dose[b] = (µg total As/g creat. × g creat./d)/BW
Meliker et al. (2010) (USA)	66	66	2.5, 3.3	0 for 35%; 16.6, 37 for 65%	68, 10	0.05, 0.09	–	–	–	µg/d, DD	dose = DI + f*(µg/d)/BW) + (1–f)*(LE*WCR)
Steinmaus et al. (2003) (USA)	23.2	69.8	2.5, 3.3	0 for 35%; 16.6, 37 for 65%	68, 10	0.05, 0.09	–	–	70.3, 9.6	mg, CE	dose = DI + f*(CE/(AGE*365)/BW) + (1–f)*(LE*WCR)
Steinmaus et al. (2013) (Chile)	66	66	2.5, 3.3	1.7, 0.09	72.3, 10	1.0, 0.30	–	–	–	µg/d, DD	dose = DI + f*(µg/d)/BW) + (1–f)*(LE*WCR)
Wu et al. (2013) (Taiwan)	–	–	–	–	64.6, 6.4	–	164, 4.86	–	62.56, 13.5	µg total As/g creat.	Dose[b] = (µg total As/g creat. × g creat./d)/BW

ADWE = average duration of well exposure; AAD = average age at diagnosis; LE = low (outside study) exposure; WCR = water consumption rate; BW = body weight; DI = dietary intake; H = height; RD = reported duration of well exposure; Age = control group average age.

[a]See Conversion Factor Validation spreadsheet for justifications for individual exposure factors.

[b]According to EPA's PBPK model (El-Masri et al., 2018a, b), iAs is eliminated almost exclusively in urine. Thus, total µg/kg-day arsenic in urine is a good approximation of µg iAs/kg-day intake, assuming arsenic intake is substantially in the form of iAs. Urinary creatinine/kg-day is estimated as = $(266.16 – 47.17*sex –2.33*BMI + 0.66*age + 0.17*age^2)*113.12/10^6$, where sex is 0 for male and 1 for female and BMI is estimated as $BW/(Height/100)^2$.

Table C-19. Meta-regression inputs and estimated effective counts for selected bladder cancer data sets, with three selected sets of dose values

Data set name (reported dose units)	Exposure ranges (in reported dose units)	Dose values for analysis (avg. daily µg/kg)[a]			Raw counts			Adjusted OR/RR and 95% CIs			Effective counts[b]		
		MLE	Low	High	Cases	Controls	Expected	Adj OR	LCL	UCL	Cases	Controls	Expected
Chen et al. (2010b) (cohort study; cumulative water exposure, µg/L-yrs)[c]	< 400	0.830	0.810	0.851	6	–	6.00	1	1	1	6.00	–	6.00
	400–1,000	1.106	1.078	1.136	3	–	2.70	1.11	0.27	4.54	2.84	–	2.56
	1,000–5,000	2.042	1.956	2.120	12	–	5.15	2.33	0.86	6.36	10.65	–	4.57
	5,000–10,000	4.40	4.65	4.91	5	–	1.33	3.77	1.13	12.6	4.72	–	1.25
	>10,000	18.20	21.60	26.15	11	–	1.47	7.49	2.7	20.8	9.56	–	1.28
Steinmaus et al. (2013) (µg/d from water)[e]	<41	1.26	1.24	1.29	32	197	–	1	1	1	32.00	80.25	–
	41–136	1.99	1.93	2.05	39	194	–	1.08	0.62	1.87	40.18	93.31	–
	137–307	3.55	3.42	3.68	64	154	–	3.06	1.75	5.35	59.12	48.45	–
	>307	10.73	8.02	15.95	97	95	–	5.85	3.41	10.05	–	–	–
Wu et al. (2013) (µg/gm Creatinine)	≤11.74	0.42	0.27	0.56	44	196	–	1	1	1	44.00	108.33	–
	11.74–20.94	0.96	0.54	1.73	63	196	–	1.42	0.9	2.25	69.52	120.54	–
	>20.94	1.77	1.18	2.85	192	202	–	4.13	2.69	6.35	166.80	99.44	–
Bates et al. (1995) (cumulative water iAs intake, mg)	<19	0.111	0.093	0.131	14	47	–	1	1	1	14.00	40.24	–
	19–33	0.116	0.094	0.139	21	36	–	1.56	0.8	3.2	18.98	34.98	–
	33–53	0.121	0.101	0.145	17	39	–	0.95	0.4	2	9.30	28.14	–
	≥53	0.141	0.114	0.176	19	38	–	1.41	0.7	2.9	16.49	33.62	–
Steinmaus et al. (2003) (cumulative Intake, mg)	<6.4	0.10	0.09	0.12	66	101	–	1	1	1	66.00	73.03	–
	6.4–82.8	0.11	0.10	0.12	57	111	–	0.77	0.48	1.24	56.96	81.85	–
	> 82.8	0.46	0.21	1.52	58	116	–	0.73	0.45	1.17	54.29	82.29	–
Bates et al. (2004) (water concentration, µg/L)	0–50	0.56	0.55	0.58	87	80	–	1	1	1	87.00	51.35	–
	51–100	1.34	0.97	1.81	8	8	–	1.11	0.3	3.7	7.58	4.03	–
	101–200	2.31	1.72	2.97	13	13	–	0.81	0.3	2	11.67	8.51	–
	>200	8.16	3.62	16.83	3	10	–	0.28	0.1	1.4	3.49	7.36	–
Meliker et al. (2010) (water intake, µg/d)	<1	0.103	0.097	0.110	189	252	–	1	1	1	189.00	210.37	–
	1–10	0.145	0.136	0.154	162	234	–	0.83	0.62	1.11	145.13	194.62	–
	>10	0.455	0.334	0.723	43	48	–	1.01	0.62	1.64	37.01	40.79	–

Data set name (reported dose units)	Exposure ranges (in reported dose units)	Dose values for analysis (avg. daily µg/kg)[a]			Raw counts			Adjusted OR/RR and 95% CIs			Effective counts[b]		
		MLE	Low	High	Cases	Controls	Expected	Adj OR	LCL	UCL	Cases	Controls	Expected
Baris et al. (2016) (Cumulative arsenic intake, mg)[d]	≤ 15.7	0.103	0.097	0.109	250	315	–	1	1	1	250	215.56	–
	>15.7–34.5	0.111	0.104	0.117	250	311	–	1.18	0.92	1.52	250.84	220.70	–
	>34.5–77.0	0.127	0.121	0.135	266	309	–	1.13	0.88	1.46	284.84	213.57	–
	>77.0–291.0	0.172	0.160	0.185	210	243	–	1.32	1	1.73	208.11	154.69	–
	>291.0–483.6	0.29	0.25	0.34	37	30	–	1.3	0.74	2.28	40.069	20.44	–
	>483.6	0.44	0.37	0.53	43	29	–	1.6	0.9	2.87	45.215	21.54	–
Chang et al. (2016) (urinary µg/gm Creatinine)	6-46	1.09	1.03	1.14			–	1	1	1	59.00	91.93	–
	46-86.8	2.29	2.22	2.36			–	0.94	0.59	1.5	55.60	92.17	–
	>86.8	5.31	4.96	5.66			–	1.52	0.98	2.37	86.18	88.34	–
Huang et al. (2018) (urinary µg/gm Creatinine)	≤ 9.78	0.21	0.21	0.23			–	1	1	1	72.00	34.09	–
	9.78-17.91	0.46	0.45	0.47			–	1.94	1.18	3.2	236.52	57.73	–
	17.91-30.28	0.79	0.77	0.80			–	2.09	1.18	3.69	130.86	29.65	–
	>30.28	1.81	1.71	1.91			–	3.52	1.77	6.96	107.05	14.40	–
Lin et al. (2018) (urinary µg/gm Creatinine)[e]	≤ 9.71	0.22	0.21	0.22			–	1	1	1	34.00	86.20	–
	9.71-17.98	0.46	0.45	0.47			–	2.02	1.25	3.27	93.73	117.65	–
	17.98-30.51	0.79	0.78	0.81			–	2.36	1.36	4.09	50.97	54.76	–
	>30.51	1.82	1.71	1.92			–	3.23	1.68	6.2	–	–	–

[a]Sets of dose values derived as per Allen et al. (2020a).
[b]Effective Counts derived as per Allen et al. (2020b).
[c]Person years of follow up for reference group = 29,599.
[d]Dose estimates and Ors are for cumulative intake (mg), unlagged.
[e]Effective counts shown are the ones used in the final meta-regression analysis based on dropping the high dose to improve model fit at low doses.

Summary of bladder cancer meta-regression results for MLE dose estimates

The settings for all Bayesian meta-regression runs summarized in the tables of this section were:

- 4 chains, each with iterations = 25,000; warmup = 21250; thin = 2; Adapt_Delta[21] = 0.9999
- post-warmup draws per chain = 1,875, total post-warmup draws = 7500.
- β_mean Gamma parameters: a = 0.52 and b = 1.12

[21]Corresponds to the target average proposal acceptance probability which is inversely related to the numerical integrator "step size" employed in Stan Hamiltonian MC.

This section provides details of the results for the hierarchical meta-regression modeling, as well as dose-response plots from non-hierarchical modeling of individual studies. Additional details regarding the hierarchical and non-hierarchical modeling results can be obtained from the EPA HERO database.

Table C-20. Summary of bladder cancer Bayesian analysis output using MLE dose estimates

Study	Parameter[a]	Mean	Standard error of mean	Standard deviation	2.50%	25%	50%	75%	97.50%
Chen et al. (2010b)	b	0.0753	0.0002	0.0199	0.0342	0.0623	0.0762	0.0888	0.1132
	μ(δ)	9.7215	0.0294	2.2747	5.898	8.0837	9.5036	11.1018	14.8568
	OR_RR[1]	1	0	0	1	1	1	1	1
	OR_RR[2]	1.021	0.0001	0.0056	1.0095	1.0173	1.0212	1.0248	1.0317
	OR_RR[3]	1.0958	0.0003	0.0264	1.0423	1.0784	1.0967	1.1136	1.1469
	OR_RR[4]	1.3364	0.0012	0.101	1.1394	1.2682	1.3374	1.4033	1.5397
	OR_RR[5]	5.183	0.0258	2.1465	2.0348	3.6435	4.8644	6.319	10.4611
Steinmaus et al. (2013)	b	0.5149	0.0014	0.1174	0.2874	0.4367	0.514	0.5942	0.7472
	vlambda[1]	1.122	0.0077	0.6547	0.2367	0.6457	0.9968	1.4519	2.7388
	vlambda[2]	1.1965	0.0083	0.6991	0.2552	0.6933	1.0617	1.5505	2.93
	vlambda[3]	0.6855	0.0048	0.4067	0.1449	0.3927	0.605	0.891	1.7085
	OR_RR[1]	1	NaN	0	1	1	1	1	1
	OR_RR[2]	1.4578	0.0015	0.1246	1.2317	1.3725	1.4515	1.5385	1.719
	OR_RR[3]	3.3568	0.0109	0.9225	1.9268	2.709	3.2313	3.8809	5.5025
Wu et al. (2013)	b	1.0394	0.0018	0.1535	0.7371	0.9359	1.0375	1.1438	1.3423
	vlambda[1]	1.0067	0.007	0.5946	0.1978	0.5684	0.895	1.3249	2.3594
	vlambda[2]	1.0439	0.0072	0.6127	0.2064	0.5873	0.9263	1.3729	2.5957
	vlambda[3]	0.9535	0.0066	0.5618	0.1902	0.5407	0.8431	1.2517	2.3079
	OR_RR[1]	1	NaN	0	1	1	1	1	1
	OR_RR[2]	1.7517	0.0017	0.1448	1.4846	1.6516	1.744	1.8463	2.0536
	OR_RR[3]	4.1705	0.0105	0.8827	2.7112	3.548	4.0707	4.7004	6.1488
Bates et al. (1995)	b	0.3279	0.0084	0.6562	−0.9798	−0.0629	0.3189	0.7091	1.6827
	vlambda[1]	1.1049	0.0066	0.5744	0.2905	0.6849	1.0054	1.4266	2.5034
	vlambda[2]	1.0991	0.0066	0.5728	0.2904	0.6819	0.988	1.4114	2.4811
	vlambda[3]	0.7707	0.0047	0.4062	0.1995	0.4748	0.6964	0.9918	1.7693

Study	Parameter[a]	Mean	Standard error of mean	Standard deviation	2.50%	25%	50%	75%	97.50%
	vlambda[4]	1.0192	0.0062	0.5328	0.2668	0.634	0.9165	1.3082	2.2799
	OR_RR[1]	1	NaN	0	1	1	1	1	1
	OR_RR[2]	1.0015	0	0.003	0.9956	0.9997	1.0014	1.0032	1.0076
	OR_RR[3]	1.0032	0.0001	0.0065	0.9904	0.9994	1.0031	1.007	1.0166
	OR_RR[4]	1.0102	0.0003	0.02	0.9708	0.9981	1.0097	1.0216	1.0521
Steinmaus et al. (2003)	b	−0.0765	0.0056	0.4408	−1.0136	−0.3634	−0.054	0.2205	0.743
	vlambda[1]	0.9982	0.0066	0.5758	0.2009	0.5745	0.8946	1.2993	2.4054
	vlambda[2]	0.9954	0.0067	0.5754	0.2009	0.5746	0.8964	1.3063	2.4075
	vlambda[3]	0.9921	0.0066	0.5752	0.1977	0.5681	0.8888	1.2984	2.3964
	OR_RR[1]	1	NaN	0	1	1	1	1	1
	OR_RR[2]	0.9995	0	0.0027	0.9937	0.9977	0.9997	1.0014	1.0046
	OR_RR[3]	0.985	0.002	0.1552	0.6928	0.8767	0.9807	1.0831	1.3087
Bates et al. (2004)	b	−0.1753	0.001	0.0878	−0.3577	−0.2327	−0.1707	−0.1145	−0.0168
	vlambda[1]	2.7656	0.0166	1.4067	0.77	1.7289	2.5241	3.5212	6.2796
	vlambda[2]	0.2729	0.0019	0.1617	0.0651	0.1552	0.2396	0.3542	0.6765
	vlambda[3]	0.5044	0.0033	0.2827	0.1254	0.2998	0.4474	0.6455	1.2082
	vlambda[4]	0.4276	0.0031	0.2684	0.0957	0.238	0.3672	0.5486	1.1005
	OR_RR[1]	1	NaN	0	1	1	1	1	1
	OR_RR[2]	0.8742	0.0007	0.0594	0.7565	0.834	0.8753	0.9146	0.987
	OR_RR[3]	0.7444	0.0013	0.113	0.5347	0.6655	0.7417	0.8185	0.971
	OR_RR[4]	0.3265	0.0026	0.2283	0.0661	0.1709	0.2736	0.4193	0.88
Meliker et al. (2010)	b	0.205	0.0061	0.4542	−0.7103	−0.0886	0.2135	0.5054	1.0775
	vlambda[1]	1.4798	0.0104	0.86	0.3029	0.8389	1.3309	1.9496	3.5581
	vlambda[2]	1.2538	0.0089	0.7278	0.2599	0.7124	1.1277	1.6403	3.0183
	vlambda[3]	0.2812	0.002	0.1668	0.0562	0.1576	0.2497	0.3695	0.6896
	OR_RR[1]	1	NaN	0	1	1	1	1	1
	OR_RR[2]	1.0088	0.0003	0.0192	0.9706	0.9963	1.009	1.0215	1.0463
	OR_RR[3]	1.0888	0.0024	0.1749	0.7785	0.9692	1.0782	1.1951	1.4622
Baris et al. (2016)	b	0.651	0.006	0.4718	−0.2435	0.3365	0.6275	0.9399	1.637
	vlambda[1]	1.4221	0.0076	0.5875	0.526	0.9965	1.3379	1.7515	2.8138
	vlambda[2]	1.5961	0.0086	0.6591	0.5957	1.1138	1.4991	1.9669	3.1668

Study	Parameter[a]	Mean	Standard error of mean	Standard deviation	2.50%	25%	50%	75%	97.50%
	vlambda[3]	1.5245	0.0081	0.6289	0.5657	1.0663	1.4303	1.8792	3.0226
	vlambda[4]	1.1321	0.0061	0.4692	0.4223	0.7864	1.0633	1.3901	2.2428
	vlambda[5]	0.1625	0.0009	0.0716	0.0573	0.1113	0.1509	0.2015	0.3386
	vlambda[6]	0.1503	0.0008	0.0666	0.0522	0.1021	0.1396	0.1867	0.3078
	OR_RR[1]	1	NaN	0	1	1	1	1	1
	OR_RR[2]	1.0051	0	0.0037	0.9981	1.0026	1.0049	1.0074	1.0129
	OR_RR[3]	1.0161	0.0002	0.0118	0.9941	1.0083	1.0155	1.0233	1.0409
	OR_RR[4]	1.0464	0.0004	0.0341	0.9834	1.0234	1.0441	1.0668	1.1192
	OR_RR[5]	1.1337	0.0013	0.1014	0.9556	1.0648	1.1243	1.1918	1.3575
	OR_RR[6]	1.2619	0.0026	0.2076	0.9211	1.1203	1.2359	1.3733	1.7376
Chang et al. (2016)	b	0.1151	0.0006	0.0508	0.0141	0.0815	0.115	0.1502	0.2131
	vlambda[1]	1.0489	0.007	0.602	0.223	0.6022	0.9381	1.3629	2.5213
	vlambda[2]	0.973	0.0065	0.5598	0.2078	0.5625	0.8688	1.2748	2.3443
	vlambda[3]	0.9846	0.0065	0.5658	0.2077	0.5669	0.8797	1.2906	2.3597
	OR_RR[1]	1	NaN	0	1	1	1	1	1
	OR_RR[2]	1.1513	0.0009	0.0705	1.0172	1.1033	1.149	1.1988	1.2933
	OR_RR[3]	1.6652	0.0043	0.3591	1.0614	1.4114	1.6267	1.8876	2.4627
Huang et al. (2018)	b	0.5908	0.0024	0.1957	0.2177	0.4572	0.5856	0.7208	0.9912
	vlambda[1]	0.7776	0.0047	0.4015	0.2009	0.4856	0.7055	0.9968	1.7186
	vlambda[2]	1.9121	0.0113	0.968	0.4961	1.2088	1.7454	2.4477	4.2099
	vlambda[3]	0.8976	0.0053	0.4577	0.2323	0.5631	0.8158	1.1513	1.9947
	vlambda[4]	0.4165	0.0027	0.2335	0.1005	0.2473	0.372	0.5354	0.9883
	OR_RR[1]	1	NaN	0	1	1	1	1	1
	OR_RR[2]	1.1635	0.0007	0.0582	1.0569	1.1232	1.1605	1.2011	1.2866
	OR_RR[3]	1.4215	0.002	0.1645	1.1356	1.3061	1.4078	1.5235	1.7842
	OR_RR[4]	2.7074	0.0106	0.8933	1.4171	2.0793	2.554	3.1711	4.8899
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

Study	Parameter[a]	Mean	Standard error of mean	Standard deviation	2.50%	25%	50%	75%	97.50%
	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

[a]The indices, e.g., OR[i] refer to the ith group in the study. The lambda values that characterize the proportion of the control population in each dose-range are computed by vlambda[i]/sum(vlambda[j]) for all i, j in the range appropriate for each study.

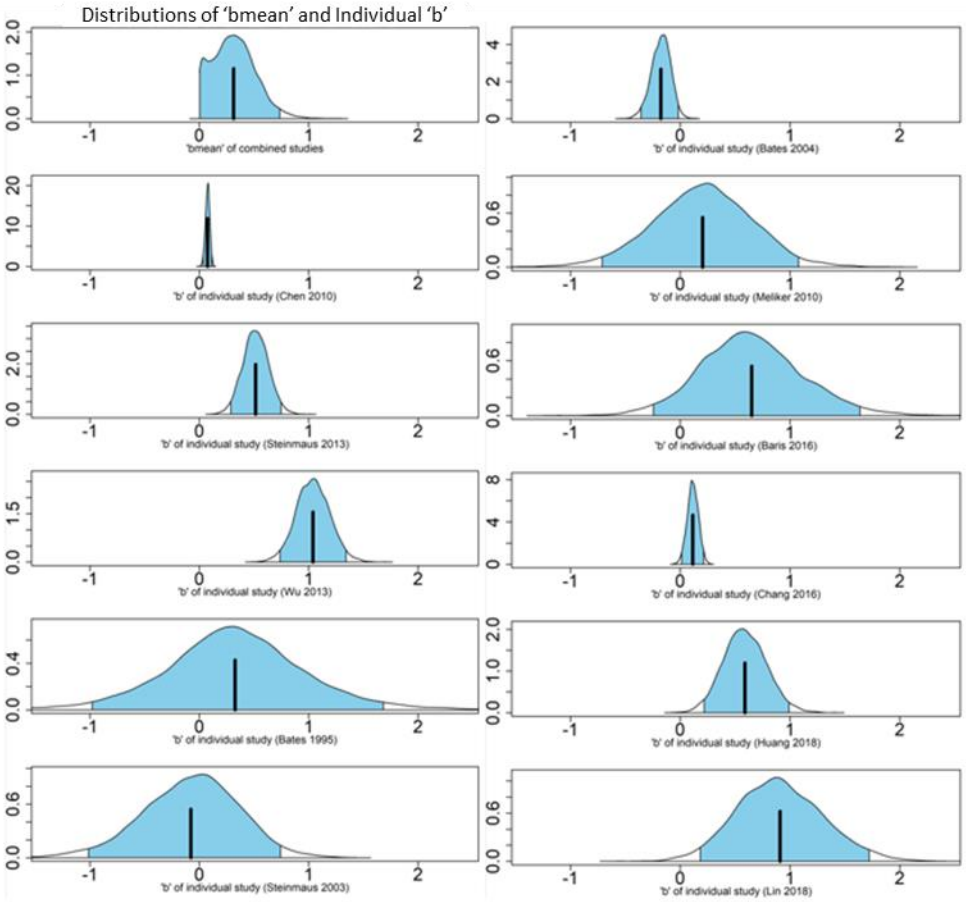


Figure C-10. Posterior distributions for bladder cancer pooled (bmean) and data-set-specific (b) logistic slope parameters, using MLE dose estimates. 95% Credible intervals are highlighted.

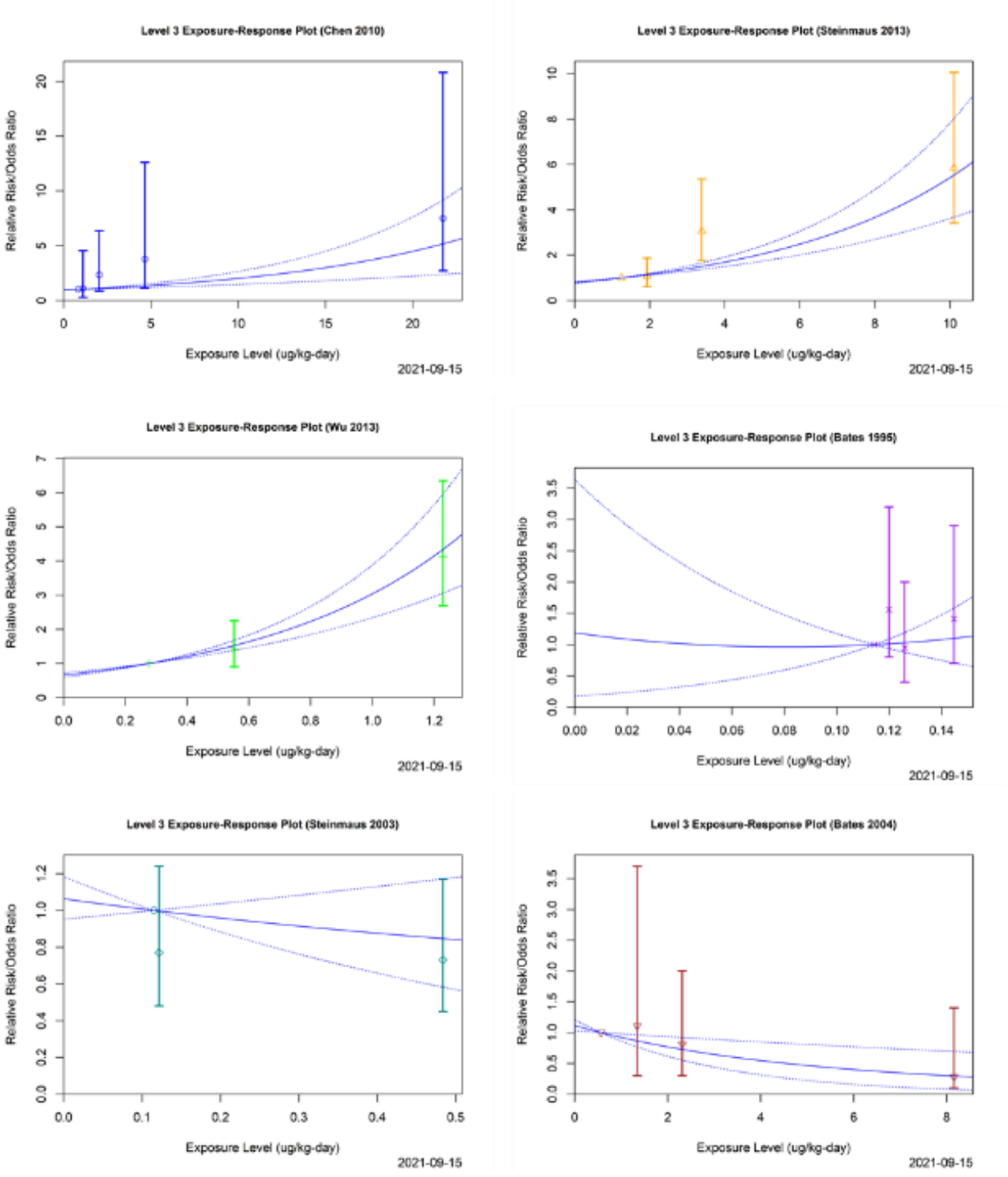


Figure C-11. Non-hierarchical meta-regression dose response curves for individual bladder cancer studies; using MLE dose estimates.

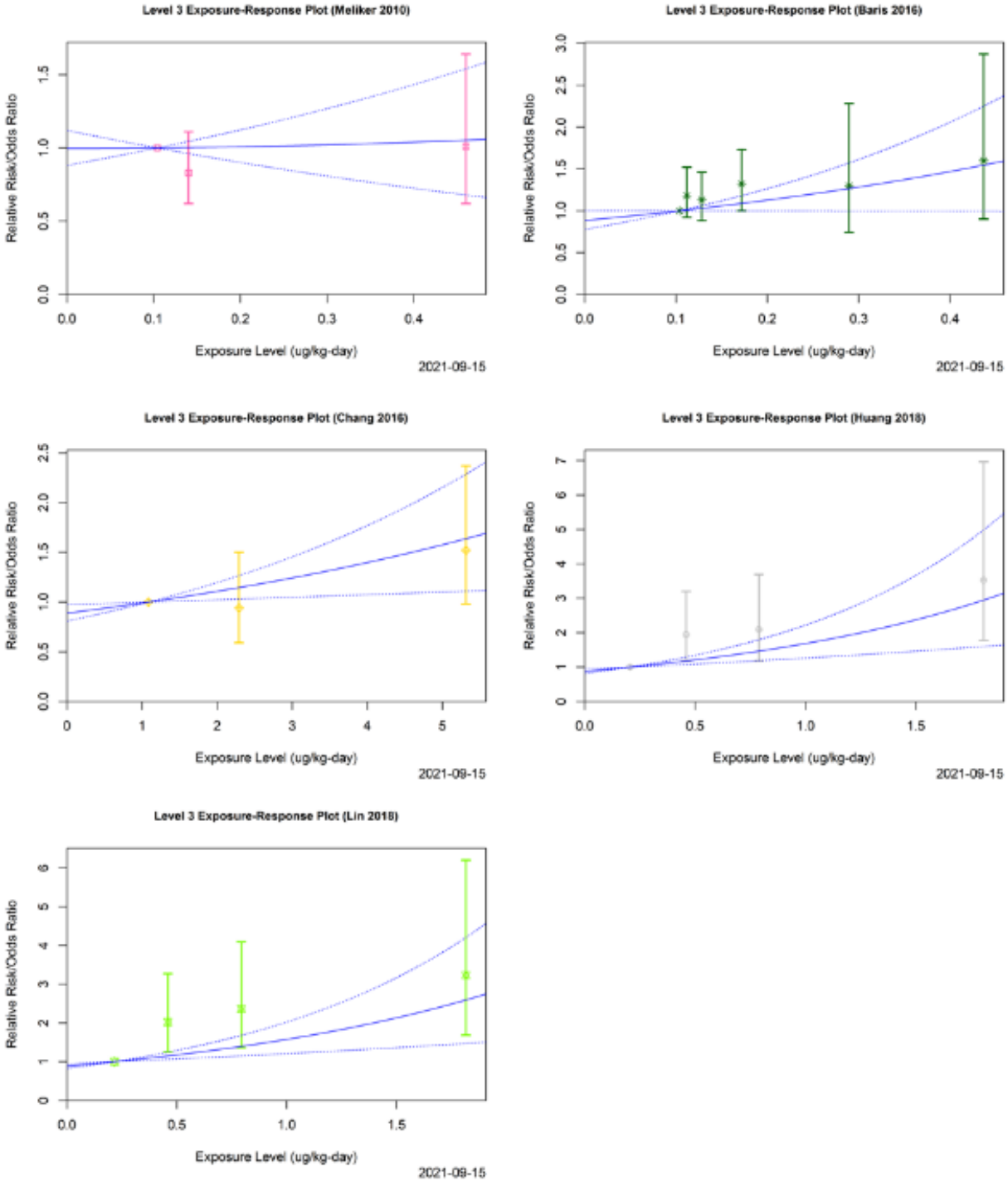


Figure C-12. Non-hierarchical meta-regression dose response curves for individual bladder cancer studies; using MLE dose estimates (cont.).

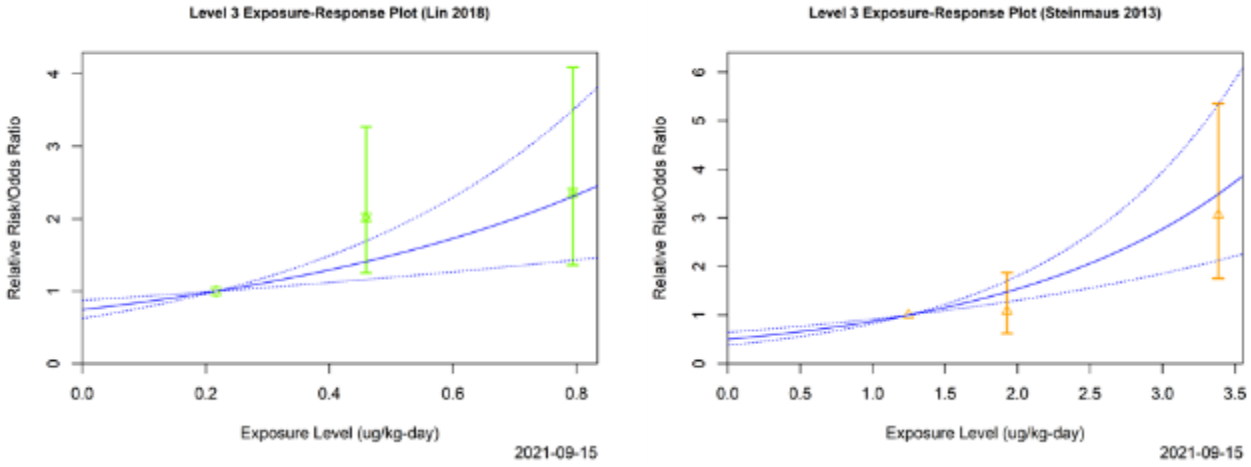


Figure C-13. Non-hierarchical meta-regression dose response curves for individual bladder cancer studies (using MLE dose estimates) where doses were dropped to improve fit.

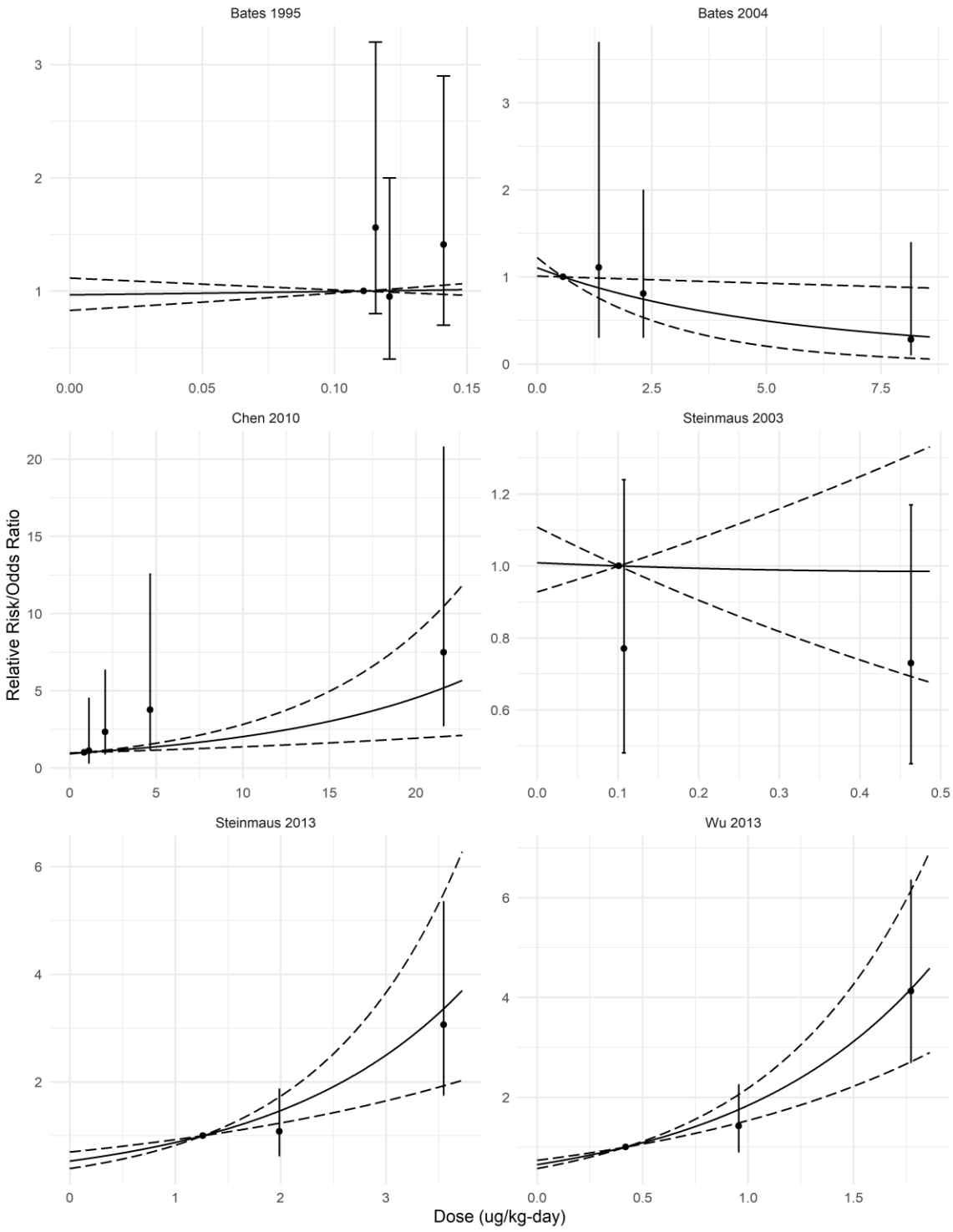


Figure C-14. Hierarchical meta-regression dose response curves for individual bladder cancer studies; using MLE dose estimates.

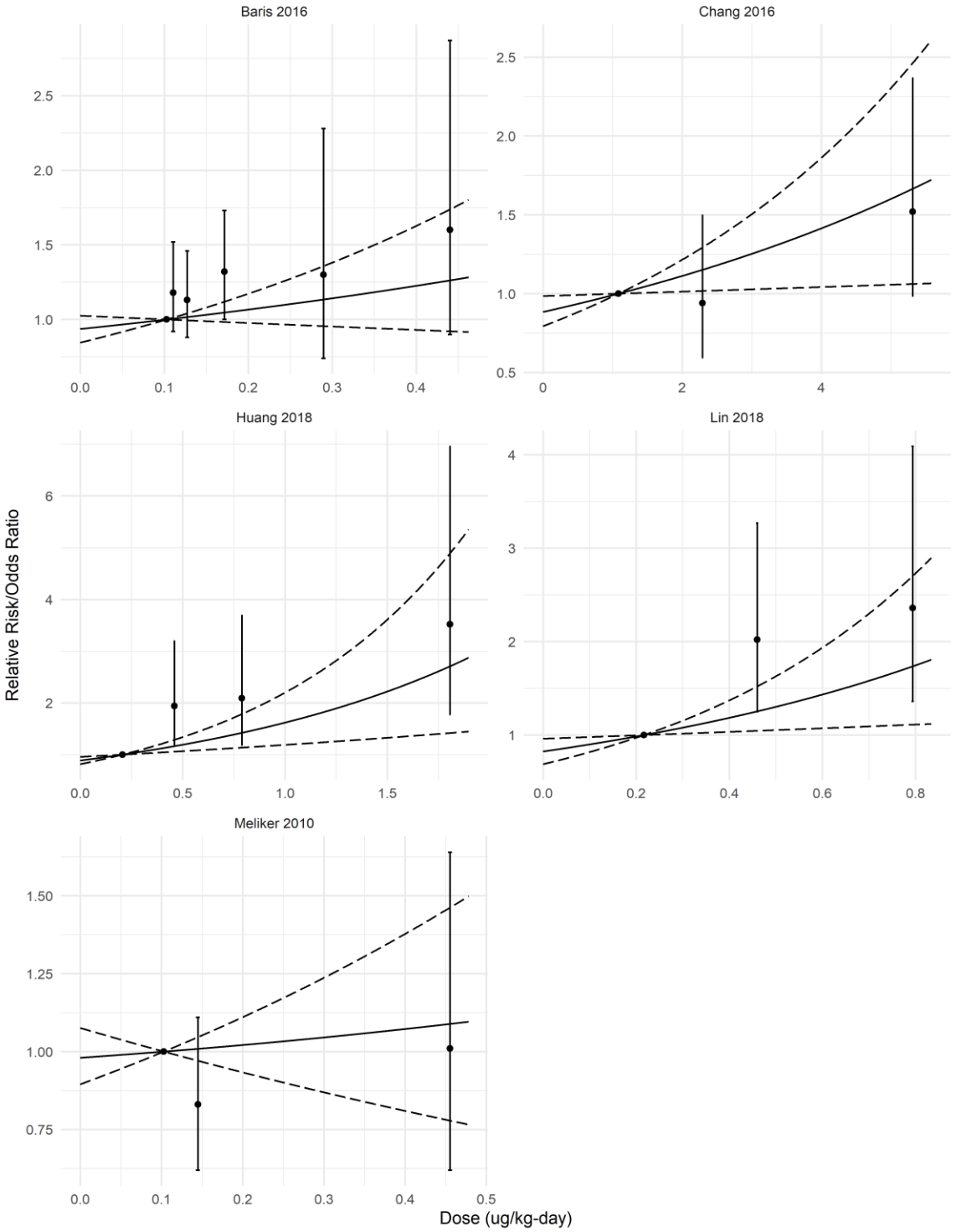


Figure C-15. Hierarchical meta-regression dose response curves for individual bladder cancer studies; using MLE dose estimates (cont.).

Bladder cancer sensitivity analyses

In addition to the evaluation of the meta-regression approach's sensitivity across endpoints to the choice of the simpler Logistic model over a more complex double Hill model that allows for non-monotonicity (see Sensitivity Analysis of Possible Non-monotonic Dose-Response Relationships), EPA has examined the sensitivity of the estimates of the association between oral iAs exposure and each meta-regression endpoint for six sources of uncertainty, as follows: (1) characterization of the exposure levels used for the dose-response modeling, (2) the choice of data sets, (3) the assumption that the general U.S. population is not appreciably exposed to iAs via inhalation, (4) considerations of alternative gamma prior distributions for b_mean, (5) the use of urine biomarker studies (if available) in the meta-regression analysis, and (6) the use of alternative exposure metrics and/or lagged analyses within studies (if applicable).

The sources of uncertainty related to dose metric values are themselves broken down into two components. The first arises because of the need to estimate a mean value for the dose groups reported in terms of ranges of values (in whatever metric). The second relates to conversion of those mean exposure values to a consistent set of units across studies, those units being average daily μg/kg. The methods used to characterize those uncertainties are described in Allen et al. (2020a). Table C-21 below summarizes the 95% confidence intervals for the meta-regression pooled b value and extra risk values for bladder cancer for the "MLE," "low," and "high" iAs dose estimates shown in Table C-20.[22] Note that, while the "low" dose estimates provide the largest extra risks, it is only 16% higher than the MLE estimate, indicating that the analysis was relatively insensitive to the uncertainties associated with dose characterization.

Table C-21. Pooled mean b and extra risk estimates from meta-regression of bladder cancer studies using MLE, "low," and "high" dose estimates

	Low dose estimates		MLE (MLE) dose estimates		High dose estimates	
	Mean b	Lifetime Extra Risk[a]	Mean b	Lifetime Extra Risk[a]	Mean b	Lifetime Extra Risk[a]
5%	0.0098	2.43E-05	0.0161	3.99E-05	0.0217	5.39E-05
Mean	0.3634	9.11E-04	0.3138	7.85E-04	0.2478	6.19E-04
95%	0.8048	2.04E-03	0.6508	1.64E-03	0.5010	1.26E-03

[a]Risk above zero dose; Estimated for a total dose of 0.13 μg iAs/kg-day, which includes an estimated 0.0365 μg iAs/kg-day background dose, 0.05 μg iAs/kg-day from diet and 0.021 μg iAs/kg-day from drinking water.

With respect to sensitivity of the estimates to choice of dataset, note that the meta-regression approach avoids the issue of study selection by pooling the results of all the datasets. Nevertheless, it is of interest to determine how influential each of those studies are on the estimate of the pooled risk. That sensitivity has been investigated by computing the pooled estimate of risk

[22]Details of the meta-regression analyses using low and high dose estimates are available from the EPA HERO database.

when each of the data sets is iteratively excluded from the analysis (i.e., a leave-one-out analysis). Table C-22 lists the pooled and study-specific mean b values when one study is iteratively left out of the analysis. As can be seen, the greatest decrease (35%) is observed when the dataset from Wu et al. (2013) is excluded, and the greatest increase (20%) is observed when the dataset from Bates (2004) is excluded.

Although inhalation of inorganic arsenic is not considered a primary route of exposure for the general public, the World Health Organization (WHO) estimates that background exposure may range from 0.02 to 0.6 μg/day in areas without substantial arsenic emissions from anthropogenic sources. Assuming an average body weight of 70 kg, this corresponds to daily intake values of 2.9×10^{-4} μg/kg-day to 8.6×10^{-3} μg/kg-day. The third sensitivity analysis involved two extra lifetable analyses wherein background inhalation components of either 4.4×10^{-3} μg/kg-day (corresponding to the midpoint of the range of reported background iAs concentrations), or 8.6×10^{-3} μg/kg-day (corresponding to the upper limit of background concentrations) were added to the original background estimate of exposure due to dietary and drinking water sources (i.e., 0.0365 μg/kg-day). Incorporation of inhalation exposures in the background estimate of total exposure also did not result in dramatically different estimates of extra risk. By definition, as the estimate of background exposure increased in the lifetable analysis, calculated extra risks must correspondingly decrease. Thus, at a 0.13 μg/kg-day dose (approximately equivalent to a 10 μg/L iAs lifetime drinking water exposure), when the assumed background exposure was either 0.0409 μg/kg-day or 0.0451 μg/kg-day, extra risks decreased to 7.84×10^{-4} or 7.83×10^{-4}, compared to 7.85×10^{-4} when no inhalation component was included in the background estimate of exposure. This corresponds to 0.1% and 0.3% decreases in extra risk, respectively.

Table C-22. Results of the leave-one-out analysis for bladder cancer datasets using the MLE dose estimate

Study left out	Mean b values (5th–95th percentile)											
	Pooled	Chen et al. (2010b)	Steinmaus et al. (2013)	Wu et al. (2013)	Bates et al. (1995)	Steinmaus (2003)	Bates (2004)	Meliker et al. (2010)	Baris et al. (2016)	Chang et al. (2016)	Huang et al. (2018)	Lin et al. (2018)
Chen et al. (2010b)	0.3546 (0.0205–0.7421)	–	0.5186 (0.3204–0.7172)	1.0519 (0.8086–1.3064)	0.3790 (−0.7355–1.5321)	−0.0863 (−0.8717–0.6364)	−0.17783 (−0.3266–0.0434)	0.2298 (−0.5834–0.9868)	0.7007 (−0.0740–1.563)	0.1145 (0.0300–0.1999)	0.6038 (0.2866–0.9452)	0.9818 (0.3430–1.6781)
Steinmaus et al. (2013)	0.2884 (0.0088–0.6638)	0.0757 (0.0417–0.1075)	–	1.0482 (0.7994–1.3056)	0.3085 (−0.8382–1.459)	−0.1346 (−0.9025–0.5690)	−0.1780 (−0.3266–0.0405)	0.1890 (−0.6110–0.9700)	0.6586 (−0.1312–1.5361)	0.1133 (0.0293–0.1958)	0.5944 (0.2743–0.9258)	0.9462 (0.3023–1.6402)
Wu et al. (2013)	0.2197 (0.0060–0.5159)	0.0754 (0.0417–0.1074)	0.4960 (0.2968–0.6921)	–	0.2286 (−0.6108–1.0836)	−0.0527 (−0.7431–0.5485)	−0.1693 (−0.3140–-0.0361)	0.1559 (−0.4931–0.7928)	0.5012 (−0.1382–1.2716)	0.1148 (0.0320–0.2000)	0.5428 (0.2286–0.8767)	0.7386 (0.1534–1.4416)
Bates et al. (1995)	0.3102 (0.0144–0.6403)	0.0755 (0.0428–0.1068)	0.5191 (0.3232–0.7174)	1.0401 (0.7876–1.2954)	–	−0.0857 (−0.8441–0.6074)	−0.1749 (−0.3182–0.0175)	0.2124 (−0.7684–1.1445)	0.7410 (−0.2342–1.8487)	0.1139 (0.0146–0.2147)	0.6082 (0.2324–1.0127)	1.0288 (0.2394–1.8648)
Steinmaus (2003)	0.4089 (0.0070–0.9233)	0.0746 (0.0352–0.1116)	0.5555 (0.3133–0.8015)	1.4064 (0.9928–1.8224)	0.4175 (−1.2062–2.0228)	–	−0.1785 (−0.3556–-0.0370)	0.2058 (−0.5585–0.9267)	0.6379 (−0.0855–1.4459)	0.1136 (0.0308–0.1994)	0.5895 (0.2670–0.9245)	0.9157 (0.2950–1.5935)
Bates (2004)	0.3903 (0.0312–0.7408)	0.0757 (0.0425–0.1069)	0.5200 (0.3285–0.7082)	1.0405 (1.2916–0.7914)	0.3970 (-0.6653–1.4489)	-0.0156 (-0.7921–0.6687)	–	0.2699 (-0.5057–1.0001)	0.6862 (-0.0490–1.5269)	0.1159 (0.0311–0.2007)	0. 5964 (0.2853–0.9241)	0.9379 (0.3400–1.6150)
Meliker et al. (2010)	0.3238 (0.0144 -0.6924)	0.0747 (0.0422 -0.1051)	0.5170 (0.3216 -0.7183)	1.0450 (0.7978 -1.2984)	0.3333 (-0.7525 -1.4069)	-0.0904 (-0.8506 -0.6007)	-0.1760 (-0.3198 --0.0369)	–	0.6596 (-0.1184 -1.4879)	0.1136 (0.0298 -0.1956)	0.5975 (0.2782 -0.9316)	0.9415 (0.3057 -1.6222)
Baris et al. (2016)	0.2770 (0.0100 -0.6191)	0.0756 (0.0424 -0.1072)	0.5171 (0.3214 -0.7134)	1.0380 (0.7880 -1.2948)	0.2918 (-0.8013 1-.3392)	-0.0923 (-0.8251 -0.5924)	-0.1771 (-0.3246 --0.0409)	0.1768 (-0.5856 -0.9052)	–	0.1143 (0.0309 -0.1984)	0.5831 (0.2674 -0.9098)	0.9057 (0.2772 -1.5810)
Chang et al. (2016)	0.3338 (0.0122 -0.7189)	0.0752 (0.0421 -0.1069)	0.5200 (0.3249 -0.7201)	1.0545 (0.8034 -1.3088)	0.3413 -(0.7827 1-.4997)	-0.1004 (-0.8905 -0.6141)	-0.1775 (-0.3263 --0.0386)	0.2155 (-0.5843 -0.9630)	0.6950 -(0.0772 1-.5433)	–	0.6031 (0.2850 -0.9412)	0.9631 (0.3088 -1.6581)

Study left out	Mean b values (5th–95th percentile)											
	Pooled	Chen et al. (2010b)	Steinmaus et al. (2013)	Wu et al. (2013)	Bates et al. (1995)	Steinmaus (2003)	Bates (2004)	Meliker et al. (2010)	Baris et al. (2016)	Chang et al. (2016)	Huang et al. (2018)	Lin et al. (2018)
Huang et al. (2018)	0.2798 (0.0078 -0.6365)	0.0753 (0.0427 -0.1073)	0.5173 (0.3227 -0.7171)	1.0438 (0.7958 -1.2999)	0.2808 -(0.8115 1-.3798)	-0.1252 (-0.9128 -0.5853)	-0.1779 (-0.3193 --0.0402)	0.1780 (-0.6023 -0.9448)	0.6490 -(0.1346 1-.4836)	0.1144 (0.0305 -0.1963)	–	0.9403 (0.2982 -1.6617)
Lin et al. (2018)	0.2492 (0.0066 -0.5603)	0.0752 (0.0426 -0.1066)	0.5115 (0.3194 -0.7107)	1.0247 (0.7739 -1.2787)	0.2713 -(0.6818 1-.2320)	-0.0817 (-0.8067 -0.5825)	-0.1767 (-0.3224 --0.0403)	0.1823 (-0.5362 -0.8764)	0.5833 -(0.1257 1-.3741)	0.1138 (0.0294 -0.1976)	0.5766 (0.2646 -0.9066)	–

[a]Pooled estimate using all studies was 0.3138 (0.0161−0.6508) (see Table C-21).

The assumption of different Gamma prior distributions for β_mean did not result in large differences in the posterior distributions of the β_mean parameter (see Table C-23). Interestingly, the alternative prior sensitivity results indicated that, for the present set of studies used in this case-example, the results of the dose-response meta-analysis are rather insensitive to assumptions on the gamma distribution prior. For example, using priors that differed with respect to the 1st percentile (i.e., 1.00001 – 20 and 1.001 – 20) resulted in the greatest differences in the mean of the posterior distribution relative to the original prior. This is due to the characteristics of the Gamma distribution, in which the greatest density with respect to probability of response is close to zero. So, when using the 1.00001 – 20 priors, the corresponding posterior mean distribution was approximately 7% lower than the results with the original prior because the 1st percentile is assumed to be ten times lower than for the original prior. Correspondingly, the 1.001 – 20 prior resulted in a posterior mean distribution approximately 8% higher than the original prior. Alternate Gamma prior distributions that differed with respect to the 99th percentile also did not differ greatly from the results using the original prior: using a prior with an upper bound of 10 (i.e., 50% lower than the original) resulted in a posterior mean approximately 2% lower, and using a prior with an upper bound of 30 (i.e., 50% higher than the original) resulted in a posterior mean approximately 2% higher than the original prior. This broadly indicates that the results of the analysis are heavily influenced by the actual data being modeled and are not inappropriately driven by the prior assumptions of the Bayesian modeling.

Table C-23. Posterior β_mean distribution values resulting from various prior Gamma distributions

Alternative prior	5th percentile	Mean	95th percentile	% Mean difference
1.00001 – 20	0.0073	0.2931	0.6330	-7%
1.0001 – 10	0.0141	0.3082	0.6472	−2%
1.0001 – 30	0.0176	0.3209	0.6675	2%
1.001 – 20	0.0375	0.3395	0.6710	8%
Original Prior(1.0001 – 20)	0.0161	0.3138	0.6508	**–**

The outcome of the meta-regression was sensitive to whether or not urinary biomarker studies were included in the modeling set. For bladder cancer, there were four urinary biomarker studies included the in the modeling set, Wu, Chang, Huang, and Lin. As can be seen in Table C-22, when Wu is left out of the modeling set, the mean logistic slope decreases approximately 30%, but when Chang, Huang, or Lin are iteratively left out, the mean logistic slope increased 6%, decreased 11%, and decreased 21%, respectively. When all four studies are excluded, the mean logistic slope decreased to 0.1362, a 57% decrease compared to the mean logistic slope estimate of 0.3138 when all studies are included in the meta-regression. Conversely, when only urine studies are used in the meta-regression, the mean logistic slope is 0.5358, a 71% increase. These results indicate that the

urinary biomarker studies are important drivers of the overall estimated association between iAs exposure and bladder cancer in this meta-regression.

The last sensitivity analysis for bladder cancer investigated the impact that alternative exposure metrics or lagged vs. unlagged analyses used in some studies had on the final meta-regression results. Baris 2016 presented multiple results in their study using either total mg or µg/day as the exposure metric and analyses lagged 40 years or unlagged. Table C-24 below shows the impact these alternative datasets in the meta-regression on the final modeling results; the greatest difference was a 30% decrease in the estimated logistic slope when the 40-year lagged mg exposure metric was used from the Baris study.

Table C-24. Posterior β_mean distribution values resulting from the inclusion of alternative datasets in the meta-regression

Alternative analysis	5th percentile	Mean	95th percentile	% Mean difference
Baris (lagged, mg)	0.0040	0.2184	0.5457	-30%
Baris (lagged, µg/d)	0.0097	0.2546	0.5563	-19%
Baris (unlagged, µg/d)	0.0069	0.2416	0.5559	-23%
Original Analysis (Baris, unlagged mg)	0.0161	0.3138	0.6508	–

Extrapolation of bladder cancer extra risk to target U.S. population

Table C-25. Lifetable rates for all-cause mortality and bladder cancer mortality and incidence

Age range	All-cause mortality rates (per 100,000)[a]	Bladder cancer mortality rates (per 100,000)[b]	Bladder cancer incidence rates (per 100,000)[b]
0–1	567	0	0
1–4	24.3	0	0
5–9	11.6	0	0
10–14	15.5	0	0
15–19	51.5	0	0.1
20–24	95.6	0	0.2
25–29	121	0	0.4
30–34	145.4	0	0.7
35–39	173.8	0.1	1.4
40–44	218.4	0.3	2.7
45–49	313.2	0.6	6
50–54	488	1.4	12.6

Age range	All-cause mortality rates (per 100,000)[a]	Bladder cancer mortality rates (per 100,000)[b]	Bladder cancer incidence rates (per 100,000)[b]
55–59	736.5	3.2	23.8
60–64	1050.2	5.8	41.5
65–69	1473.5	9.5	68.6
70–74	2206.9	16.7	100.2
75–79	3517.8	27	135.4
80–84	5871.7	47.8	165.2

[a]National Vital Statistics Report, Volume 68, Number 9, 2/16/2016. Final data for 2017: https://www.cdc.gov/nchs/data/nvsr/nvsr68/nvsr68_09-508.pdf.
[b]SEER cancer statistics for 2017: https://gis.cdc.gov/Cancer/USCS/DataViz.html.

Oral Lung Cancer

Lung cancer study and dataset selection

Table C-26. Data sets selected for oral exposure lung cancer dose-response Bayesian meta-regression

Study	Study design	Location	Exposure/ Dose metric	Estimate of iAs exposure group mean µg/kg-d intake range (Estimate of mean U.S. equivalent µg/L drinking water range)[a]	Health outcome/endpoint	Description	Limitations
Argos et al. (2014)	Cohort	Bangladesh	Creatinine-adjusted urinary arsenic (µg/g)	2.08–21.22 187–1,927	Lung cancer identified by trained physician via verbal autopsy questionnaire followed by review by panel of physicians.	Large cohort study (90 lung cancer deaths, total cohort size = 26,043) of Bangladeshi adults exposed to high levels of arsenic via drinking water; urinary total arsenic concentrations were measured from baseline spot urine samples; the analysis controlled for major confounders including smoking	Exposure estimates were based on a one-time baseline urine measurement; high level of detection for urinary arsenic compared to other urinary studies; relatively short follow-up time compared to other cohort studies included in meta-analysis
García-Esquinas et al. (2013)	Cohort	United States (Arizona, Oklahoma, North and South Dakota)	Creatinine-adjusted total urinary arsenic (µg/g)	0.139–0.585 10.8–51.4	Trachea, bronchus, and lung tumors as identified by trained nosologist from death certificates and medical examiner reports (if available)	Large cohort study (78 lung cancer cases, total cohort size = 4,549) of Native Americans in multiple states exposed to relatively low levels of arsenic via drinking water and food; urinary total arsenic concentrations were measured from baseline spot urine samples; the analysis controlled for major confounders including smoking	Exposure estimates were based on a one-time baseline urine measurement; cohort size relatively small compared to other cohorts included in meta-analysis
Chen et al. (2010a)	Cohort	NE Taiwan	Cumulative As exposure (µg/L-yrs)	0.76–23.26 (67.3–2,113)	Histologically confirmed lung cancers identified from Taiwan national cancer registry	Large cohort study (6,888 subjects with exposure measurements), individual well As levels measured for 85% of subjects. Broad exposure range, well-documented case ascertainment, good follow up (12 yrs), controlled for major covariates.	No notable limitations

Study	Study design	Location	Exposure/ Dose metric	Estimate of iAs exposure group mean µg/kg-d intake range (Estimate of mean U.S. equivalent µg/L drinking water range)[a]	Health outcome/endpoint	Description	Limitations
D'Ippoliti et al. (2015)	Cohort	Central Italy	Drinking water concentration (µg/L)	0.16–0.43 (12.7–37.3)	Identification of trachea, bronchus, and lung cancer from Mortality Registry of the Lazio, Italy region	Very large retrospective cohort study (138,800 subjects), individual iAs levels available for 90% of subjects based on residential history. Arsenic exposures were low and comparable to US populations, controlled for major covariates	Smoking controlled for on the municipal level via smoking sale information
Dauphiné et al. (2013)	Case-Control	United States (California, Nevada)	Cumulative As exposure (µg/L-yrs)	0.11–3.82 (7.3–345)	Histological confirmation of lung cancer from hospital records or state level cancer registries	Moderately (196 cases, 359 controls) large study of U.S. population exposed to mostly low levels of arsenic in water. Historical residential history, drinking water consumption questionnaire, and municipal drinking water/well As measurements used to estimate cumulative As exposure; major confounders adjusted for in final analyses	Possible recall bias (~47% of study questionnaires filled out by relatives/next-of-kin
Ferreccio et al. (2000)	Case-Control	N. Chile	Average water As concentration (µg/L)	1.1–6.7 (98–607)	Histologically confirmed lung cancer cases from public hospital records	Moderately (151 cases, 419 controls) large study of Chilean population exposed to As in municipal drinking water supplies; well-documented historical water As concentrations with good resolution in the low-medium dose range; The subject cohort has been the subject of a number of studies of As-related cancer and covariate interactions	Use of hospital controls; period of high exposure occurred many yrs prior to study period (1958−1970), use of average As water concentrations during 1930−1994 could lead to exposure misclassification

Study	Study design	Location	Exposure/ Dose metric	Estimate of iAs exposure group mean µg/kg-d intake range (Estimate of mean U.S. equivalent µg/L drinking water range)[a]	Health outcome/endpoint	Description	Limitations
Steinmaus et al. (2013)	Case-Control	N. Chile	Cumulative As exposure (µg/L-yrs)	1.3–10.8 (116–980)	Lung cancer cancers from all pathologists, hospitals, and radiologists in study area	Large case-control study (306 cases, 640 controls), well-documented historical water As exposures, good resolution in low-moderate exposure range. Residential and water use histories are used to estimate As intakes. The subject cohort has been the subject of a number of studies of As-related cancer and covariate interactions	Relied on municipal water As measurements for exposure estimates, but unique characteristics of study area (lack of alternative sources), suggest this is not a major source of uncertainty
Mostafa et al. (2008)	Case-Control	Bangladesh	Average well water As concentration (µg/L)	Smokers: 1.7–10.8 (153–980) Non-smokers: 1.7–10.8 (153–980)	Lung cancer identified via cytology following needle biopsy	Large case control study (2,755 cases, 1,173 controls) of Bangladeshi adults exposed to As via tube wells; smokers and non-smokers analyzed separately	Basing As exposure metric on average concentration of wells within a subjects home district could lead to exposure misclassification

[a]Estimated from µg/kg-d ranges (see Table C-29 assuming mean U.S. dietary background of 0.05 µg/kg-d (Xue et al., 2010) and mean U.S. water consumption rate of 0.014 L/kg-d (see (U.S. EPA, 2011), Table 3-1, "All Ages").

Comparison of studies selected for EPA meta-regression and studies used in earlier meta-analyses

EPA found considerable overlap between the studies included in the EPA meta-regression analysis and those identified in earlier meta-analysis (see Table C-27). Of the eight studies chosen by EPA, a core group of five studies were chosen for all (Dauphiné et al., 2013; Steinmaus et al., 2013; Chen et al., 2010a) or for all but one (D'Ippoliti et al., 2015; Mostafa et al., 2008) of the meta-analyses published after them. Studies selected for the earlier meta-analyses that were not used by EPA tended to be either (1) superseded by later analyses of the same cohorts, or (2) based on a dose metric that EPA decided not to be sufficiently reliable.

Table C-27. Comparison of study selection for EPA lung cancer meta-regression compared to earlier meta-analyses

Study	EPA meta-regression analysis	Begum et al. (2012)	Lynch et al. (2017)	Shao et al. (2021)
Argos et al. (2014)	✓			
Chen et al. (2004)		✓		
Chen et al. (2010a)	✓	✓	✓	✓
Chiou et al. (1995)		✓	✓	
Dauphiné et al. (2013)	✓		✓	✓
D'Ippoliti et al. (2015)	✓		✓	
Ferreccio et al. (2000)	✓			
García-Esquinas et al. (2013)	✓			
Heck et al. (2009)		✓		
Mostafa et al. (2008)	✓		✓	✓
Smith et al. (2009)		✓	✓	✓
Steinmaus et al. (2013)	✓		✓	✓

Chiou et al. (1995): EPA chose not to use data from this study because it was based in the southwest Taiwan "endemic" area. Exposure levels were generally quite high, and the incidence of Blackfoot Disease and potential poor nutrition in the study subjects led EPA not to include the data.

Smith et al. (2009): This study was not included in EPA's meta-analysis as the oral data included in Smith et al. (2009) is simply the data earlier reported in Ferreccio et al. (2000). Ferreccio et al. (2000) is included in EPA's meta-analysis.

Heck et al. (2009): EPA's rationale for not selecting this study was that the reported dose-metric (toenail arsenic concentrations) could not reliably be converted to equivalent arsenic intake. While limited data concerning empirical relationships between toenail arsenic and water arsenic are available, there is no generally accepted approach for estimating arsenic intake from toenail levels (EPA's PBPK model does not include a toenail compartment).

Chen et al. (2004): EPA's rationale for not selecting this study was two-fold: (1) this study included townships previously investigated in Chiou et al. (1995) and the concerns regarding exposure levels and incidence of Blackfoot Disease pertain to this study as well; and (2) the four N.E. Taiwan townships included in Chen et al. (2004) are also included in the analysis by Chen et al. (2010a). Chen et al. (2010a) has more years of follow-up than Chen et al. (2004) and presents As exposure as cumulative exposure, and therefore was judged by EPA to be the superior study for inclusion in the meta-analysis.

Finally, two studies were selected by EPA that were not included in any of the previous meta-analysis: Argos et al. (2014) and García-Esquinas et al. (2013). These studies were published after the Begum et al. (2012) meta-analysis and were urine biomarker studies from which EPA was able to estimate daily average intake with support from the EPA PBPK model (El-Masri et al., 2018a, b). All previously published meta-analyses focused on drinking water studies.

While there are differences in the modeling approaches used by EPA and earlier meta-analyses, differing results can be attributed largely to study and data selection. As for bladder cancer, while the Lynch et al. (2017) approach differed from EPA's approach with respect to the exposure metric modeled and the lifetime adjustment method used, when the Lynch et al. (2017) dataset was evaluated by both approaches, the lung cancer extra risk predictions were nearly identical (data not shown).

Lung cancer study-specific dose conversions

The study-specific dose conversions and confidence interval estimations were derived in Excel workbooks with the Yasai add-in to do Monte Carlo simulations. Each study required a potentially different set of assumptions for the dose conversions. The study-specific conversion assumptions and results are provided in the Excel files, which are included in the health outcome-specific intake uncertainty folders of Supplemental Material available from the EPA HERO database. The following tables summarize the input equations and assumptions used in the Monte Carlo analyses (see Table C-28) and the best, low, and high exposure and μg/kg-day dose estimates (see Table C-30) for each of the studies used in EPA's lung cancer meta-regression analyses.

Table C-28. Equations and assumptions for estimating µg/kg-day doses from oral lung cancer studies[a]

Citation (Country)	ADWE (yrs)	AAD (yrs)	LE, SD (µg/L)	WCR, SD (mL/kg-d)	BW, SD (kg)	DI, SD	BMI, SD (kg/m^2)	RD, SD (yrs)	AGE, SD (yrs)	Exposure or dose metric	Equation
Argos et al. (2014) (Bangladesh)	–	–	–	–	62.5, 8.8	–	19.7, 3.15	–	37.6, 9.35	µg total As/g creat.	dose[b] = (µg total As/g creat. × g creat./d)/BW
Chen et al. (2010a) (NE Taiwan)	42	65	5, 15	34.5, 23.3	–	0.65, 0.33	–	42, 15	–	µg/L-yrs, CE	dose = DI + (f*(CE-Val*WCR)/RDWE) + ((1–f) * (LE*WCR))
Dauphiné et al. (2013) (USA)	39	69	2.5, 3.3	0 for 35%; 16.6, 37 for 65%	–	0.05, 0.09	–	39, 10	–	µg/L-yrs, CE	dose = DI + (f*(CE-Val*WCR)/RDWE) + ((1–f) * (LE*WCR))
D'Ippoliti et al. (2015) (Italy)	39.5	66	2.5, 3.3	0 for 35%; 16.6, 37 for 65%	–	0.07, 0.07	–	–	–	µg/L, WE	dose = DI + f*(CE-Val*WCR) + (1–f) * (LE*WCR)
Ferreccio et al. (2000) (Chile)	63	63	2.5, 3.3	24.3, 13	–	1.00, 0.3	–	–	–	µg/L, WE	dose = DI + f*(CE-Val*WCR) + (1–f) * (LE*WCR)
García-Esquinas et al. (2013) (USA)	–	–	–	–	68, 10	–	30.9, 6.3	–	56.2, 8	µg total As/g creat.	dose[b] = (µg total As/g creat. × g creat./d)/BW
Mostafa et al. (2008) Smokers (Bangladesh)	61	61	2.5, 3.3	61.8, 26.8	–	1.4, 0.33	–	–	–	µg/L, WE	dose = DI + f*(CE-Val*WCR) + (1–f) * (LE*WCR)
Mostafa et al. (2008) Non-smokers (Bangladesh)	61	61	2.5, 3.3	61.8, 26.8	–	1.4, 0.33	–	–	–	µg/L, WE	dose = DI + f*(CE-Val*WCR) + (1–f) * (LE*WCR)

Citation (Country)	ADWE (yrs)	AAD (yrs)	LE, SD (µg/L)	WCR, SD (mL/kg-d)	BW, SD (kg)	DI, SD	BMI, SD (kg/m^2)	RD, SD (yrs)	AGE, SD (yrs)	Exposure or dose metric	Equation
Steinmaus et al. (2013) (Chile)	66	66	2.5, 3.3	1.7, 0.9 (L/d)	68, 10	1.00, 0.3	–	–	–	µg/d, DD	dose = DI + (f*(CE-Val/BW)) + ((1–f) * (LE*WCR)/BW)

ADWE=average duration of well exposure; AAD=average age at diagnosis; LE=low (outside study) exposure; WCR=water consumption rate; BW=body weight; DI=dietary intake; H=height; RD=reported duration of well exposure; Age=control group average age.

[a]See Conversion Factor Validation spreadsheet for justifications for individual exposure factors.

[b]According to EPA's PBPK model (El-Masri et al., 2018a, b), iAs is eliminated almost exclusively in urine. Thus, total µg/kg-day arsenic in urine is a good approximation of µg iAs/kg-day intake, assuming arsenic intake is substantially in the form of iAs. Urinary creatinine/kg-day is estimated as = (266.16 – 47.17*sex - 2.33*BMI + 0.66*age + 0.17*age^2)*113.12/10^6, where sex is 0 for male and 1 for female and BMI is estimated as BW/(Height/100)^2.

Table C-29. Meta-regression inputs and estimated effective counts for select lung cancer data sets (oral exposure), with three selected sets of dose values

Data set (reported dose units)	Exposure ranges	Dose values for analysis (avg. daily µg/kg)[a]			Raw counts			Adjusted OR/RR and 95% CIs			Effective counts[b]		
		MLE	Low	High	Cases	Controls	Expected	Adj OR	LCL	UCL	Cases	Controls	Expected
Argos et al. (2014) (µg/g urinary iAs)	0–132.4	2.084	2.048	2.119	23	–	23	1	1	1	23	–	23
	132.5–331.9	5.981	5.895	6.080	36	–	22.1	1.63	0.96	2.75	34.96	–	21.45
	≥332	21.215	20.197	22.480	31	–	19.3	1.61	0.93	2.76	29.83	–	18.53
García-Esquinas et al. (2013) (µg/g urinary iAs)	0–6.91	0.139	0.138	0.140	27	–	27	1	1	1	27	–	27
	6.91–13.32	0.284	0.283	0.290	20	–	21.3	0.94	0.51	1.72	16.91	–	17.99
	≥13.32	0.585	0.569	0.600	31	–	17	1.82	1	3.32	17.65	–	9.70
Chen et al. (2010a) (µg/L-yrs)	0–100	0.76	0.74	0.78	43	–	43	1	1	1	43	–	43
	100–1,000	0.98	0.95	1.01	32	–	49.2	0.65	0.41	1.02	32.47	–	49.95
	1,000–5,000	2.14	2.05	2.23	51	–	56	0.91	0.6	1.36	49.21	–	54.08
	5,000–10,000	4.96	4.67	5.26	23	–	14.4	1.6	0.96	2.65	22.81	–	14.26
	≥10,000	23.26	20.54	26.30	29	–	16.3	1.78	1.11	2.85	28.89	–	16.23
D'Ippoliti et al. (2015) (µg/L)-Males	≤10	0.1629	0.1542	0.1728	283	–	283	1	1	1	283	–	63
	10–20	0.2310	0.2144	0.2488	259	–	176.2	1.47	1.17	1.86	95.68	–	65.09
	≥20	0.4257	0.3883	0.4684	469	–	256.3	1.83	1.41	2.39	68.55	–	37.46
D'Ippoliti et al. (2015) (µg/L)-Females[d]	≤10	0.1629	0.1542	0.1728	63	–	63	1	1	1	63.00	63.00	63.00
	10–20	0.2310	0.2144	0.2488	69	–	38.3	1.8	1.23	2.66	43.78	24.32	43.78
	≥20	0.4257	0.3883	0.4684	100	–	59.2	1.69	1.18	2.42	–	–	–
Dauphiné et al. (2013) (µg/L-yrs)	0–0.1	0.11	0.09	0.12	70	113	–	1	1	1	70	57.12	–
	0.11–299	0.13	0.11	0.16	114	232	–	0.75	0.48	1.15	107.3	116.73	–
	≥2,400	3.82	0.95	11.62	12	14	–	1.2	0.45	3.22	11.22	7.63	–
Ferreccio et al. (2000) (µg/L)[d]	0–10	1.11	1.07	1.16	9	104	–	1	1	1	9.00	43.94	–
	10–29	1.38	1.28	1.49	5	39	–	1.6	0.5	5.3	5.80	17.70	–
	30–49	1.80	1.62	2.00	8	23	–	3.9	1.2	12.3	8.23	10.30	–
	50–199	3.10	2.86	3.35	50	124	–	5.2	2.3	11.7	53.87	50.58	–
	200–400	6.69	6.17	7.24	79	129	–	8.9	4.0	19.6	–	–	–

Data set (reported dose units)	Exposure ranges	Dose values for analysis (avg. daily µg/kg)[a]			Raw counts			Adjusted OR/RR and 95% CIs			Effective counts[b]		
		MLE	Low	High	Cases	Controls	Expected	Adj OR	LCL	UCL	Cases	Controls	Expected
Steinmaus et al. (2013) (µg/d)	0–41	1.26	1.23	1.29	64	197	–	1	1	1	64	98.66	–
	41–136	1.99	1.93	2.05	56	194	–	0.87	0.55	1.36	56.73	100.52	–
	137–307	3.55	3.42	3.67	76	154	–	1.24	0.78	1.98	58.75	73.04	–
	≥307	10.76	8.43	14.52	110	95	–	3.16	1.98	5.03	99.01	48.30	–
Mostafa et al. (2008) (non-smokers) (µg/L)	0–10	1.73	1.66	1.80	85	69	–	1	1	1	85	60.84	–
	11–50	2.80	2.70	2.91	241	208	–	0.9	0.62	1.33	232.54	184.95	–
	51–100	5.08	4.55	5.69	45	33	–	1.1	0.62	1.96	43.73	28.46	–
	101–400	10.84	9.78	11.96	145	128	–	0.94	0.62	1.41	147.04	111.97	–
Mostafa et al. (2008) (smokers) (µg/L)	0–10	1.73	1.68	1.78	269	117	–	1	1	1	269	101.82	–
	11–50	2.80	2.71	2.88	1062	368	–	1.25	0.96	1.62	1,105.43	304.47	–
	51–100	5.08	4.64	5.59	163	51	–	1.37	0.92	2.03	169.69	46.89	–
	101–400	10.77	9.87	11.69	745	199	–	1.65	1.25	2.18	812.90	186.49	–

[a]Sets of dose values derived as per Allen et al. (2020a).
[b]Effective counts derived as per Allen et al. (2020b).
[c]Person years of reference group follow up for (Argos et al., 2014), Chen et al. (2010a), D'Ippoliti et al. (2015) Males and D'Ippoliti et al. (2015) Females were 73386, 19060, 20033, 379421 and 392439, respectively.
[d]Effective counts shown are the ones used in the final meta-regression analysis based on dropping the high dose to improve model fit at low doses.

Summary of lung cancer meta-regression results for MLE dose estimates

The settings for all Bayesian meta-regression runs summarized in the tables of this section were:

- 4 chains, each with iterations = 25000; warmup = 21250; thin = 2; Adapt_Delta[23] = 0.9999
- post-warmup draws per chain = 1875, total post-warmup draws = 7500.
- β_mean Gamma parameters: a = 0.52 and b = 1.12

This section provides details of the results for the hierarchical meta-regression modeling, as well as dose-response plots from non-hierarchical modeling of individual studies. Additional details regarding the hierarchical and non-hierarchical modeling results can be obtained from the EPA HERO database.

[23]Corresponds to the target average proposal acceptance probability which is inversely related to the numerical integrator "step size" employed in Stan Hamiltonian MC.

Table C-30. Summary of lung cancer (oral exposure) Bayesian analysis output using best dose estimates

Study	Parameter[a]	Mean	Standard error of mean	Standard deviation	2.50%	25%	50%	75%	97.50%
Argos et al. (2014)	b	0.0193	0.0001	0.0121	−0.0049	0.0112	0.0194	0.0276	0.0423
	μ(δ)	26.8472	0.0442	3.4697	20.7293	24.4199	26.5955	29.0494	34.2131
	OR_RR[1]	1	0	0	1	1	1	1	1
	OR_RR[2]	1.0793	0.0006	0.0507	0.9811	1.0447	1.0786	1.1136	1.1792
	OR_RR[3]	1.4856	0.0041	0.343	0.9108	1.2394	1.4501	1.696	2.2463
García-Esquinas et al. (2013)	b	0.6436	0.0091	0.7417	−0.8382	0.1599	0.6314	1.1292	2.0998
	μ(δ)	27.3459	0.0439	3.4495	21.0519	24.9703	27.1586	29.5385	34.6519
	OR_RR[1]	1	0	0	1	1	1	1	1
	OR_RR[2]	1.1206	0.0013	0.0879	0.9795	1.0564	1.1112	1.1752	1.3154
	OR_RR[3]	1.4455	0.0055	0.3624	0.9385	1.183	1.3813	1.6399	2.3154
Chen et al. (2010a)	b	0.0318	0.0001	0.009	0.0137	0.0259	0.0322	0.0379	0.0487
	μ(δ)	38.8661	0.0373	2.9519	33.297	36.794	38.7738	40.8362	44.8856
	OR_RR[1]	1	0	0	1	1	1	1	1
	OR_RR[2]	1.007	0	0.002	1.003	1.0057	1.0071	1.0083	1.0107
	OR_RR[3]	1.0448	0.0002	0.0129	1.0189	1.0362	1.0452	1.0535	1.0692
	OR_RR[4]	1.1438	0.0005	0.043	1.059	1.1148	1.1446	1.1725	1.2265
	OR_RR[5]	2.0844	0.005	0.4171	1.3588	1.7885	2.0589	2.3414	2.9772
D'Ippoliti et al. (2015) 5 - Males	b	1.5689	0.0118	0.6368	0.3035	1.127	1.5975	2.0187	2.761
	μ(δ)	299.5895	0.1833	13.7074	273.4724	290.3073	299.2361	308.7424	327.1693
	OR_RR[1]	1	0	0	1	1	1	1	1
	OR_RR[2]	1.1137	0.0009	0.0482	1.0209	1.0797	1.1148	1.1472	1.2067
	OR_RR[3]	1.5308	0.0046	0.2545	1.0829	1.3444	1.5211	1.6989	2.0642
D'Ippoliti et al. (2015)- Females	b	0.9071	0.0161	0.9924	−0.4505	0.2448	0.6998	1.3479	3.4159
	μ(δ)	70.9693	0.0761	5.8361	60.1416	66.8662	70.7562	74.6935	83.1585
	OR_RR[1]	1	0	0	1	1	1	1	1
	OR_RR[2]	1.0662	0.0012	0.0764	0.9698	1.0168	1.0488	1.0961	1.2618
Dauphiné et al. (2013)	b	0.0812	0.0015	0.1235	−0.1594	−0.0005	0.0795	0.1659	0.3225
	vlambda[1]	1.0531	0.0074	0.6258	0.2073	0.5978	0.93	1.3731	2.5768
	vlambda[2]	1.8481	0.0129	1.0915	0.3728	1.0547	1.6433	2.4108	4.5222
	vlambda[3]	0.1398	0.0011	0.0982	0.0229	0.0708	0.1165	0.1832	0.3885
	OR_RR[1]	1	0	0	1	1	1	1	1
	OR_RR[2]	1.0016	0	0.0025	0.9968	1	1.0016	1.0033	1.0064
	OR_RR[3]	1.5025	0.009	0.7262	0.5531	0.9981	1.3437	1.8524	3.3139
	b	0.6939	0.0027	0.1862	0.3181	0.5711	0.6964	0.8191	1.0457

Study	Parameter[a]	Mean	Standard error of mean	Standard deviation	2.50%	25%	50%	75%	97.50%
Ferreccio et al. (2000)	vlambda[1]	1.346	0.0083	0.6815	0.3659	0.8501	1.233	1.7055	2.9794
	vlambda[2]	0.5887	0.0038	0.3145	0.1516	0.3594	0.5334	0.753	1.3428
	vlambda[3]	0.4323	0.0028	0.2352	0.1094	0.2635	0.3909	0.5509	1.0078
	vlambda[4]	1.6379	0.0101	0.8317	0.4435	1.0426	1.5028	2.064	3.6539
	OR_RR[1]	1	NaN	0	1	1	1	1	1
	OR_RR[2]	1.205	0.0009	0.0598	1.0886	1.1647	1.2044	1.2445	1.3221
	OR_RR[3]	1.6204	0.0029	0.2058	1.243	1.4779	1.6102	1.7511	2.0447
	OR_RR[4]	4.2475	0.0208	1.5994	1.8814	3.1103	3.9899	5.0913	7.987
Steinmaus et al. (2013)	b	0.1312	0.0003	0.0229	0.0867	0.1158	0.1311	0.1469	0.1763
	vlambda[1]	1.2734	0.0079	0.6476	0.3413	0.8021	1.1555	1.6204	2.8294
	vlambda[2]	1.1875	0.0073	0.6026	0.3204	0.7475	1.0856	1.5157	2.6202
	vlambda[3]	0.9144	0.0056	0.4643	0.2425	0.578	0.8319	1.1659	2.0479
	vlambda[4]	0.6069	0.0039	0.3165	0.1573	0.3797	0.5495	0.7754	1.3669
	OR_RR[1]	1	NaN	0	1	1	1	1	1
	OR_RR[2]	1.1004	0.0002	0.0184	1.0652	1.088	1.1002	1.1129	1.137
	OR_RR[3]	1.3515	0.0008	0.0709	1.2192	1.303	1.3494	1.399	1.4962
	OR_RR[4]	3.5611	0.0092	0.7847	2.2793	3.0049	3.4746	4.0375	5.3378
Mostafa et al. (2008) (non-smokers)	b	0.0011	0.0002	0.0182	−0.0348	−0.0111	0.0014	0.0134	0.0366
	vlambda[1]	0.6577	0.0041	0.3374	0.1749	0.4139	0.6022	0.8334	1.5032
	vlambda[2]	1.8688	0.0114	0.9428	0.5056	1.1856	1.7097	2.3773	4.1808
	vlambda[3]	0.3272	0.002	0.1694	0.0849	0.2045	0.2977	0.4188	0.7373
	vlambda[4]	1.1549	0.0071	0.5858	0.3111	0.7349	1.0614	1.4626	2.5602
	OR_RR[1]	1	NaN	0	1	1	1	1	1
	OR_RR[2]	1.0013	0.0002	0.0196	0.9632	0.9881	1.0015	1.0145	1.0402
	OR_RR[3]	1.0054	0.0007	0.0612	0.8898	0.9635	1.0047	1.0458	1.1306
	OR_RR[4]	1.0235	0.002	0.1702	0.728	0.9037	1.0129	1.1294	1.3962
Mostafa et al. (2008) (smokers)	b	0.0418	0.0001	0.0122	0.0176	0.0336	0.0417	0.05	0.0658
	vlambda[1]	0.5733	0.0037	0.2915	0.1556	0.3617	0.5221	0.7344	1.2701
	vlambda[2]	1.9532	0.0123	0.9854	0.534	1.2267	1.7822	2.5068	4.3177
	vlambda[3]	0.3013	0.0019	0.1533	0.0812	0.188	0.2761	0.3865	0.6746
	vlambda[4]	1.1477	0.0073	0.5824	0.312	0.7169	1.0521	1.4657	2.5407
	OR_RR[1]	1	NaN	0	1	1	1	1	1
	OR_RR[2]	1.0456	0.0002	0.0136	1.019	1.0365	1.0456	1.0548	1.0727
	OR_RR[3]	1.1509	0.0006	0.0469	1.0608	1.1192	1.15	1.1822	1.2463
	OR_RR[4]	1.4674	0.0019	0.1618	1.1727	1.3554	1.4585	1.5714	1.8127
Pooled β_mean		0.3153	0.0042	0.2434	0.0038	0.1288	0.2724	0.4453	0.8968

Study	Parameter[a]	Mean	Standard error of mean	Standard deviation	2.50%	25%	50%	75%	97.50%
β_sigma		0.715	0.0073	0.3765	0.1788	0.4634	0.6518	0.887	1.6554

[a]The indices, e.g., OR[i] refer to the ith group in the study. The lambda values that characterize the proportion of the control population in each dose-range are computed by vlambda[i]/sum(vlambda[j]) for all i,j in the range appropriate for each study.

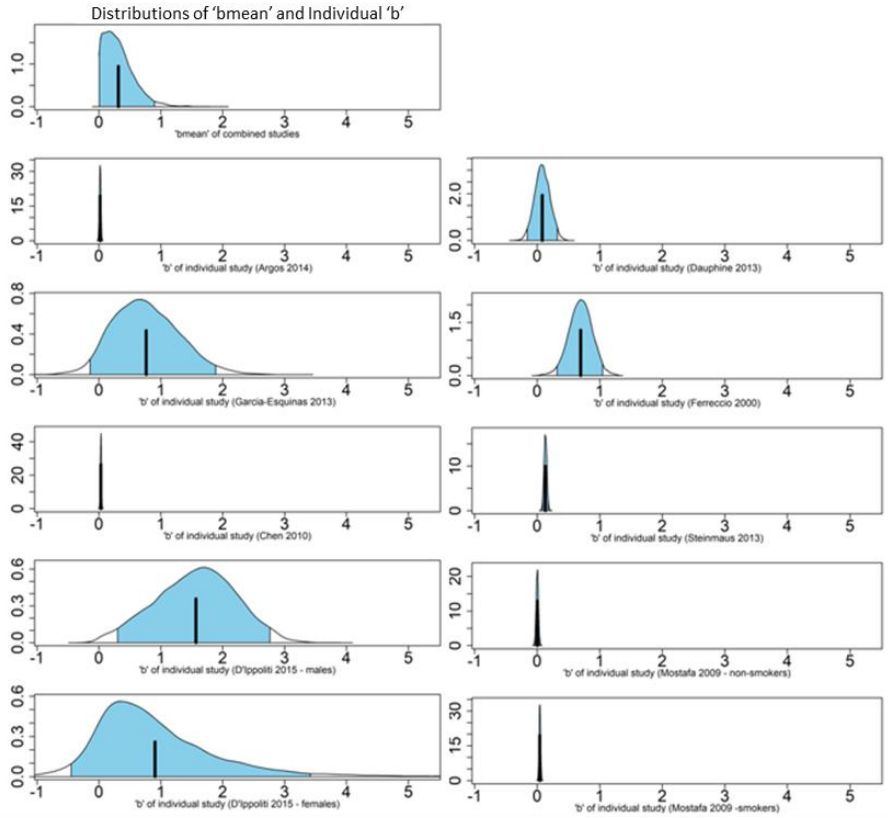


Figure C-16. Posterior distributions for lung cancer pooled (bmean) and data-set-specific (b) logistic slope parameters, using best dose estimates. 95% Credible intervals are highlighted.

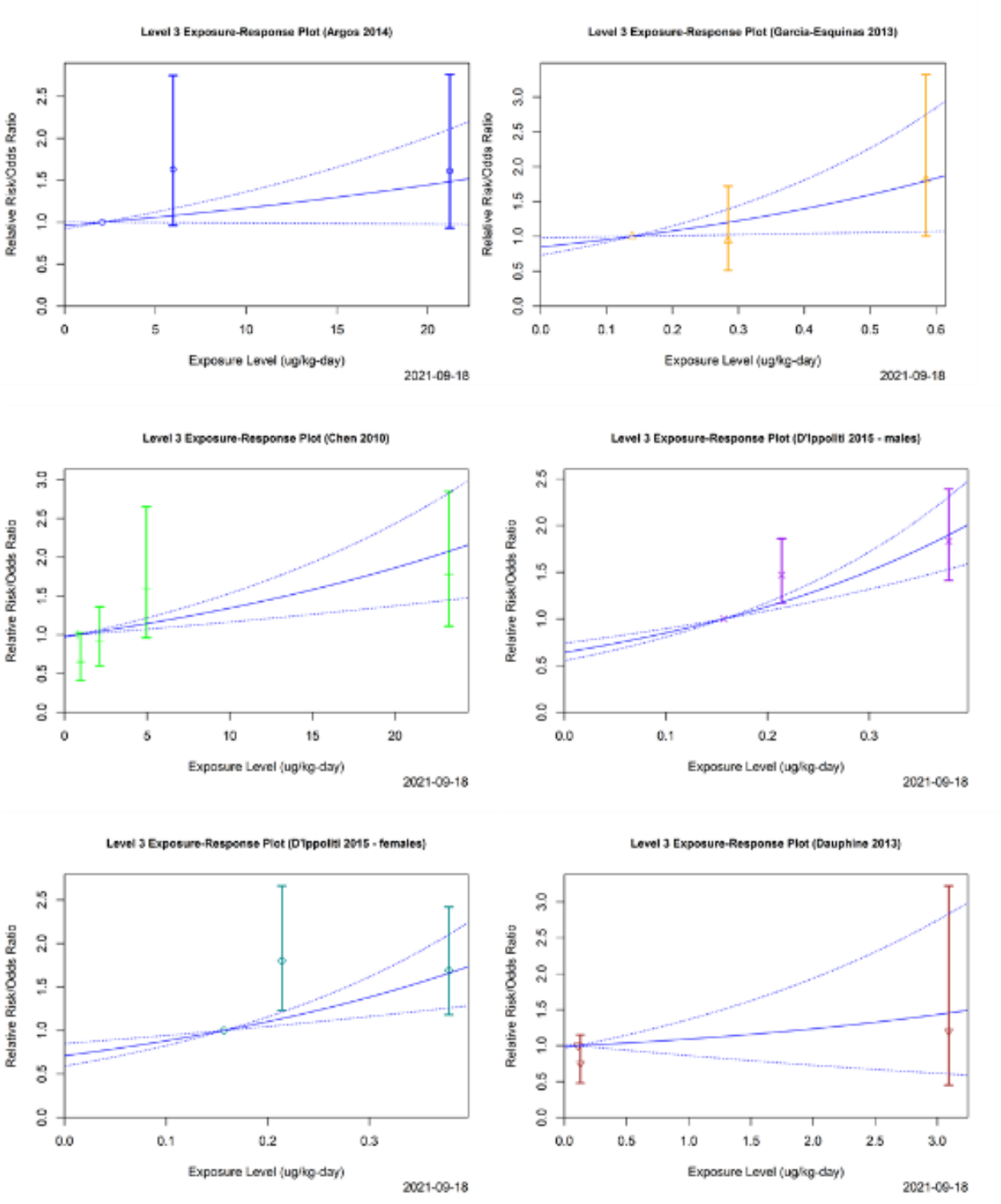


Figure C-17. Non-hierarchical meta-regression dose response curves for individual lung cancer studies.

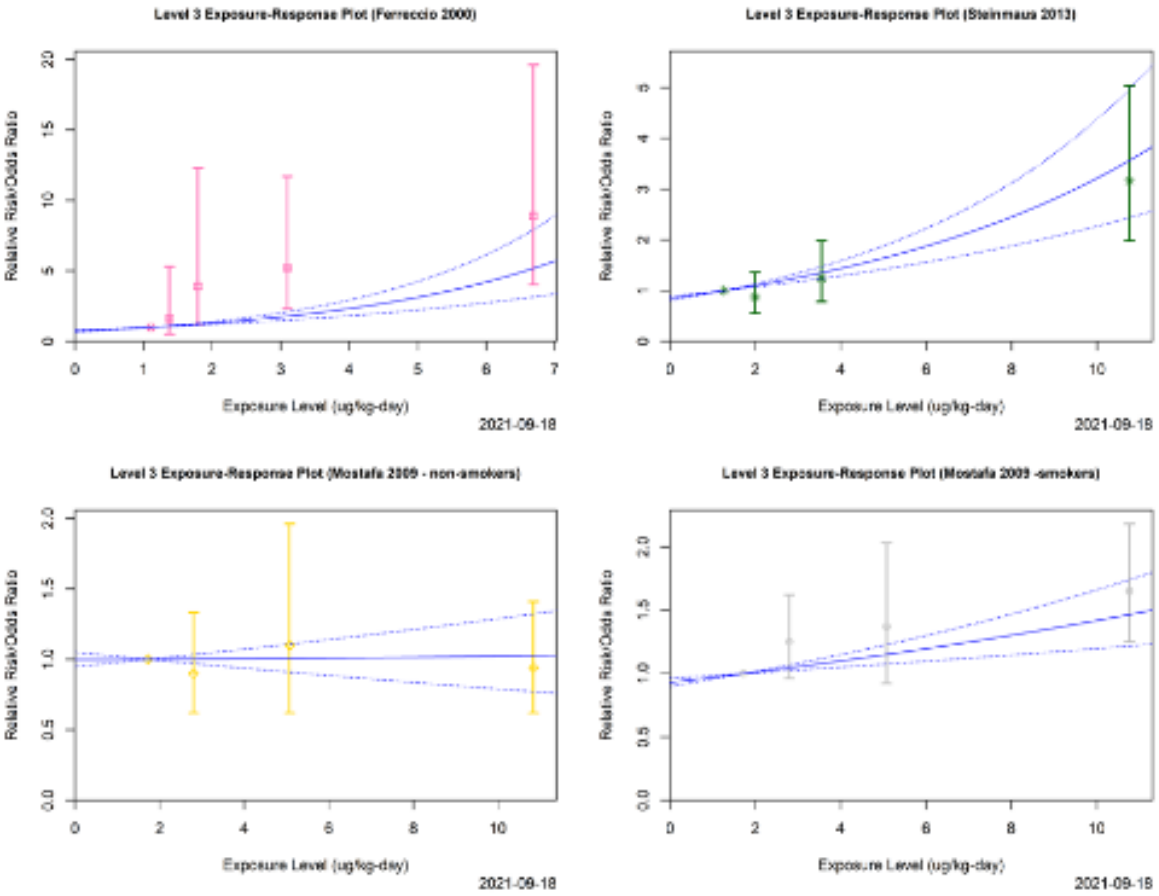


Figure C-18. Non-hierarchical meta-regression dose response curves for individual lung cancer studies (cont.).

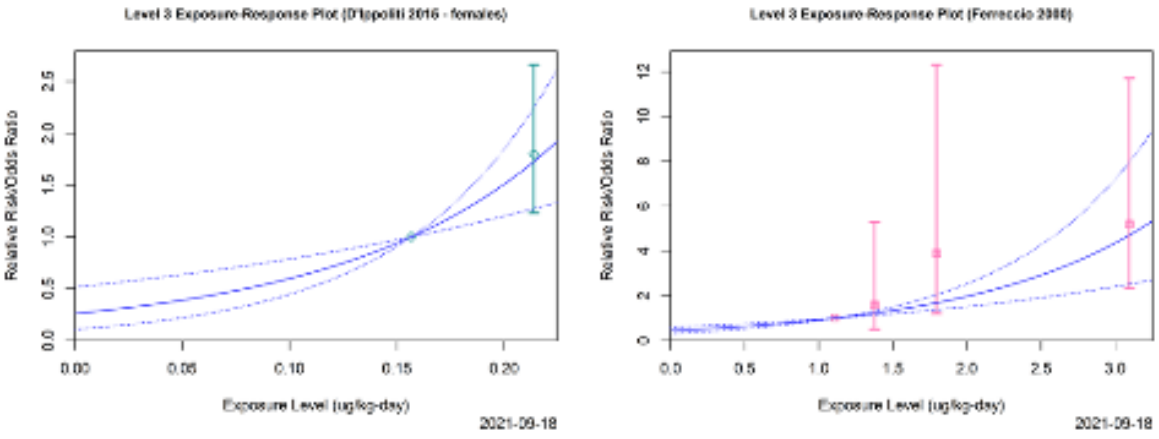


Figure C-19. Non-hierarchical meta-regression dose response curves for individual lung cancer studies where doses were dropped to improve fit.

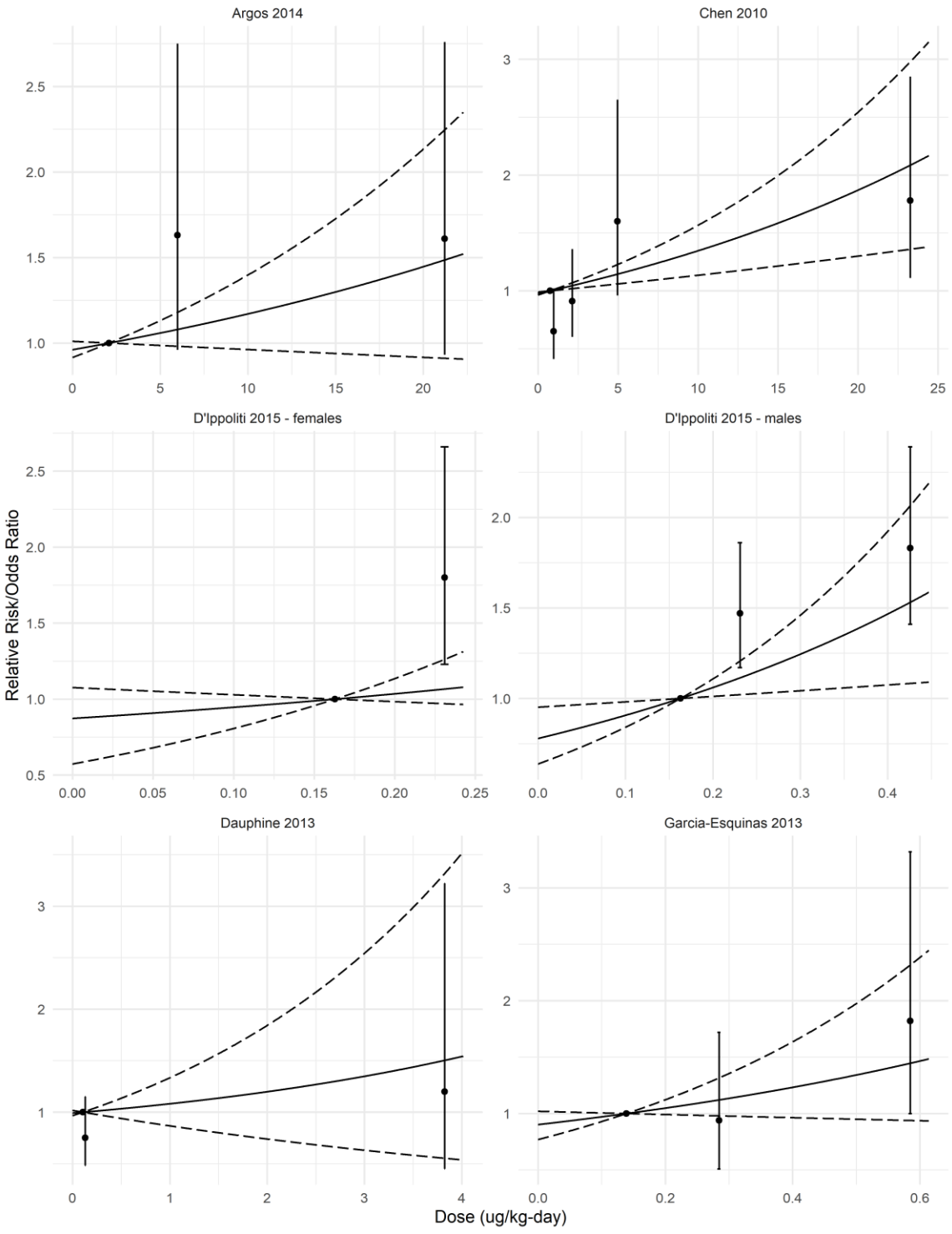


Figure C-20. Hierarchical meta-regression dose response curves for individual lung cancer studies.

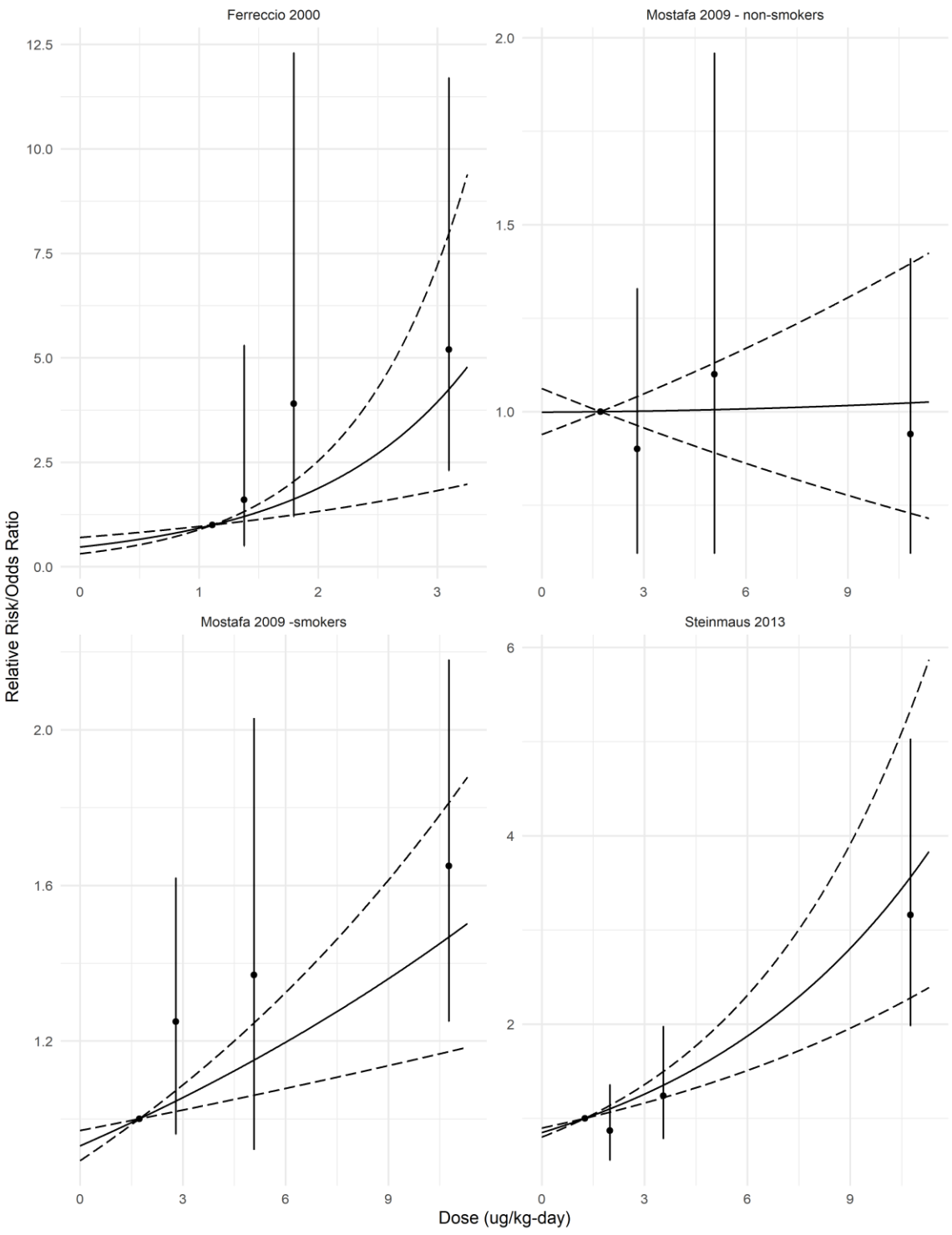


Figure C-21. Hierarchical meta-regression dose response curves for individual lung cancer studies (cont.).

Lung cancer sensitivity analyses

In addition to the evaluation of the meta-regression approach's sensitivity across endpoints to the choice of the simpler Logistic model over a more complex double Hill model that allows for non-monotonicity (see Sensitivity Analysis of Possible Non-monotonic Dose-Response Relationships), EPA has examined the sensitivity of the estimates of the association between oral iAs exposure and lung cancer for five sources of uncertainty. The first relates to the choices made with respect to the characterization of the exposure levels used for the dose-response modeling. The second addresses sensitivity to choice of data sets. The third addresses the assumption that the general US population is not exposed to iAs via inhalation. The fourth addresses considerations of alternative gamma prior distributions for b_mean. The fifth addresses the use of urine biomarker studies in the meta-regression analysis.

The sources of uncertainty related to dose metric values are themselves broken down into two components. The first arises because of the need to estimate a mean value for the dose groups reported in terms of ranges of values (in whatever metric). The second relates to conversion of those mean exposure values to a consistent set of units across studies, those units being average daily μg/kg. The methods used to characterize those uncertainties are described in Allen et al. (2020a). Table C-31 below summarizes the 95% confidence intervals for the meta-regression pooled b value and extra risk values for bladder cancer for the MLE, "low," and "high" iAs dose estimates shown in Table C-29. Note that, while the "low" dose estimates provide the largest extra risks, the extra risk values are not appreciably different across the different dose estimates, indicating that the analysis was relatively insensitive to the uncertainties associated with dose characterization.

With respect to sensitivity of the estimates to choice of dataset, note that the meta-regression approach avoids the issue of study selection by pooling the results of all the datasets. Nevertheless, it is of interest to determine how influential each of those studies are on the estimate of the pooled risk. That sensitivity has been investigated by computing the pooled estimate of risk when each of the data sets is iteratively excluded from the analysis (i.e., a leave-one-out analysis). Table C-32 lists the pooled and study-specific mean b values when one study is iteratively left out of the analysis. As can be seen, the greatest decrease (75%) is observed when the dataset from Ferreccio et al. (2000) is excluded, and the greatest increase (23%) is observed when the dataset from Mostafa et al. (2008) excluded.

Table C-31. Pooled mean b and extra risk estimates from meta-regression of lung cancer studies using MLE, "low," and "high" dose estimates

	Low dose estimates		MLE dose estimates		High dose estimates	
	Mean b	Lifetime extra risk[a]	Mean b	Lifetime extra risk[a]	Mean b	Lifetime extra risk[a]
5%	0.0140	1.06E-04	0.0135	1.03E-04	0.0092	6.96E-05
Mean	0.3735	2.86E-03	0.3153	2.41E-03	0.2804	2.14E-03
95%	0.8896	6.90E-03	0.7697	5.95E-03	0.6993	5.40E-03

[a]Risk above zero dose; Estimated for a total dose of 0.13 µg iAs/kg-day, which includes an estimated 0.0365 µg iAs/kg-day background dose, 0.02 µg iAs/kg-day from diet and 0.0165 µg iAs/kg-day from drinking water.

Although inhalation of inorganic arsenic is not considered a primary route of exposure for the general public, the World Health Organization (WHO) estimates that background exposure may range from 0.02 to 0.6 µg/day in areas without substantial arsenic emissions from anthropogenic sources. Assuming an average body weight of 70 kg, this corresponds to daily intake values of 2.9×10^{-4} µg/kg-day to 8.6×10^{-3} µg/kg-day. The third sensitivity analysis involved two extra lifetable analyses wherein background inhalation components of either 4.4×10^{-3} µg/kg-day (corresponding to the midpoint of the range of reported background iAs concentrations), or 8.6×10^{-3} µg/kg-day (corresponding to the upper limit of background concentrations) were added to the original background estimate of exposure due to dietary and drinking water sources (i.e., 0.0365 µg/kg-day). Incorporation of inhalation exposures in the background estimate of total exposure also did not result in dramatically different estimates of extra risk. By definition, as the estimate of background exposure increased in the lifetable analysis, calculated extra risks must correspondingly decrease. Thus, at a 0.13 µg/kg-day dose (approximately equal to a 10 µg/L iAs lifetime drinking water exposure), when the assumed background exposure was either 0.0409 µg/kg-day or 0.0451 µg/kg-day, extra risks decreased to 2.406×10^{-3} or 2.403×10^{-3}, compared to 2.410×10^{-3} when no inhalation component was included in the background estimate of exposure. This corresponds to 0.2% and 0.3% decreases in extra risk, respectively.

Table C-32. Results of the leave-one-out analysis for oral lung cancer datasets using the MLE dose estimate

Study left out	Mean b values (5th–95th percentile)										
	Pooled	Argos et al. (2014)	García-Esquinas et al. (2013)	Chen et al. (2010a)	D'Ippoliti et al. (2015)–males	D'Ippoliti et al. (2015)–females	Dauphiné et al. (2013)	Ferreccio et al. (2000)	Steinmaus et al. (2013)	Mostafa et al. (2008)–non-smokers	Mostafa et al. (2008)–smokers
Argos et al. (2014)	0.3803 (0.0148 -0.9149)	–	0.8825 (0.0288 -1.7973)	0.0316 (0.0164 -0.0457)	1.7948 (0.8022 -2.7233)	1.2385 (-0.2522 3-.5399)	0.0824 (-0.1246 -0.2935)	0.7190 (0.4328 -1.0059)	0.1310 (0.0935 -0.1686)	0.0016 (-0.0282 -0.0318)	0.0419 (0.0223 -0.0621)
García-Esquinas et al. (2013)	0.2637 (0.0071 -0.6897)	0.0192 (-0.0013 -0.0390)	–	0.0316 (0.0161 -0.0459)	1.4932 (0.3262 -2.5257)	0.8379 (-0.2682 -2.7399)	0.0801 (-0.1267 0.2850	0.6784 (0.3469 -0.9887)	0.1314 (0.0943 -0.1692)	0.0011 (-0.0285 -0.0306)	0.0419 (0.0224 -0.0617)
Chen et al. (2010a)	0.3878 (0.0155 -0.9334)	0.0195 (-0.0002 -0.0389)	0.8796 (0.0186 -1.8164)	–	1.7857 (0.7771 -2.7004)	1.2201 (-0.2429 -3.4501)	0.0813 (-0.1202 -0.2845)	0.7207 (0.4423 -1.0080)	0.1313 (0.0941 -0.1687)	0.0011 (-0.0282 -0.0309)	0.0418 (0.0224 -0.0619)
D'Ippoliti et al. (2015) – males	0.0994 (0.0042 -0.2632)	0.0199 (-0.0002 -0.0391)	0.1996 (-0.0997 -0.7163)	0.0318 (0.0167 -0.0465)	–	0.1595 (-0.1687 -0.6510)	0.0737 (-0.0801 -0.2448)	0.3933 (0.0751 -0.7624)	0.1280 (0.0912 -0.1656)	0.0032 (-0.0261 -0.0335)	0.0421 (0.0223 -0.0616)
D'Ippoliti et al. (2015) – females	0.2561 (0.0087 -0.6465)	0.0194 (-0.0006 -0.0388)	0.6823 (-0.0492 -1.5932)	0.0317 (0.0169 -0.0459)	1.4483 (0.3858 -2.4425)	–	0.0790 (-0.1219 -0.2867)	0.6803 (0.3718 -0.9747)	0.1307 (0.0936 -0.1679)	0.0013 (-0.0280 -0.0306)	0.0420 (0.0222 -0.0621)
Dauphiné et al. (2013)	0.3775 (0.0099 -0.9195)	0.0193 (-0.0008 -0.0385)	0.8815 (0.0013 -1.8490)	0.0317 (0.0162 -0.0460)	1.7786 (0.7568 -2.6884)	1.2184 (-0.2352 -3.5067)	–	0.7196 (0.4349 -1.0117)	0.1311 (0.0939 -0.1688)	0.0017 (-0.0274 -0.0311)	0.0419 (0.0222 -0.0615)
Ferreccio et al. (2000)	0.1065 (0.0041 -0.4625)	0.0203 (0.0008 -0.0392)	0.2454 (-0.0510 -1.2314)	0.0320 (0.0171 -0.0461)	0.4883 (-0.0112 -2.1886)	0.2991 (-0.0804 -1.6995)	0.0579 (-0.0695 -0.2117)	–	0.1201 (0.0792 -0.1613)	0.0048 (-0.0259 -0.0345)	0.0417 (0.0226 -0.0611)
Steinmaus et al. (2013)	0.3784 (0.0099 -0.9292)	0.0191 (-0.0005 -0.0379)	0.8722 (0.0015 -1.8169)	0.0316 (0.0164 -0.0456)	1.7828 (0.7937 -2.6790)	1.2224 (-0.2541 -3.4820)	0.0800 (-0.1260 -0.2902)	0.7183 (0.4388 -1.0059)	–	0.0012 (-0.0279 -0.0312)	0.0417 (0.0220 -0.0618)
Mostafa et al. (2008) – non-smokers	0.3858 (0.0135 -0.9181)	0.0191 (-0.0010 -0.0387)	0.8764 (0.0083 -1.8217)	0.0314 (0.0165 -0.0459)	1.7846 (0.7748 -2.7058)	1.2329 (-0.2293 -3.5033)	0.0804 (-0.1211 -0.2901)	0.7184 (0.4381 -1.0068)	0.1312 (0.0945 -0.1688)	–	0.0417 (0.0218 -0.0614)

Study left out	Mean b values (5th–95th percentile)										
	Pooled	Argos et al. (2014)	García-Esquinas et al. (2013)	Chen et al. (2010a)	D'Ippoliti et al. (2015)–males	D'Ippoliti et al. (2015)–females	Dauphiné et al. (2013)	Ferreccio et al. (2000)	Steinmaus et al. (2013)	Mostafa et al. (2008)–non-smokers	Mostafa et al. (2008)–smokers
Mostafa et al. (2008) – smokers	0.3740 (0.0104 -0.9142)	0.0194 (-0.0006 -0.0386)	0.8592 (-0.0017 -1.8003)	0.0315 (0.0163 -0.0460)	1.7797 (0.7694 -2.7086)	1.1890 (-0.2653 -3.3322)	0.0810 (-0.1221 -0.2905)	0.7170 (0.4349 -1.0040)	0.1311 (0.0941 -0.1685)	0.0011 (-0.0279 -0.0309)	–

[a]Pooled estimate using all studies was 0.3153 (0.0135−0.7697) (see Table C-31).

The assumption of different Gamma prior distributions for β_mean did not result in large differences in the posterior distributions of the β_mean parameter (see Table C-33). Interestingly, the alternative prior sensitivity results indicated that, for the present set of studies used in this case-example, the results of the dose-response meta-analysis are rather insensitive to assumptions on the gamma distribution prior. For example, using priors that differed with respect to the 1st percentile (i.e., 1.00001 – 20 and 1.001 – 20) resulted in the greatest differences in the mean of the posterior distribution relative to the original prior. This is due to the characteristics of the Gamma distribution, in which the greatest density with respect to probability of response is close to zero. So, when using the 1.00001 – 20 prior, the corresponding posterior mean distribution was approximately 9% lower than the results with the original prior because the 1st percentile is assumed to be ten times lower than for the original prior. Correspondingly, the 1.001 – 20 prior resulted in a posterior mean distribution approximately 10% higher than the original prior. Alternate Gamma prior distributions that differed with respect to the 99th percentile also did not differ greatly from the results using the original prior: using a prior with an upper bound of 10 (i.e., 50% lower than the original) resulted in a posterior mean approximately 6% lower and using a prior with an upper bound of 30 (i.e., 50% higher than the original) resulted in a posterior mean approximately 3% higher. This broadly indicates that the results of the analysis are heavily influenced by the actual data being modeled and are not inappropriately driven by the prior assumptions of the Bayesian modeling.

Table C-33. Posterior β_mean distribution values resulting from various prior Gamma distributions

Alternative prior	5th percentile	Mean	95th percentile	% Mean difference
1.00001 – 20	0.0027	0.2881	0.7330	−9%
1.0001 – 10	0.0099	0.2963	0.7479	−6%
1.0001 – 30	0.0119	0.3262	0.7940	3%
1.001 – 20	0.0317	0.3468	0.7935	10%
Original Prior (1.0001 – 20)	0.0135	0.3153	0.7697	–

The last sensitivity analysis investigated to what degree the inclusion of urinary biomarker studies influenced the modeled association between iAs intake and lung cancer. For lung cancer, there were only two urinary biomarker studies included the in modeling set, (Argos et al., 2014) and (García-Esquinas et al., 2013). As can be seen in Table C-32, when these studies are left out individually, the mean estimate of the logistic slope increases 21% to 0.3803 when (Argos et al., 2014) is excluded and decreases 16% to 0.2637 when (García-Esquinas et al., 2013) is excluded. When both of the urine studies are excluded, the mean logistic slope estimate increases to 0.3342, a 6% increase over the mean logistic slope estimate of 0.3153 when all studies are included in the meta-regression.

Extrapolation of lung cancer extra risk to target U.S. population

Table C-34. Lifetable rates for all-cause mortality and lung cancer mortality and incidence

Age range	All-cause mortality rates (per 100,000)[a]	Lung cancer mortality rates (per 100,000)[b]	Lung cancer incidence rates (per 100,000)[b]
0–1	567	0	0
1–4	24.3	0	0.1
5–9	11.6	0	0
10–14	15.5	0	0
15–19	51.5	0	0.1
20–24	95.6	0	0.3
25–29	121	0.1	0.6
30–34	145.4	0.4	1.3
35–39	173.8	1.1	2.6
40–44	218.4	3.1	6.5
45–49	313.2	8.5	16.5
50–54	488	24.4	44.4
55–59	736.5	54.6	96.1
60–64	1050.2	87.7	149.1
65–69	1473.5	132.1	223.9
70–74	2206.9	198.2	319.3
75–79	3517.8	266	391.2
80–84	5871.7	309.7	395.2

[a]All cause mortality: 2017 numbers, https://www.cdc.gov/nchs/data/nvsr/nvsr68/nvsr68_09-508.pdf.
[b]Cancer numbers: 2017 numbers, https://gis.cdc.gov/Cancer/USCS/DataViz.html.

Diabetes

Diabetes study and dataset selection

Table C-35 describes the studies selected for the diabetes dose-response Bayesian meta-regression. The Rangel-Moreno et al. (2022) was considered,[24] but as not included in the final analysis due to an extreme non-monotonic response, only evaluating Type II diabetes cases separately for hypertensive and non-hypertensive females and only requiring a self-diagnosis for classifying cases. No objective diagnostic measures were used, and the frequency or quality of their physician care was not determined suggesting the potential for under reporting (e.g., from patients for which diabetes exists but was undiagnosed, uncertain, or known but denied).

[24] An alternative Bayesian meta-regression including this study was performed and is available in the Supplemental Material available from the EPA HERO database.

Table C-35. Data sets selected for oral exposure diabetes dose-response Bayesian meta-regression

Study	Study design	Location	Exposure/ dose metric	Estimate of iAs exposure group mean µg/kg-d intake range (Estimate of mean U.S. equivalent µg/L drinking water range)[a]	Health outcome/endpoint	Description	Limitations
Grau-Perez et al. (2017)	Cohort	United States (Arizona, Oklahoma, North and South Dakota)	Creatinine-adjusted urinary arsenic (µg/g)	0.066–0.276 4.2–23.3	Incident type II diabetes defined as fasting glucose ≥ 126 mg/dL, self-reported physician diagnosis or self-reported use of insulin or oral diabetes treatment	Medium-sized cohort study (125 diabetes cases, total cohort 1,838) of Native American adults exposed to arsenic via drinking water; urinary total arsenic concentrations were measured from baseline spot urine samples; the analysis controlled for major confounders including smoking	Exposure estimates were based on a one-time baseline urine measurement; relatively short follow-up time
James et al. (2013)	Cohort	United States (Colorado)	Cumulative As exposure (µg/L)	0.13–0.6 10–52.7	Incident type II diabetes based on self-report (with medical records verification) or fasting glucose test	Large study of randomly selected participants from the San Luis Valley Diabetes Study (SLVDS) (120 cases, 548 total subjects). Estimates of lifetime exposure obtained from residential history linked to geospatial model of predicted iAs in groundwater. Model adjusted for appropriate covariates, including ethnicity, gender, socioeconomic status, education, BMI, smoking, age, alcohol consumption, and physical activity level.	Collected water samples from just 61% of participant residences. Uncertainty associated with geospatial model estimates of arsenic concentrations not well characterized. Fasting glucose test based on WHO standard (≥ 140 mg/dL) during the time that the SLVDS study was conducted (1984–1998), which differs from the current standard (≥ 126 mg/dL)

Study	Study design	Location	Exposure/ dose metric	Estimate of iAs exposure group mean µg/kg-d intake range (Estimate of mean U.S. equivalent µg/L drinking water range)[a]	Health outcome/endpoint	Description	Limitations
Coronado-González et al. (2007)	Case-Control (case-cohort)	Mexico	Creatinine-adjusted urinary arsenic (µg/g)	1.303–4.561 117–413	Type II diabetes diagnosed after 2 consecutive fasting blood glucose tests ≥ 126 mg/dL	Case-cohort study (200 cases, 200 controls) drawn from a larger cross-sectional study. Urinary total arsenic concentrations were measured from baseline spot urine samples; the analysis controlled for major confounders including age, sex, hypertension, family history of diabetes, obesity, and serum lipids.	Smoking was not controlled for explicitly in the logistic regression as a confounding variable; however, the study authors did report that they found "no association between smoking … and the occurrence of diabetes" and that "cases and controls were comparable to the cross-sectional study participants by …. smoking." Other limitations included lack of temporality, dietary patterns and education was not available, and the possibility that diabetes influences arsenic metabolism and/or concentrations (reverse causation).

Study	Study design	Location	Exposure/ dose metric	Estimate of iAs exposure group mean µg/kg-d intake range (Estimate of mean U.S. equivalent µg/L drinking water range)[a]	Health outcome/endpoint	Description	Limitations
Pan et al. (2013)	Case-control	Bangladesh	Drinking water concentration (µg/L)	1.5–23.20 135–2107	Individuals were defined as type II diabetes cases if their hemoglobin A1c levels were 6.5% or higher	Large case-control study of 84 cases and 827 controls drawn from a larger 1,800 participant case-control study. Drinking water concentrations were obtained for every individual in the study. Model adjusted for appropriate covariates including age, sex, BMI, smoking, and skin lesions.	Sensitivity analyses indicate suggest some selection bias (primary results remained robust in sensitivity analysis), no information on physical activity levels or caloric intakes were available, possibility of some prevalent cases of diabetes included in the analysis, possibility of other nutritional deficiencies which may impact diabetes and/or arsenic toxicity

Study	Study design	Location	Exposure/ dose metric	Estimate of iAs exposure group mean µg/kg-d intake range (Estimate of mean U.S. equivalent µg/L drinking water range)[a]	Health outcome/endpoint	Description	Limitations
							Smoking was not controlled for explicitly in the logistic regression as a confounding variable; however, the study authors did report that they found "no association between smoking … and the occurrence of diabetes" and that "cases and controls were comparable to the cross-sectional study participants by …. smoking." Other limitations included lack of temporality, dietary patterns and education was not available, and the possibility that diabetes influences arsenic metabolism and/or concentrations (reverse causation).

[a]Estimated from µg/kg-d ranges (see Table C-37) assuming mean U.S. dietary background of 0.05 µg/kg-d (Xue et al., 2010) and mean U.S. water consumption rate of 0.014 L/kg-d U.S. EPA (2011), [see Table 3-1, "All Ages"].

Comparison of studies selected for EPA meta-regression and studies used in earlier meta-analyses

Wang et al. (2014) performed the only meta-analyses comparable to the EPA meta-regression approach in that it involved meta-regression modeling of multiple studies of the relation between type II diabetes and inorganic arsenic exposure. It differed from the EPA analysis in that it included cross-sectional studies and studies conducted of the iAs endemic region of SW Taiwan region which, as previously discussed, were excluded from the EPA analysis due to their high degree of uncertainty and questionable relevance. Of the four diabetes studies used in the EPA analysis, two were included in the Wang et al. (2014) analysis (James et al., 2013; Coronado-González et al., 2007), but the two later publications (Grau-Perez et al., 2017; Pan et al., 2013) were not.

Diabetes study-specific dose conversions

The study-specific dose conversions and confidence interval estimations were derived in Excel workbooks with the Yasai add-in to do Monte Carlo simulations. Each study required a potentially different set of assumptions for the dose conversions. The study-specific conversion assumptions and results are provided in the Excel files, which are included in the health outcome-specific intake uncertainty folders of Supplemental Material available from the EPA HERO database. The following tables summarize the input equations and assumptions used in the Monte Carlo analyses (see Table C-36) and the MLE, low and high exposure and µg/kg-day dose estimates (see Table C-37) for each of the studies used in EPA's lung cancer meta-regression analyses.

Table C-36. Equations and assumptions for estimating µg/kg-day doses from diabetes studies[a]

Citation (country)	ADWE (yrs)	AAD (yrs)	LE, SD (µg/L)	WCR, SD (mL/kg-d)	BW, SD (kg)	DI, SD	BMI, SD (kg/m2)	RD, SD (yrs)	AGE, SD (yrs)	Exposure or dose metric	Equation
Coronado-González et al. (2007)	–	–	–	–	68, 10	–	27.4, 4.3	–	52.1 13.5	µg total As/g creat.	Doseb = (µg total As/g creat. × g creat./d)/BW
Grau-Perez et al. (2017)	–	–	–	–	68, 10	–	30.9, 6.3	–	56.2, 8	µg total As/g creat.	Doseb = (µg total As/g creat. × g creat./d)/BW
James et al. (2013)	56	56	25., 3.3	17, 37	–	0.05, 0.09	–	–	–	µg/L, WE	dose = DI + f*(CE-Val*WCR) + (1– f)*(LE*WCR)

Citation (country)	ADWE (yrs)	AAD (yrs)	LE, SD (µg/L)	WCR, SD (mL/kg-d)	BW, SD (kg)	DI, SD	BMI, SD (kg/m2)	RD, SD (yrs)	AGE, SD (yrs)	Exposure or dose metric	Equation
Pan et al. (2013)	34.1	34.1	2.5, 3.3	61.8, 26.8	–	1.44, 0.33	–	–	–	µg/L, WE	dose = DI + f*(CE-Val*WCR) + (1– f)*(LE*WCR)

ADWE=average duration of well exposure; AAD=average age at diagnosis; LE=low (outside study) exposure; WCR=water consumption rate; BW=body weight; DI=dietary intake; H=height; RD=reported duration of well exposure; Age=control group average age.

[a]See Conversion Factor Validation spreadsheet for justifications for individual exposure factors.

[b]According to EPA's PBPK model (El-Masri et al., 2018a, b), iAs is eliminated almost exclusively in urine. Thus, total µg/kg-day arsenic in urine is a good approximation of µg iAs/kg-day intake, assuming arsenic intake is substantially in the form of iAs. Urinary creatinine/kg-day is estimated as = (266.16 – 47.17*sex - 2.33*BMI + 0.66*age + 0.17*age^2)*113.12/10^6, where sex is 0 for male and 1 for female and BMI is estimated as BW/(Height/100)^2.

Table C-37. Meta-regression inputs and estimated effective counts for selected diabetes data sets, with three selected sets of dose values

Data set (reported dose units)	Exposure ranges	Dose values for analysis (avg. daily µg/kg)[a]			Raw counts			Adjusted OR/RR and 95% CIs			Effective counts[b]		
		MLE	Low	High	Cases	Controls	Expected	Adj OR	LCL	UCL	Cases	Controls	Expected
Grau-Perez et al. (2017) (µg/g)	≤3.3	0.066	0.066	0.066	30	–	30	1	1	1	30	–	30
	3.3–5.8	0.129	0.128	0.133	36	–	31.6	1.14	0.67	1.95	24.43	–	21.43
	>5.8	0.276	0.257	0.297	59	–	28.9	2.04	1.19	3.49	23.81	–	11.67
James et al. (2013) (µg/L-yr)	1–4	0.13	0.12	0.15	31	–	31	1	1	1	31	–	31
	4–8	0.18	0.16	0.21	31	–	27.9	1.11	0.82	1.95	60.32	–	54.34
	8–20	0.28	0.23	0.35	36	–	25.4	1.42	0.94	2.48	34.49	–	24.29
	>20	0.60	0.46	0.81	43	–	27.7	1.55	1	2.51	43.75	–	28.23
Coronado-González et al. (2007) (µg/g)	<63.5	1.303	1.294	1.311	36	67	–	1	1	1	36	48.64	–
	63.5–104	2.354	2.300	2.526	70	67	–	2.16	1.23	3.79	76.26	47.7	–
	>104	4.561	3.925	5.593	94	66	–	2.84	1.64	4.92	102.69	48.85	–
Pan et al. (2013) (µg/L)[d]	≤1.7	1.50	1.46	1.53	11	217	–	1	1	1	11	50.97	–
	1.8–15.5	1.80	1.76	1.85	19	208	–	1.92	0.84	4.35	21.6	52.13	–
	15.6–170	4.48	4.16	4.86	24	203	–	3.07	1.38	6.85	29.42	44.4	–
	170–1,050	23.20	21.15	25.50	28	199	–	4.51	2.01	10.09	–	–	–

[a]Sets of dose values derived as per Allen et al. (2020a).

[b]Effective counts derived as per Allen et al. (2020b).

[c]Person years of reference group follow up for Grau-Perez and James were 2,590 and 1,301, respectively.

[d]Effective counts shown are the ones used in the final meta-regression analysis based on dropping the high dose to improve model fit at low doses.

Summary of diabetes meta-regression results for MLE dose estimates

The settings for all Bayesian meta-regression runs summarized in the tables of this section were:

- 4 chains, each with iterations = 25000; warmup = 21250; thin = 2; Adapt_Delta[25] = 0.99999999
- post-warmup draws per chain = 1875, total post-warmup draws = 7500.
- β_mean Gamma parameters: a = 0.52 and b = 1.12

This section provides details of the results for the hierarchical meta-regression modeling, as well as dose-response plots from non-hierarchical modeling of individual studies. Additional details regarding the hierarchical and non-hierarchical modeling results can be obtained from the EPA HERO database.

Table C-38. Summary of diabetes Bayesian analysis output using MLE dose estimates

Study	Parameter[a]	Mean	Standard error of mean	Standard deviation	2.50%	25%	50%	75%	97.50%
Grau-Perez et al. (2017) (μg/g)	b	0.8319	0.0171	0.9268	−0.119	0.2587	0.4502	1.1173	3.368
	μ(δ)	35.5257	0.0659	4.7157	26.6438	32.3542	35.3929	38.5208	45.2777
	OR_RR[1]	1	0	0	1	1	1	1	1
	OR_RR[2]	1.0549	0.0012	0.0643	0.9926	1.0162	1.0284	1.072	1.2341
	OR_RR[3]	1.2126	0.0051	0.2829	0.9756	1.055	1.0977	1.2602	2.01
James et al. (2013) (μg/L-yr)	b	0.5255	0.0058	0.3614	−0.0049	0.2698	0.4324	0.7444	1.3741
	μ(δ)	35.5269	0.0468	3.4628	28.8331	33.215	35.4492	37.8535	42.4942
	OR_RR[1]	1	0	0	1	1	1	1	1
	OR_RR[2]	1.0251	0.0003	0.0175	0.9998	1.0127	1.0204	1.0354	1.0665
	OR_RR[3]	1.079	0.0009	0.0567	0.9993	1.039	1.0633	1.1114	1.2156
	OR_RR[4]	1.2866	0.0036	0.2262	0.9978	1.1302	1.2166	1.4005	1.8594
Coronado-González et al. (2007) (μg/g)	b	0.2735	0.0009	0.0775	0.1236	0.222	0.273	0.3253	0.4283
	vlambda[1]	0.8928	0.0069	0.5307	0.1705	0.5039	0.7923	1.1685	2.1796
	vlambda[2]	1.1221	0.0087	0.658	0.2205	0.6424	0.9974	1.4721	2.7187
	vlambda[3]	0.9425	0.0073	0.5588	0.1827	0.5363	0.8336	1.2368	2.3002
	OR_RR[1]	1	NA	0	1	1	1	1	1

[25]Corresponds to the target average proposal acceptance probability which is inversely related to the numerical integrator "step size" employed in Stan Hamiltonian MC.

Study	Parameter[a]	Mean	Standard error of mean	Standard deviation	2.50%	25%	50%	75%	97.50%
	OR_RR[2]	1.3374	0.0012	0.1093	1.1387	1.2628	1.3324	1.4076	1.5686
	OR_RR[3]	2.5167	0.0073	0.6497	1.4957	2.0613	2.434	2.8857	4.0367
Pan et al. (2013) (μg/L)	b	0.8319	0.0171	0.9268	−0.119	0.2587	0.4502	1.1173	3.368
	vlambda[1]	0.9943	0.0074	0.5773	0.2093	0.571	0.8822	1.2909	2.4253
	vlambda[2]	1.1542	0.0087	0.6696	0.2472	0.6608	1.0213	1.5261	2.8275
	vlambda[3]	0.9135	0.0069	0.5381	0.19	0.5209	0.8098	1.1848	2.2412
	OR_RR[1]	1	NA	0	1	1	1	1	1
	OR_RR[2]	1.0894	0.0004	0.0332	1.0257	1.0672	1.0886	1.1108	1.1563
	OR_RR[3]	2.3991	0.0084	0.7364	1.2811	1.8861	2.2896	2.7884	4.1223
Pooled β_mean		**0.346**	**0.004**	**0.2784**	**0.0058**	**0.1786**	**0.2918**	**0.4252**	**1.1016**
β_sigma		**0.591**	**0.0152**	**0.7786**	**0.0089**	**0.1101**	**0.3088**	**0.7773**	**2.7332**

[a]The indices, e.g., OR[i] refer to the ith group in the study. The lambda values that characterize the proportion of the control population in each dose-range are computed by vlambda[i]/sum(vlambda[j]) for all i,j in the range appropriate for each study.

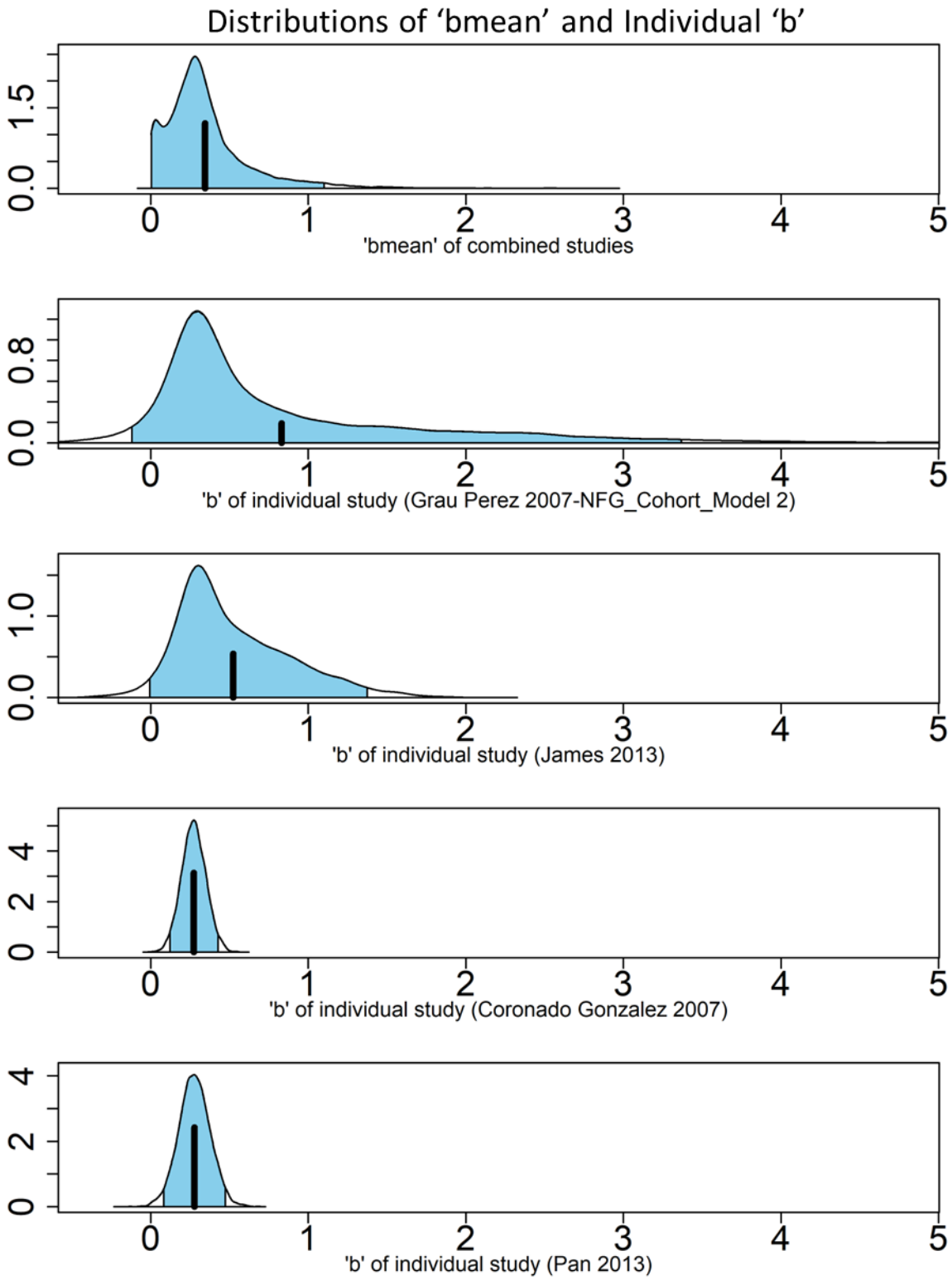


Figure C-22. Posterior distributions for diabetes pooled (bmean) and data-set-specific (b) logistic slope parameters, using MLE dose estimates. 95% Credible intervals are highlighted.

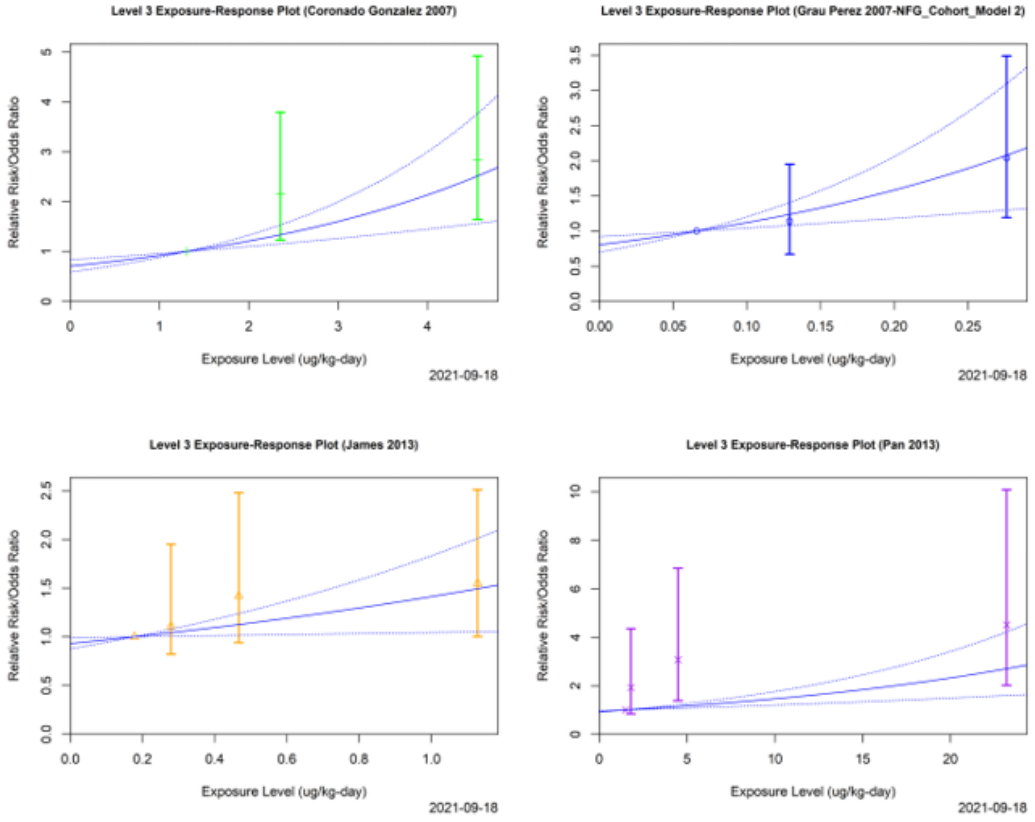


Figure C-23. Non-hierarchical meta-regression dose response curves for individual diabetes studies.

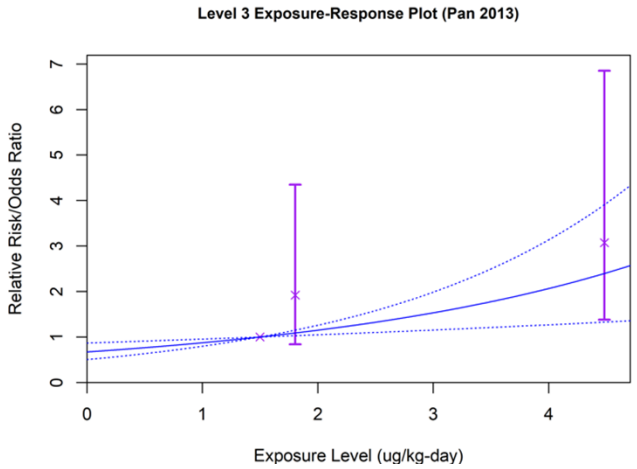


Figure C-24. Non-hierarchical meta-regression dose response curves for individual diabetes studies where doses were dropped to improve fit.

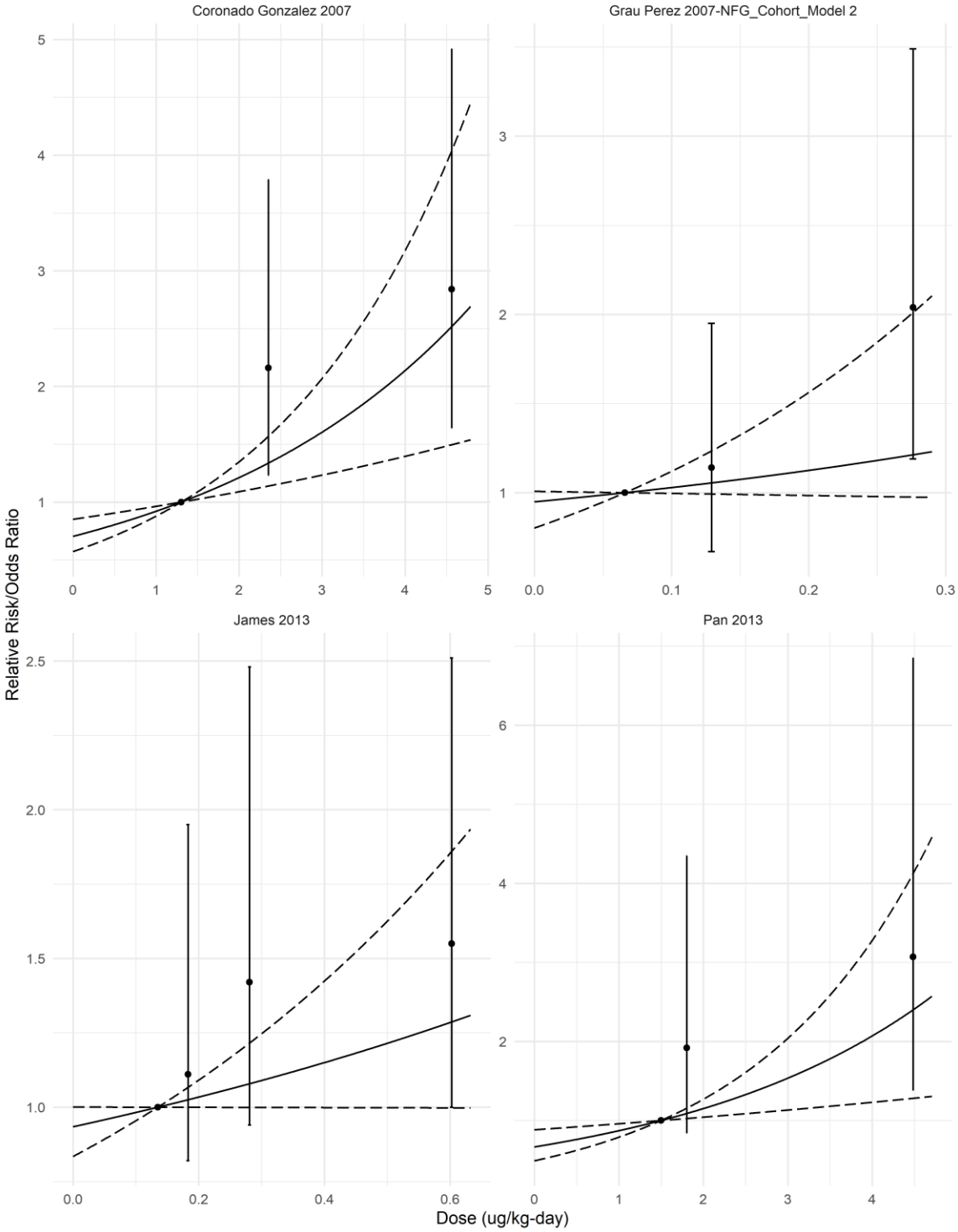


Figure C-25. Hierarchical meta-regression dose response curves for individual diabetes studies.

Diabetes sensitivity analyses

In addition to the evaluation described in Section Y.1.5 of the meta-regression approach's sensitivity across endpoints to the choice of the simpler Logistic model over a more complex double Hill model that allows for non-monotonicity, EPA has examined the sensitivity of the estimates of the association between oral iAs exposure and type II diabetes for five sources of uncertainty. The first relates to the choices made with respect to the characterization of the exposure levels used for the dose-response modeling. The second addresses sensitivity to choice of data sets. The third addresses the assumption that the general US population is not exposed to iAs via inhalation. The fourth addresses considerations of alternative gamma prior distributions for b_mean. The fifth addresses the use of urine biomarker studies in the meta-regression analysis.

The sources of uncertainty related to dose metric values are themselves broken down into two components. The first arises because of the need to estimate a mean value for the dose groups reported in terms of ranges of values (in whatever metric). The second relates to conversion of those mean exposure values to a consistent set of units across studies, those units being average daily μg/kg. The methods used to characterize those uncertainties are described in Allen et al. (2020a). Table C-39 below summarizes the 95% confidence intervals for the meta-regression pooled b value and extra risk values for bladder cancer for the MLE, "low," and "high" iAs dose estimates shown in Table C-37. Note that, while the "low" dose estimates provide the largest extra risks, the extra risk values are not appreciably different across the different dose estimates, indicating that the analysis was relatively insensitive to the uncertainties associated with dose characterization.

Table C-39. Pooled mean b and extra risk estimates from meta-regression of diabetes studies using MLE, "low," and "high" dose estimates

	Low dose estimates		MLE dose estimates		High dose estimates	
	Mean b	Lifetime Extra Risk[a]	Mean b	Lifetime Extra Risk[a]	Mean b	Lifetime Extra Risk[a]
5%	0.0176	9.13E-04	0.0215	1.12E-03	0.0119	6.17E-04
Mean	0.4113	2.13E-02	0.3460	1.79E-02	0.2820	1.46E-02
95%	1.0572	5.44E-02	0.8987	4.63E-02	0.7348	3.80E-02

[a]Risk above zero dose; Estimated for a total dose of 0.13 μg iAs/kg-day, which includes an estimated 0.0365 μg iAs/kg-day background dose, 0.02 μg iAs/kg-day from diet and 0.0165 μg iAs/kg-day from drinking water.

With respect to sensitivity of the estimates to choice of dataset, note that the meta-regression approach avoids the issue of study selection by pooling the results of all the datasets. Nevertheless, it is of interest to determine how influential each of those studies are on the estimate of the pooled risk. That sensitivity has been investigated by computing the pooled estimate of risk when each of the data sets is iteratively excluded from the analysis (i.e., a leave-one-out analysis). Table C-40 lists the pooled and study-specific mean b values when one study is iteratively left out of the analysis. As can be seen, the greatest decrease (24%) is observed when the dataset from Grau-

Perez et al. (2017) is excluded, and the greatest increase (36%) is observed when the dataset from Pan et al. (2013) is excluded.

Table C-40. Results of the leave-one-out analysis for diabetes datasets using the MLE dose estimate

Study left out	Mean b values (5th–95th percentile)				
	Pooled	Grau-Perez et al. (2017)	James et al. (2013)	Coronado-González et al. (2007) (µg/g)	Pan et al. (2013)
Grau-Perez et al. (2017)	0.2706 (0.0105–0.5987)	–	0.4354 (0.0593–1.0608)	0.2691 (0.1464–0.3928)	0.2715 (0.1112–0.4352)
James et al. (2013)	0.3330 (0.0080–0.9948)	1.0738 (-0.0256–3.6050)	–	0.2685 (0.1418–0.3986)	0.2716 (0.1054–0.4454)
Coronado-González et al. (2007)	0.4642 (0.0057–1.3769)	1.6312 (0.0574–4.0481)	0.7134 (0.0974–1.4071)	–	0.2800 (0.1048–0.4588)
Pan et al. (2013)	0.4691 (0.0074–1.3787)	1.6372 (0.0644–4.0941)	0.7080 (0.0856–1.4148)	0.2751 (0.1454–0.4095)	–

[a]Pooled estimate using all studies was 0.3460 (0.0215–0.8987) (see Table C-38).

Although inhalation of inorganic arsenic is not considered a primary route of exposure for the general public, the World Health Organization (WHO) estimates that background exposure may range from 0.02 to 0.6 µg/day in areas without substantial arsenic emissions from anthropogenic sources. Assuming an average body weight of 70 kg, this corresponds to daily intake values of 2.9×10^{-4} µg/kg-day to 8.6×10^{-3} µg/kg-day. The third sensitivity analysis involved two extra lifetable analyses wherein background inhalation components of either 4.4×10^{-3} µg/kg-day (corresponding to the midpoint of the range of reported background iAs concentrations), or 8.6×10^{-3} µg/kg-day (corresponding to the upper limit of background concentrations) were added to the original background estimate of exposure due to dietary and drinking water sources (i.e., 0.0365 µg/kg-day). Incorporation of inhalation exposures in the background estimate of total exposure also did not result in dramatically different estimates of extra risk. By definition, as the estimate of background exposure increased in the lifetable analysis, calculated extra risks must correspondingly decrease. Thus, at a 0.13 µg/kg-day iAs dose, when the assumed background exposure was either 0.0409 µg/kg-day or 0.0451 µg/kg-day, extra risks decreased to 1.792×10^{-2} or 1.791×10^{-2}, compared to 1.794×10^{-2} when no inhalation component was included in the background estimate of exposure. This corresponds to 0.1% and 0.2% decreases in extra risk, respectively.

Finally, the assumption of different Gamma prior distributions for β_mean did not result in large differences in the posterior distributions of the β_mean parameter (see Table C-41). Interestingly, the alternative prior sensitivity results indicated that, for the present set of studies used in this case-example, the results of the dose-response meta-analysis are rather insensitive to

assumptions on the gamma distribution prior. For example, using priors that differed with respect to the 1st percentile (i.e., 1.00001 – 20 and 1.001 – 20) resulted in the greatest differences in the mean of the posterior distribution relative to the original prior. This is due to the characteristics of the Gamma distribution, in which the greatest density with respect to probability of response is close to zero. So, when using the 1.00001 – 20 prior, the corresponding posterior mean distribution was approximately 5% lower than the results with the original prior because the 1st percentile is assumed to be ten times lower than for the original prior. Correspondingly, the 1.001 – 20 prior resulted in a posterior mean distribution approximately 11% higher than the original prior. Alternate Gamma prior distributions that differed with respect to the 99th percentile also did not differ greatly from the results using the original prior: using a prior with an upper bound of 10 (i.e., 50% lower than the original) resulted in a posterior mean approximately 6% lower and using a prior with an upper bound of 30 (i.e., 50% higher than the original) resulted in a posterior mean approximately 3% higher. This broadly indicates that the results of the analysis are heavily influenced by the actual data being modeled and are not inappropriately driven by the prior assumptions of the Bayesian modeling.

Table C-41. Posterior β_mean distribution values resulting from various prior Gamma distributions

Alternative prior	5th percentile	Mean	95th percentile	% Mean Difference
1.00001 – 20	0.0044	0.3280	0.8471	−5%
1.0001 – 10	0.0171	0.3240	0.7871	−6%
1.0001 – 30	0.0185	0.3563	0.9132	3%
1.001 – 20	0.0485	0.3839	0.9441	11%
Original Prior (1.0001 – 20)	0.0215	0.346	0.8987	–

The last sensitivity analysis investigated to what degree the inclusion of urinary biomarker studies influenced the modeled association between iAs intake and type II diabetes. For diabetes, there were only two urinary biomarker studies included in the modeling set, (Grau-Perez et al., 2017) and (Coronado-González et al., 2007). As can be seen in Table C-40, when these studies are left out individually, the mean estimate of the logistic slope decreases from 0.346 to 0.2706 when (Grau-Perez et al., 2017) is excluded and increases to 0.4642 when (Coronado-González et al., 2007) is excluded. This pattern is expected as Grau-Perez is a low-dose study and Coronado-Gonzalez is a moderate- to high-dose study. When both of the urine studies are excluded, the mean logistic slope estimate decreases to 0.3261, a 6% decrease over the mean logistic slope estimate of 0.346 when all studies are included in the meta-regression.

Extrapolation to target U.S. population

Approximate lifetable lifetime risk approach for diabetes

The posterior distribution for the "pooled" (average) value of the logistic slope parameter, β_mean, was used with a summary value of 40% for the U.S. lifetime probability of developing type II diabetes (Gregg et al., 2014)[26] as the input to a lifetable calculation of the lifetime probability of diabetes as a function of iAs dose (average daily μg/kg).

Diseases of the Circulatory System

Study and dataset selection

[26]For diabetes, age-stratified morbidity and mortality values were not available; therefore, a summary estimate of the lifetime probability of developing type II diabetes was used instead.

Table C-42. Data sets selected for meta-regressions of DCS outcomes[a]

Study (Study type)	Outcome (ascertainment)	Population (exposure/ dose metric)	N (follow-up)[b]	Group mean µg iAs/kg-d range (U.S. equivalent µg/L drinking water range)[c]	Description	Limitations[d]
CVD and IHD Incidence Studies						
Chen et al. (2013) Case-cohort	CVD and IHD incidence (Clinical exam: ECG and cardiac enzymes; Verbal autopsy, medical records, ICD-10: 100–199)	Matlab, Bangladesh 18–75 y 43% men (µg/L Drinking water)	1109 (~6 yrs)	1.8–2.8 (125–911)	Large case-cohort study of 369 incident fatal and nonfatal cases of CVD, including 148 stroke cases and 211 cases of heart disease, and a sub-cohort of 1,109 subjects randomly selected from the 11,224 participants in Bangladesh Health Effects of Arsenic Longitudinal Study (HEALS). Related iAs in drinking water to cases of CVD, CHD and stroke. 20 wells monitored for 3 yrs showed stable As concentrations over time. Controlled for age, sex, BMI, smoking, hypertension, occupation, education, income, diabetes status, hypertension and change in urinary status between visits.	High exposure levels. No follow-up. Only 3 exposure categories. Used arsenic level in index well assessed at baseline. Average duration of index well use was 7.4 yrs prior to baseline, accounting for just 20% of each participant's lifetime. 12% of participants did not exclusively use baseline well. Verbal autopsy may involve some misclassification and non-fatal cases relied on participant visits to field clinic.
James et al. (2015) Case-cohort	IHD incidence (Non-fatal: Self-report on yearly follow-up phone calls, and medical record review Fatal: Obituary monitoring and death certificate searches (ICD-9: 410–414))	Colorado, USA 20–74 y 46% male (µg/L Drinking water)	555 (~<10–14 yrs)	0.2–0.8 (11–54)	Large study of randomly selected participants from the San Luis Valley Diabetes Study (SLVDS) with a documented CHD event prior to 1998 (96 cases, 459 controls). Estimates of lifetime exposure obtained from residential history linked to geospatial model of predicted iAs in groundwater and drinking-water samples collected from kitchen tap at time of interview. Model adjusted for appropriate covariates, including age, sex, socioeconomic status, BMI, physical activity, smoking status, alcohol consumption, serum lipid levels, and micronutrient intake.	Collected water samples from just 64% of participant residences. Uncertainty associated with geospatial model estimates of arsenic concentrations not well characterized. Authors collected information on intake in order to estimate lifetime dose, but dose estimates did not correlate well with response or with speciated arsenic concentrations in urine samples collected from 1984–1991.

Study (Study type)	Outcome (ascertainment)	Population (exposure/ dose metric)	N (follow-up)[b]	Group mean µg iAs/kg-d range (U.S. equivalent µg/L drinking water range)[c]	Description	Limitations[d]
Moon et al. (2013) Prospective cohort	CVD and IHD incidence (Non-fatal: Self-report, clinical follow-up exams, medical records Fatal: Death certificate searches, medical records, informant interviews, ICD-9: 410–414)	Arizona, Oklahoma, and North and South Dakota, USA 45–74 yr 40% male (µg/g creatinine, Urine)	3575 (~15 yrs)	0.18–0.64 (9.3–42)	American Indian participants (ages 45–74 at baseline) from large prospective cohort study of 3,575 U.S. Strong Heart Study American Indians exposed to low levels of iAs. Cohort had relatively high pre-existing rate of diabetes and CVD. Obtained one creatinine adjusted urinary arsenic measurement for all participants, and 3 measurements over 10 yrs for a subset of 380 participants. Models adjusted for appropriate covariates age, sex, education, smoking, BMI, LDL cholesterol. Also presented modeling results with diabetes and hypertension treated as covariates.	Relatively high pre-existing rate of diabetes and CVD could have confounded results. Daily intake estimates were based on one urinary sample per individual and individual levels in drinking water were unavailable; temporal reproducibility of urine measurements in subset of 380 participants (3 repeated samples over 10 yrs) was 0.64 (95% CI, 0.60 to 0.69).
Wade et al. (2015) Case-control	IHD incidence[e] (Nonfatal only: Standard clinical criteria, including angina, ECG, echocardiogram, and cardiac enzymes)	Inner Mongolia, China 18–70 yr 70% men (µg/L Drinking water)	298 cases/275 controls	0.8–2.9 (54–204)	Case-control study of adults with CVD and controls from Hang-Hou hospital (298 cases, 275 controls). Water samples collected from primary drinking water source, and subjects assigned a water arsenic exposure based on arsenic concentration of this water source; for shared wells or municipal water, a single sample was used to represent arsenic exposures. Model adjusted for age, sex, education, smoking, BMI, occupation, alcohol use, family history of hypertension, diabetes, or heart disease.	Moderate to high exposure levels. Study only examined non-fatal events.

Study (Study type)	Outcome (ascertainment)	Population (exposure/ dose metric)	N (follow-up)[b]	Group mean µg iAs/kg-d range (U.S. equivalent µg/L drinking water range)[c]	Description	Limitations[d]
Fatal CVD and IHD Studies						
Chen et al. (2011) Prospective cohort	Fatal CVD and IHD (Verbal autopsy, medical records, ICD-10: 100–199)	Bangladesh 18–75 yr 43% men (µg/L water and µg/g creatinine, urine)	11746 (~6 yrs)	2.0–15.1 (139–1,075)	Health Effects of Arsenic Longitudinal Study (HEALS) of 11,746 participants residing in study area for ≥5 yrs. Drinking water iAs concentration calculated from well water samples from 5,966 contiguous wells in the area. Adjusted for age, sex, education, BMI, smoking, change in arsenic between visits.	High exposure levels. Limited follow-up. No details on individual level exposures. Only examined fatal events.
D'Ippoliti et al. (2015) Retrospective cohort	Fatal CVD and IHD (Death certificate registry, ICD-9: 390–459; 410–414)	Italy Mean 33 yr 50% men (µg/L Drinking water)	165609 (~40 yrs)	0.2–0.7 (11–46)	Retrospective cohort study of residents in 8 high and 9 low iAs municipalities (165,609 total). Cumulative iAs (CAI) estimated by multiplying iAs concentrations from each subject's residence by time lived at each address and by average water intake, summed up for all residencies since birth. Model adjusted for age, calendar period, SES, occupation in the ceramic industry (individual); smoking sales and radon exposure (municipal level).	Did not measure individual household exposures. Limited follow-up rate. Only examined fatal events.
Moon et al. (2013) Prospective cohort	Fatal CVD and IHD (Fatal: Death certificate searches, medical records, informant interviews, ICD-9: 410–414)	Arizona, Oklahoma, and N and S Dakota, USA 45–74 yr 40% male (µg/g creatinine, Urine)	3575 (~15 yrs)	0.18–0.64 (9.3–42)	See above under "CVD and IHD Incidence Studies"	

Study (Study type)	Outcome (ascertainment)	Population (exposure/ dose metric)	N (follow-up)[b]	Group mean µg iAs/kg-d range (U.S. equivalent µg/L drinking water range)[c]	Description	Limitations[d]
Sohel et al. (2009) Prospective cohort	Fatal CVD (Verbal autopsy, ICD-10: 100–199)	Matlab, Bangladesh 15–75 yr 50% men (µg/day Drinking water)	115903 (~10 yrs)	1.5–22.0 (104–1,568)	Large prospective cohort study of 93,415 subjects with nonaccidental deaths 1991–2000. Mean household exposure calculated for each calendar yr from 1970; based on information obtained from the current population present in that specific household for each yr; if data were missing for a specific household, the corresponding information was derived on the compound level. Adjusted for age, sex, education, asset score.	High exposure levels. Exposure levels based on limited and uncertain historical information. Only examined fatal events.
Wade et al. (2009) Retrospective cohort	Fatal CVD and IHD (Verbal autopsy, medical records and physician interview (ICD-10: 100–109, 20–51)	Inner Mongolia, China 0–>80 yr 50% men (Drinking water)	12334 (~6 yrs)	0.7–12.7 (46–904)	Study of deceased subjects from village with history of high iAs in drinking water (n=12,600). Drinking water iAs exposure calculated from single well water sample collected from each household; results below LOD assigned one-half of LOD. Adjusted for age, sex, education, smoking, alcohol use, farm work.	Moderate to high exposure levels. Exposure levels estimated from single well sample and limited attempt to ascertain historical information. Only examined fatal events.

[a]Some studies investigated multiple DCS outcomes.

[b]Number of persons at baseline for cohort studies, number of persons in the sub-cohort at baseline for case-cohort studies and number of cases and non-cases for case-control studies.

[c]Estimated from µg/kg-d ranges (see Table C-45) assuming mean U.S. dietary background of 0.05 µg/kg-d (Xue et al., 2010) and mean U.S. water consumption rate of 0.014 L/kg-d (U.S. EPA, 2011), (see Table 3-1, "All Ages").

[d]Some studies offered models that adjust for hypertension and diabetes. This might be considered a limitation if simpler models are not also provided. EPA prefers models that do not treat these diseases as covariates because of the possibility that they are in the pathological pathway for CVD caused by arsenic.

[e]Wade et al. (2015) included 16 cases of cardiomyopathy (<4%), which may not be associated with IHD.

Comparison of studies selected for EPA meta-regression and studies used in earlier meta-analyses

Moon et al. (2017) updated a prior meta-analysis of CVD health outcomes (Moon et al., 2012). The Moon et al. (2017) meta-analysis uses high quality studies (see Table C-43) to estimate the relationship between levels of arsenic in drinking water and relative risks for incidence of and fatality from clinical CVD endpoints (all CVD, CHD, and stroke) in the adult general population. They excluded studies of childhood exposures, occupational exposures uncommon in the general population (e.g., arsenic trioxide), case reports or case series, preclinical CVD outcomes, ecological studies (or studies analyzed as group level data), studies with prevalent outcomes, and studies that reported results with fewer than three exposure categories. They identified one prospective cohort study of CHD and stroke (Wang et al., 2005) that reported the results of additional follow-up of two previously described cohorts (Chiou et al., 1997; Chen et al., 1996) from the arsenic-endemic areas of Taiwan combined with a cohort of Taiwan residents exposed to low levels of arsenic in drinking water. They included this study in their systematic review but excluded it from the meta-analysis because the study was not peer reviewed and did not report the number of person-years necessary to calculate the effective number of cases and noncases.[27]

Table C-43. Moon et al. (2017) meta-analysis; arsenic exposure vs. CVD, CHD or stroke[a]

Study	Design	Population	Exposure assessment	Outcome	Adjustment factors
High arsenic in drinking water (At least one exposure group ≥100 µg/L)					
Rahman et al. (2014)	Prospective cohort	Matlab, Bangladesh	Individual drinking water (µg/L)	Fatal stroke	Age, sex, education, SES
Chen et al. (2013)	Case-cohort	Araihazar, Bangladesh	TWA household drinking water (µg/L)	Non-fatal and fatal CVD, CHD, and stroke	Age, sex, education, BMI, smoking, hypertension, diabetes, change in arsenic between visits
Chen et al. (2011)	Prospective cohort	Araihazar, Bangladesh	Spot urine (µg/g creatinine) and TWA drinking water (µg/L)	Fatal CVD, CHD, and stroke	Age, sex, education, BMI, smoking, change in arsenic between visits
Sohel et al. (2009)	Prospective cohort	Matlab, Bangladesh	TWA household drinking water (µg/L)	Fatal CVD	Age, sex, education, asset score
Wade et al. (2009)	Retrospective cohort	Inner Mongolia, China	Household drinking water (µg/L)	Fatal CVD, CHD, stroke	Age, sex, education, smoking, alcohol use, farm work
Wang et al. (2005)[a]	Prospective cohort, extern. comparison	SW, NE, and low arsenic Taiwan townships	Village, household, and municipal water (µg/L)	Fatal CVD	Age, sex, smoking

[27]This study is not included in the EPA meta-regression analyses for these reasons and also because it combined populations with very different exposure scenarios (e.g., tap water systems were installed to replace well water in the 1970s in southwestern Taiwan versus in the 1990s in northeastern Taiwan).

Study	Design	Population	Exposure assessment	Outcome	Adjustment factors
Chen et al. (1996)	Prospective cohort	SW Taiwan	Village drinking water	Fatal CHD	Age, sex, smoking, BMI, lipids, hypertension, diabetes
Low-moderate arsenic in drinking water (All exposure groups <100 µg/L)					
D'Ippoliti et al. (2015)	Administrative retrospective cohort	Lazio, Italy	Predicted household drinking water (µg/L)	Fatal CVD, CHD, stroke[a]	Age, calendar period, SES, ceramic industry occupation (individual); smoking sales and radon exposure (municipal)
James et al. (2015)	Prospective case-cohort	Colorado, USA	Household drinking water Predicted TWA household drinking water (µg/L)	Nonfatal and fatal incidence of CHD	Age, sex, income, Hispanic ethnicity, smoking, alcohol use, BMI, sedentary physical activity, family history of CHD, diabetes, LDL cholesterol, TG, HDL cholesterol, folate, selenium
Wade et al. (2015)	Hospital-based case-Control	Inner Mongolia, China	Household drinking water (µg/L)	Nonfatal CHD[b]	Age, sex, education, smoking, BMI, occupation, alcohol use; family history of hypertension, diabetes, or heart disease
Farzan et al. (2015)	Prospective case-control	New Hampshire, USA	Toenail (µg/g)	Fatal CVD, CHD, stroke	Age, sex, education, smoking (pack-yrs), cancer status (case vs. control)
Moon et al. (2013)	Prospective cohort	Arizona, N Dakota, S Dakota, Oklahoma, USA	Spot urine (µg/g creatinine)	Nonfatal and fatal CVD, CHD, and stroke	Age, sex, education, smoking, BMI, LDL cholesterol

Adapted from (Moon et al., 2017).

TWA = time-weighted average, CVD = cardiovascular disease, CHD = coronary heart disease, LDL = low-density lipoprotein, HDL = high-density lipoprotein, TG = triglycerides, BMI = body mass index, SES = socioeconomic status.

[a]This study was excluded from the final meta-analysis because it was not peer reviewed and did not report the number of person-years necessary to calculate the effective number of cases and noncases.

[b]Wade et al. (2015) included 16 cases of cardiomyopathy (<4%), in addition to acute or previous myocardial infarction.

The CVD and IHD studies selected by EPA for meta-regression analyses (see Section 2.5.2 of the iAs assessment) differ from the studies considered in the (Moon et al., 2017) analysis only with respect to EPA exclusion of (Farzan et al., 2015) study of fatal CVD and IHD (and toenail studies of other health outcomes) due to high level of uncertainty in extrapolating from toenail concentrations to intake (dose). While limited data concerning empirical relationships between toenail arsenic and water arsenic are available, there is no generally accepted approach for estimating arsenic intake from toenail levels, and EPA's PBPK model does not include a toenail compartment.

While study selection was similar between the (Moon et al., 2017) analysis and the EPA meta-regression, methods differed in a number of ways, including the models used, exposure

metric modeled, the reference exposure assumed, and the response metric modeled.[28] However, despite these methodological differences, the conclusions of the two meta-analyses are similar. Although the assumed drinking water reference exposures were different,[29] both analyses predict a substantial increase in risk of CVD incidence and IHD incidence within increasing levels of inorganic iAs exposure.

Study-specific dose conversions

The study-specific dose conversions and confidence interval estimations were derived in Excel workbooks with the Yasai add-in to do Monte Carlo simulations. Each study required a potentially different set of assumptions for the dose conversions. The study-specific conversion assumptions and results are provided in the Excel files, which are included in the health outcome-specific intake uncertainty folders of Supplemental Material available from the EPA HERO database. Table C-44 summarizes the input equations and assumptions used in the Monte Carlo analyses and Table C-45 shows the MLE, low and high exposure and µg/kg-day dose estimates for each of the studies used in EPA's DCS meta-regression analyses. Table C-46 presents additional information provided by the authors of (Moon et al., 2013) on temporal variability in the urine levels of 386 study participants that was also used in EPA's Monte Carlo analysis of uncertainty in extrapolating dose from the urine levels reported in the (Moon et al., 2013) publication.

Table C-44. Equations and assumptions for estimating µg/kg-day doses from oral DCS studies[a]

Citation (Country)	ADWE (yrs)	AAD (yrs)	LE, 3SD (µg/L)	WCR, 3SD (mL/kg-d)	BW, 3SD (kg)	DI, 3SD	BMI, 3SD (kg/m²)	RD, 3SD (yrs)	AGE, SD (yrs)	Exposure or dose metric	Equation
Chen et al. (2011) (Bangladesh)	–	–	–	–	62.5, 26.4	–	19.7, 9.45[a]	–	37.6, 28	µg total As/g creat.	Dose[b] = (µg total As/g creat. × g creat./d)/BW
Chen et al. (1996) (SW Taiwan)	16	57	5, 45	34.5, 69.6	–	1.4, 1.0	–	16, 42	–	µg/L-yrs, CE	dose = DI + f*WCR*CE/RD + (1–f)*WCR*LE
Chen et al. (2013) (Bangladesh)	54	54	5, 10	61.8, 80.5	–	1.4, 1.0	–	–	–	µg/L, WE	dose = DI + f*WCR*WE + (1–f)*WCR*LE
D'Ippoliti et al. (2015) (Italy)	46	46	5, 10	14, 30	–	0.1, 0.9	–	–	–	µg/L, WE	dose = DI + f*WCR*WE + (1–f)*WCR*LE

[28]Moon et al. (2017) estimated the pooled association between log-transformed water arsenic (log-linear) and restricted cubic splines of log-transformed water arsenic (non-linear) and the relative risk of each CVD endpoint. They modeled log relative risk of each CVD endpoint, assuming both a constant log-linear association (log-transformed arsenic concentrations) and a flexible non-linear association (restricted cubic splines with knots at the 10th, 50th and 90th percentiles of log-transformed arsenic).
[29]EPA used a reference exposure of 1.5 µg /L and Moon et al. (2017) used a reference exposure of 10 µg/L.

Citation (Country)	ADWE (yrs)	AAD (yrs)	LE, 3SD (µg/L)	WCR, 3SD (mL/kg-d)	BW, 3SD (kg)	DI, 3SD	BMI, 3SD (kg/m²)	RD, 3SD (yrs)	AGE, SD (yrs)	Exposure or dose metric	Equation
James et al. (2015) (USA)	65	65	1.5, 12	14, 30	–	0.05, 0.27	–	–	–	µg/L, WE	dose = DI + f*WCR*WE + (1–f)*WCR*LE
Moon et al. (2013) (USA)	–	–	–	–	68, 30	–	30.8, 18.9	–	56.2, 24	µg total As/g creat.	Dose[b] = (µg total As/g creat. × g creat./d)/BW
Sohel et al. (2009) (Bangladesh)	67	67	5, 10	61.8, 80.5	–	1.4, 1.0	–	–	–	µg/L, WE	dose = DI + f*WCR*WE + (1–f)*WCR*LE
Wade et al. (2009) (China)	66	66	5, 10	34.5, 69.6	–	0.65, 1.0	–	–	–	µg/L, WE	dose = DI + f*WCR*WE + (1–f)*WCR*LE
Wade et al. (2015) (China)	56	56	5, 10[g]	34.5, 69.6	–	0.65, 1.0	–	–	–	µg/L, WE	dose = DI + f*WCR*WE + (1–f)*WCR*LE

ADWE=average duration of well exposure; AAD=average age at diagnosis; LE=low (outside study) exposure; WCR=water consumption rate; BW=body weight; DI=dietary intake; H=height; RD=reported duration of well exposure; Age=control group average age.

[a]See Conversion Factor Validation spreadsheet for justifications for individual exposure factors.

[b]According to EPA's PBPK model (El-Masri et al., 2018a, b), iAs is eliminated almost exclusively in urine. Thus, total µg/kg-day arsenic in urine is a good approximation of µg iAs/kg-day intake, assuming arsenic intake is substantially in the form of iAs. Urinary creatinine/kg-day is estimated as = (266.16 – 47.17*sex - 2.33*BMI + 0.66*age + 0.17*age^2)*113.12/10^6, where sex is 0 for male and 1 for female and BMI is estimated as BW/(Height/100)^2.

Table C-45. Meta-regression inputs and estimated effective counts for DCS data sets, with three sets of dose values

Data set (exposure units)/ person yrs[a]	Exposure ranges	Doses (µg/kg-d)[b]			Health outcome	Raw counts			Adjusted OR/RR and 95% CIs			Effective counts[c]		
		MLE	Low	High		Cases	Control	Expected	Adj OR	LCL	UCL	Cases	Control	Expected
Chen et al. (2011) (µg/g creatinine) 20,064	6.6–105.9	1.95	1.95	1.95	Fatal CVD	44	–	44	1	1	1	44	–	44
					Fatal IHD	17	–	17	1	1	1	17	–	17
	105.9–199	4.13	4.10	4.15	Fatal CVD	48	–	41.7	1.15	0.77	1.72	51.8	–	45.0
					Fatal IHD	18	–	14.0	1.29	0.66	2.51	17.5	–	13.5
	199–351.8	7.30	7.25	7.35	Fatal CVD	54	–	34.6	1.56	1.03	2.38	43.6	–	28.0

Data set (exposure units)/ person yrs[a]	Exposure ranges	Doses (µg/kg-d)[b]			Health outcome	Raw counts			Adjusted OR/RR and 95% CIs			Effective counts[c]		
		MLE	Low	High		Cases	Control	Expected	Adj OR	LCL	UCL	Cases	Control	Expected
					Fatal IHD	17	–	11.6	1.47	0.72	3.01	13.5	–	9.2
	351.8–1,100	15.07	14.91	15.24	Fatal CVD	46	–	29.7	1.55	1.01	2.37	40.6	–	26.2
					Fatal IHD	17	–	8.9	1.9	0.91	3.98	12.1	–	6.4
Chen et al. (2013) (µg/L)[d] 2,823	7.20	1.80	1.76	1.83	CVD Inc.	114	–	114	1	1	1	114	–	114
					IHD Inc.	61	–	61	1	1	1	61	–	61
	59.90	4.48	4.36	4.62	CVD Inc.	120	–	120.0	1	0.67	1.5	29.9	–	29.9
					IHD Inc.	72	–	61.0	1.18	0.75	1.84	27.8	–	23.5
	222.80	12.80	12.36	13.28	CVD Inc.	132	–	88.6	1.49	1.06	2.11	45.3	–	30.4
					IHD Inc.	75	–	48.7	1.54	1.02	2.31	36.9	–	24.0
D'Ippoliti et al. (2015) (µg/L)[e, f] 771,860-CVD 713,276-IHD	6.5 ± 2.8	0.16	0.15	0.17	Fatal CVD	2752	–	2752	1	1	1	2752	–	2752
					Fatal IHD	684	–	684	1	1	1	684	–	684
	13.7 ± 2.6	0.23	0.21	0.25	Fatal CVD	2115	–	1652.3	1.28	1.08	1.51	144.0	–	112.5
					Fatal IHD	573	–	409.3	1.4	1.19	1.64	191.1	–	136.5
	34.5 ± 19.7	0.43	0.39	0.47	Fatal CVD	3514	–	2583.8	1.36	1.06	1.74	64.0	–	47.1
					Fatal IHD	1014	–	694.5	1.46	1.07	2.01	41.0	–	28.1
James et al. (2015) (µg/L)[d] 4,806	1–20	0.20	0.19	0.22	IHD Inc.	58	–	58	1	1	1	58	–	58
	20–30	0.45	0.34	0.61	IHD Inc.	18	–	14.6	1.23	0.56	2.18	9.7	–	7.9
	30–45	0.62	0.38	1.00	IHD Inc.	16	–	7.3	2.18	1.23	4.02	13.5	–	6.2
	45–88	0.82	0.31	1.77	IHD Inc.	4	–	1.3	3.1	1.1	9.11	3.7	–	1.2
Moon et al. (2013) (µg/g creatinine)[d] 12,146 – for CVD and IHD incidence	0–5.8	0.18	0.17	0.18	CVD Inc.	265	–	265	1	1	1	265	–	265
					IHD Inc.	202	–	202	1	1	1	202	–	202
					Fatal CVD	86.0	–	86.0	1	1	1	86.0	–	86.0
					Fatal IHD	68	–	68	1	1	1	68	–	68
	5.8–9.7	0.23	0.22	0.24	CVD Inc.	297	–	260.5	1.14	0.95	1.35	234.6	–	205.8
					IHD Inc.	206	–	196.2	1.05	0.86	1.28	187.2	–	178.3

Data set (exposure units)/ person yrs[a]	Exposure ranges	Doses (µg/kg-d)[b]			Health outcome	Raw counts			Adjusted OR/RR and 95% CIs			Effective counts[c]		
		MLE	Low	High		Cases	Control	Expected	Adj OR	LCL	UCL	Cases	Control	Expected
13,616 – for CVD and IHD fatality					Fatal CVD	95	–	84.8	1.12	0.83	1.52	82.0	–	73.2
					Fatal IHD	67	–	67.7	0.99	0.7	1.41	58.1	–	58.7
	9.7–15.7	0.33	0.32	0.34	CVD Inc.	291	–	277.1	1.05	0.87	1.26	194.0	–	184.8
					IHD Inc.	197	–	207.4	0.95	0.77	1.19	135.5	–	142.6
					Fatal CVD	115	–	91.3	1.26	0.92	1.73	69.8	–	55.4
					Fatal IHD	87	–	73.7	1.18	0.83	1.69	55.0	–	46.6
	15.7–20	0.64	0.62	0.66	CVD Inc.	331	–	250.8	1.32	1.09	1.59	181.7	–	137.7
					IHD Inc.	241	–	185.4	1.3	1.04	1.62	127.7	–	98.2
					Fatal CVD	143	–	86.7	1.65	1.2	2.27	67.5	–	40.9
					Fatal IHD	119	–	69.6	1.71	1.19	2.44	53.1	–	31.0
Sohel et al. (2009) (µg/d)[d] 114,068	0–10	1.50	1.48	1.52	Fatal CVD	147	–	147	1	1	1	147	–	147
	10–49	3.01	2.97	3.06	Fatal CVD	168	–	163.1	1.03	0.82	1.29	152.5	–	148.1
	50–149	6.38	6.26	6.51	Fatal CVD	463	–	399.1	1.16	0.96	1.4	406.3	–	350.3
	150–299	12.08	11.84	12.35	Fatal CVD	318	–	258.5	1.23	1.01	1.51	268.6	–	218.4
	300–500	22.00	21.51	22.49	Fatal CVD	115	–	83.9	1.37	1.07	1.77	103.3	–	75.4
Wade et al. (2009) (µg/L)[d] 14,636	0–5	0.73	0.72	0.75	Fatal CVD	97	–	97	1	1	1	97	–	97
					Fatal IHD	44	–	44	1	1	1	44	–	44
	5–20	1.03	1.00	1.06	Fatal CVD	42	–	58.3	0.72	0.32	1.6	6.3	–	8.8
					Fatal IHD	26	–	24.3	1.07	0.64	1.78	22.0	–	20.6
	20–100	1.80	1.75	1.84	Fatal CVD	113	–	143.0	0.79	0.34	1.86	5.6	–	7.1
					Fatal IHD	72	–	59.0	1.22	0.82	1.82	53.6	–	44.0

Data set (exposure units)/ person yrs[a]	Exposure ranges	Doses (µg/kg-d)[b]			Health outcome	Raw counts			Adjusted OR/RR and 95% CIs			Effective counts[c]		
		MLE	Low	High		Cases	Control	Expected	Adj OR	LCL	UCL	Cases	Control	Expected
	100–300	5.48	5.24	5.74	Fatal CVD	24	–	38.7	0.62	0.1	3.7	1.2	–	1.9
					Fatal IHD	17	–	11.0	1.55	0.88	2.73	16.5	–	10.6
	300–500	12.71	10.91	14.68	Fatal CVD	2	–	1.2	1.7	0.51	5.72	2.7	–	1.6
					Fatal IHD	2	–	0.8	2.47	0.5	12.18	1.6	–	0.63
Wade et al. (2015) (µg/L) Case-control	0–10	0.77	0.73	0.82	IHD Inc.	168	137	–	1	1	1	168	–	168
	10–39	1.28	1.20	1.36	IHD Inc.	105	131	–	1.23	0.78	1.93	192.8	–	45.7
	40–208	2.95	1.87	4.39	IHD Inc.	15	4	–	4.05	1.1	14.99	35.6	–	2.6

[a]Person years of reference group follow up; obtained from (Moon et al., 2017), supplemental table 2.

[b]Sets of dose values derived as per (Allen et al., 2020a).

[c]Effective counts derived as per (Allen et al., 2020b).

[d]Author reported means without SDs are presented in (Moon et al., 2017), supplemental table 2. These means are used directly in EPA's analysis. Sensitivity analyses indicate dose estimations do not vary substantially with variance in the exposure group means. Hence, the benefit of using actual reported means is believed to outweigh the benefit of sampling from a presumed distribution.

[e]Authors reported means with SDs. The mean and SE for each exposure group were used to generate random values for the MC analysis.

[f]Ns reported in Section X.1 were obtained from authors by (Hobbie et al., 2020) (see Table S-15). Adjusted RR values for combined males and female responses were obtained from (Moon et al., 2017), Supplemental Table 2.

Table C-46. Strong heart study arsenic concentrations at phase I (1989–1991, baseline) and change over phase II (1993–1995) and phase III (1998–1999), stratified by baseline exposure level groups as in (Moon et al., 2013)[a]

	N	Phase I concentrations (baseline)	Phase II vs. Phase I change	Phase III vs. Phase I change
<5.8 µg/g	114	4.18 (1.04)	1.10 (3.12)	1.65 (4.18)
5.8–9.7 µg/g	115	7.72 (1.17)	−0.53 (4.48)	0.02 (5.12)
9.8–15.7 µg/g	69	12.65 (1.73)	−2.60 (4.41)	−1.11 (5.82)
>15.7 µg/g	88	24.79 (10.12)	−8.80 (9.56)	−4.63 (13.88)
Overall	386	11.45 (9.22)	−2.32 (6.86)	−0.77 (8.25)

[a]Data are mean (SD) of urine arsenic concentrations divided by urine creatinine levels, expressed as mg/g. Arsenic concentration is assessed as the sum of iAs, MMA, and DMA.

Summary of DCS meta-regression results for MLE dose estimates

The settings for the Bayesian meta-regression runs summarized in the tables of this section were run with:

- 4 chains, each with iterations = 25000 (30,000 for fatal IHD and IHD Incidence analyses that use All and High Dose studies); warmup=21250 (26,250 for fatal IHD and IHD Incidence analyses that use All and High Dose studies); thin = 2; Adapt_Delta[30] = 0.9999
- post-warmup draws per chain = 1875, total post-warmup draws = 7500.
- β_mean Gamma parameters: a = 0.52 and b = 1.12

This section provides details of the results for the hierarchical meta-regression modeling, as well as dose-response plots from non-hierarchical modeling of individual studies. Additional details regarding the hierarchical and non-hierarchical modeling results can be obtained from the EPA HERO database.

[30]Corresponds to the target average proposal acceptance probability which is inversely related to the numerical integrator "step size" employed in Stan Hamiltonian MC.

CVD Incidence – All Studies

Table C-47. Summary of CVD incidence (all studies) Bayesian analysis output; MLE dose estimates

Parameter	Mean	Se_mean	SD	2.50%	25%	50%	75%	97.50%	N_eff	Rhat
bmean	0.2305	0.0048	0.2788	0.0006	0.0399	0.1396	0.3163	0.9961	3428	1.0005
b_sigma	0.8872	0.0205	1.1148	0.0525	0.2794	0.5227	1.0418	4.1466	2966	1.0011
b0[1]	−0.3549	0.0089	0.5117	−1.6833	−0.5668	−0.1857	−0.007	0.2127	3336	1.0003
b0[2]	0.5379	0.0103	0.6469	−0.646	0.1106	0.4468	0.9086	1.9723	3966	1.0004
mu_ref[1]	113.1477	0.0964	7.67	98.7498	107.8552	112.9425	118.2242	128.7426	6324	1
mu_ref[2]	272.8586	0.1524	10.4519	252.8473	265.4576	272.7714	280.1152	293.437	4704	1.0006
b[1]	0.037	0.0002	0.0161	0.0049	0.0263	0.0374	0.0478	0.0686	7160	0.9998
b[2]	0.4593	0.0035	0.2054	0.045	0.324	0.4617	0.6016	0.8535	3505	1.0009
p[1]	0.0401	0	0.0027	0.035	0.0382	0.04	0.0419	0.0456	6324	1
p[2]	0.0441	0	0.0027	0.0389	0.0422	0.0441	0.0459	0.0494	6751	1
p[3]	0.0595	0.0001	0.0088	0.0436	0.0534	0.0592	0.065	0.0779	7422	0.9999
p[4]	0.0225	0	0.0009	0.0208	0.0219	0.0225	0.0231	0.0242	4704	1.0006
p[5]	0.023	0	0.0008	0.0216	0.0225	0.023	0.0235	0.0245	5925	1.0003
p[6]	0.0241	0	0.0008	0.0227	0.0236	0.0241	0.0246	0.0256	7066	0.9997
p[7]	0.0278	0	0.0021	0.0237	0.0263	0.0277	0.0292	0.032	4070	1.0004
pr[1]	0.0401	0	0.0027	0.035	0.0382	0.04	0.0419	0.0456	6324	1
pr[2]	0.0401	0	0.0027	0.035	0.0382	0.04	0.0419	0.0456	6324	1
pr[3]	0.0401	0	0.0027	0.035	0.0382	0.04	0.0419	0.0456	6324	1
pr[4]	0.0225	0	0.0009	0.0208	0.0219	0.0225	0.0231	0.0242	4704	1.0006
pr[5]	0.0225	0	0.0009	0.0208	0.0219	0.0225	0.0231	0.0242	4704	1.0006
pr[6]	0.0225	0	0.0009	0.0208	0.0219	0.0225	0.0231	0.0242	4704	1.0006
pr[7]	0.0225	0	0.0009	0.0208	0.0219	0.0225	0.0231	0.0242	4704	1.0006
OR_RR[1]	1	0	0	1	1	1	1	1	7137	0.9995
OR_RR[2]	1.101	0.0005	0.0456	1.0128	1.07	1.101	1.131	1.1936	7158	0.9998
OR_RR[3]	1.4929	0.003	0.2498	1.0532	1.317	1.4784	1.6469	2.0414	7147	0.9999
OR_RR[4]	1	0	0	1	1	1	1	1	476	0.9995
OR_RR[5]	1.0245	0.0002	0.0111	1.0024	1.0172	1.0246	1.0321	1.0459	3524	1.0009
OR_RR[6]	1.0745	0.0006	0.0343	1.007	1.0516	1.0743	1.0979	1.1418	3560	1.0009
OR_RR[7]	1.2384	0.0019	0.1158	1.0208	1.1593	1.2344	1.3156	1.4752	3669	1.0009
astar	−3.8542	0.0011	0.0675	−3.9862	−3.9009	−3.8546	−3.8076	−3.7228	3444	1.001
lp__	2830.513	0.054	2.508	2824.258	2829.189	2830.952	2832.307	2834.17	2156	1.0031

Samples were drawn using NUTS(diag_e) Sat Jul 09 19:34:04 2022. For each parameter, n_eff is a crude measure of effective sample size, and Rhat is the potential scale reduction factor on split chains (at convergence, Rhat = 1). There were two divergent transitions after warmup.

Study Key:

1. Chen et al. (2013)
2. Moon et al. (2013)

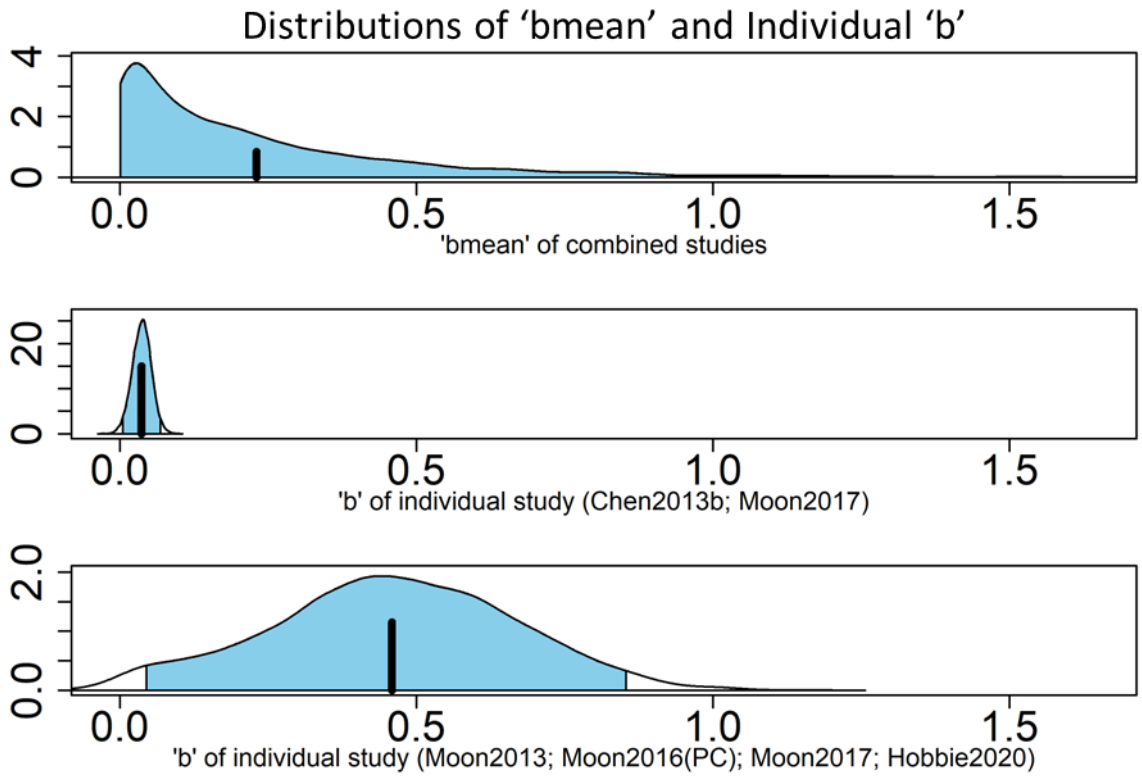


Figure C-26. Posterior distributions for CVD incidence pooled (bmean) and data-set-specific (b) logistic slope parameters, using MLE dose estimates and all studies. 95% Credible intervals are highlighted.

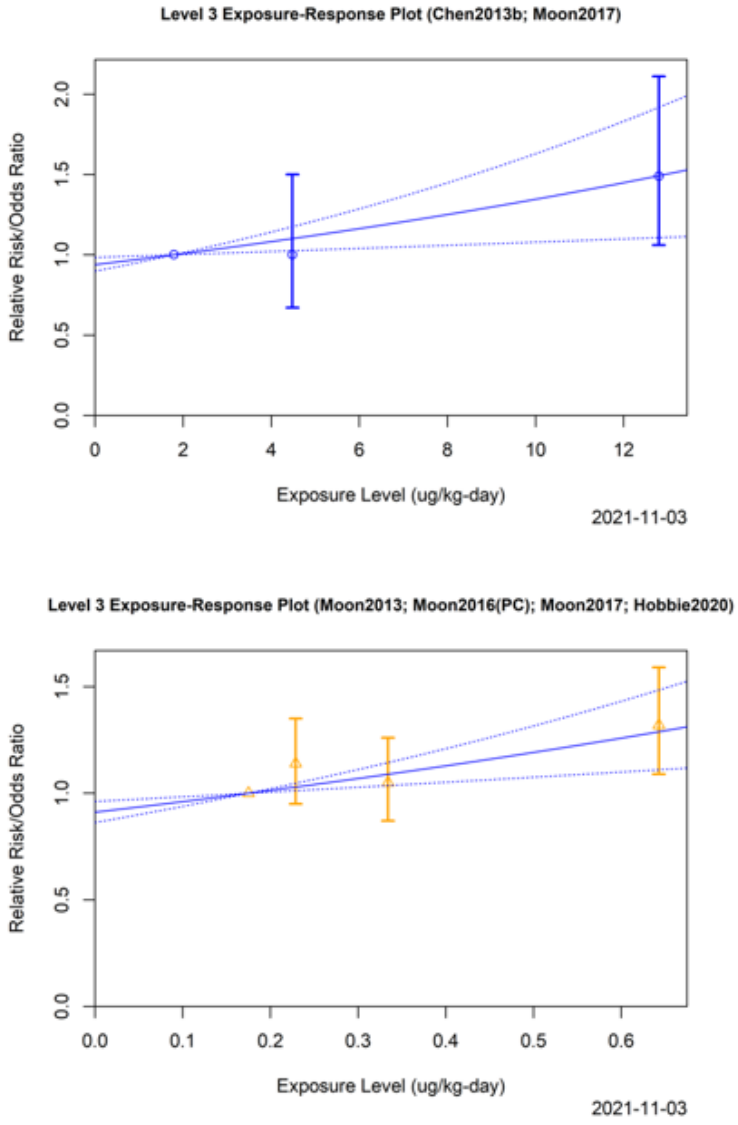


Figure C-27. Non-hierarchical meta-regression dose response curves for individual CVD incidence studies.

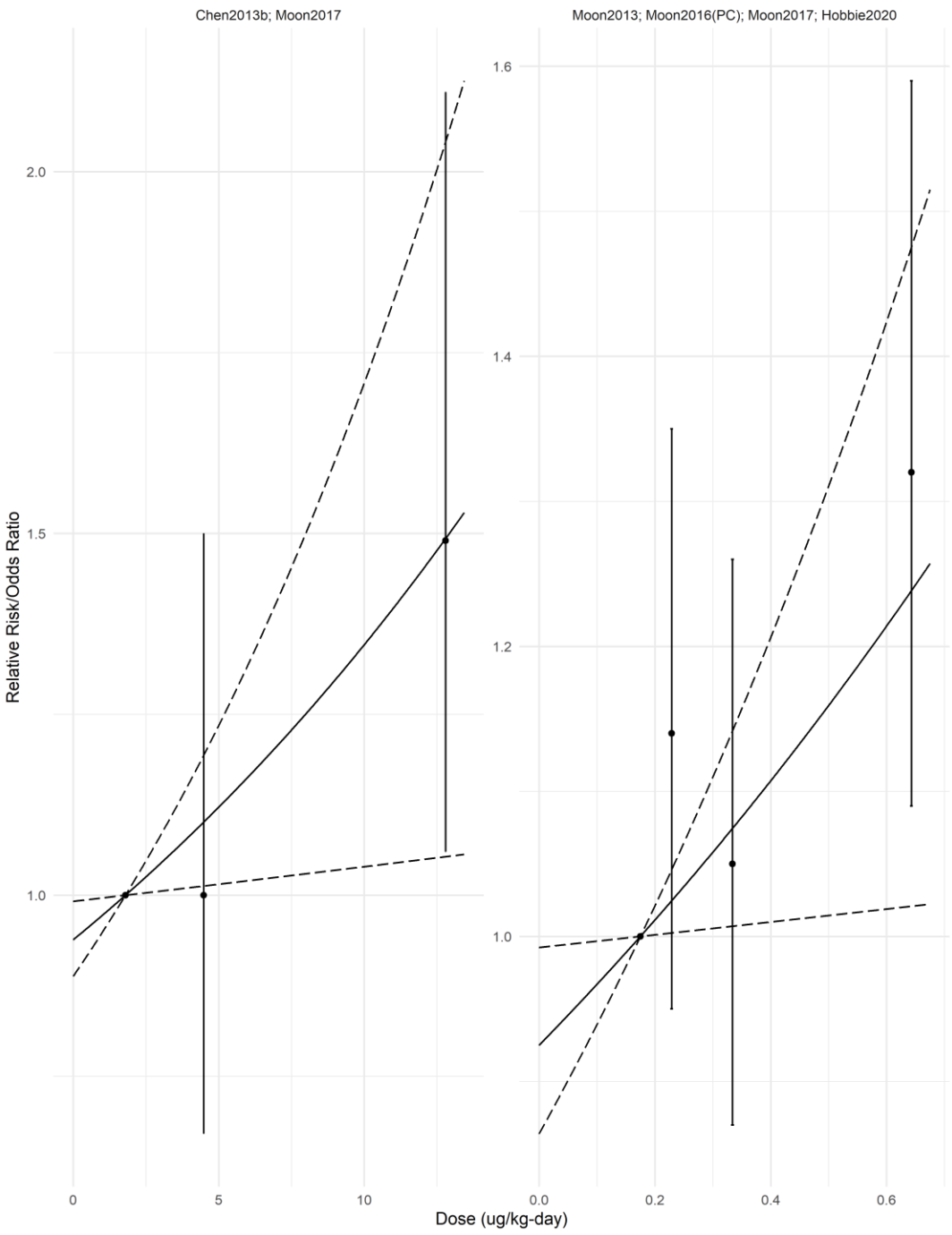


Figure C-28. Hierarchical (all studies) meta-regression dose response curves for individual CVD incidence studies.

CVD Incidence – Low Exposure Studies

Table C-48. Summary of CVD incidence (Moon et al., 2013) (low exp study) Bayesian analysis output; MLE dose estimates

	Mean	Se_mean	Sd	2.50%	25%	50%	75%	97.50%	N_eff	Rhat
Moon et al. (2013)	0.54	0	0.19	0.16	0.41	0.54	0.66	0.9	5732	1
Moon et al. (2013) mu_ref	270.44	0.13	9.93	251.65	263.7	270.02	276.88	290.68	6073	1
OR_RR[1]	1	0	0	1	1	1	1	1	370	1
OR_RR[2]	1.03	0	0.01	1.01	1.02	1.03	1.04	1.05	5729	1
OR_RR[3]	1.09	0	0.03	1.03	1.07	1.09	1.11	1.15	5726	1
OR_RR[4]	1.28	0	0.11	1.08	1.21	1.28	1.35	1.51	5718	1

Samples were drawn using NUTS (diag_e) at Wed Nov 03 09:25:47 2021.
For each parameter, n_eff is a crude measure of effective sample size, and Rhat is the potential scale reduction factor on split chains (at convergence, Rhat = 1).

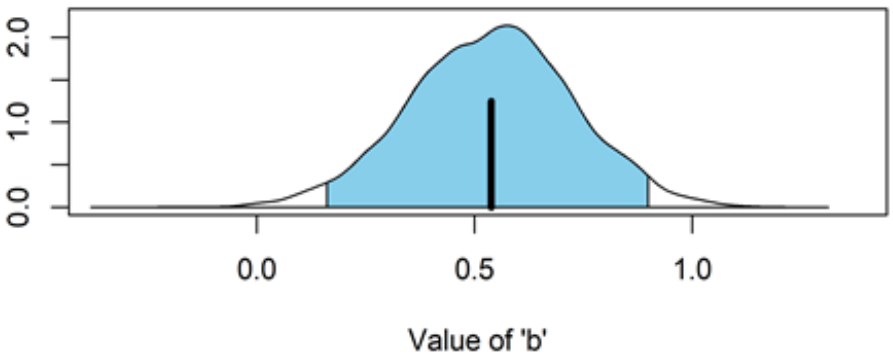


Figure C-29. Posterior distributions for CVD incidence pooled (bmean) and data-set-specific (b) logistic slope parameters, using MLE dose estimates and low dose studies. 95% Credible intervals are highlighted.

CVD Incidence – High Exposure Studies

Table C-49. Summary of CVD incidence (high exp studies) Bayesian analysis output; MLE dose estimate

	Mean	Se_mean	Sd	2.50%	25%	50%	75%	97.50%	N_eff	Rhat
Chen et al. (2013)b	0.04	0	0.02	0	0.03	0.04	0.05	0.07	6293	1

	Mean	Se_mean	Sd	2.50%	25%	50%	75%	97.50%	N_eff	Rhat
Chen et al. (2013) mu_ref	113.08	0.1	7.67	98.71	107.75	112.83	118.21	128.72	6461	1
OR_RR[1]	1	0	0	1	1	1	1	1	7565	1
OR_RR[2]	1.1	0	0.05	1.01	1.07	1.1	1.13	1.19	6292	1
OR_RR[3]	1.49	0	0.25	1.04	1.32	1.48	1.65	2.01	6302	1

Samples were drawn using NUTS (diag_e) at Wed Nov 03 09:25:47 2021.
For each parameter, n_eff is a crude measure of effective sample size, and Rhat is the potential scale reduction factor on split chains (at convergence, Rhat = 1).

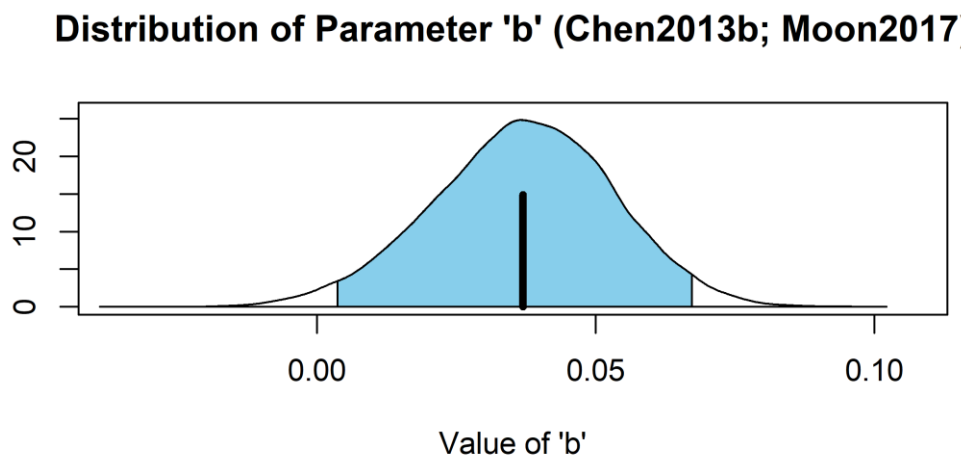


Figure C-30. Posterior distributions for CVD incidence pooled (bmean) and data-set-specific (b) logistic slope parameters, using MLE dose estimates and high dose studies. 95% Credible intervals are highlighted.

IHD Incidence – All Studies

Table C-50. Summary of IHD incidence (all studies) Bayesian analysis output; MLE dose estimates

Parameter	Mean	Se_mean	Sd	2.50%	25%	50%	75%	97.50%	N_Eff	Rhat
bmean	0.3442	0.0045	0.2975	0.0023	0.1166	0.286	0.4923	1.1074	4384	1.0004
b_sigma	0.7295	0.009	0.5859	0.1204	0.3598	0.5807	0.9208	2.2502	4264	1
b0[1]	−0.6017	0.0089	0.5908	−2.001	−0.9494	−0.4657	−0.1121	0.0786	4387	1.0002
b0[2]	0.9699	0.0098	0.7889	−0.622	0.4671	0.9582	1.4871	2.5192	6450	0.9998
b0[3]	0.2497	0.0085	0.5992	−0.9362	−0.0933	0.2389	0.5898	1.5401	4977	1.0002
b0[4]	0.2305	0.0084	0.596	−0.9519	−0.1146	0.2136	0.562	1.5114	5063	1.0005
mu_ref[2]	60.6558	0.0732	5.8966	49.8018	56.5655	60.466	64.4911	72.869	6493	0.9997
mu_ref[3]	200.0929	0.1017	8.3292	184.0542	194.5124	199.9171	205.5117	217.2227	6705	1
vlambda[1]	1.5263	0.0117	0.8929	0.3144	0.8737	1.3511	2.0028	3.7233	5817	1.0003
vlambda[2]	1.3949	0.0107	0.8092	0.2895	0.7987	1.2426	1.8281	3.418	5692	1.0005
vlambda[3]	0.1257	0.0012	0.0942	0.02	0.061	0.1021	0.164	0.3678	5832	1.0001
b[1]	0.0401	0.0002	0.0179	0.0043	0.0282	0.0403	0.0526	0.0745	7265	1
b[2]	1.0088	0.0088	0.5834	0.0453	0.5622	0.9669	1.4046	2.2395	4363	0.9999
b[3]	0.4644	0.0029	0.2141	0.0462	0.3177	0.4652	0.6085	0.8787	5596	0.9999
b[4]	0.4568	0.003	0.2267	0.0455	0.2992	0.4439	0.6032	0.9313	5730	0.9997
p[1]	0.0218	0	0.002	0.0181	0.0205	0.0218	0.0232	0.026	6831	0.9999
p[2]	0.0242	0	0.0019	0.0207	0.0229	0.0242	0.0254	0.028	6944	0.9998
p[3]	0.0338	0.0001	0.0054	0.0243	0.03	0.0335	0.0372	0.0452	7307	0.9999
p[4]	0.0126	0	0.0012	0.0104	0.0118	0.0126	0.0134	0.0152	6493	0.9997
p[5]	0.0162	0	0.0022	0.0124	0.0146	0.0161	0.0176	0.0212	5503	1
p[6]	0.0195	0.0001	0.0044	0.0129	0.0162	0.0189	0.0221	0.0299	5059	0.9999
p[7]	0.0243	0.0001	0.0083	0.0132	0.0181	0.0226	0.0287	0.0451	5080	0.9999
p[8]	0.0165	0	0.0007	0.0152	0.016	0.0165	0.0169	0.0179	6705	1
p[9]	0.0169	0	0.0006	0.0157	0.0165	0.0169	0.0173	0.0181	7222	0.9999
p[10]	0.0177	0	0.0006	0.0164	0.0173	0.0177	0.0182	0.019	7417	0.9997
p[11]	0.0204	0	0.0017	0.0173	0.0193	0.0204	0.0216	0.0239	6594	0.9998
pr[1]	0.0218	0	0.002	0.0181	0.0205	0.0218	0.0232	0.026	6831	0.9999
pr[2]	0.0218	0	0.002	0.0181	0.0205	0.0218	0.0232	0.026	6831	0.9999
pr[3]	0.0218	0	0.002	0.0181	0.0205	0.0218	0.0232	0.026	6831	0.9999
pr[4]	0.0126	0	0.0012	0.0104	0.0118	0.0126	0.0134	0.0152	6493	0.9997
pr[5]	0.0126	0	0.0012	0.0104	0.0118	0.0126	0.0134	0.0152	6493	0.9997
pr[6]	0.0126	0	0.0012	0.0104	0.0118	0.0126	0.0134	0.0152	6493	0.9997

Parameter	Mean	Se_mean	Sd	2.50%	25%	50%	75%	97.50%	N_Eff	Rhat
pr[7]	0.0126	0	0.0012	0.0104	0.0118	0.0126	0.0134	0.0152	6493	0.9997
pr[8]	0.0165	0	0.0007	0.0152	0.016	0.0165	0.0169	0.0179	6705	1
pr[9]	0.0165	0	0.0007	0.0152	0.016	0.0165	0.0169	0.0179	6705	1
pr[10]	0.0165	0	0.0007	0.0152	0.016	0.0165	0.0169	0.0179	6705	1
pr[11]	0.0165	0	0.0007	0.0152	0.016	0.0165	0.0169	0.0179	6705	1
OR_RR[1]	1	0	0	1	1	1	1	1	7028	0.9995
OR_RR[2]	1.1124	0.0006	0.0524	1.0112	1.0769	1.1118	1.1482	1.2163	7252	1
OR_RR[3]	1.5639	0.0035	0.2987	1.0468	1.353	1.5398	1.7541	2.2133	7204	1
OR_RR[4]	1	0	0	1	1	1	1	1	7655	0.9995
OR_RR[5]	1.2942	0.0028	0.1905	1.0112	1.148	1.2679	1.4115	1.7307	4586	0.9999
OR_RR[6]	1.5621	0.0057	0.3948	1.0189	1.2617	1.4911	1.7856	2.5121	4754	0.9999
OR_RR[7]	1.9554	0.0105	0.7382	1.0278	1.4045	1.792	2.3294	3.8196	4954	0.9999
OR_RR[8]	1	0	0	1	1	1	1	1	7760	0.9995
OR_RR[9]	1.0249	0.0002	0.0116	1.0024	1.0169	1.0249	1.0327	1.0476	5605	0.9999
OR_RR[10]	1.0759	0.0005	0.036	1.0072	1.0509	1.0754	1.0998	1.1472	5624	0.9999
OR_RR[11]	1.2436	0.0016	0.1224	1.0215	1.1571	1.2381	1.3224	1.4962	5679	0.9999
OR_RR[12]	1	NaN	0	1	1	1	1	1	NaN	NaN
OR_RR[13]	1.2704	0.002	0.1499	1.0234	1.1646	1.2536	1.3595	1.6068	5756	0.9996
OR_RR[14]	3.0862	0.0235	1.7987	1.1044	1.922	2.6363	3.7326	7.6419	5843	0.9996
astar	−4.1715	0.0009	0.07	−4.3088	−4.2168	−4.1718	−4.1245	−4.0337	5790	1
lp__	1547.242	0.0613	3.2853	1539.707	1545.406	1547.62	1549.573	1552.485	2869	1.0003

Samples were drawn using NUTS (diag_e) at Aug 10 20:55:07 2022.
For each parameter, n_eff is a crude measure of effective sample size, and Rhat is the potential scale reduction factor on split chains (at convergence, Rhat = 1). There were 3 divergent transitions after warmup.

Study Key:

1. Chen et al. (2013)
2. James et al. (2015)
3. Moon et al. (2013)
4. Wade et al. (2015)

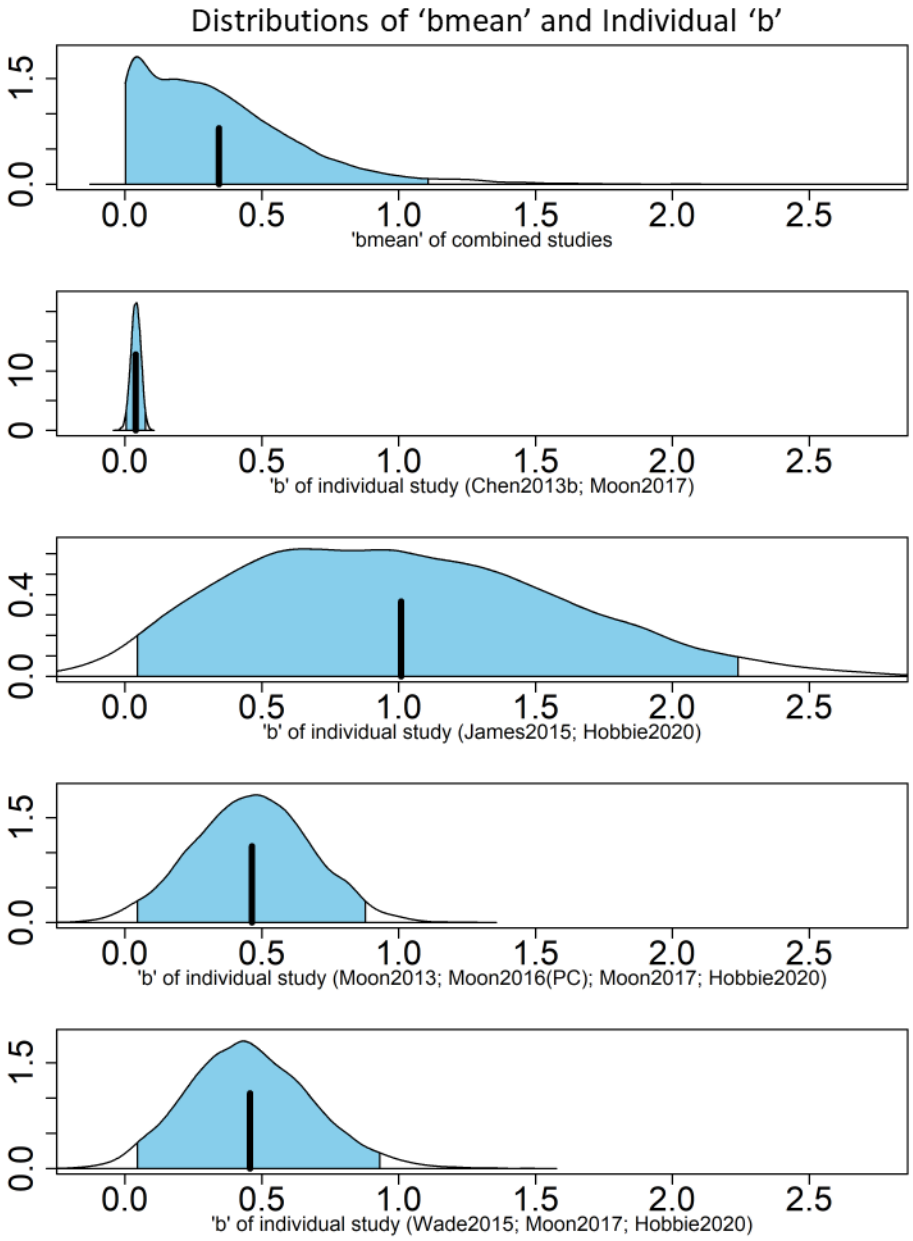


Figure C-31. Posterior distributions for IHD incidence pooled (bmean) and data-set-specific (b) logistic slope parameters; using MLE dose estimates and all studies. 95% Credible intervals are highlighted.

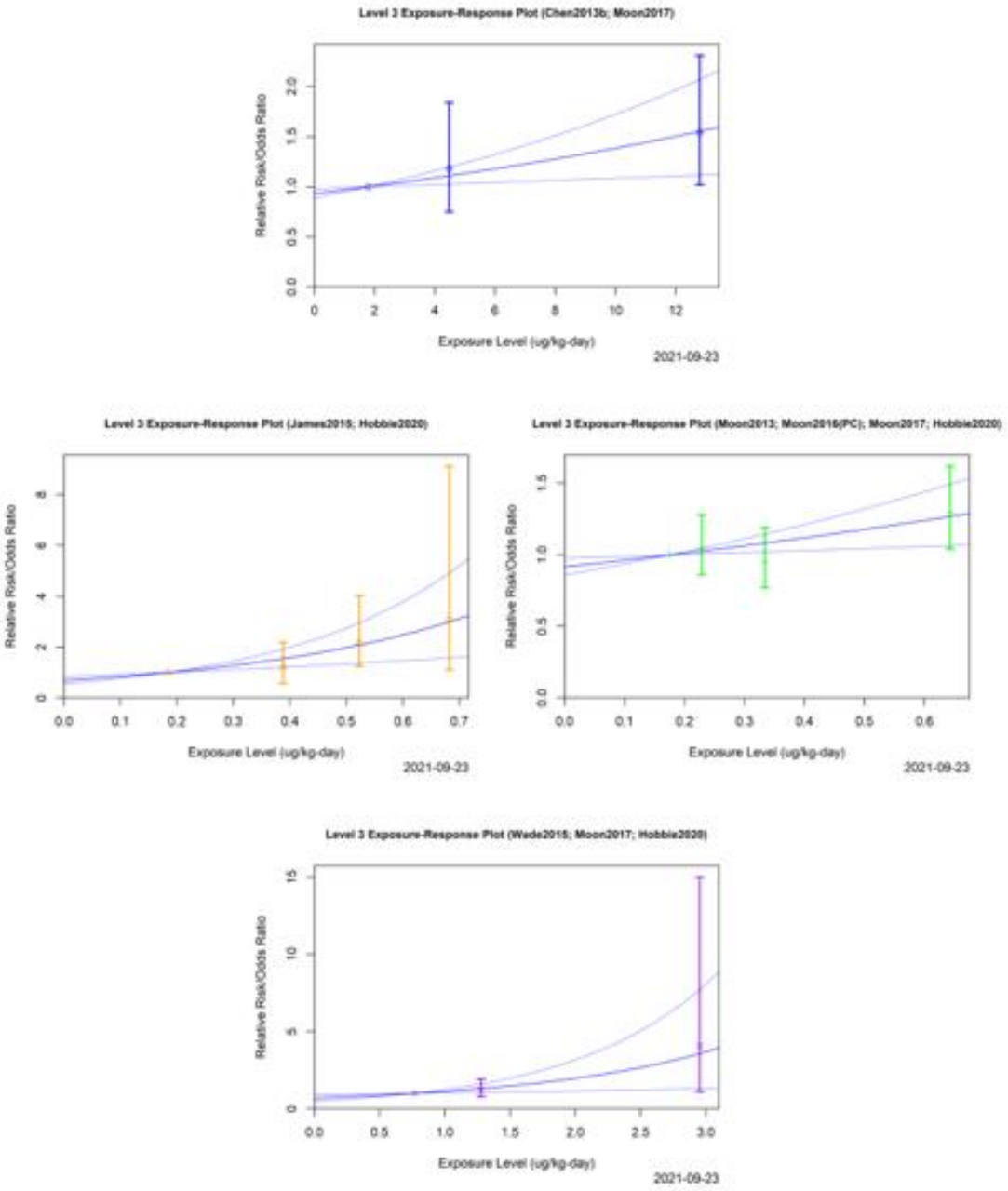


Figure C-32. Non-hierarchical meta-regression dose response curves for individual IHD incidence studies.

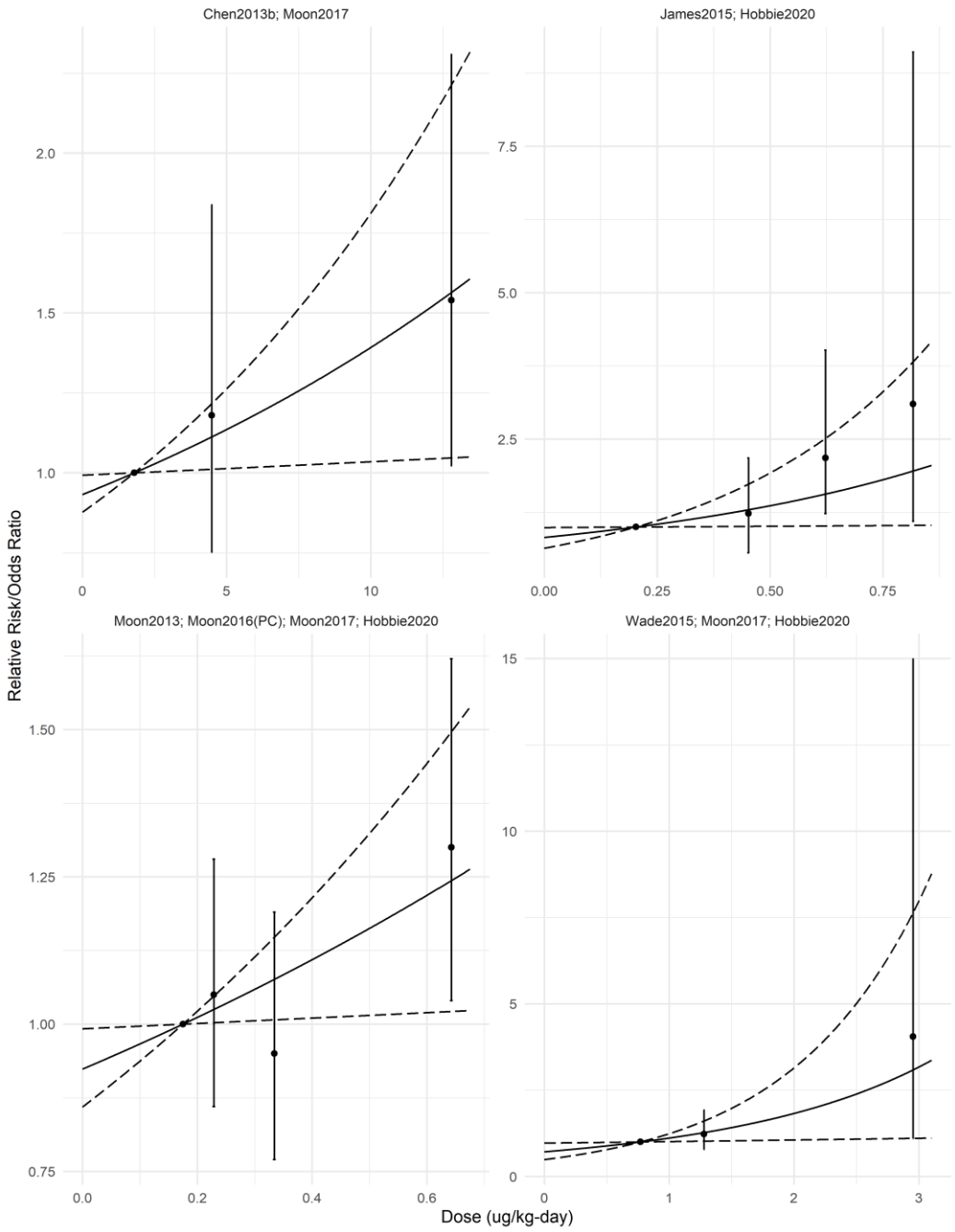


Figure C-33. Hierarchical (all studies) meta-regression dose response curves for individual IHD incidence studies.

IHD Incidence – Low Exposure Studies

Table C-51. Summary of IHD incidence (low exp studies) Bayesian analysis output; MLE dose estimates

Parameter	Mean	Se_mean	Sd	2.50%	25%	50%	75%	97.50%	N_eff	Rhat
bmean	0.5221	0.0072	0.5258	0.0013	0.1044	0.3733	0.781	1.8577	5407	1.0007
b_sigma	2.0074	0.0334	2.1922	0.1113	0.7729	1.4137	2.4954	7.3252	4314	1.0002
James et al. (2015) b[1]	0.7476	0.01	0.6724	-0.526	0.3308	0.6915	1.1378	2.2246	4565	1.0013
Moon et al. (2013) b[2]	-0.0519	0.0077	0.5285	-1.386	-0.2555	0.0481	0.2204	0.8562	4665	1.0011
mu_ref[1]	59.1682	0.0784	6.0246	48.2644	54.9583	58.9	63.1225	71.5849	5906	1.0009
mu_ref[2]	199.2287	0.104	8.3612	183.217	193.4565	199.1934	204.7349	215.8966	6466	1.0002
b[1]	1.6456	0.0122	0.7502	0.2745	1.0857	1.6422	2.1823	3.0947	3785	1.0012
b[2]	0.5092	0.0027	0.2187	0.0758	0.3585	0.5123	0.6566	0.9405	6712	1.0001
p[1]	0.0123	0	0.0013	0.01	0.0114	0.0123	0.0131	0.0149	5906	1.0009
p[2]	0.0172	0	0.0024	0.013	0.0155	0.0171	0.0188	0.0222	5218	1.0002
p[3]	0.0217	0.0001	0.0049	0.0139	0.0181	0.0212	0.0248	0.0321	4746	1.0004
p[4]	0.0289	0.0001	0.0097	0.0147	0.0215	0.0274	0.0345	0.0509	4832	1.0004
p[5]	0.0164	0	0.0007	0.0151	0.0159	0.0164	0.0169	0.0178	6466	1.0002
p[6]	0.0168	0	0.0006	0.0157	0.0164	0.0168	0.0173	0.0181	6403	1.0002
p[7]	0.0178	0	0.0006	0.0165	0.0173	0.0178	0.0182	0.019	6751	1.0002
p[8]	0.0208	0	0.0017	0.0175	0.0196	0.0207	0.0219	0.0244	7024	1.0001
pr[1]	0.0123	0	0.0013	0.01	0.0114	0.0123	0.0131	0.0149	5906	1.0009
pr[2]	0.0123	0	0.0013	0.01	0.0114	0.0123	0.0131	0.0149	5906	1.0009
pr[3]	0.0123	0	0.0013	0.01	0.0114	0.0123	0.0131	0.0149	5906	1.0009
pr[4]	0.0123	0	0.0013	0.01	0.0114	0.0123	0.0131	0.0149	5906	1.0009
pr[5]	0.0164	0	0.0007	0.0151	0.0159	0.0164	0.0169	0.0178	6466	1.0002
pr[6]	0.0164	0	0.0007	0.0151	0.0159	0.0164	0.0169	0.0178	6466	1.0002
pr[7]	0.0164	0	0.0007	0.0151	0.0159	0.0164	0.0169	0.0178	6466	1.0002
pr[8]	0.0164	0	0.0007	0.0151	0.0159	0.0164	0.0169	0.0178	6466	1.0002
OR_RR[1]	1	0	0	1	1	1	1	1	7227	0.9995
OR_RR[2]	1.4082	0.0033	0.2142	1.0568	1.2441	1.3911	1.5508	1.862	4141	1.0009
OR_RR[3]	1.7842	0.0068	0.4523	1.096	1.4362	1.7277	2.0675	2.7929	4390	1.0008
OR_RR[4]	2.3852	0.013	0.8937	1.1442	1.7016	2.2306	2.8998	4.4822	4698	1.0006
OR_RR[5]	1	0	0	1	1	1	1	1	7074	0.9995
OR_RR[6]	1.0274	0.0001	0.0119	1.004	1.0191	1.0275	1.0354	1.0511	6717	1.0001
OR_RR[7]	1.0835	0.0005	0.037	1.0119	1.0576	1.0833	1.1081	1.1584	6729	1.0001

Parameter	Mean	Se_mean	Sd	2.50%	25%	50%	75%	97.50%	N_eff	Rhat
OR_RR[8]	1.2697	0.0015	0.1273	1.0354	1.179	1.2651	1.3517	1.5397	6763	1.0001
astar	-4.1838	0.0009	0.0716	-4.3236	-4.2323	-4.1837	-4.1351	-4.0421	6534	1.0001
lp__	1842.591	0.0445	2.2824	1837.119	1841.296	1842.985	1844.299	1845.855	2633	1.002

Samples were drawn using NUTS (diag_e) at Thu Sep 23 08:14:51 2021.
For each parameter, n_eff is a crude measure of effective sample size, and Rhat is the potential scale reduction factor on split chains (at convergence, Rhat = 1).

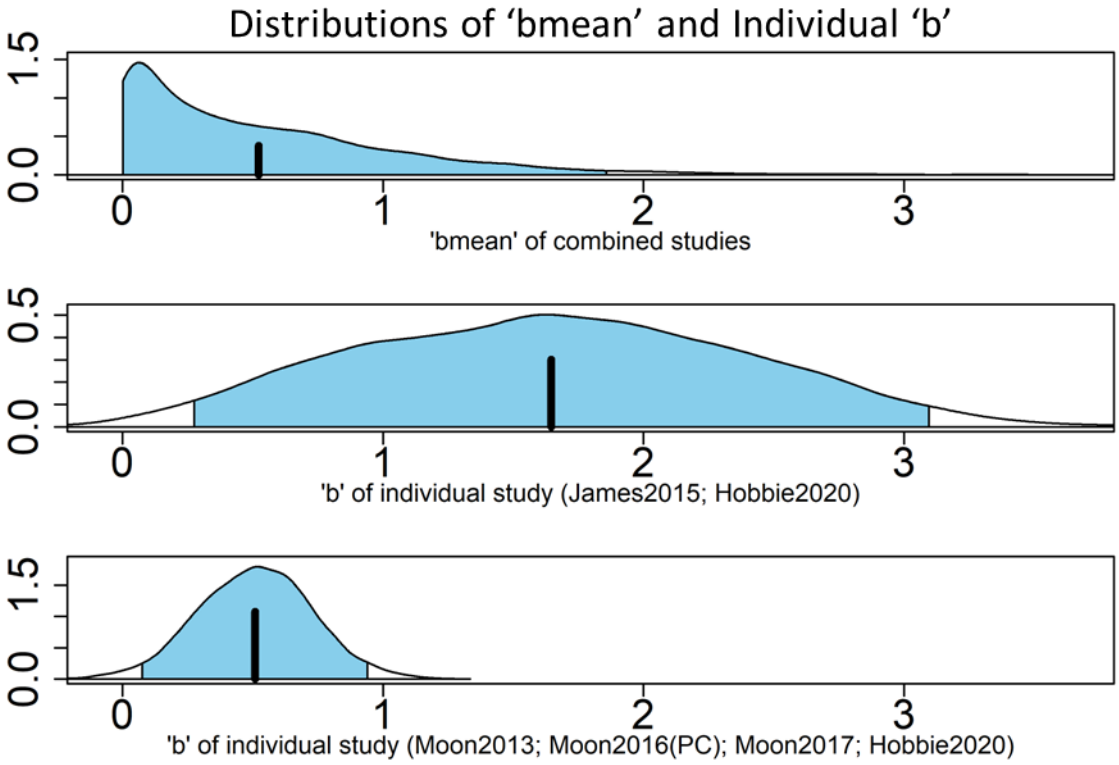


Figure C-34. Posterior distributions for IHD incidence pooled (bmean) and data-set-specific (b) logistic slope parameters, using MLE dose estimates and low dose studies. 95% Credible intervals are highlighted.

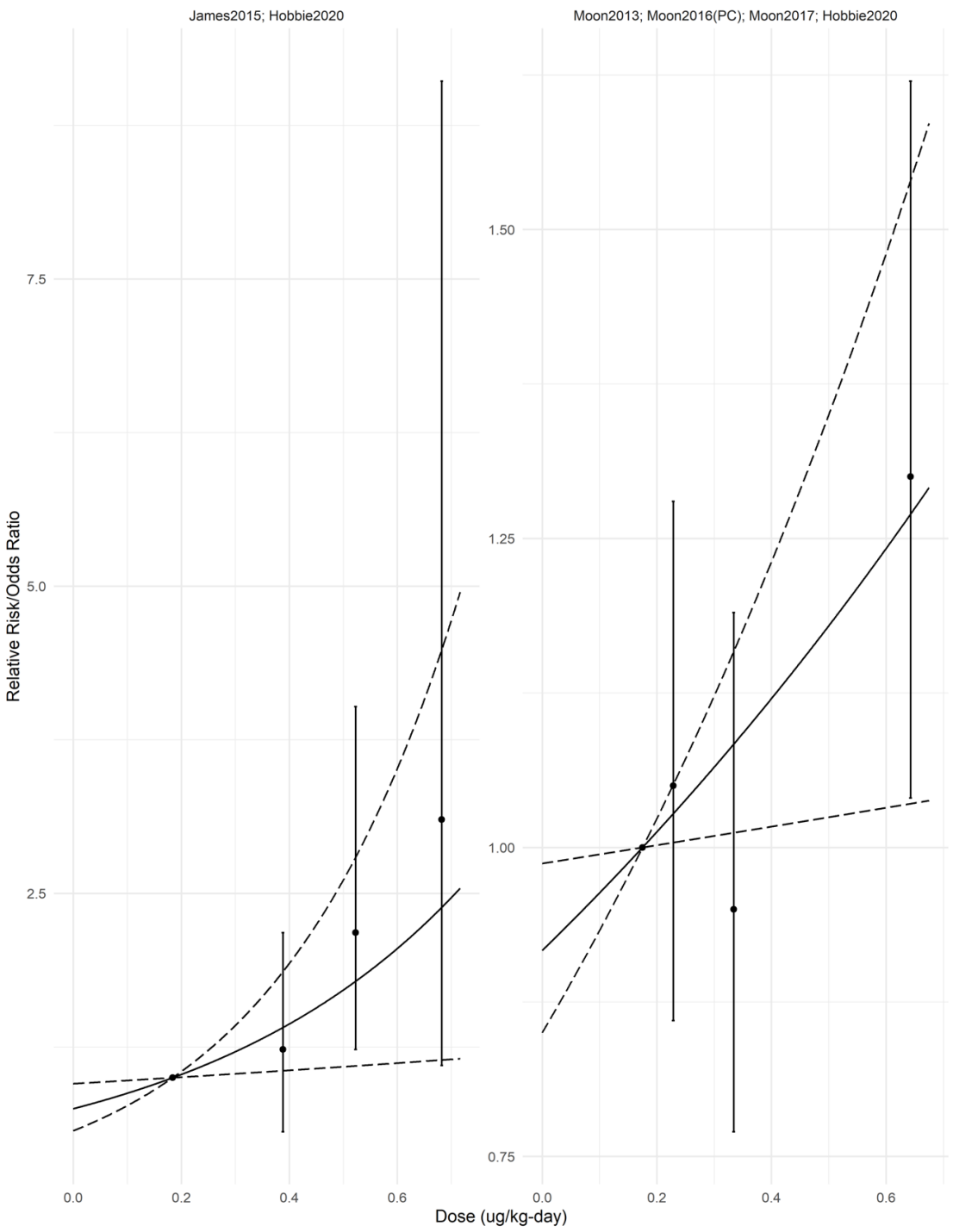


Figure C-35. Hierarchical (low dose studies) meta-regression dose response curves for individual IHD incidence studies.

IHD Incidence – High Exposure Studies

Table C-52. Summary of IHD incidence (high exp studies) Bayesian analysis output; MLE dose estimates

Parameter	Mean	Se_mean	Sd	2.50%	25%	50%	75%	97.50%	N_Eff	Rhat
bmean	0.1968	0.0045	0.2621	0.0005	0.0316	0.1016	0.2614	0.9211	3377	1.0009
b_sigma	0.7134	0.0192	1.0091	0.0137	0.1705	0.3889	0.8269	3.4958	2753	1.0018
Chen et al. (2013) b[1]	-0.3186	0.0096	0.5686	-1.754	-0.5781	-0.163	0.0118	0.6	3538	1.001
Wade et al. (2015) b[2]	0.4306	0.0104	0.7066	-0.9499	0.0135	0.3564	0.8365	1.9444	4620	1.0001
mu_ref[1]	61.8575	0.0712	5.6441	51.605	57.919	61.5908	65.5134	73.7086	6285	1.0002
vlambda[1]	1.4715	0.0127	0.8577	0.3024	0.8583	1.3007	1.9235	3.5731	4574	1.0004
vlambda[2]	1.3971	0.012	0.8038	0.2888	0.8172	1.2402	1.8131	3.3452	4483	1.0003
vlambda[3]	0.1471	0.0017	0.1071	0.0223	0.0706	0.1195	0.1947	0.4296	4060	1.0005
b[1]	0.0393	0.0002	0.0177	0.0039	0.0275	0.0393	0.0514	0.0741	7115	0.9998
b[2]	0.3555	0.004	0.2485	-0.011	0.1553	0.3351	0.5209	0.8847	3904	1.001
p[1]	0.0219	0	0.002	0.0183	0.0205	0.0218	0.0232	0.0261	6285	1.0002
p[2]	0.0243	0	0.0019	0.0208	0.023	0.0242	0.0255	0.0281	6673	1
p[3]	0.0336	0.0001	0.0054	0.024	0.0299	0.0333	0.0371	0.0451	7704	0.9997
pr[1]	0.0219	0	0.002	0.0183	0.0205	0.0218	0.0232	0.0261	6285	1.0002
pr[2]	0.0219	0	0.002	0.0183	0.0205	0.0218	0.0232	0.0261	6285	1.0002
pr[3]	0.0219	0	0.002	0.0183	0.0205	0.0218	0.0232	0.0261	6285	1.0002
OR_RR[1]	1	0	0	1	1	1	1	1	7331	0.9995
OR_RR[2]	1.1099	0.0006	0.0518	1.0104	1.0749	1.1087	1.1447	1.2149	7130	0.9998
OR_RR[3]	1.5496	0.0035	0.2945	1.0433	1.3427	1.523	1.7332	2.2029	7177	0.9999
OR_RR[4]	1	NaN	0	1	1	1	1	1	NaN	NaN
OR_RR[5]	1.2083	0.0025	0.1582	0.9944	1.0823	1.1861	1.3037	1.569	4126	1.001
OR_RR[6]	2.5497	0.0235	1.6732	0.9762	1.4038	2.0788	3.1187	6.9016	5058	1.0006
astar	-3.8732	0.0014	0.1131	-4.0911	-3.9506	-3.8731	-3.7965	-3.6466	6416	1.0002
lp__	-296.957	0.0608	2.8724	-303.531	-298.696	-296.545	-294.844	-292.577	2235	1.0024

Samples were drawn using NUTS(diag_e) at Thu Oct 14 16:01:17 2021.
For each parameter, n_eff is a crude measure of effective sample size, and Rhat is the potential scale reduction factor on split chains (at convergence, Rhat = 1).

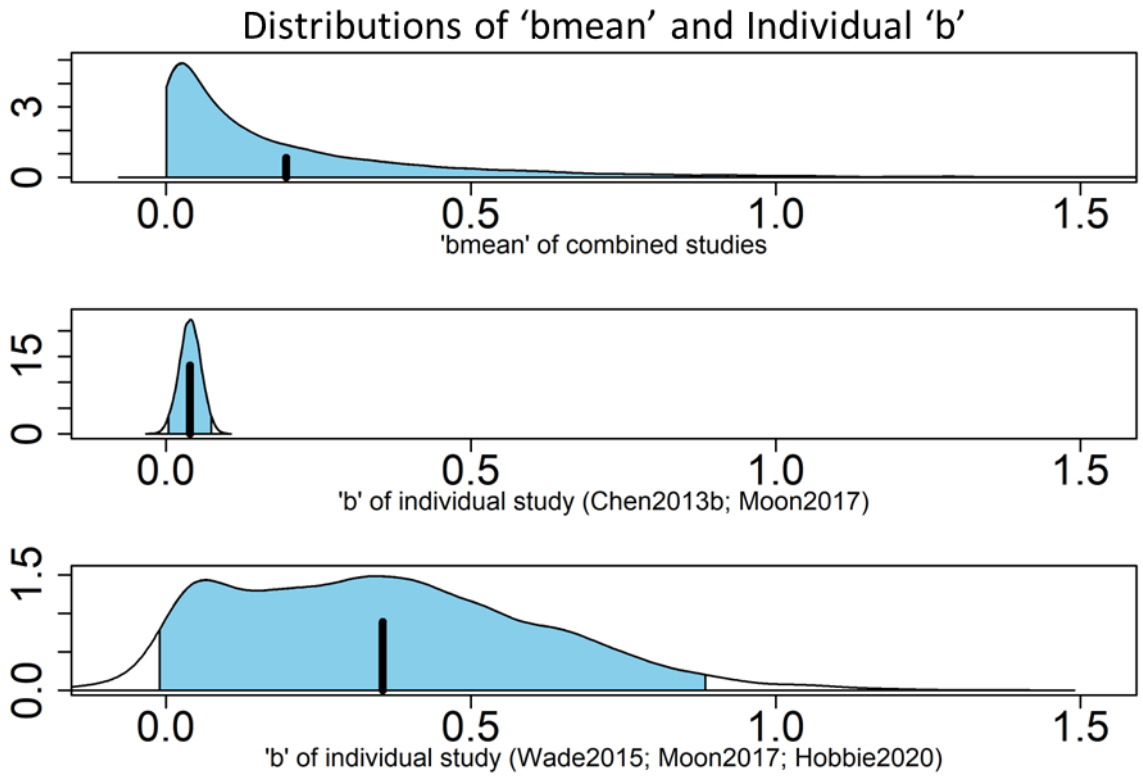


Figure C-36. Posterior distributions for IHD incidence pooled (bmean) and data-set-specific (b) logistic slope parameters, using MLE dose estimates and high dose studies. 95% Credible intervals are highlighted.

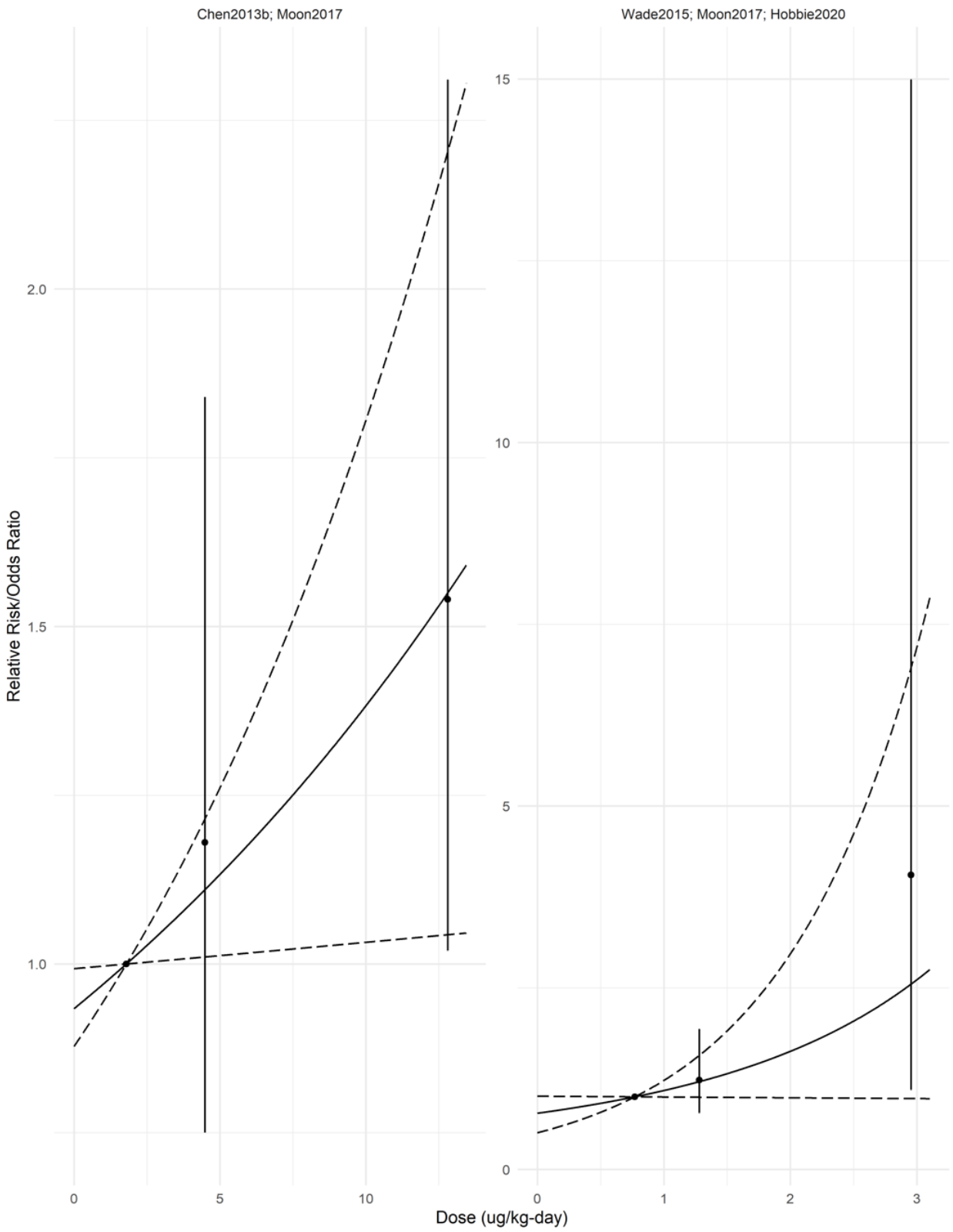


Figure C-37. Hierarchical (high dose studies) meta-regression dose response curves for individual IHD incidence studies.

Fatal CVD – All Studies

Table C-53. Summary of fatal CVD (all studies) Bayesian analysis output; MLE dose estimates

Parameter	Mean	Se_mean	Sd	2.50%	25%	50%	75%	97.50%	N_eff	Rhat
bmean	0.2408	0.0062	0.2457	0.001	0.0421	0.1725	0.3655	0.859	1582	1.0016
b_sigma	0.6417	0.0152	0.4693	0.0084	0.3568	0.5815	0.8399	1.7668	956	1.0011
b0[1]	−0.3225	0.0121	0.4886	−1.3434	−0.605	−0.2616	−0.0269	0.7466	1637	1.0019
b0[2]	0.9884	0.0159	0.7897	−0.7403	0.5242	1.0117	1.4929	2.5022	2471	1.0013
b0[3]	−0.3846	0.0089	0.4978	−1.4663	−0.6707	−0.3185	−0.0727	0.6091	3105	1.0015
b0[4]	0.8577	0.0139	0.7291	−0.6785	0.4409	0.8368	1.2854	2.3219	2746	1.0014
b0[5]	−0.4171	0.0076	0.4542	−1.4766	−0.6794	−0.3308	−0.0811	0.1948	3577	1.0009
mu_ref[1]	47.0443	0.0514	4.301	39.274	44.0196	46.8626	49.8728	56.0428	7012	1.0007
mu_ref[2]	2766.665	0.4411	37.2461	2694.166	2741.608	2765.928	2790.778	2842.539	7129	1.0001
mu_ref[3]	94.979	0.0809	6.8013	82.0456	90.3236	94.7424	99.4282	109.0339	7063	0.9999
mu_ref[4]	91.8088	0.1733	6.5987	79.629	87.212	91.4407	96.0481	105.5046	1449	1.0015
mu_ref[5]	151.9457	0.0767	6.4119	139.6558	147.5322	151.8905	156.2135	164.5978	6989	0.9999
b[1]	0.0335	0.0002	0.0141	0.0059	0.0239	0.0337	0.043	0.0606	6826	1.001
b[2]	0.874	0.0182	0.5271	0.0048	0.4931	0.9045	1.2581	1.846	836	1.0016
b[3]	0.0158	0.0006	0.0533	−0.1021	−0.0145	0.0194	0.0515	0.1095	7046	1.0001
b[4]	0.7484	0.0149	0.4016	0.0091	0.4921	0.7957	1.0383	1.4414	725	1.0041
b[5]	0.0158	0.0001	0.0049	0.0061	0.0126	0.0159	0.0191	0.0256	6854	0.9999
p[1]	0.0025	0	0.0002	0.0021	0.0023	0.0025	0.0027	0.003	7012	1.0007
p[2]	0.0027	0	0.0002	0.0023	0.0025	0.0027	0.0028	0.0031	7133	1.0005
p[3]	0.003	0	0.0002	0.0026	0.0028	0.003	0.0031	0.0034	7227	1.0001
p[4]	0.0039	0	0.0006	0.0029	0.0035	0.0039	0.0043	0.005	7035	1.0007
p[5]	0.0036	0	0	0.0035	0.0036	0.0036	0.0036	0.0037	7162	0.9998
p[6]	0.0038	0	0.0001	0.0036	0.0037	0.0038	0.0039	0.0041	946	1.001
p[7]	0.0046	0	0.0006	0.0036	0.0041	0.0046	0.005	0.0059	935	1.0011
p[8]	0.0065	0	0.0005	0.0056	0.0062	0.0065	0.0068	0.0074	7063	0.9999
p[9]	0.0065	0	0.0005	0.0057	0.0062	0.0065	0.0068	0.0075	7080	1.0001
p[10]	0.0066	0	0.0005	0.0055	0.0062	0.0066	0.007	0.0077	7129	1.0004
p[11]	0.0072	0	0.0017	0.004	0.006	0.0071	0.0082	0.0108	7342	1.0002
p[12]	0.0093	0.0001	0.0055	0.002	0.0055	0.0082	0.0119	0.0233	7516	1
p[13]	0.0067	0	0.0005	0.0058	0.0064	0.0067	0.0071	0.0077	1449	1.0015
p[14]	0.007	0	0.0004	0.0062	0.0067	0.007	0.0073	0.0079	2623	1.0005
p[15]	0.0076	0	0.0004	0.0068	0.0073	0.0076	0.0079	0.0084	5033	1.0004

Parameter	Mean	Se_mean	Sd	2.50%	25%	50%	75%	97.50%	N_eff	Rhat
p[16]	0.0096	0	0.0014	0.0071	0.0087	0.0097	0.0106	0.0123	913	1.0035
p[17]	0.0013	0	0.0001	0.0012	0.0013	0.0013	0.0014	0.0014	6989	0.9999
p[18]	0.0014	0	0.0001	0.0013	0.0013	0.0014	0.0014	0.0015	6969	0.9999
p[19]	0.0014	0	0	0.0014	0.0014	0.0014	0.0015	0.0015	6880	1
p[20]	0.0016	0	0.0001	0.0015	0.0015	0.0016	0.0016	0.0017	7057	1
p[21]	0.0018	0	0.0001	0.0016	0.0017	0.0018	0.0019	0.0021	6744	0.9999
pr[1]	0.0025	0	0.0002	0.0021	0.0023	0.0025	0.0027	0.003	7012	1.0007
pr[2]	0.0025	0	0.0002	0.0021	0.0023	0.0025	0.0027	0.003	7012	1.0007
pr[3]	0.0025	0	0.0002	0.0021	0.0023	0.0025	0.0027	0.003	7012	1.0007
pr[4]	0.0025	0	0.0002	0.0021	0.0023	0.0025	0.0027	0.003	7012	1.0007
pr[5]	0.0036	0	0	0.0035	0.0036	0.0036	0.0036	0.0037	7129	1.0001
pr[6]	0.0036	0	0	0.0035	0.0036	0.0036	0.0036	0.0037	7129	1.0001
pr[7]	0.0036	0	0	0.0035	0.0036	0.0036	0.0036	0.0037	7129	1.0001
pr[8]	0.0065	0	0.0005	0.0056	0.0062	0.0065	0.0068	0.0074	7063	0.9999
pr[9]	0.0065	0	0.0005	0.0056	0.0062	0.0065	0.0068	0.0074	7063	0.9999
pr[10]	0.0065	0	0.0005	0.0056	0.0062	0.0065	0.0068	0.0074	7063	0.9999
pr[11]	0.0065	0	0.0005	0.0056	0.0062	0.0065	0.0068	0.0074	7063	0.9999
pr[12]	0.0065	0	0.0005	0.0056	0.0062	0.0065	0.0068	0.0074	7063	0.9999
pr[13]	0.0067	0	0.0005	0.0058	0.0064	0.0067	0.0071	0.0077	1449	1.0015
pr[14]	0.0067	0	0.0005	0.0058	0.0064	0.0067	0.0071	0.0077	1449	1.0015
pr[15]	0.0067	0	0.0005	0.0058	0.0064	0.0067	0.0071	0.0077	1449	1.0015
pr[16]	0.0067	0	0.0005	0.0058	0.0064	0.0067	0.0071	0.0077	1449	1.0015
pr[17]	0.0013	0	0.0001	0.0012	0.0013	0.0013	0.0014	0.0014	6989	0.9999
pr[18]	0.0013	0	0.0001	0.0012	0.0013	0.0013	0.0014	0.0014	6989	0.9999
pr[19]	0.0013	0	0.0001	0.0012	0.0013	0.0013	0.0014	0.0014	6989	0.9999
pr[20]	0.0013	0	0.0001	0.0012	0.0013	0.0013	0.0014	0.0014	6989	0.9999
pr[21]	0.0013	0	0.0001	0.0012	0.0013	0.0013	0.0014	0.0014	6989	0.9999
OR_RR[1]	1	0	0	1	1	1	1	1	7657	0.9995
OR_RR[2]	1.0758	0.0004	0.0329	1.0128	1.0532	1.0758	1.0978	1.1405	6842	1.0011
OR_RR[3]	1.1988	0.0011	0.0901	1.0318	1.1359	1.1968	1.2578	1.3815	6865	1.0011
OR_RR[4]	1.5756	0.0035	0.2915	1.0798	1.3669	1.5537	1.755	2.2084	6921	1.0012
OR_RR[5]	1.0053	0.0001	0.0032	1	1.003	1.0055	1.0077	1.0113	838	1.0016
OR_RR[6]	1.0676	0.0014	0.0416	1.0004	1.0371	1.0692	1.0975	1.1462	860	1.0015
OR_RR[7]	1.2763	0.0059	0.1804	1.0013	1.1412	1.2741	1.4005	1.639	932	1.0012
OR_RR[8]	1	0	0	1	1	1	1	1	7430	0.9995
OR_RR[9]	1.0048	0.0002	0.0157	0.9704	0.9958	1.0057	1.0153	1.0327	7066	1.0001

Parameter	Mean	Se_mean	Sd	2.50%	25%	50%	75%	97.50%	N_eff	Rhat
OR_RR[10]	1.0184	0.0007	0.0565	0.8978	0.9848	1.0208	1.0559	1.1226	7116	1.0001
OR_RR[11]	1.1102	0.0031	0.2663	0.6176	0.934	1.096	1.2747	1.674	7322	1
OR_RR[12]	1.444	0.01	0.8681	0.296	0.8418	1.26	1.8431	3.6458	7500	0.9999
OR_RR[13]	1	0	0	1	1	1	1	1	7450	0.9995
OR_RR[14]	1.041	0.0008	0.0223	1.0005	1.0266	1.0434	1.0571	1.0801	738	1.0041
OR_RR[15]	1.1277	0.0026	0.0709	1.0014	1.0807	1.1338	1.1782	1.2556	762	1.0039
OR_RR[16]	1.4394	0.009	0.2622	1.0042	1.2563	1.4465	1.619	1.9509	846	1.0035
OR_RR[17]	1	0	0	1	1	1	1	1	7440	0.9995
OR_RR[18]	1.0243	0.0001	0.0077	1.0093	1.0193	1.0243	1.0293	1.0395	6854	0.9999
OR_RR[19]	1.0807	0.0003	0.026	1.0302	1.0634	1.0806	1.0976	1.1329	6853	0.9999
OR_RR[20]	1.1839	0.0007	0.0617	1.0667	1.1424	1.1827	1.2236	1.3102	6851	0.9998
OR_RR[21]	1.3903	0.0017	0.1406	1.1332	1.2942	1.3842	1.4784	1.6878	6844	0.9998
astar	−6.6443	0.0006	0.0479	−6.7387	−6.6774	−6.6436	−6.6119	−6.5516	6950	0.9999
lp__	6131.497	0.2286	5.2034	6118.377	6129.344	6132.873	6135.131	6138.279	518	1.004

Samples were drawn using NUTS (diag_e) at Thu Aug 11 8:54:19 2022.
For each parameter, n_eff is a crude measure of effective sample size, and Rhat is the potential scale reduction factor on split chains (at convergence, Rhat = 1). There was 1 diverge transition after warmup.

Study Key:

1. Chen et al. (2011)
2. D'Ippoliti et al. (2015)
3. Wade et al. (2009)
4. Moon et al. (2013)
Sohel et al. (2009) b[5]

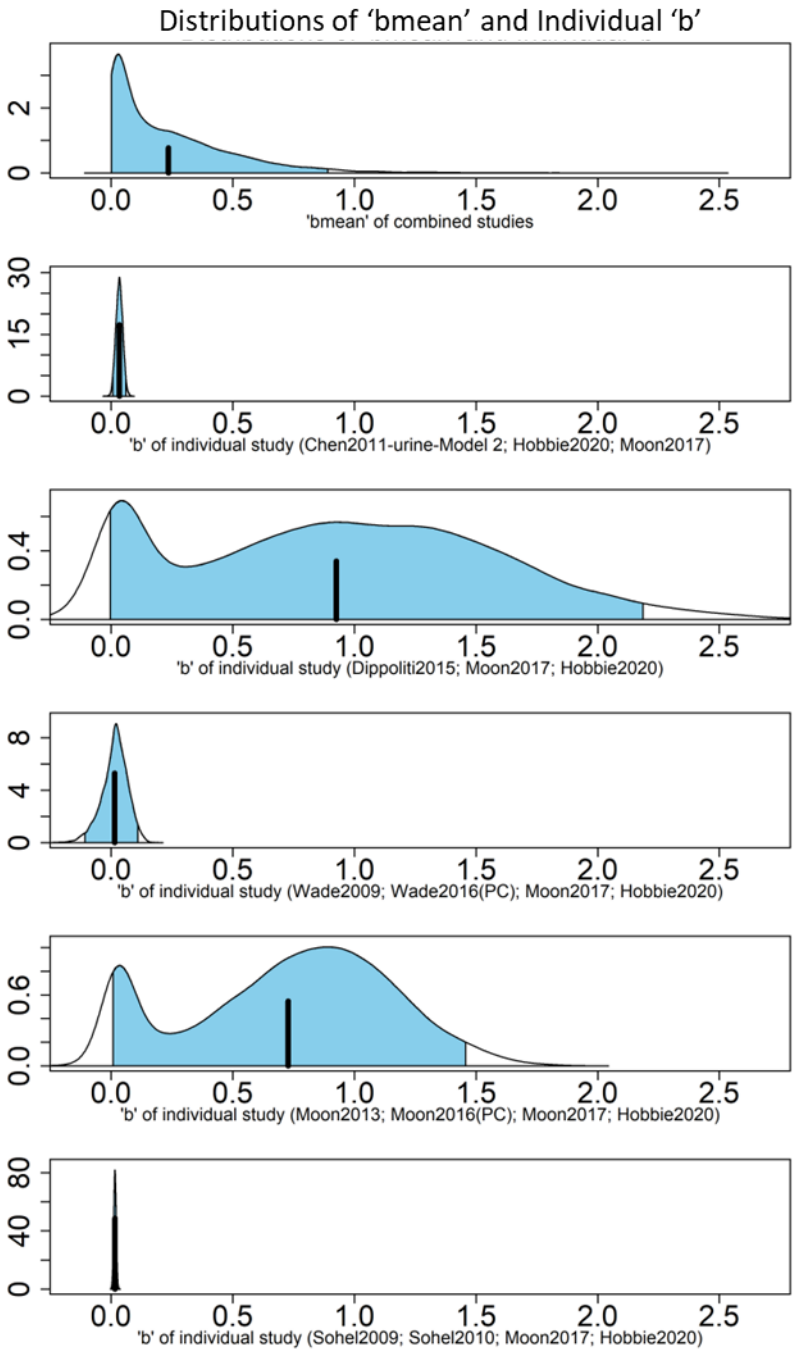


Figure C-38. Posterior distributions for fatal CVD pooled (bmean) and data-set-specific (b) logistic slope parameters, using MLE dose estimates and all studies. 95% Credible intervals are highlighted.

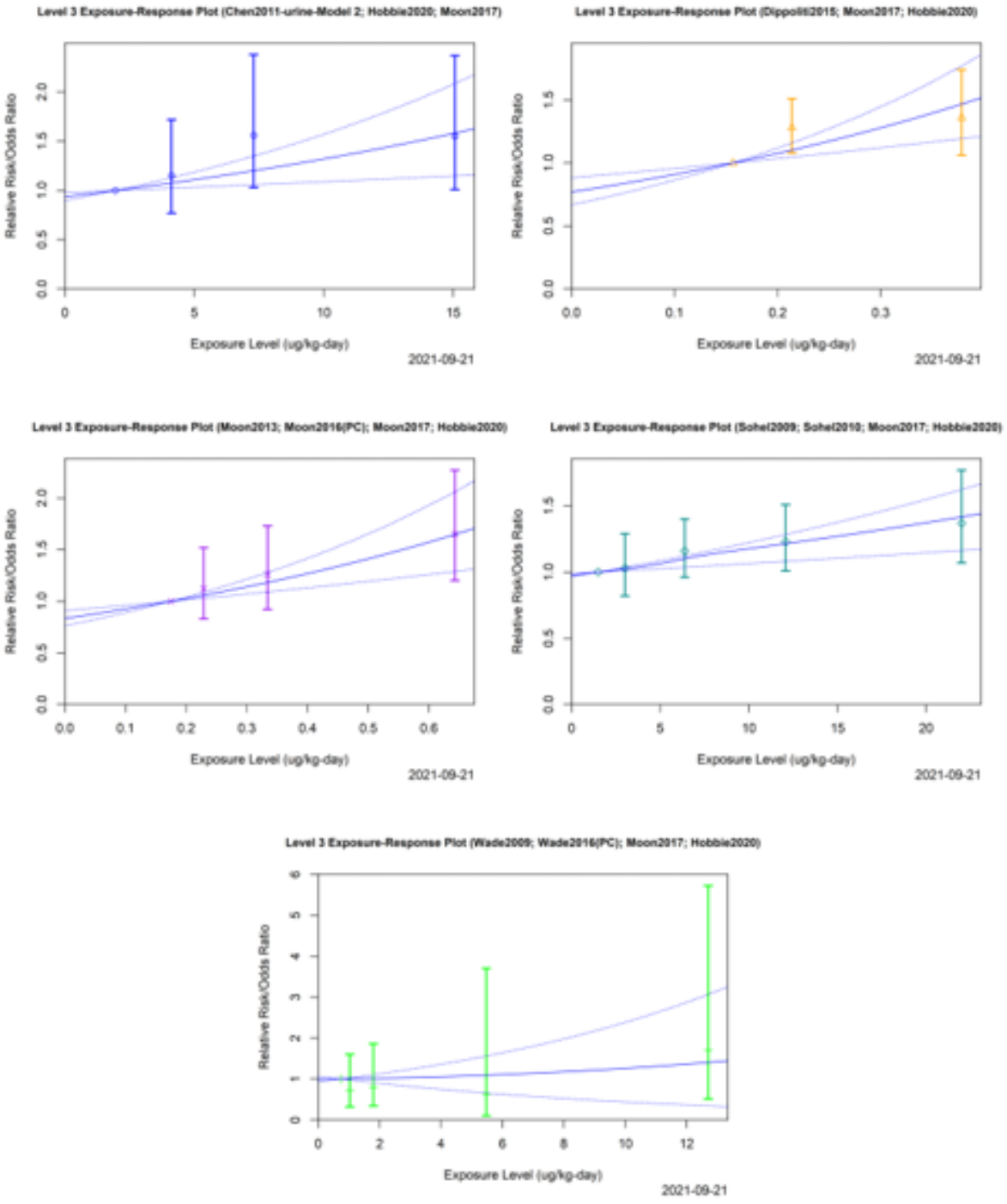


Figure C-39. Non-hierarchical meta-regression dose response curves for individual fatal CVD studies.

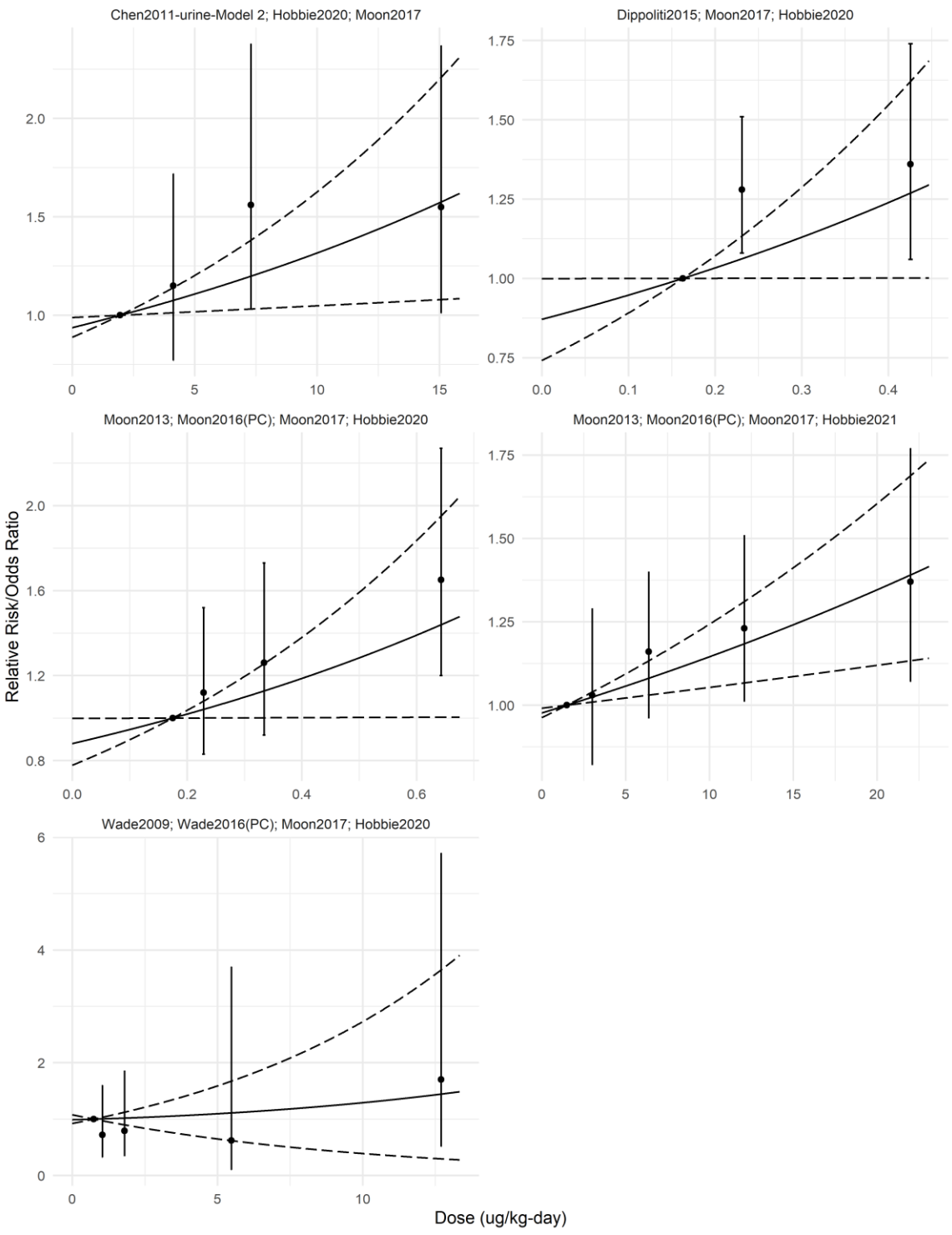


Figure C-40. Hierarchical (all studies) meta-regression dose response curves for individual fatal CVD studies.

Fatal CVD – Low Exposure Studies

Table C-54. Summary of fatal CVD (low exp studies) Bayesian analysis output; MLE dose estimates

Parameter	Mean	Se_mean	Sd	2.50%	25%	50%	75%	97.50%	N_eff	Rhat
bmean	0.6889	0.0087	0.5678	0.0032	0.1733	0.613	1.0892	1.8907	4300	1.0011
b_sigma	1.6353	0.0281	1.8396	0.0494	0.5241	1.1237	2.1072	6.3815	4288	1.0005
D'Ippoliti et al. (2015) b[1]	0.5622	0.0098	0.6874	-0.9085	0.2011	0.5356	0.9453	1.9738	4943	1.0004
Moon et al. (2013) b[2]	0.2063	0.0097	0.6572	-1.3448	-0.0664	0.2462	0.5677	1.4507	4574	1.0003
mu_ref[1]	2761.857	0.479	37.776	2687.166	2736.123	2761.729	2787.507	2835.857	6220	1.0001
mu_ref[2]	88.5171	0.0717	5.8236	77.4784	84.5487	88.3808	92.3162	100.3784	6591	0.9998
b[1]	1.451	0.0067	0.5051	0.5276	1.095	1.427	1.788	2.4955	5717	1
b[2]	1.0325	0.0036	0.3033	0.4253	0.8299	1.0382	1.2388	1.6206	7062	1
p[1]	0.0036	0	0	0.0035	0.0035	0.0036	0.0036	0.0037	6220	1.0001
p[2]	0.0039	0	0.0001	0.0037	0.0038	0.0039	0.004	0.0041	6619	1.0003
p[3]	0.005	0	0.0006	0.004	0.0046	0.0049	0.0053	0.0062	6100	1.0001
p[4]	0.0065	0	0.0004	0.0057	0.0062	0.0065	0.0068	0.0074	6591	0.9998
p[5]	0.0069	0	0.0004	0.0061	0.0066	0.0069	0.0071	0.0077	6675	0.9998
p[6]	0.0076	0	0.0004	0.0069	0.0074	0.0076	0.0079	0.0085	7186	0.9998
p[7]	0.0105	0	0.0012	0.0083	0.0097	0.0105	0.0113	0.013	7626	1
pr[1]	0.0036	0	0	0.0035	0.0035	0.0036	0.0036	0.0037	6220	1.0001
pr[2]	0.0036	0	0	0.0035	0.0035	0.0036	0.0036	0.0037	6220	1.0001
pr[3]	0.0036	0	0	0.0035	0.0035	0.0036	0.0036	0.0037	6220	1.0001
pr[4]	0.0065	0	0.0004	0.0057	0.0062	0.0065	0.0068	0.0074	6591	0.9998
pr[5]	0.0065	0	0.0004	0.0057	0.0062	0.0065	0.0068	0.0074	6591	0.9998
pr[6]	0.0065	0	0.0004	0.0057	0.0062	0.0065	0.0068	0.0074	6591	0.9998
pr[7]	0.0065	0	0.0004	0.0057	0.0062	0.0065	0.0068	0.0074	6591	0.9998
OR_RR[1]	1	0	0	1	1	1	1	1	7300	0.9995
OR_RR[2]	1.0865	0.0004	0.0313	1.0305	1.0643	1.0846	1.1071	1.1525	5740	1
OR_RR[3]	1.3858	0.0021	0.1563	1.1235	1.2732	1.3699	1.4834	1.7335	5810	1
OR_RR[4]	1	0	0	1	1	1	1	1	6820	0.9995
OR_RR[5]	1.0569	0.0002	0.0171	1.023	1.0453	1.0571	1.0685	1.0905	7070	1
OR_RR[6]	1.1784	0.0007	0.0564	1.0694	1.14	1.1781	1.2161	1.2916	7086	1
OR_RR[7]	1.6303	0.0027	0.229	1.2182	1.4698	1.6188	1.7765	2.1194	7127	1
astar	-5.2122	0.0013	0.1068	-5.4221	-5.2835	-5.2124	-5.1399	-5.0034	6639	0.9999
lp__	1490.337	0.039	2.1412	1485.288	1489.093	1490.635	1491.922	1493.548	3022	1.0012

Samples were drawn using NUTS (diag_e) at Fri Oct 08 09:21:56 2021.
For each parameter, n_eff is a crude measure of effective sample size, and Rhat is the potential scale reduction factor on split chains (at convergence, Rhat = 1).

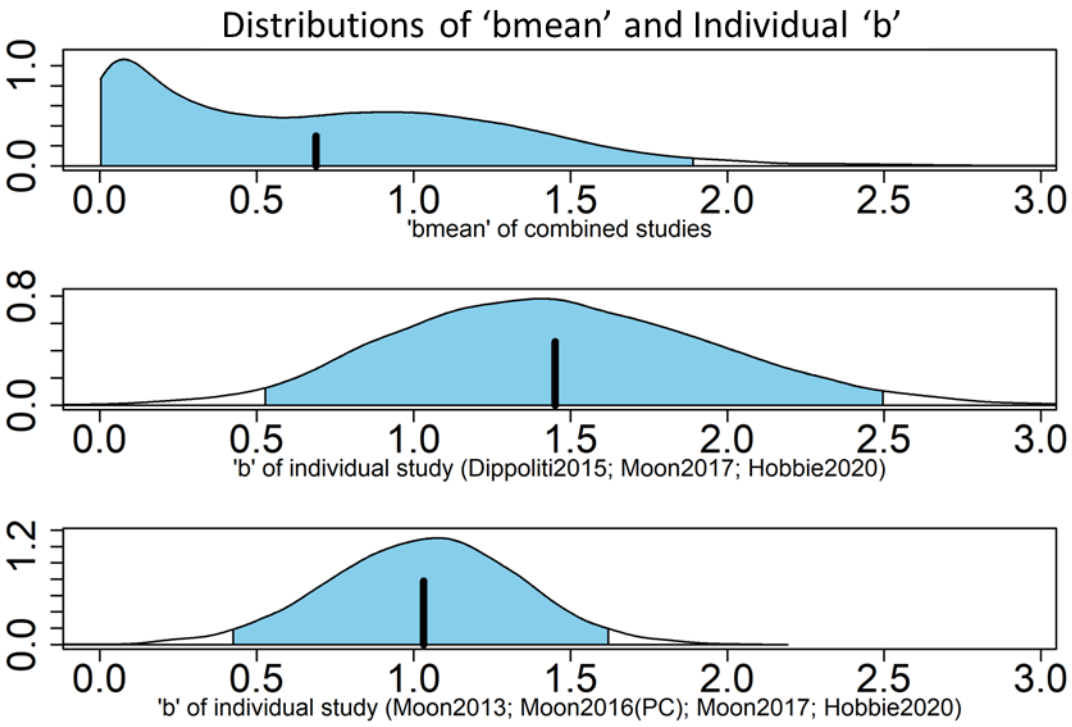


Figure C-41. Posterior distributions for fatal CVD pooled (bmean) and data-set-specific (b) logistic slope parameters, using MLE dose estimates and low dose studies. 95% Credible intervals are highlighted.

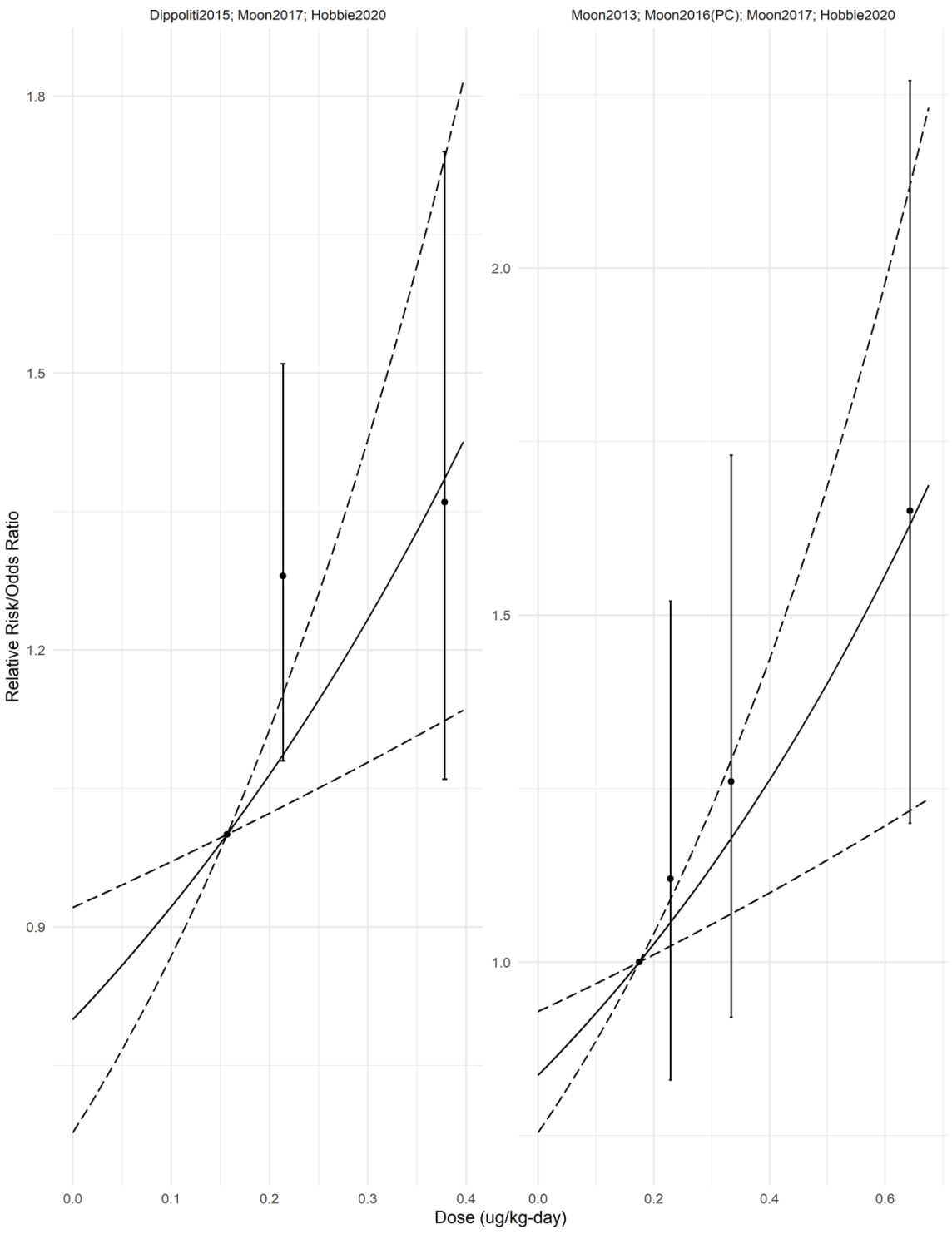


Figure C-42. Hierarchical (low dose studies) meta-regression dose response curves for individual CVD incidence studies.

Fatal CVD – High Exposure Studies

Table C-55. Summary of fatal CVD (high exp studies) Bayesian analysis output; MLE dose estimates

Parameter	Mean	Se_mean	Sd	2.50%	25%	50%	75%	97.50%	N_eff	Rhat
bmean	0.0287	0.0052	0.0577	0.0002	0.0101	0.0187	0.0296	0.103	125	1.0349
b_sigma	0.046	0.0064	0.0903	0.001	0.01	0.0216	0.0449	0.2585	196	1.0232
Chen et al. (2011) b[1]	0.3055	0.011	0.7585	-1.1908	-0.1568	0.2753	0.765	1.9086	4785	1.0007
Wade et al. (2009) b[2]	-0.0205	0.0115	0.8755	-1.7314	-0.5853	-0.0327	0.5411	1.7416	5828	1.0001
Sohel et al. (2009) b[3]	-0.2	0.0114	0.7152	-1.7104	-0.6353	-0.1255	0.2295	1.1663	3944	1.0003
mu_ref[1]	48.153	0.0653	4.2497	40.0994	45.2465	48.0391	50.9659	56.6231	4235	1.0005
mu_ref[2]	95.0264	0.0954	6.8142	82.6915	90.2448	94.749	99.582	108.7563	5106	0.9999
mu_ref[3]	151.6311	0.0813	6.3869	139.6426	147.2613	151.4061	155.8693	164.5664	6178	1.0003
b[1]	0.0281	0.0002	0.0131	0.0047	0.0187	0.0272	0.0369	0.0558	4653	0.9997
b[2]	0.0203	0.0005	0.0298	-0.0444	0.0072	0.0196	0.0345	0.0847	3088	1.001
b[3]	0.0161	0.0001	0.0049	0.0066	0.0128	0.0162	0.0194	0.0254	7032	1.0003
p[1]	0.0026	0	0.0002	0.0021	0.0024	0.0026	0.0027	0.003	4235	1.0005
p[2]	0.0027	0	0.0002	0.0023	0.0026	0.0027	0.0029	0.0031	4289	1.0006
p[3]	0.003	0	0.0002	0.0026	0.0028	0.003	0.0031	0.0034	5224	1.0004
p[4]	0.0037	0	0.0005	0.0028	0.0033	0.0037	0.004	0.0048	5574	0.9997
p[5]	0.0065	0	0.0005	0.0056	0.0062	0.0065	0.0068	0.0074	5106	0.9999
p[6]	0.0065	0	0.0005	0.0057	0.0062	0.0065	0.0068	0.0075	5796	0.9998
p[7]	0.0066	0	0.0005	0.0057	0.0063	0.0066	0.007	0.0076	6557	0.9996
p[8]	0.0072	0	0.0011	0.0052	0.0066	0.0071	0.0078	0.0096	5708	1.0002
p[9]	0.0088	0.0001	0.0032	0.0038	0.007	0.0082	0.0098	0.0172	3567	1.0008
p[10]	0.0013	0	0.0001	0.0012	0.0013	0.0013	0.0014	0.0014	6178	1.0003
p[11]	0.0014	0	0.0001	0.0013	0.0013	0.0014	0.0014	0.0015	6126	1.0004
p[12]	0.0014	0	0	0.0014	0.0014	0.0014	0.0015	0.0015	7173	1.0005
p[13]	0.0016	0	0.0001	0.0015	0.0015	0.0016	0.0016	0.0017	7943	1.0006
p[14]	0.0019	0	0.0001	0.0016	0.0018	0.0019	0.0019	0.0021	7568	1.0004
pr[1]	0.0026	0	0.0002	0.0021	0.0024	0.0026	0.0027	0.003	4235	1.0005
pr[2]	0.0026	0	0.0002	0.0021	0.0024	0.0026	0.0027	0.003	4235	1.0005
pr[3]	0.0026	0	0.0002	0.0021	0.0024	0.0026	0.0027	0.003	4235	1.0005
pr[4]	0.0026	0	0.0002	0.0021	0.0024	0.0026	0.0027	0.003	4235	1.0005
pr[5]	0.0065	0	0.0005	0.0056	0.0062	0.0065	0.0068	0.0074	5106	0.9999

Parameter	Mean	Se_mean	Sd	2.50%	25%	50%	75%	97.50%	N_eff	Rhat
pr[6]	0.0065	0	0.0005	0.0056	0.0062	0.0065	0.0068	0.0074	5106	0.9999
pr[7]	0.0065	0	0.0005	0.0056	0.0062	0.0065	0.0068	0.0074	5106	0.9999
pr[8]	0.0065	0	0.0005	0.0056	0.0062	0.0065	0.0068	0.0074	5106	0.9999
pr[9]	0.0065	0	0.0005	0.0056	0.0062	0.0065	0.0068	0.0074	5106	0.9999
pr[10]	0.0013	0	0.0001	0.0012	0.0013	0.0013	0.0014	0.0014	6178	1.0003
pr[11]	0.0013	0	0.0001	0.0012	0.0013	0.0013	0.0014	0.0014	6178	1.0003
pr[12]	0.0013	0	0.0001	0.0012	0.0013	0.0013	0.0014	0.0014	6178	1.0003
pr[13]	0.0013	0	0.0001	0.0012	0.0013	0.0013	0.0014	0.0014	6178	1.0003
pr[14]	0.0013	0	0.0001	0.0012	0.0013	0.0013	0.0014	0.0014	6178	1.0003
OR_RR[1]	1	0	0	1	1	1	1	1	7151	0.9995
OR_RR[2]	1.0633	0.0004	0.0304	1.0103	1.0415	1.0608	1.0833	1.1287	4674	0.9997
OR_RR[3]	1.1646	0.0012	0.0824	1.0256	1.1051	1.1562	1.2173	1.3467	4709	0.9997
OR_RR[4]	1.4663	0.0037	0.2593	1.0639	1.2778	1.4275	1.6199	2.0748	4805	0.9997
OR_RR[5]	1	0	0	1	1	1	1	1	7575	0.9995
OR_RR[6]	1.006	0.0002	0.0088	0.987	1.0021	1.0058	1.0102	1.0253	3053	1.001
OR_RR[7]	1.0222	0.0006	0.032	0.9542	1.0076	1.021	1.0371	1.0936	2986	1.001
OR_RR[8]	1.1111	0.003	0.1551	0.8111	1.0345	1.097	1.1764	1.4903	2748	1.0011
OR_RR[9]	1.3529	0.01	0.5045	0.5894	1.0893	1.2629	1.5058	2.7275	2534	1.0013
OR_RR[10]	1	0	0	1	1	1	1	1	6676	0.9995
OR_RR[11]	1.0247	0.0001	0.0075	1.01	1.0196	1.0248	1.0298	1.0392	7034	1.0003
OR_RR[12]	1.082	0.0003	0.0256	1.0325	1.0645	1.0822	1.0994	1.1318	7040	1.0003
OR_RR[13]	1.187	0.0007	0.0609	1.0718	1.145	1.1866	1.2278	1.3075	7049	1.0003
OR_RR[14]	1.3972	0.0017	0.1388	1.1437	1.2998	1.3929	1.4882	1.681	7064	1.0003
astar	-6.6468	0.0006	0.0476	-6.7397	-6.6794	-6.6473	-6.6148	-6.5532	6223	1.0003
lp__	4638.017	0.0525	2.6316	4631.973	4636.464	4638.3	4639.895	4642.3	2515	1.0009

Samples were drawn using NUTS (diag_e) at Tue Sep 21 19:06:51 2021.
For each parameter, n_eff is a crude measure of effective sample size, and Rhat is the potential scale reduction factor on split chains (at convergence, Rhat = 1).

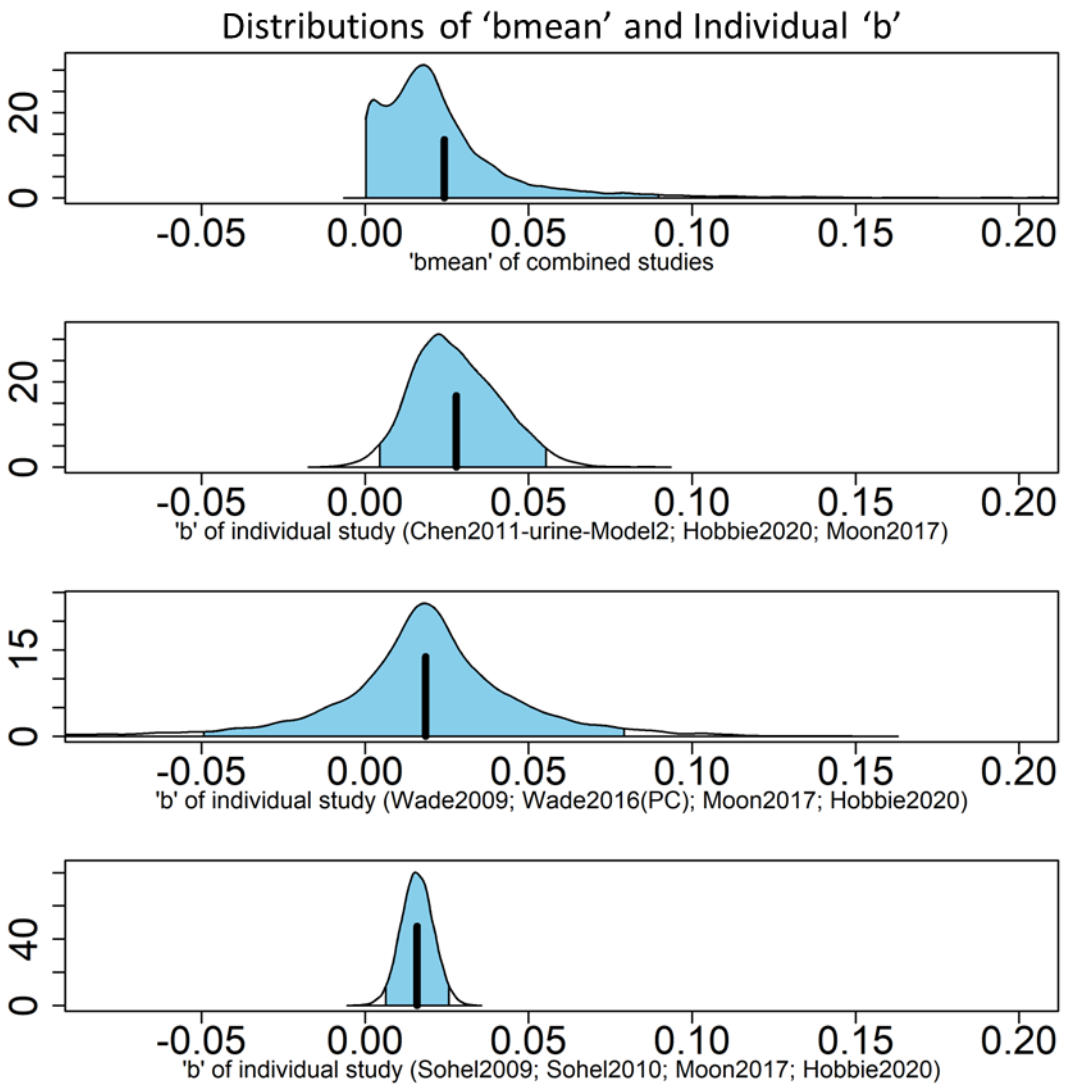


Figure C-43. Posterior distributions for fatal CVD pooled (bmean) and data-set-specific (b) logistic slope parameters, using MLE dose estimates and high dose studies. 95% Credible intervals are highlighted.

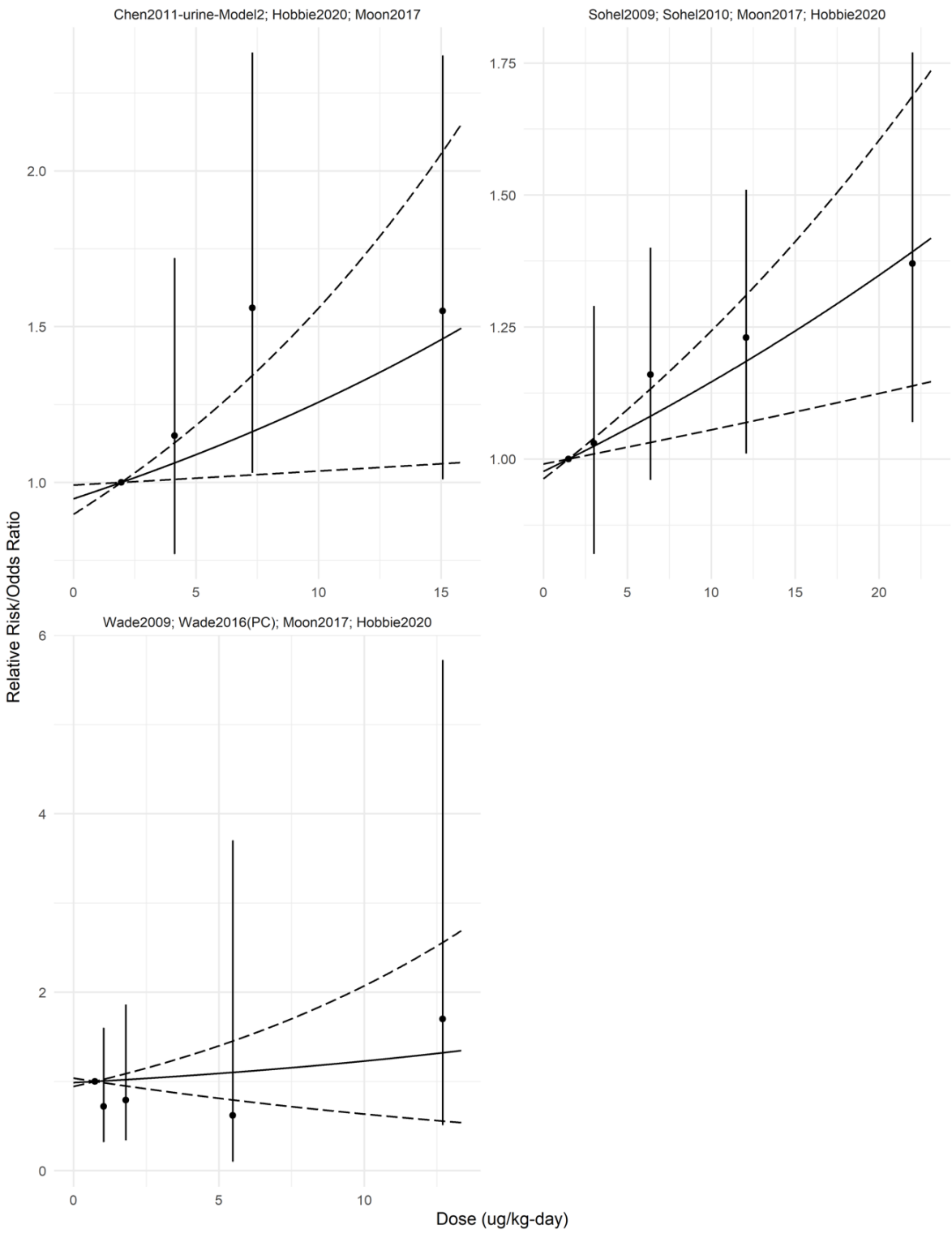


Figure C-44. Hierarchical (high dose studies) meta-regression dose response curves for individual fatal CVD studies.

Fatal IHD – All Studies

Table C-56. Summary of fatal IHD (all studies) Bayesian analysis output; MLE dose estimates

Parameter	Mean	Se_mean	Sd	2.50%	25%	50%	75%	97.50%	N_eff	Rhat
bmean	0.2408	0.0062	0.2457	0.001	0.0421	0.1725	0.3655	0.859	1582	1.0016
b_sigma	0.6417	0.0152	0.4693	0.0084	0.3568	0.5815	0.8399	1.7668	956	1.0011
b0[1]	−0.3225	0.0121	0.4886	−1.3434	−0.605	−0.2616	−0.0269	0.7466	1637	1.0019
b0[2]	0.9884	0.0159	0.7897	−0.7403	0.5242	1.0117	1.4929	2.5022	2471	1.0013
b0[3]	−0.3846	0.0089	0.4978	−1.4663	−0.6707	−0.3185	−0.0727	0.6091	3105	1.0015
b0[4]	0.8577	0.0139	0.7291	−0.6785	0.4409	0.8368	1.2854	2.3219	2746	1.0014
b0[5]	−0.4171	0.0076	0.4542	−1.4766	−0.6794	−0.3308	−0.0811	0.1948	3577	1.0009
mu_ref[1]	47.0443	0.0514	4.301	39.274	44.0196	46.8626	49.8728	56.0428	7012	1.0007
mu_ref[2]	2766.665	0.4411	37.2461	2694.166	2741.608	2765.928	2790.778	2842.539	7129	1.0001
mu_ref[3]	94.979	0.0809	6.8013	82.0456	90.3236	94.7424	99.4282	109.0339	7063	0.9999
mu_ref[4]	91.8088	0.1733	6.5987	79.629	87.212	91.4407	96.0481	105.5046	1449	1.0015
mu_ref[5]	151.9457	0.0767	6.4119	139.6558	147.5322	151.8905	156.2135	164.5978	6989	0.9999
b[1]	0.0335	0.0002	0.0141	0.0059	0.0239	0.0337	0.043	0.0606	6826	1.001
b[2]	0.874	0.0182	0.5271	0.0048	0.4931	0.9045	1.2581	1.846	836	1.0016
b[3]	0.0158	0.0006	0.0533	−0.1021	−0.0145	0.0194	0.0515	0.1095	7046	1.0001
b[4]	0.7484	0.0149	0.4016	0.0091	0.4921	0.7957	1.0383	1.4414	725	1.0041
b[5]	0.0158	0.0001	0.0049	0.0061	0.0126	0.0159	0.0191	0.0256	6854	0.9999
p[1]	0.0025	0	0.0002	0.0021	0.0023	0.0025	0.0027	0.003	7012	1.0007
p[2]	0.0027	0	0.0002	0.0023	0.0025	0.0027	0.0028	0.0031	7133	1.0005
p[3]	0.003	0	0.0002	0.0026	0.0028	0.003	0.0031	0.0034	7227	1.0001
p[4]	0.0039	0	0.0006	0.0029	0.0035	0.0039	0.0043	0.005	7035	1.0007
p[5]	0.0036	0	0	0.0035	0.0036	0.0036	0.0036	0.0037	7162	0.9998
p[6]	0.0038	0	0.0001	0.0036	0.0037	0.0038	0.0039	0.0041	946	1.001
p[7]	0.0046	0	0.0006	0.0036	0.0041	0.0046	0.005	0.0059	935	1.0011
p[8]	0.0065	0	0.0005	0.0056	0.0062	0.0065	0.0068	0.0074	7063	0.9999
p[9]	0.0065	0	0.0005	0.0057	0.0062	0.0065	0.0068	0.0075	7080	1.0001
p[10]	0.0066	0	0.0005	0.0055	0.0062	0.0066	0.007	0.0077	7129	1.0004
p[11]	0.0072	0	0.0017	0.004	0.006	0.0071	0.0082	0.0108	7342	1.0002

Parameter	Mean	Se_mean	Sd	2.50%	25%	50%	75%	97.50%	N_eff	Rhat
p[12]	0.0093	0.0001	0.0055	0.002	0.0055	0.0082	0.0119	0.0233	7516	1
p[13]	0.0067	0	0.0005	0.0058	0.0064	0.0067	0.0071	0.0077	1449	1.0015
p[14]	0.007	0	0.0004	0.0062	0.0067	0.007	0.0073	0.0079	2623	1.0005
p[15]	0.0076	0	0.0004	0.0068	0.0073	0.0076	0.0079	0.0084	5033	1.0004
p[16]	0.0096	0	0.0014	0.0071	0.0087	0.0097	0.0106	0.0123	913	1.0035
p[17]	0.0013	0	0.0001	0.0012	0.0013	0.0013	0.0014	0.0014	6989	0.9999
p[18]	0.0014	0	0.0001	0.0013	0.0013	0.0014	0.0014	0.0015	6969	0.9999
p[19]	0.0014	0	0	0.0014	0.0014	0.0014	0.0015	0.0015	6880	1
p[20]	0.0016	0	0.0001	0.0015	0.0015	0.0016	0.0016	0.0017	7057	1
p[21]	0.0018	0	0.0001	0.0016	0.0017	0.0018	0.0019	0.0021	6744	0.9999
pr[1]	0.0025	0	0.0002	0.0021	0.0023	0.0025	0.0027	0.003	7012	1.0007
pr[2]	0.0025	0	0.0002	0.0021	0.0023	0.0025	0.0027	0.003	7012	1.0007
pr[3]	0.0025	0	0.0002	0.0021	0.0023	0.0025	0.0027	0.003	7012	1.0007
pr[4]	0.0025	0	0.0002	0.0021	0.0023	0.0025	0.0027	0.003	7012	1.0007
pr[5]	0.0036	0	0	0.0035	0.0036	0.0036	0.0036	0.0037	7129	1.0001
pr[6]	0.0036	0	0	0.0035	0.0036	0.0036	0.0036	0.0037	7129	1.0001
pr[7]	0.0036	0	0	0.0035	0.0036	0.0036	0.0036	0.0037	7129	1.0001
pr[8]	0.0065	0	0.0005	0.0056	0.0062	0.0065	0.0068	0.0074	7063	0.9999
pr[9]	0.0065	0	0.0005	0.0056	0.0062	0.0065	0.0068	0.0074	7063	0.9999
pr[10]	0.0065	0	0.0005	0.0056	0.0062	0.0065	0.0068	0.0074	7063	0.9999
pr[11]	0.0065	0	0.0005	0.0056	0.0062	0.0065	0.0068	0.0074	7063	0.9999
pr[12]	0.0065	0	0.0005	0.0056	0.0062	0.0065	0.0068	0.0074	7063	0.9999
pr[13]	0.0067	0	0.0005	0.0058	0.0064	0.0067	0.0071	0.0077	1449	1.0015
pr[14]	0.0067	0	0.0005	0.0058	0.0064	0.0067	0.0071	0.0077	1449	1.0015
pr[15]	0.0067	0	0.0005	0.0058	0.0064	0.0067	0.0071	0.0077	1449	1.0015
pr[16]	0.0067	0	0.0005	0.0058	0.0064	0.0067	0.0071	0.0077	1449	1.0015
pr[17]	0.0013	0	0.0001	0.0012	0.0013	0.0013	0.0014	0.0014	6989	0.9999
pr[18]	0.0013	0	0.0001	0.0012	0.0013	0.0013	0.0014	0.0014	6989	0.9999
pr[19]	0.0013	0	0.0001	0.0012	0.0013	0.0013	0.0014	0.0014	6989	0.9999
pr[20]	0.0013	0	0.0001	0.0012	0.0013	0.0013	0.0014	0.0014	6989	0.9999
pr[21]	0.0013	0	0.0001	0.0012	0.0013	0.0013	0.0014	0.0014	6989	0.9999

Parameter	Mean	Se_mean	Sd	2.50%	25%	50%	75%	97.50%	N_eff	Rhat
OR_RR[1]	1	0	0	1	1	1	1	1	7657	0.9995
OR_RR[2]	1.0758	0.0004	0.0329	1.0128	1.0532	1.0758	1.0978	1.1405	6842	1.0011
OR_RR[3]	1.1988	0.0011	0.0901	1.0318	1.1359	1.1968	1.2578	1.3815	6865	1.0011
OR_RR[4]	1.5756	0.0035	0.2915	1.0798	1.3669	1.5537	1.755	2.2084	6921	1.0012
OR_RR[5]	1.0053	0.0001	0.0032	1	1.003	1.0055	1.0077	1.0113	838	1.0016

Samples were drawn using NUTS(diag_e) at Thu Aug 11 20:54:19 2022.
For each parameter, n_eff is a crude measure of effective sample size, and Rhat is the potential scale reduction factor on split chains (at convergence, Rhat = 1).

Study Key:

1. Chen et al. (2011)
2. D'Ippoliti et al. (2015)
3. Wade et al. (2009)
4. Moon et al. (2013)

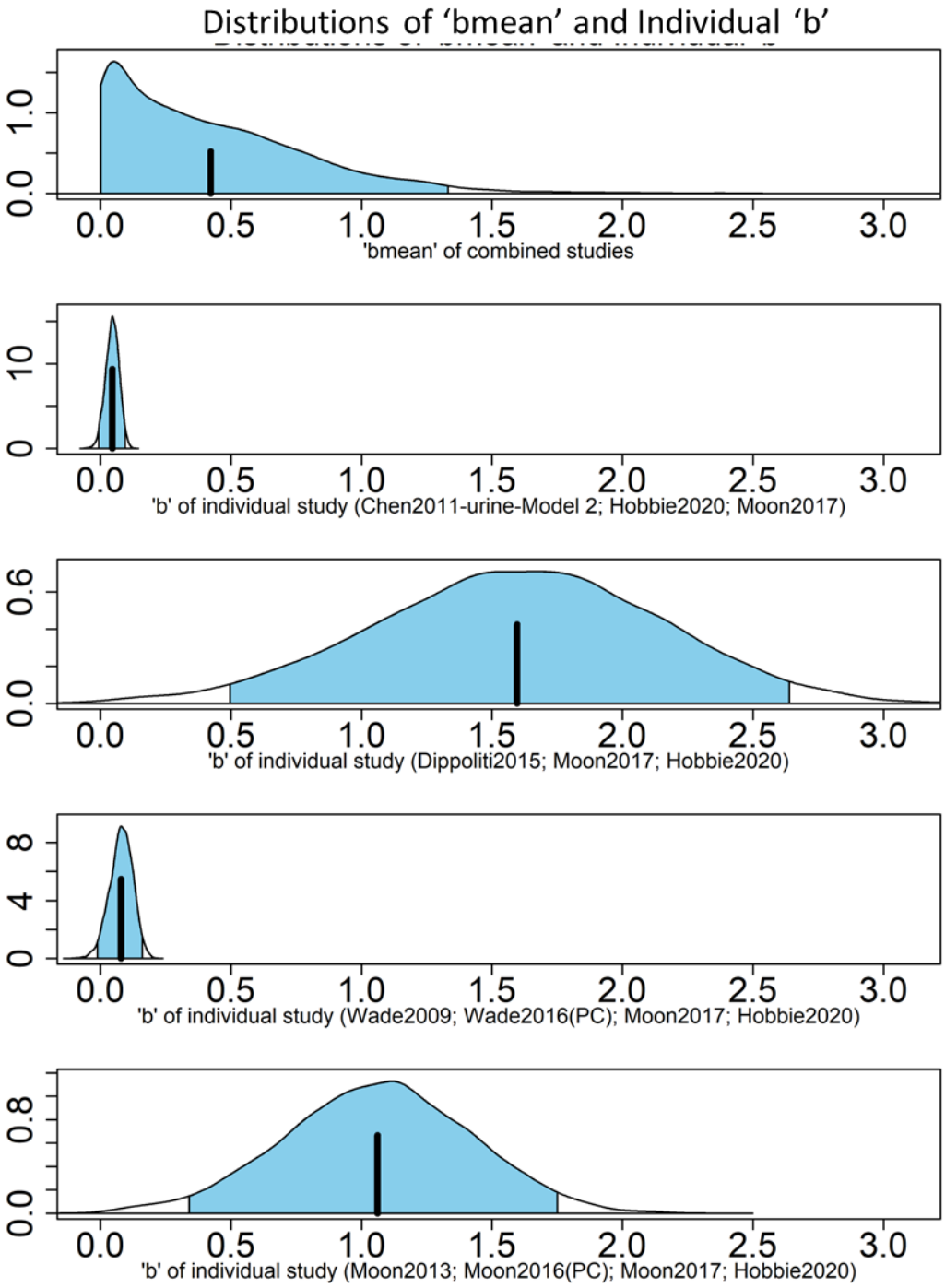


Figure C-45. Posterior distributions for fatal IHD pooled (bmean) and data-set-specific (b) logistic slope parameters; using MLE dose estimates and all studies. 95% Credible intervals are highlighted.

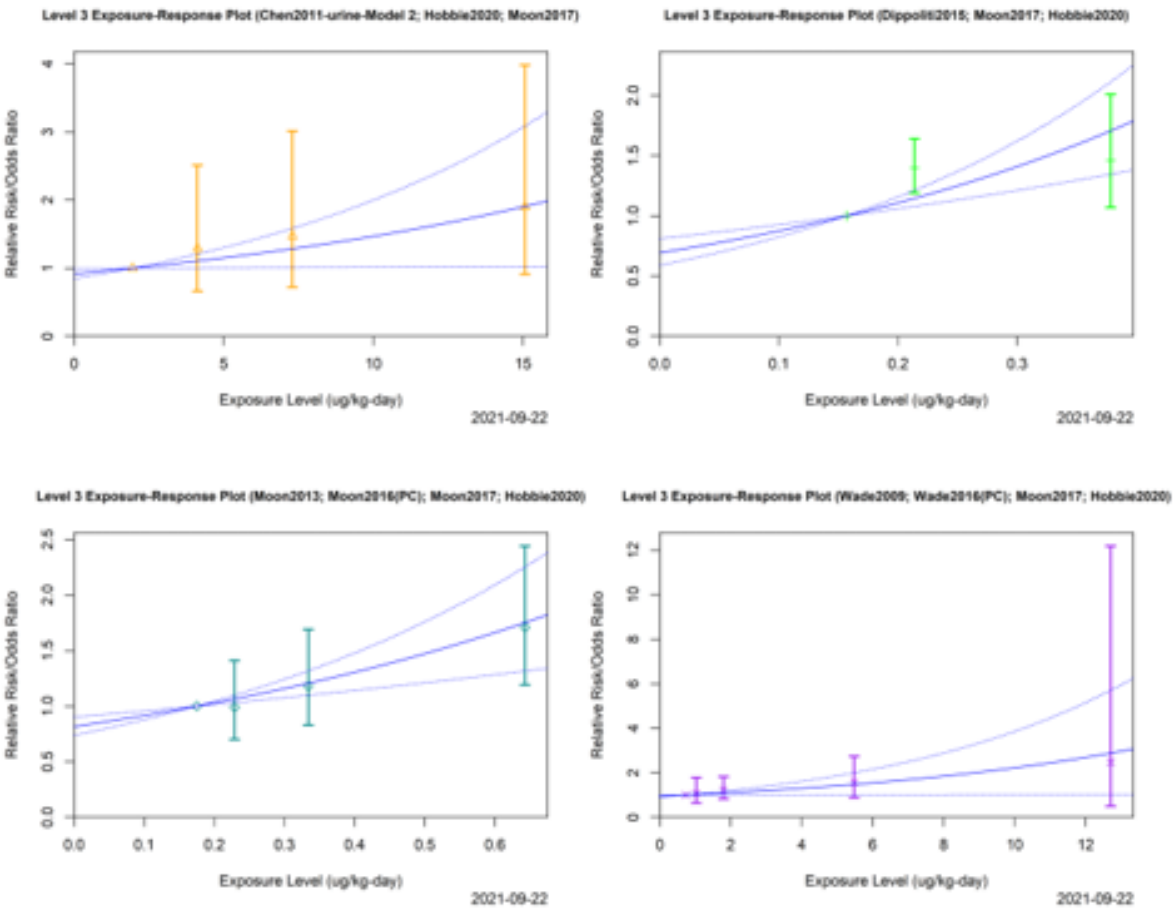


Figure C-46. Non-hierarchical meta-regression dose response curves for individual fatal IHD studies.

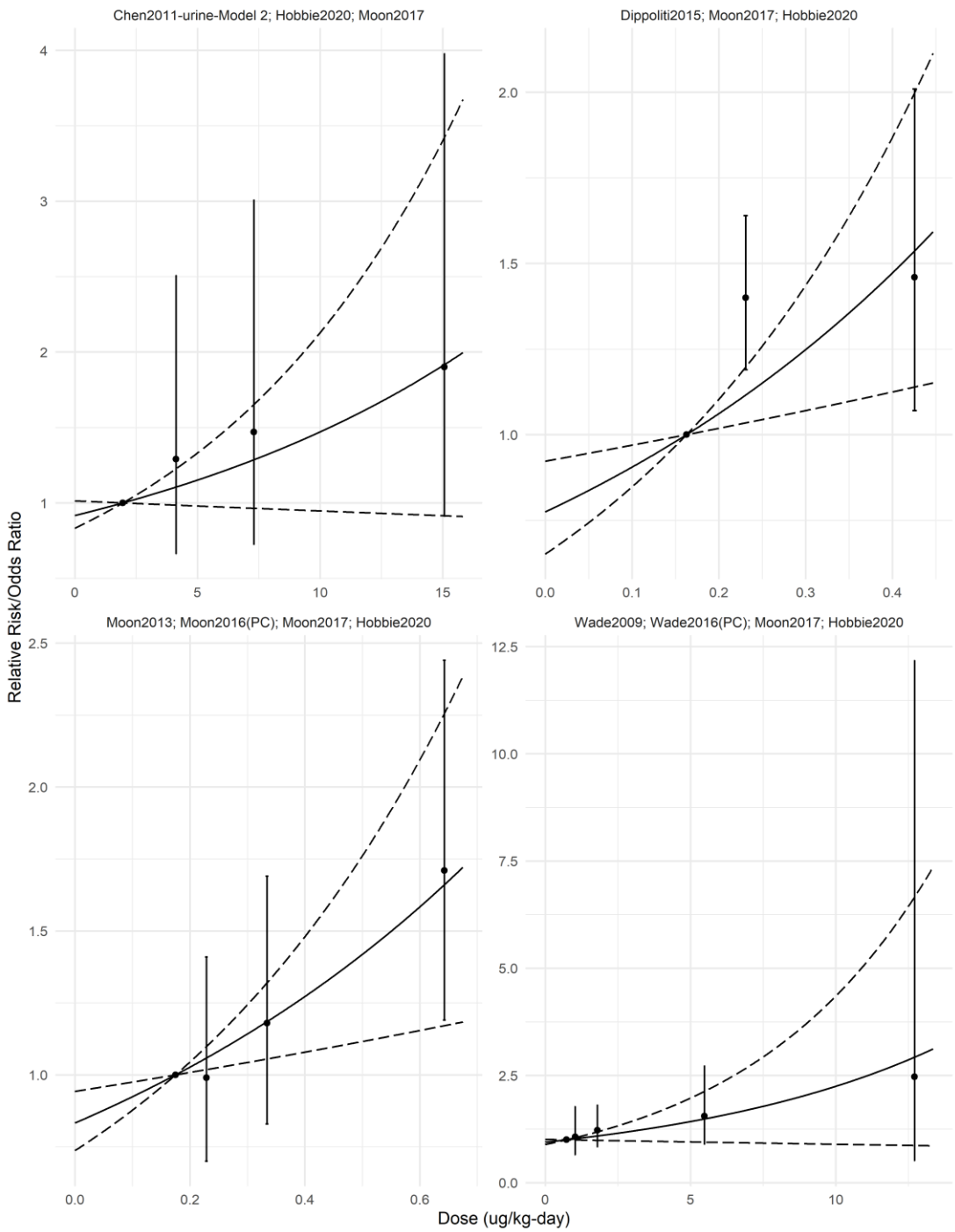


Figure C-47. Hierarchical (all studies) meta-regression dose response curves for individual fatal IHD studies.

Fatal IHD – Low Exposure Studies

Table C-57. Summary of fatal IHD (low exp studies) Bayesian analysis output; MLE dose estimates

Parameter	Mean	Se_mean	Sd	2.50%	25%	50%	75%	97.50%	N_eff	Rhat
bmean	0.7427	0.0109	0.6838	0.0012	0.1359	0.5709	1.2135	2.2986	3947	1.0002
b_sigma	2.2771	0.0352	2.2939	0.133	0.9335	1.6801	2.8554	7.9695	4257	1.0005
D'Ippoliti et al. (2015) b[1]	0.773	0.0093	0.6484	-0.496	0.3699	0.7215	1.1559	2.1761	4902	0.9998
Moon et al. (2013) b[2]	0.177	0.0089	0.5864	-1.2829	-0.0324	0.2276	0.4974	1.2092	4378	0.9997
mu_ref[1]	701.82	0.257	20.7672	660.9869	687.8653	701.395	715.4994	743.8336	6528	1.0001
mu_ref[2]	66.6257	0.0637	4.9747	57.2624	63.1866	66.3875	69.9335	77.0194	6100	1.0004
b[1]	2.0895	0.0085	0.6371	0.9138	1.641	2.0865	2.5299	3.3332	5655	0.9999
b[2]	1.1687	0.0042	0.3412	0.5023	0.9397	1.1699	1.4026	1.8302	6740	0.9999
p[1]	0.0009	0	0	0.0009	0.0009	0.0009	0.0009	0.001	6526	1.0001
p[2]	0.001	0	0	0.0009	0.001	0.001	0.0011	0.0011	6225	0.9997
p[3]	0.0015	0	0.0002	0.0011	0.0013	0.0014	0.0016	0.0019	5967	0.9998
p[4]	0.0049	0	0.0004	0.0042	0.0046	0.0049	0.0051	0.0057	6100	1.0004
p[5]	0.0052	0	0.0003	0.0046	0.005	0.0052	0.0054	0.0059	6114	1.0003
p[6]	0.0059	0	0.0004	0.0052	0.0056	0.0059	0.0061	0.0066	6374	1.0001
p[7]	0.0085	0	0.0011	0.0065	0.0077	0.0084	0.0092	0.0107	6951	0.9997
pr[1]	0.0009	0	0	0.0009	0.0009	0.0009	0.0009	0.001	6528	1.0001
pr[2]	0.0009	0	0	0.0009	0.0009	0.0009	0.0009	0.001	6528	1.0001
pr[3]	0.0009	0	0	0.0009	0.0009	0.0009	0.0009	0.001	6528	1.0001
pr[4]	0.0049	0	0.0004	0.0042	0.0046	0.0049	0.0051	0.0057	6100	1.0004
pr[5]	0.0049	0	0.0004	0.0042	0.0046	0.0049	0.0051	0.0057	6100	1.0004
pr[6]	0.0049	0	0.0004	0.0042	0.0046	0.0049	0.0051	0.0057	6100	1.0004
pr[7]	0.0049	0	0.0004	0.0042	0.0046	0.0049	0.0051	0.0057	6100	1.0004
OR_RR[1]	0.9998	0	0.0001	0.9997	0.9997	0.9998	0.9998	0.9999	5655	0.9999
OR_RR[2]	1.1273	0.0005	0.041	1.0535	1.0981	1.1264	1.1553	1.2094	5725	0.9999
OR_RR[3]	1.6043	0.003	0.2283	1.2243	1.4382	1.5873	1.751	2.0917	5906	0.9999

Parameter	Mean	Se_mean	Sd	2.50%	25%	50%	75%	97.50%	N_eff	Rhat
OR_RR[4]	1	0	0	1	1	1	1	1	7448	0.9995
OR_RR[5]	1.0647	0.0002	0.0195	1.0272	1.0516	1.0646	1.078	1.103	6748	0.9999
OR_RR[6]	1.2048	0.0008	0.065	1.0826	1.1602	1.2032	1.2484	1.3358	6767	0.9999
OR_RR[7]	1.743	0.0034	0.2769	1.263	1.5479	1.7222	1.9188	2.3402	6819	1
astar	-5.5224	0.0015	0.1204	-5.7588	-5.6032	-5.523	-5.4421	-5.2861	6310	1.0002
lp__	1416.76	0.0389	2.1351	1411.668	1415.503	1417.117	1418.362	1419.914	3017	1.0004

Samples were drawn using NUTS(diag_e) at Thu Sep 23 00:16:18 2021.
For each parameter, n_eff is a crude measure of effective sample size, and Rhat is the potential scale reduction factor on split chains (at convergence, Rhat = 1).

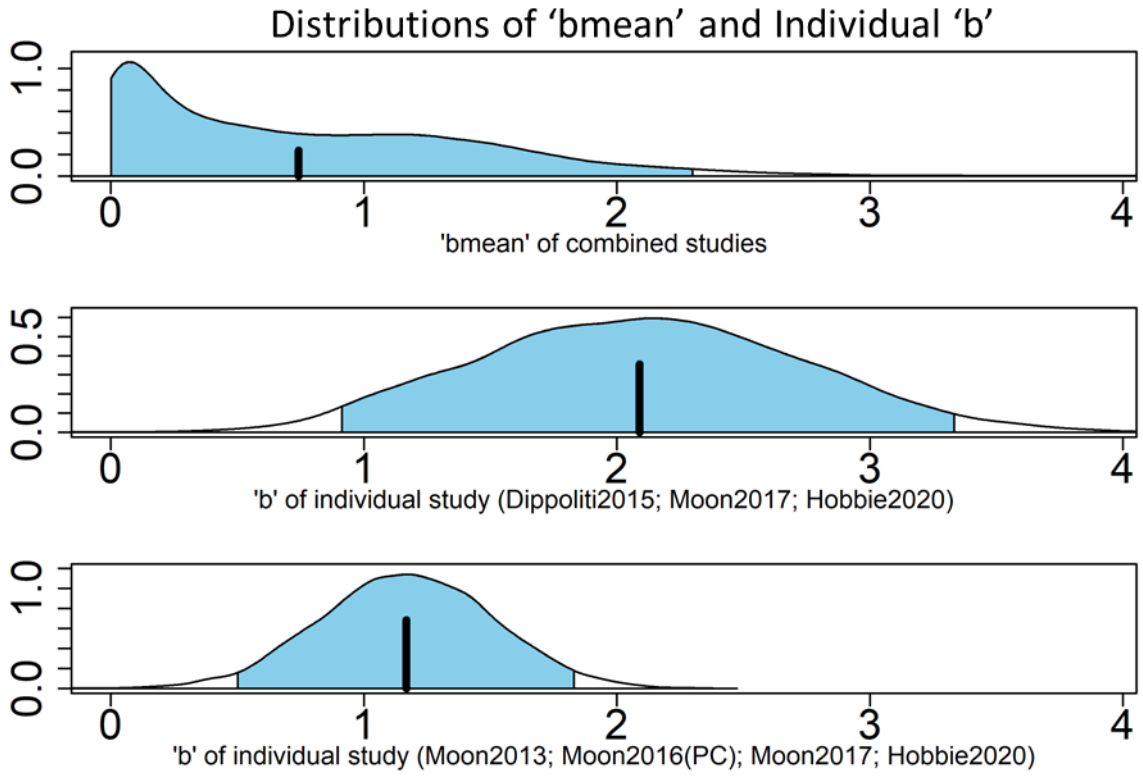


Figure C-48. Posterior distributions for fatal IHD pooled (bmean) and data-set-specific (b) logistic slope parameters, using MLE dose estimates and low dose studies. 95% Credible intervals are highlighted.

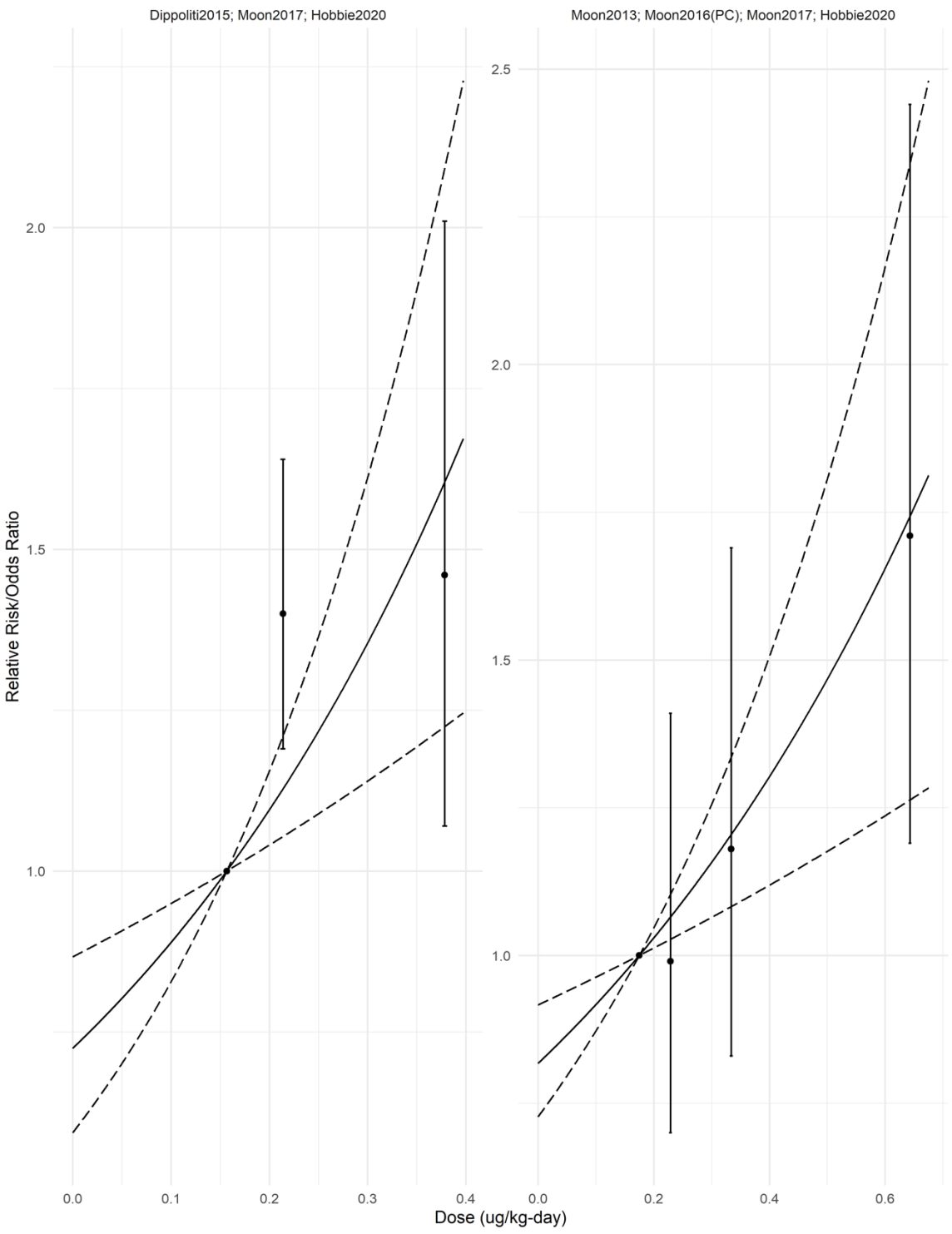


Figure C-49. Hierarchical (low dose studies) meta-regression dose response curves for individual fatal IHD studies.

Fatal IHD – High Exposure Studies

Table C-58. Summary of fatal IHD (high exp studies) Bayesian analysis output; MLE dose estimates

Parameter	Mean	Se_mean	Sd	2.50%	25%	50%	75%	97.50%	N_eff	Rhat
bmean	0.0735	0.0021	0.0952	0.0005	0.0216	0.0499	0.0871	0.321	2002	1.0024
b_sigma	0.1999	0.0117	0.3764	0.003	0.03	0.0747	0.1933	1.2754	1043	1.003
Chen et al. (2011) b[2]	-0.0979	0.0105	0.6818	-1.5731	-0.464	-0.0502	0.259	1.3111	4207	1.0001
Wade et al. (2009) b[3]	0.1267	0.0117	0.7282	-1.3432	-0.2777	0.0833	0.517	1.6954	3850	1.0006
mu_ref[1]	18.2948	0.0379	2.8425	13.2568	16.3129	18.118	20.0819	24.3986	5633	0.9998
mu_ref[2]	46.9216	0.0556	4.2606	39.0315	43.9739	46.7599	49.6851	55.7788	5873	1
b[1]	0.0463	0.0003	0.0242	-0.0012	0.03	0.0465	0.0632	0.0935	6166	0.9997
b[2]	0.0671	0.0005	0.04	-0.0083	0.0401	0.066	0.0934	0.1472	5440	1.0003
p[1]	0.001	0	0.0002	0.0007	0.0009	0.001	0.0011	0.0013	5633	0.9998
p[2]	0.0011	0	0.0001	0.0008	0.001	0.0011	0.0012	0.0014	5845	1
p[3]	0.0012	0	0.0002	0.001	0.0011	0.0012	0.0013	0.0016	6686	1.0003
p[4]	0.0018	0	0.0005	0.0011	0.0015	0.0018	0.0021	0.0028	6882	1
p[5]	0.0032	0	0.0003	0.0027	0.003	0.0032	0.0034	0.0038	5873	1
p[6]	0.0033	0	0.0003	0.0027	0.0031	0.0033	0.0034	0.0038	6002	1
p[7]	0.0034	0	0.0003	0.0029	0.0032	0.0034	0.0036	0.004	6247	0.9999
p[8]	0.0044	0	0.0008	0.0032	0.0039	0.0044	0.0049	0.0061	5835	1.0001
p[9]	0.0078	0	0.0037	0.0031	0.0052	0.007	0.0095	0.0171	5870	1.0004
pr[1]	0.001	0	0.0002	0.0007	0.0009	0.001	0.0011	0.0013	5633	0.9998
pr[2]	0.001	0	0.0002	0.0007	0.0009	0.001	0.0011	0.0013	5633	0.9998
pr[3]	0.001	0	0.0002	0.0007	0.0009	0.001	0.0011	0.0013	5633	0.9998
pr[4]	0.001	0	0.0002	0.0007	0.0009	0.001	0.0011	0.0013	5633	0.9998
pr[5]	0.0032	0	0.0003	0.0027	0.003	0.0032	0.0034	0.0038	5873	1
pr[6]	0.0032	0	0.0003	0.0027	0.003	0.0032	0.0034	0.0038	5873	1
pr[7]	0.0032	0	0.0003	0.0027	0.003	0.0032	0.0034	0.0038	5873	1
pr[8]	0.0032	0	0.0003	0.0027	0.003	0.0032	0.0034	0.0038	5873	1
pr[9]	0.0032	0	0.0003	0.0027	0.003	0.0032	0.0034	0.0038	5873	1
OR_RR[1]	1	0	0	1	1	1	1	1	6210	0.9995
OR_RR[2]	1.1074	0.0007	0.0582	0.9975	1.0673	1.1062	1.1472	1.2251	6174	0.9997
OR_RR[3]	1.2914	0.0021	0.1672	0.9938	1.1736	1.2818	1.4017	1.6474	6185	0.9996
OR_RR[4]	1.9288	0.0079	0.6213	0.9848	1.4811	1.8387	2.2895	3.4018	6212	0.9996
OR_RR[5]	1	0	0	1	1	1	1	1	6916	0.9995

Parameter	Mean	Se_mean	Sd	2.50%	25%	50%	75%	97.50%	N_eff	Rhat
OR_RR[6]	1.0201	0.0002	0.012	0.9976	1.0119	1.0197	1.028	1.0444	5444	1.0003
OR_RR[7]	1.0746	0.0006	0.0456	0.9912	1.0434	1.0724	1.104	1.1688	5458	1.0003
OR_RR[8]	1.3978	0.0036	0.268	0.9615	1.2086	1.3662	1.555	2.0047	5539	1.0004
OR_RR[9]	2.4901	0.0168	1.2675	0.9057	1.6125	2.1959	3.041	5.7481	5720	1.0005
astar	-5.7929	0.0014	0.1072	-6.0063	-5.8638	-5.7921	-5.721	-5.5817	5613	1.0001
lp__	299.7174	0.0563	2.5116	294.1297	298.2163	299.9519	301.4268	304.1562	1987	1.0003

Samples were drawn using NUTS(diag_e) at Tue Oct 26 15:29:36 2021.
For each parameter, n_eff is a crude measure of effective sample size, and Rhat is the potential scale reduction factor on split chains (at convergence, Rhat = 1).

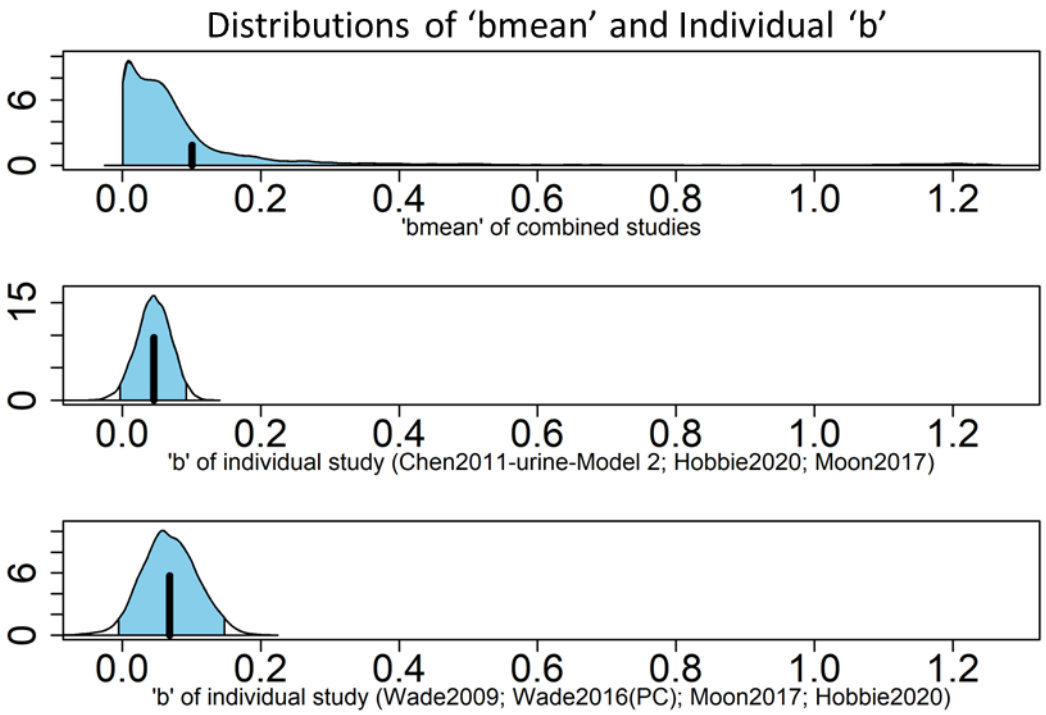


Figure C-50. Posterior distributions for fatal IHD pooled (bmean) and data-set-specific (b) logistic slope parameters; using MLE dose estimates and high dose studies. 95% Credible intervals are highlighted.

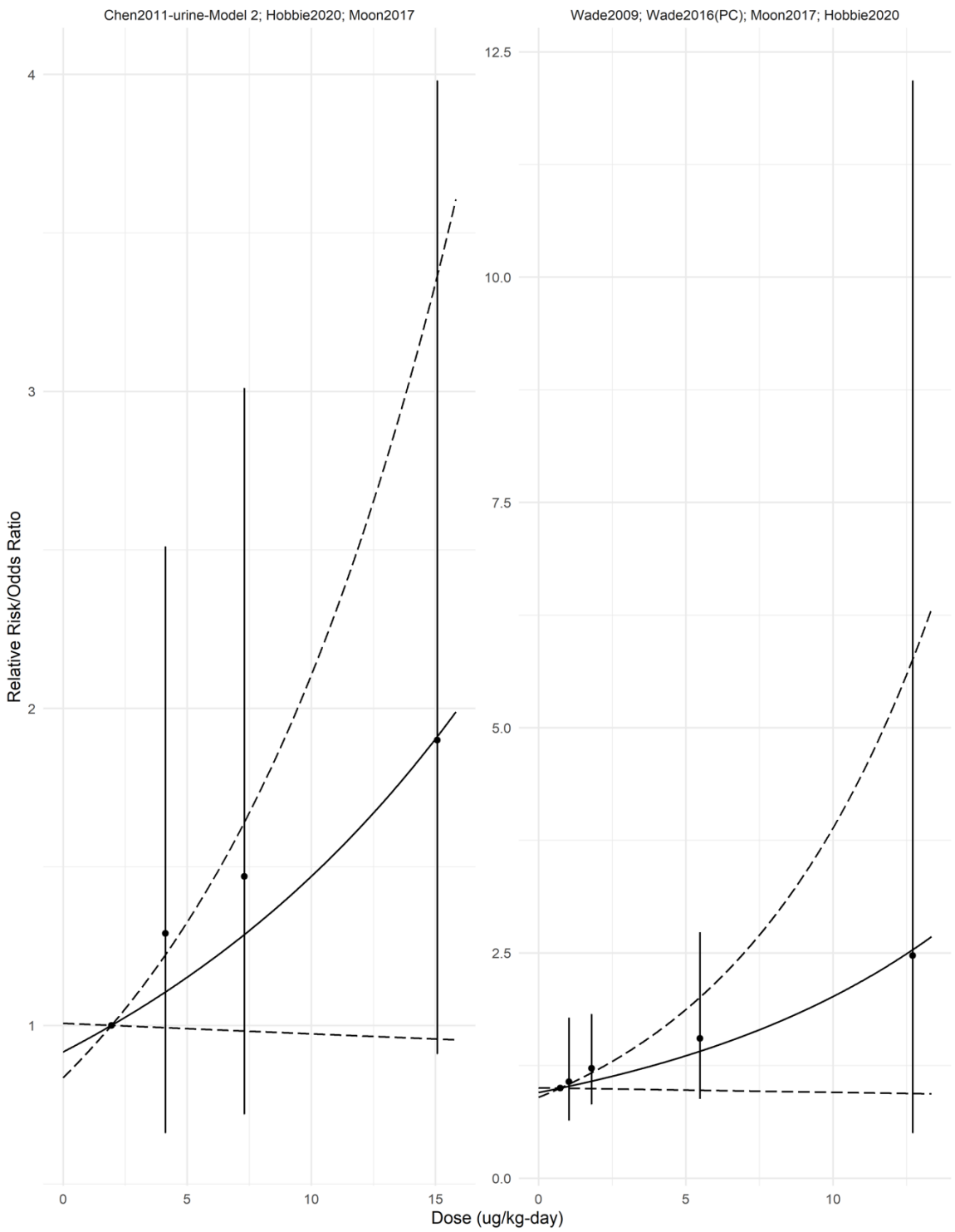


Figure C-51. Hierarchical (high dose studies) meta-regression dose response curves for individual fatal IHD studies.

Model fit/Convergence for DCS meta-regressions

The meta-regression results shown above for each of the four DCS health outcomes indicate different β_mean estimates for analyses using all studies, only low-dose studies, and only high-dose studies. Overall, the Stan® software used to perform the meta-regression modeling indicates model fit/convergence (when including all studies and in the sub analyses) was not as good for the DCS outcomes relative to the bladder cancer, lung cancer, and diabetes meta-regressions. An indicator of model convergence the Stan software provides is the number of divergent transitions in the Hamiltonian Markov chain.[31] The software reported no divergent transitions the EPA bladder cancer, lung cancer, and diabetes meta-regressions. Divergent transitions were reported, however, for some DCS meta-regressions (see Table C-59).

As shown in Table C-59, Stan reported a high number of divergent transitions when only high-dose studies were included in the meta-regressions, indicating a questionable fit/convergence for these meta-regressions. Few divergent transitions were reported when all studies or only low-dose studies were included, indicating adequate fit/convergence. The low-dose study meta-regressions relied on just two studies or just one study in the case of CVD incidence, however, and the use of only low-dose studies did not significantly improve the fit/convergence when compared to the use of all studies. Further, the use of all studies increases confidence in and precision of the meta-regression results, making accurate reflections of the true U.S. population variability more likely. For these reasons, the full set of studies was used to estimate lifetime extra risks for each DCS health outcome (see next section).

Table C-59. DCS meta-regression settings and divergent transitions

Health outcome/studies included	Iterations[a]	Divergent transitions
CVD incidence/all studies	25,000	2
CVD incidence/only low-dose study	25,000	Individual Study
CVD incidence/only high-dose study	25,000	Individual Study
IHD incidence/all studies	30,000	3
IHD incidence/only low-dose studies	25,000	0
IHD incidence/only high-dose studies	30,000	24
CVD fatal/all studies	25,000	1
CVD fatal/only low-dose studies	25,000	1
CVD fatal/only high-dose studies	50,000	38
IHD Fatal/all studies	30,000	0
IHD fatal/only low-dose studies	30,000	1
IHD fatal/only high-dose studies	50,000	93

[a]All meta-regressions were run using the same settings/options, including the same number of post-warmup iterations (7,500), but the total number of iterations was increased above 25,000 in some cases in an attempt to reduce the number of divergences to less than 8 (< 0.1% of the post-warmup iterations). Divergences could not be reduced below 8 for MRs involving just high-dose studies.

[31]Betancourt (2018). https://arxiv.org/pdf/1701.02434.pdf.

DCS sensitivity analyses

EPA has examined the sensitivity of the estimates of the association between oral iAs exposure and DCS for five sources of uncertainty. The first relates to the choices made with respect to the characterization of the exposure levels used for the dose-response modeling. The second addresses sensitivity to choice of data sets. The third addresses the assumption that the general US population is not exposed to iAs via inhalation. The fourth addresses considerations of alternative gamma prior distributions for b_mean. The fifth addresses the use of urine biomarker studies in the meta-regression analysis.

The sources of uncertainty related to dose metric values are themselves broken down into two components. The first arises because of the need to estimate a mean value for the dose groups reported in terms of ranges of values (in whatever metric). The second relates to conversion of those mean exposure values to a consistent set of units across studies, those units being average daily μg/kg. The methods used to characterize those uncertainties are described in (Allen et al., 2020a). Table C-60 below summarizes the 95% confidence intervals for the meta-regression pooled b value and extra risk values for bladder cancer for the MLE, "low," and "high" iAs dose estimates shown in Table C-45. Note that, while the "low" dose estimates provide the largest extra risks, the extra risk values are not appreciably different across the different dose estimates, indicating that the analysis was relatively insensitive to the uncertainties associated with dose characterization.

Table C-60. Pooled mean b and extra risk estimates from meta-regression of DCS studies using MLE, "low," and "high" dose estimates

	Low dose estimates		MLE dose estimates		High dose estimates	
	Mean b	**Lifetime extra risk[a]**	**Mean b**	**Lifetime extra risk[a]**	**Mean b**	**Lifetime extra risk[a]**
CVD incidence						
5%	0.0018	1.65E-04	0.0022	2.04E-04	0.0026	2.36E-04
Mean	0.2405	2.17E-02	0.2305	2.08E-02	0.2404	2.17E-02
95%	0.8063	7.12E-02	0.7797	6.89E-02	0.8305	7.33E-02
IHD incidence						
5%	0.0063	3.29E-04	0.0068	3.55E-04	0.0066	3.46E-04
Mean	0.3428	1.78E-02	0.3442	1.78E-02	0.2690	1.40E-02
95%	1.0011	5.16E-02	0.8998	4.64E-02	0.6572	3.40E-02
Fatal CVD						
5%	0.0035	7.38E-05	0.0034	7.23E-05	0.0030	6.42E-05
Mean	0.2499	5.34E-03	0.2408	5.14E-03	0.2144	4.57E-03
95%	0.7692	1.66E-02	0.7105	1.53E-02	0.6566	1.41E-02
Fatal IHD						

	Low dose estimates		MLE dose estimates		High dose estimates	
	Mean b	Lifetime extra risk[a]	Mean b	Lifetime extra risk[a]	Mean b	Lifetime extra risk[a]
5%	0.0058	5.93E-05	0.0053	5.46E-05	0.0052	5.33E-05
Mean	0.4494	4.65E-03	0.4228	4.38E-03	0.3996	4.13E-03
95%	1.2571	1.33E-02	1.1607	1.22E-02	1.1041	1.16E-02

[a]Risk above zero dose; Estimated for a total dose of 0.13 µg iAs/kg-day, which includes an estimated 0.0365 µg iAs/kg-day background dose, 0.02 µg iAs/kg-day from diet and 0.0165 µg iAs/kg-day from drinking water.

With respect to sensitivity of the estimates to choice of dataset, note that the meta-regression approach avoids the issue of study selection by pooling the results of all the datasets. Nevertheless, it is of interest to determine how influential each of those studies are on the estimate of the pooled risk. That sensitivity has been investigated by computing the pooled estimate of risk when each of the data sets is iteratively excluded from the analysis (i.e., a leave-one-out analysis). Table C-61 to Table C-64 list the pooled and study-specific mean b values when one study is iteratively left out of the analysis. As can be seen, for CVD incidence, for which there are only two studies, the mean b estimate for (Chen et al., 2013) is 93% lower than the mean b estimate for (Moon et al., 2013). For meta-regressions involving more datasets, the greatest decrease (86%) is observed for fatal CVD when the dataset from (Moon et al., 2013) is excluded, and the greatest increase (53%) is observed For Fatal CVD when the dataset from (Wade et al., 2009) is excluded.

Table C-61. Results of the leave-one-out analysis for CVD incidence datasets using the MLE dose estimate

Study left out	Mean b values (5th–95th percentile)		
	Pooled	Chen et al. (2013)	Moon et al. (2013)
Chen et al. (2013)	–	–	0.54 (0.23–0.85)
Moon et al. (2013)	–	0.04 (0.01–0.06)	–

[a]Pooled estimate using all studies was 0.2305 (0.0022–0.7797) (see Table C-47).

Table C-62. Results of the leave-one-out analysis for IHD incidence datasets using the MLE dose estimate

Study left out	Mean b values (5th–95th percentile)				
	Pooled	Chen et al. (2013)	James et al. (2015)	Moon et al. (2013)	Wade et al. (2015)
Chen et al. (2013)	0.5009 (0.0105–1.248)	–	1.299 (0.2972–2.598)	0.5085 (0.1702–0.8456)	0.5136 (0.1423–0.8990)

Study left out	Mean b values (5th–95th percentile)				
	Pooled	Chen et al. (2013)	James et al. (2015)	Moon et al. (2013)	Wade et al. (2015)
James et al. (2015)	0.2249 (0.003–0.6470)	0.0399 (0.0097–0.0688)	–	0.3970 (0.0464–0.7743)	0.3845 (0.0462–0.7742)
Moon et al. (2013)	0.3648 (0.0007–1.4285)	0.0394 (0.0039–0.0727)	1.329 (0.0102–2.88)	–	0.4667 (0.0289–0.9772)
Wade et al. (2015)	0.3753 (0.004–1.167)	0.0395 (0.0091–0.0692)	1.374 (0.141–2.702)	0.4770 (0.103–0.8405)	–

[a]Pooled estimate using all studies was 0.3442 (0.0068–0.8998) (see Table C-50).

Table C-63. Results of the leave-one-out analysis for fatal CVD datasets using the MLE dose estimate

Study left out	Mean b values (5th–95th percentile)					
	Pooled	Chen et al. (2011)	D'Ippoliti et al. (2015)	Wade et al. (2009)	Moon et al. (2013)	Sohel et al. (2009)
Chen et al. (2011)	0.3486 (0.003–0.9923)	–	1.252 (0.3201–2.255)	0.0144 (−0.085–0.0995)	0.9151 (0.3708–1.425)	0.0156 (0.0074–0.0236)
D'Ippoliti et al. (2015)	0.0659 (0.0012–0.294)	0.0303 (0.009–0.0532)	–	0.0203 (−0.049–0.0846)	0.245 (−0.009–1.022)	0.0159 (0.008–0.0242)
Wade et al. (2009)	0.3603 (0.0046–1.021)	0.0338 (0.0105–0.0561)	1.233 (0.2538–2.162)	–	0.9169 (0.3297–1.434)	0.0157 (0.0074–0.0239)
Moon et al. (2013)	0.0327 (0.0009–0.1035)	0.0285 (0.0087–0.0517)	0.1046 (−0.0222–0.629)	0.0199 (−0.032–0.0726)	–	0.0160 (0.0079–0.024)
Sohel et al. (2009)	0.3572 (0.0053–1.004)	0.0340 (0.011–0.0562)	1.261 (0.3622–2.172)	0.0128 (−0.0897–0.096)	0.9256 (0.3879–1.4266)	–

[a]Pooled estimate using all studies was 0.2408 (0.0034–0.7105) (see Table C-53).

Table C-64. Results of the leave-one-out analysis for fatal IHD datasets using the MLE dose estimate

Study left out	Mean b values (5th–95th percentile)				
	Pooled	Chen et al. (2011)	D'Ippoliti et al. (2015)	Wade et al. (2009)	Moon et al. (2013)
Chen et al. (2011)	0.5308 (0.0056–1.505)	–	2.022 (0.9418–3.081)	0.0793 (−0.042–0.1493)	1.120 (0.5621–1.680)
D'Ippoliti et al. (2015)	0.2281 (0.0026–0.7447)	0.04566 (−0.016–0.0862)	–	0.0778 (0.0052–0.1474)	0.776 (0.051–1.495)
Wade et al. (2009)	0.5329 (0.0047–1.517)	0.0452 (−0.002–0.0863)	2.016 (0.9062–3.101)	–	1.126 (0.5462–1.691)
Moon et al. (2013)	0.3422	0.0453	1.671	0.0777	–

Study left out	Mean b values (5th–95th percentile)				
	Pooled	Chen et al. (2011)	D'Ippoliti et al. (2015)	Wade et al. (2009)	Moon et al. (2013)
	(0.0027–1.153)	(−0.0026–0.0868)	(0.0574–2.969)	(0.0035–0.1469)	

[a]Pooled estimate using all studies was 0.4228 (0.0053–1.1607) (see Table C-56).

Although inhalation of inorganic arsenic is not considered a primary route of exposure for the general public, the World Health Organization (WHO) estimates that background exposure may range from 0.02 to 0.6 μg/day in areas without substantial arsenic emissions from anthropogenic sources. Assuming an average body weight of 70 kg, this corresponds to daily intake values of 2.9×10^{-4} μg/kg-day to 8.6×10^{-3} μg/kg-day. The third sensitivity analysis involved two extra lifetable analyses wherein background inhalation components of either 4.4×10^{-3} μg/kg-day (corresponding to the midpoint of the range of reported background iAs concentrations), or 8.6×10^{-3} μg/kg-day (corresponding to the upper limit of background concentrations) were added to the original background estimate of exposure due to dietary and drinking water sources (i.e., 0.0365 μg/kg-day). Incorporation of inhalation exposures in the background estimate of total exposure also did not result in dramatically different estimates of extra risk. By definition, as the estimate of background exposure increased in the lifetable analysis, calculated extra risks must correspondingly decrease. Thus, for all four DCS health outcomes analyzed, at a 0.13 μg/kg-day iAs dose (approximately equal to a lifetime drinking water exposure of 10 μg/L), when the assumed background exposure was either 0.0409 μg/kg-day or 0.0451 μg/kg-day, the maximum percentage decreases in extra risks were 0.2% (4.37×10^{-3}) and 0.5% (4.36×10^{-3}) for fatal IHD compared to 4.38×10^{-3} when no inhalation component was included in the background estimate of exposure.

Finally, the assumption of different Gamma prior distributions for β_mean did not result in large differences in the posterior distributions of the β_mean parameter (see Table C-65 to Table C-68). Interestingly, the alternative prior sensitivity results indicated that, for the present set of studies used in this case-example, the results of the dose-response meta-analysis are rather insensitive to assumptions on the gamma distribution prior. For example, using priors that differed with respect to the 1st percentile (i.e., 1.00001 – 20 and 1.001 – 20) resulted in the greatest differences in the mean of the posterior distribution relative to the original prior. This is due to the characteristics of the Gamma distribution, in which the greatest density with respect to probability of response is close to zero. So, when using the 1.00001 – 20 prior, the corresponding posterior mean distributions were an average of 15% lower across the four DCS outcomes than the results with their original prior because the 1st percentile is assumed to be ten times lower than for the original prior. Correspondingly, the 1.001 – 20 prior posterior mean distributions were an average of 12% higher across the four DCS outcomes than their original priors. Alternate Gamma prior distributions that differed with respect to the 99th percentile also did not differ greatly from the results using the original prior: using a prior with an upper bound of 10 (i.e., 50% lower than the

original) resulted in posterior means that were an average of 10.5% lower across the four DCS outcomes, and using a prior with an upper bound of 30 (i.e., 50% higher than the original) resulted in posterior means that were an average of 6% higher across the four DCS outcomes. This broadly indicates that the results of the analysis are heavily influenced by the actual data being modeled and are not inappropriately driven by the prior assumptions of the Bayesian modeling.

Table C-65. Posterior β_mean distribution values for CVD incidence resulting from various prior Gamma distributions

Alternative prior	5th percentile	Mean	95th percentile	% Mean difference
1.00001 – 20	0.0004	0.1960	0.7053	−15%
1.0001 – 10	0.0020	0.2070	0.6912	−10%
1.0001 – 30	0.0024	0.2384	0.7950	3%
1.001 – 20	0.0083	0.2858	0.8743	24%
Original Prior (1.0001 – 20)	0.0022	0.2305	0.7797	–

Table C-66. Posterior β_mean distribution values for IHD incidence resulting from various prior Gamma distributions

Alternative prior	5th percentile	Mean	95th percentile	% Mean difference
1.00001 – 20	0.0017	0.3175	0.9190	−8%
1.0001 – 10	0.0058	0.3206	0.8853	−7%
1.0001 – 30	0.0059	0.3678	0.9946	7%
1.001 – 20	0.0243	0.3966	0.9996	15%
Original Prior (1.0001 – 20)	0.0068	0.3442	0.8998	–

Table C-67. Posterior β_mean distribution values for fatal CVD resulting from various prior Gamma distributions

Alternative prior	5th percentile	Mean	95th percentile	% Mean difference
1.00001 – 20	0.0006	0.1995	0.6915	−17%
1.0001 – 10	0.0029	0.2320	0.7296	−4%
1.0001 – 30	0.0024	0.2355	0.7696	-2%
1.001 – 20	0.0094	0.2793	0.7997	16%
Original Prior (1.0001 – 20)	0.0034	0.2408	0.7105	–

Table C-68. Posterior β_mean distribution values for fatal IHD resulting from various prior Gamma distributions

Alternative prior	5th percentile	Mean	95th percentile	% Mean difference
1.00001 – 0	0.0014	0.3994	1.195	−6%
1.0001 – 10	0.0045	0.3962	1.122	−6%

Alternative prior	5th percentile	Mean	95th percentile	% Mean difference
1.0001 – 30	0.0051	0.4505	1.281	7%
1.001 – 20	0.0190	0.4970	1.278	18%
Original Prior (1.0001 – 20)	0.0053	0.4228	1.161	–

The last sensitivity analysis investigated to what degree the inclusion of urinary biomarker studies influenced the modeled association between iAs intake and the four DCS health outcomes. As shown in Table C-61, removal of the only CVD incidence urinary study (Moon et al., 2013) had the biggest meta-regression impact because the bmean estimate of 0.04 for the only other study (Chen et al., 2011) was 93% lower than the 0.54 bmean estimated for (Moon et al., 2013). As shown in Table C-62, removal of the only IHD incidence urinary study (Moon et al., 2013) resulted in a moderate 7% increase in the bmean. Removal of both the (Chen et al., 2011) and (Moon et al., 2013) urinary studies resulted in a bmean decrease of 6% for fatal CVD and a bmean increase of 11% for fatal IHD. For fatal CVD, removal of the (Chen et al., 2011) study increased the bmean by 48% and removal of the (Moon et al., 2013) study decreased the bmean by 86% (see Table C-63). Individual removal of either study from the fatal IHD meta-regression resulted in a 23–24% increase in the bmean (see Table C-64). This pattern is expected as (Moon et al., 2013) is a low-dose study and (Chen et al., 2011) is a high-dose study (see Table C-43).

Extrapolation to target U.S. population

Approximate lifetable lifetime risk approach for CVD and IHD incidence

The posterior distribution for the "pooled" (average) value of the logistic slope parameter, β_mean, was used with U.S. all-cause mortality and CVD and IHD mortality rates as input to a lifetable calculation of the lifetime probability of fatality from these health outcomes as a function of iAs dose (average daily μg/kg). For CVD and IHD incidence, because lifetables are not available, the logistic slope parameter, β_mean, was used with a summary value for the U.S. lifetime probability of developing CVD and IHD[32] to estimate the lifetime probability developing these CVD and IHD incidence as a function of iAs dose (average daily μg/kg). The methodology is described in (Allen et al., 2020b). The exposure scenario used for these extrapolations posits a continuous, full lifetime exposure to a constant iAs dose. The CVD and IHD incidence background lifetime probabilities for the lifetable data used in the analyses are estimated to be 0.7 (Leening et al., 2014) for CVD incidence[33] and 0.4 for IHD incidence (Lloyd-Jones et al., 1999).[34]

[32]For CVD and IHD incidence, age-stratified morbidity and mortality values were not available; therefore, a summary estimate of the lifetime probability of developing these health outcomes were used instead.
[33]Leening et al. (2014) reported similar lifetime risk of CVD at an index age of 55 years for men (67.1%) and women (66.4%) living in Rotterdam, the Netherlands.
[34]Lloyd-Jones et al. (1999) reported lifetime risks of IHD (CHD) at an index age of 40 years for men (48.6%) and women (31.7%) enrolled in large Framingham Heart Study.

Lifetable lifetime risk algorithm approach for fatal CVD

Table C-69. Lifetable rates for all-cause mortality and CVD mortality

Age range	All-cause mortality rates (per 100,000)[a]	CVD mortality rates (per 100,000)[b]	Adjusted CVD mortality rates (per 100,000)[c]
0–1	567	10.7	0
1–4	24.3	1.2	0
5–9	11.6	0.7	0
10–14	15.5	0.7	0
15–19	51.5	2.6	2.6
20–24	95.6	2.6	2.6
25–29	121	10.1	10.1
30–34	145.4	10.1	10.1
35–39	173.8	32.2	32.2
40–44	218.4	32.2	32.2
45–49	313.2	95.9	95.9
50–54	488	95.9	95.9
55–59	736.5	237.2	237.2
60–64	1050.2	237.2	237.2
65–69	1473.5	505.60	505.6
70–74	2206.9	505.60	505.6
75–79	3517.8	1,391.30	1391.3
80–84	5871.7	1,391.30	1391.3

[a]National Vital Statistics Report (2019), Volume 68, Number 9, Final Data for 2017, Table 2, "All Races–Both Sexes" (https://www.cdc.gov/nchs/data/nvsr/nvsr68/nvsr68_09-508.pdf).
[b]National Vital Statistics Report (2019), Volume 68, Number 9, Final Data for 2017, Table 7, "Major cardiovascular diseases" (I00–I78).
[c]Assumes CVD mortality from low level arsenic exposure would not occur prior to 15 yrs of age.

Lifetable Lifetime Risk Algorithm Approach for Fatal IHD

Table C-70. Lifetable rates for all-cause mortality and IHD mortality

	All-cause mortality rates (per 100,000)[a]	IHD mortality rates (per 100,000)[b]	IHD mortality rates (per 100,000)[c]
0–1	594.7	0	0
1–4	25.5	0	0
5–9	13	0	0
10–14	13	0	0
15–19	64.8	0.3	0.3

	All-cause mortality rates (per 100,000)[a]	IHD mortality rates (per 100,000)[b]	IHD mortality rates (per 100,000)[c]
20–24	64.8	0.3	0.3
25–29	106.1	2.4	2.4
30–34	106.1	2.4	2.4
35–39	172	12.3	12.3
40–44	172	12.3	12.3
45–49	406.1	48.5	48.5
50–54	406.1	48.5	48.5
55–59	860	121.1	121.1
60–64	860	121.1	121.1
65–69	1,802.10	258.1	258.1
70–74	1,802.10	258.1	258.1
75–79	4,648.10	683.5	683.5
80–84	4,648.10	683.5	683.5

[a]National Vital Statistics Report, 2016, Table 11, Volume 64, Number 2, 2/16/2016, 2013 rates for "All causes" (http://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_02.pdf).
[b]Table 11, National Vital Statistics Report, 2013 rates for "Ischemic heart diseases" (I20–I25).
[c]Assumes IHD mortality from low level arsenic exposure would not occur prior to 15 yrs of age.

C.2. DOSE-RESPONSE ANALYSIS FOR NEUROCOGNITIVE EFFECTS

C.2.1. Screening of Studies that Evaluate Neurodevelopmental Endpoints

As discussed in Section 1.2 of the assessment, EPA conducted a screening of 11 health outcomes with published relative risk (RR) estimates, but neurodevelopmental effects could not be analyzed with this screening approach because all of the measured responses are continuous outcomes (e.g., IQ) (Hobbie et al., 2020). This Appendix will address study selection and dose-response analysis EPA conducted for neurodevelopmental effects, particularly neurocognitive endpoints.

Table C-71 describes 26 studies that evaluated relationships between arsenic exposure and neurocognitive endpoints, such as effects on intelligence scores, motor skills, or behavioral traits. These studies possess a number of characteristics that differ from the studies of cancer and other dichotomous endpoints, and thus the screening methods used to identify neurocognitive studies for dose-response analysis differed from those applied to other endpoints. Besides the previously mentioned lack of published RRs, major differences in the studies include the predominance of continuous endpoints (such as IQ scores), and the frequent use of cross-sectional study design for evaluating neurodevelopmental effects in children and infants. Thus, the aim of screening neurocognitive studies was more focused on rating them with regard to overall quality and determining which studies could furnish data for the dose-response analyses described in Appendix C and summarized in assessment Section 1.5.

The initial screening process for neurocognitive studies was very similar to that described above for the other endpoints, with markdowns assigned to all studies that were not initially excluded. One exception was that cross-sectional studies were not automatically subject to "Initial Exclusion"; cross-sectional design was considered appropriate for evaluating neurocognitive effects, particular where developmental effects were being evaluated in infants or children. The secondary screening process (assigning markdowns) was also similar to that described by (Hobbie et al., 2020) for other endpoints, except that the meaning and scoring approach was changed for some markdown criteria. First, the "endpoint" markdown criteria were assigned markdown ratings based primarily on whether the test instruments used to measure cognitive effects validated and appropriate, rather than whether incidence or mortality was reported. Second, the "Sufficient number of subjects, cases" markdown was modified to "Sufficient cases," because, as noted above, most of the studies evaluated continuous endpoints, and thus the number of "cases" was not a primary outcome. This criterion served as a proxy for the power of a given study to detect differences in, for example, mean IQ scores across exposure groups. Also, the "Subjects, cases, reported" markdown was removed, subsumed into "Sufficient cases."

Finally, the "All data available for evaluation" criterion was emphasized; unlike other endpoints, all studies received markdown scores for data availability, and the "S", "LS", and "NS" ratings were included in the total markdown scores for each study. This approach was employed because the dose-response methodology applied for neurocognitive endpoints (which involved explicit evaluation of covariates and alternative multivariate models) was more demanding than the relative risk calculations performed for the other endpoints. As shown in Table C-71, inclusion of this criterion strongly effects the relative markdown totals for the MLE studies (those with the lowest numbers of markdowns).

Table C-71. Neurocognitive exposure-response study selection

Study	Initial screen. rec.	Rationale for initial exclusion	Endpoint[a]	Exposure		Est. adj[b]. (Smoking, gender, age)	Number exp. grps.	Exposure		Ref. grp. represent.	Sufficient subjects	Mark-downs[c]	All data available for DR	Data pro-vided by author	Final rec.
				Ascertain.	Uncertainty			Metric	Timing, Dur.						
Adams et al. (2013)	exclude	not exp. study; comp. means of single blood, RBC, urine measurements of autistic and neurotypical children (5–16 yr. old); very limited dose-response information; might contain info useful for Tier 2 due to evaluation of different internal dose metrics (blood, urine, RBC) and unique endpoint (autism)										NA			
Calderón et al. (2001)	exclude	only provided 2 mean doses (urinary levels) and 2 mean responses (WISC-RM test results); consider for Tier 2 meta-regr. if										NA			

Study	Initial screen. rec.	Rationale for initial exclusion	Endpoint[a]	Exposure		Est. adj[b]. (Smoking, gender, age)	Number exp. grps.	Exposure		Ref. grp. represent.	Sufficient subjects	Mark-downs[c]	All data available for DR	Data pro-vided by author	Final rec.
				Ascertain.	Uncertainty			Metric	Timing, Dur.						
		appropriate for combination with other similar studies													
Hamadani et al. (2010)	consider		S	S	S	S	NA (regression)	S	S	NA	S	2	NS (only unadjusted scores + regression coefficients)	No	exclude
Hamadani et al. (2011)	consider		S	S	S	S	NA (regression)	S (U)	S	NA	S	2	NS (only unadjusted scores + regression coefficients)	No	exclude
Hsieh et al. (2014)	consider		S	S	S–LS	S	S–LS	S	S–LS	S[d]	S–LS	4.5	NS (unadjusted statistics and histograms	No	exclude
Khan et al. (2012)	exclude	Mn study of impact of Mn exp. on academic achievement										NA			

Study	Initial screen. rec.	Rationale for initial exclusion	Endpoint[a]	Exposure		Est. adj[b]. (Smoking, gender, age)	Number exp. grps.	Exposure		Ref. grp. represent.	Sufficient subjects	Mark-downs[c]	All data available for DR	Data pro-vided by author	Final rec.
				Ascertain.	Uncertainty			Metric	Timing, Dur.						
		scores; no As dose-response information provided, although authors claim As had no impact on academic achievement scores and did not confound results													
Nahar et al. (2014a)	consider		S	S	S–LS	S-LS	NA (regression)	S	S-LS	NA	S	3.5	LS (unadjusted means and histograms, regression predictions)	No	exclude
Nahar et al. (2014b)	consider		S	S	S–LS	S-LS	S[e]	S	LS	S[e]	S	3	LS (unadjusted means, histograms, and trend chart)	No	exclude
Onicescu et al. (2014)	exclude	modeling results, not										NA			

Study	Initial screen. rec.	Rationale for initial exclusion	Endpoint[a]	Exposure		Est. adj[b]. (Smoking, gender, age)	Number exp. grps.	Exposure		Ref. grp. represent.	Sufficient subjects	Mark-downs[c]	All data available for DR	Data pro-vided by author	Final rec.
				Ascertain.	Uncertainty			Metric	Timing, Dur.						
		amenable to dose-response analysis; subjects obtained from Medicaid records, no information provided on methods; exp. interpolated based on measured levels in specific areas, but specific analytic methods not reported													
Parajuli et al. (2014)	consider		S	S	S-LS	S	NA (regression)	LS (cord blood)	S	NA	S	3.5	NS (no, no exp. levels presented)	No	exclude
Parajuli et al. (2015a)	exclude	small no. subjects, cord blood arsenic measurements (also lead), regr. analysis only (change in score)										NA			
Parajuli et al. (2015b)	exclude	same pop. as above, but										NA			

Study	Initial screen. rec.	Rationale for initial exclusion	Endpoint[a]	Exposure		Est. adj[b]. (Smoking, gender, age)	Number exp. grps.	Exposure		Ref. grp. represent.	Sufficient subjects	Mark-downs[c]	All data available for DR	Data pro-vided by author	Final rec.
				Ascertain.	Uncertainty			Metric	Timing, Dur.						
		measured again at 36 mos. (above is at 24 mos.)													
Parvez et al. (2011)	exclude	same study and cohort as Wasserman et al. (2011) but examined motor function; high-quality study examining As and Mn relationship, but provides only 2 As doses (urinary, well levels and blood levels); consider for Tier 2 meta-regr. if appropriate for combination with other similar studies										NA			
Rocha-Amador et al. (2007)	exclude	unless individual data obtained; reports exp. mean and SD for As urine levels and IQ corr. coeff. for 3 pops., but gives										NA			

Study	Initial screen. rec.	Rationale for initial exclusion	Endpoint[a]	Exposure		Est. adj[b]. (Smoking, gender, age)	Number exp. grps.	Exposure		Ref. grp. represent.	Sufficient subjects	Mark-downs[c]	All data available for DR	Data pro-vided by author	Final rec.
				Ascertain.	Uncertainty			Metric	Timing, Dur.						
		no mean or SD for IQ scores													
Rodríguez-Barranco et al. (2016)	consider		S	S	S-LS	S	NA (regression)	S	LS	NA	S	3.5	NS (no; only betas provided)	No	exclude
Roy et al. (2011)	consider		S-LS	S (U)	S–LS	S	S[e]	S (U)	LS	S[e]	S	4	NS (no means and standard deviations reported by exp. Group)	No	exclude
Tofail et al. (2009)	consider		S	S–LS	S	S	S[e]	S (U)	S–LS (U)	S[e]	S	2	LS (unadjusted means, regression coefficients	No	exclude
Tsai et al. (2003)	exclude	several limitations: small sample sizes, high potential for occupational co-exp. to (farming) pesticides and										NA			

Study	Initial screen. rec.	Rationale for initial exclusion	Endpoint[a]	Exposure		Est. adj[b]. (Smoking, gender, age)	Number exp. grps.	Exposure		Ref. grp. represent.	Sufficient subjects	Mark-downs[c]	All data available for DR	Data pro-vided by author	Final rec.
				Ascertain.	Uncertainty			Metric	Timing, Dur.						
		other chemicals; questionable applicability of occupational neuro tests to general pop. and to children													
Vibol et al. (2015)	exclude	most results evaluated by site (control, moderately contaminated, highly contaminated), but also examined hair arsenic levels (& a few other metals)										NA			
von Ehrenstein et al. (2007)	consider		S	S	S	S	S–LS	S	S	NA	S (continuous response)	2.5	NS (no means and standard deviations reported by exp. Group)	No	exclude
Wang et al. (2006)	exclude	important limitations: high As exp. uncertainty and co-exp. to										NA			

Study	Initial screen. rec.	Rationale for initial exclusion	Endpoint[a]	Exposure		Est. adj[b]. (Smoking, gender, age)	Number exp. grps.	Exposure		Ref. grp. represent.	Sufficient subjects	Mark-downs[c]	All data available for DR	Data pro-vided by author	Final rec.
				Ascertain.	Uncertainty			Metric	Timing, Dur.						
		fluoride (also suspected of causing IQ effects)													
Wasserman et al. (2004)	consider		S	S	S-LS	S	NA (regression)	S–LS	S-LS	NA	S	1.5	S (Not shown in article but provided by authors)	Yes	include
Wasserman et al. (2007)	consider		S	S (U, drinking water)	S-LS	S	S[e]	S (U, drinking water)	S-LS	S[e]	S	3	(NS) Not provided	No	exclude
Wasserman et al. (2011)	exclude	high-quality study of As-Mn relationship, but provides only 2 As doses (urinary, well levels and blood levels); consider for Tier 2 meta-regr. if appropriate for combination with other similar studies										NA			
Wasserman et al. (2014)	consider		S	S	S	LS[f]	S	S	S–LS	S[e]	S	1.5	S (Not shown in article but	Yes	include

Study	Initial screen. rec.	Rationale for initial exclusion	Endpoint[a]	Exposure		Est. adj[b]. (Smoking, gender, age)	Number exp. grps.	Exposure		Ref. grp. represent.	Sufficient subjects	Mark-downs[c]	All data available for DR	Data pro-vided by author	Final rec.
				Ascertain.	Uncertainty			Metric	Timing, Dur.						
													provided by authors)		
Wright et al. (2006)	exclude	exp. measured in terms of hair metals levels, incl. arsenic; no other exp. measurements taken										NA			

S=suitable; LS= less suitable; NS=not suitable

[a]Based on validity of measurement technique.

[b]Adjustment for smoking not relevant for some studies of infants, children.

[c]Total markdown score includes contribution from "all data available."

[d]Case-control study of dichotomous endpoint.

[e]Quartile comparison of mean scores.

[f]Adjusted for SES, maternal characteristics, and other covariates, but not for lead exposure.

C.2.2. Neurocognitive Effects Exposure-Response Modeling Results

As shown in Table C-71, all but two of the studies were marked down (LS, NS) because they did not provide sufficient data to support dose-response analysis. Therefore, EPA conducted dose-response analyses for only two studies (Wasserman et al., 2014; Wasserman et al., 2004) for which the authors provided raw data on exposures, outcomes, and covariates.

Wasserman et al. (2004)

Wasserman et al. (2014) recruited 201 10-year-olds from a random draw of families in the HEALS (Health Effects of Arsenic Longitudinal Study) cohort in Araihazar, Bangladesh. The HEALS cohort is known to have had long-term exposures to medium-high levels of arsenic in drinking water, which is obtained primarily from residential wells in the area (Ahsan et al., 2006) In the IQ study, arsenic exposure was characterized using residential (household) well water arsenic concentrations and speciated urinary arsenic measurements for each subject. Blood lead and hemoglobin measurements were obtained from approximately half of the children (108). Data were collected from each household concerning covariates including housing quality (roof type), television access, father's occupation and mother's age and IQ. Age, gender, height, weight, BMI, and head circumference were also recorded for each subject.

The primary outcome measures in the study were IQ scores based on subsets of questions from the Wechsler Intelligence Scale for Children, Version III. Items were removed or edited to improve cultural relevance. Results were reported as Full-Scale, Verbal, and Performance IQ raw scores; the raw test results were also normed using standard procedures, but statistical analyses were performed based on the raw scores because the norming process (derived for European and North American children) was not considered reliable for the Bangladeshi subjects.

Population characteristics and exposure metrics

Population characteristics for the (Wasserman et al., 2004) are provided in Table 1 of the article. In terms of physical characteristics, the Bangladeshi children are small compared to European norms (mean head circumference < 2nd percentile, mean height and BMI < 5th percentile.) However, hemoglobin levels were not depressed (12.6 ± 0.4 gm/dL), suggesting that the population was not severely iron or protein deficient. Urinary creatinine levels (43.3 ± 34.1 mg/dL) in the (Wasserman et al., 2004) cohort are also approximately equal to the 10th percentile value for U.S. children of the same age [42.8 mg/dL, (Barr et al., 2005)]. The lower levels are presumably due to the lower body weights and presumed lower muscle mass in the Bangladeshi children.

Approximately 64% of the children's fathers reported employment, as "factory, business, or other paid job," the remainder being farmers (23%) or "missing" (11%). About 74% of families lived in houses with tin roofs, indicative of a (locally) mid-range social status and wealth, and 35% of children had access to television.

Household well water arsenic concentrations were 117.8 ± 145.2 µg/L (mean, ± standard deviation), ranging from .094–790, geometric mean = 24.3 µg/L. The measured urinary arsenic levels were 116.6 ± 148.8 µg/L and 296.6 ± 277.2 µg /gm creatinine. Log-transformed household water and creatinine-adjusted urinary arsenic were strongly and significantly correlated (R = 0.36, $p < 0.001$.) The authors also measured manganese concentrations in household wells (1,368 ± 927 µg/L.) The mean blood lead measurement in 108 children was 10.1 µg/dL, with a standard deviation of 3.3 µg/dL.

Results

The authors focused their analysis on raw test scores owing to the uncertainties associated with the lack of validated norming procedures for the specific test population. Raw scores on all three tests were found to be correlated with arsenic exposure within quartiles ranked by drinking water arsenic levels (see Table C-72). For Full-Scale and Performance IQ, exposure-response relationships across the quantiles were monotonic and the mean scores of the 2nd through 4th quartiles were statistically different from those in the low exposure group in univariate analyses. For Verbal IQ, the difference among quartiles was smaller, and was not statistically significant except in the 4th (highest exposure) quartile.

Table C-72. Water concentrations and raw IQ scores by quartile

Water arsenic concentration range, µg/L	Mean, median water arsenic concentration, µg/L	Full-scale IQ raw score (mean ± std. dev.)	Performance IQ raw score (mean ± std. dev.)	Verbal IQ raw score (mean ± std. dev.)
0.1–5.5	0.99, 0.49	79.4 ± 20.6	61.7 ± 17.5	17.6 ± 5.1
5.6–50.0	25.3, 25.6	69.5 ± 22.2*	52.5 ± 17.7*	17.0 ± 5.4
50.1–176	108.1, 103.5	67.8 ± 18.4*	51.5 ± 15.4*	16.3 ± 5.1
177–790	333, 316	65.6 ± 19.7*	50.2 ± 17.1*	15.3 ± 4.9*

Note: * indicates that the mean IQ score for a given group is significantly different (t-test, $p < 0.05$) from the referent (low-exposure) subjects.

After adjustment for important ("core") sociodemographic and individual covariates (subject height and head circumference, housing quality, mother's education, mother's IQ score), the differences between mean Full-Scale and Performance IQ raw scores were significantly different from the low-exposure group only in the 3rd and 4th quartiles. That is, mean Full-Scale and Performance IQ were found to be significantly reduced in subjects with water arsenic concentrations greater than 50 µg/L, compared to those with drinking water concentrations of 5.5 µg/L or less. The reduction in adjusted mean Verbal IQ score in the 4th quartile (water arsenic > 177 µg/L) was only marginally significant ($p < 0.1$) compared to the referent group. The differences on adjusted mean IQ across water arsenic quartiles is illustrated in Figure 1 from the original article.

The authors also performed regression analysis in which log-transformed water arsenic concentrations were included in the model as continuous variables, along with the same "core" variables noted above. The results of the regression analyses are summarized in Table C-73. It can be seen that the regression coefficients for (log) water arsenic were relatively large and statistically significant predictors of both Full-Scale and Performance IQ; the coefficients indicate that for each natural log change in water arsenic (approximately 2.7-fold), individual Full-Scale and Performance IQ are predicted to decrease by approximately 1.64 and 1.45 points, respectively. In contrast, the coefficient representing the association between log water arsenic and verbal IQ is smaller, and not statistically significant.

Table C-73. Adjusted regression coefficients for log(water arsenic)

Test result	Adjusted β	Standard error	t	*p*-value	R^2
Full-Scale	−1.64	0.498	−3.29	0.0011	0.32
Performance	−1.45	0.423	−3.41	0.0008	0.29
Verbal	−0.193	0.130	−1.48	0.14	0.23

Table C-74 shows the predicted changes in IQ test scores associated with specific concentrations of arsenic in drinking water. For Full-Scale and Performance IQ, the differences in scores range from about −2.3 to approximately −6.4 across the range of water arsenic concentrations from 5 to 50 μg/L. The numbers in parentheses are standardized mean differences from referent groups, that is, they indicate the approximate difference from the referent group in terms of the numbers of referent group standard deviations. It can be seen that predicted changes in IQ associated with arsenic, although statistically significant, are relatively small relative to the observed variability in individual IQ values. Table C-74 shows the observed Full-Scale IQ values in the exposure range 0–100 μg/L, along with the values predicted by the multivariate regression model based on log water arsenic.

Table C-74. Predicted reductions in IQ test scores associated with water arsenic exposures

Water arsenic concentration	5 μg/L	10 μg/L	50 μg/L
Full-Scale	−2.637 (0.13)*	−3.773 (0.18)	−6.410 (0.31)
Performance	−2.326 (0.13)	−3.328 (0.19)	−5.655 (0.32)
Verbal	−0.311 (0.06)	−0.445 (0.09)	−0.755 (0.15)

Note: Numbers in parentheses are standardized mean differences from referent groups.

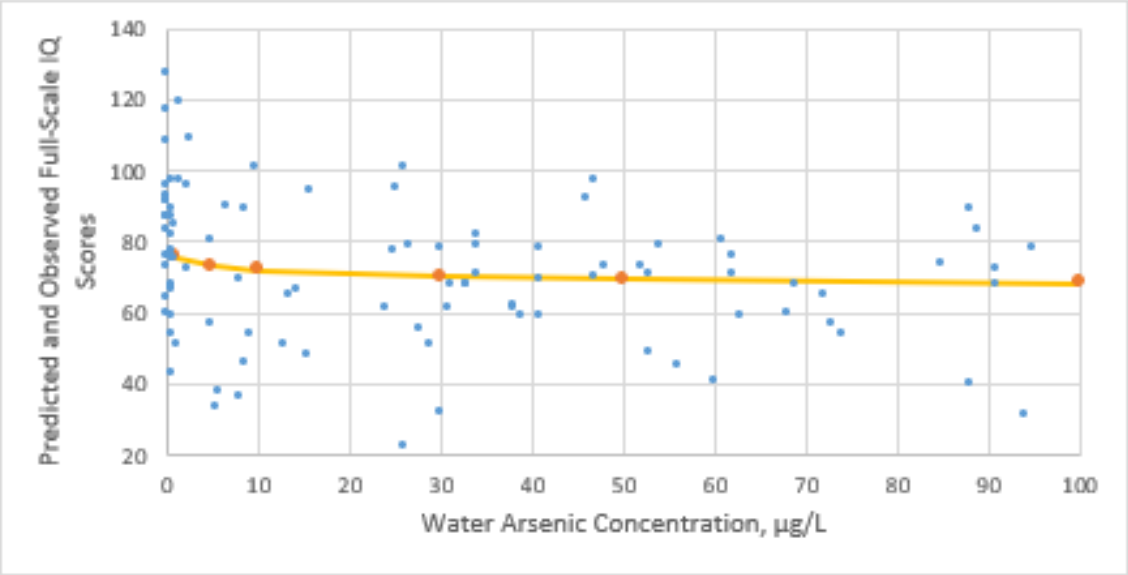


Figure C-52. Comparison of observed and predicted IQ scores in the Wasserman et al. (2004) cohort.

The predicted IQ changes should be interpreted cautiously, since they are all calculated relative to a baseline concentration of 1 µg/L, which is conventionally used in such situations. Because the log-linear models estimated by the regressions are very strongly curved at low exposures, the assumed baseline value makes a large difference in the predicted IQ impacts. Figure 2 in (Wasserman et al., 2004) clearly illustrates the extreme curvature of the model predictions at low exposures.

Multiple regression analyses were repeated including creatinine-adjusted urinary arsenic as a continuous variable. Coefficients were negative for all three of the test scores but failed to achieve statistical significance at the $p < 0.05$ level. The authors also investigated the potential role of metabolic differences, and co-exposures to lead and mercury. They found that the proportions of the inorganic arsenic, MMA, and DMA in urine were not significant predictors of IQ when included in the core model. Similarly, blood lead and mercury concentrations were not found to be significantly associated with IQ scores in the subset of subjects where they had been measured, whether or not water arsenic was included.

Dose-response considerations

Wasserman et al. (2004) report robust associations between household water arsenic concentrations and the results in two of three intelligence tests administered to Bangladeshi children. Based on these data, it is possible to develop approximate estimates of the amount of arsenic ingested in water by the exposed subjects. This exercise is inevitable imprecise, however, because the amounts of water ingested by individual subjects are not known and need to be

estimated based on studies of similar populations elsewhere. In addition, there is always the question of what proportion of drinking water the subjects actually received from the "index" wells, and how much came from other sources. Given that the subjects were children, and that residential mobility is low among the study population (Ahsan et al., 2006), it seems likely that the subjects obtained a large proportion of their drinking water from the identified household wells.

The average water consumption rates for adults in the HEALS cohort were 2.9 L/day for males and 3.1 L/day for females (Ahsan et al., 2006). Given the generally low body weights in the cohort, this corresponds to mean water intake approximately 0.065 L/kg-day. This is approximately 4.6-fold higher than the estimated mean adult water intake among U.S. adults of 0.014 L/kg-day (U.S. EPA, 2011), probably due to climatic differences. Other studies (Rahman et al., 2009a; Chowdhury et al., 2000) have also reported daily adult water intakes in Bangladesh in the same range (2.5–4.0 L), without reporting consumption per body weight. However, Hossain et al. (2013) studies age-specific water intake pattern in a similar rural population in West Bengal, India. The authors reported mean average direct water intakes of 3.95, 3.03 and 2.14 L/day for adult males, females, and children; the population average water consumption was 0.078 L/kg-day (including children.)

The above data provide an approximate basis for estimating water consumption rates (and hence water arsenic intake) in the Wasserman et al. (2004) subjects. Based on the data collected by Hossain et al. (2013) it appears that water consumption in children aged 10 is about 2.2 L/day, raising to an average of approximately 3.5 L/day during adulthood (see their Figure 1.) While the water consumption expected for these children is this about 63% of adults, their body weights are also lower. Using the HEALS data as a guide, it can be calculated that the average adult body weight is 47 kg (data not shown), while the mean body weight in the Wasserman et al. (2004) study (recruited from the families of HEALS participants) is 22 kg. Combining these two ratios suggests that the water consumption in the Wasserman et al. (2004) subjects (children) was about 1.34 times that of adults in the same cohort, or about (1.34 * 0.065 ~ 0.087) L/kg-day. As noted above, it is difficult to estimate the degree of uncertainty surrounding this estimate but rounding (upwards) to one significant figure is probably appropriate; thus, we estimate the approximate water consumption in the Wasserman et al. (2004) cohort as being on the order of 0.09 L/kg-day. This implies that the daily arsenic dose associated with each 1 µg/L increment of arsenic in drinking water would be approximately 0.09 µg/kg-day.

As noted above, Wasserman et al. (2004) found significant reductions in covariate-adjusted Full-Scale and Performance IQ scores in subjects exposed to drinking water arsenic concentrations > 50 µg/L compared to the referent group with exposures < 5 µg/L. Using the conversion factor derived in the previous paragraph, this suggests a LOAEL of approximately 4.5 µg/kg-day direct water arsenic intake for changes in IQ scores. This estimate is probably low, because it neglects likely contributions from diet, including both arsenic in food and "indirect" (cooking) water arsenic intake as well. A number of studies have attempted to derive estimates of dietary arsenic intake in

Bangladesh and in similar populations (Rahman et al., 2009b; Kile et al., 2007). These authors have found wide variations in the relative proportions of inorganic arsenic intake from diet and drinking water, with major factors that influence the balance including the relative concentrations of arsenic in raw rice, vegetables, and drinking water, the absolute concentration of arsenic in cooking water, the specific cooking method used to prepare foods, and arsenic speciation in rice and vegetables. While drinking water tends to be the dominant source of inorganic arsenic where water is highly contaminated (> than 100 µg/L), diet can contribute substantially to total intake if water concentrations are lower.

Because the water arsenic concentrations are so highly variable in the Wasserman et al. (2004) cohort, and because individual dietary data are lacking, it is not possible to reliably estimate the additional arsenic intake above that from drinking water. (Kile et al., 2007) estimated that the average dietary inorganic arsenic intake for adult females in a similar Bangladeshi population was 48 µg/day. EPA's analysis of the HEALS data (not shown) suggests a "background" dietary arsenic intake of approximately 62 µg/day in adults with low water arsenic concentrations. Scaled for relative body weight (and assuming no major differences in body weight), this suggests dietary inorganic arsenic intake in the Wasserman et al. (2004) subjects of between 22–30 µg/day, or 1.0–1.3 µg/kg-day.

In addition, Hossain et al. (2013) estimated that indirect water consumption in Bengalese children was approximately 1.1 L/day, approximately 50% of the direct intake. This would add another approximately 0.045 L/kg-day water consumption, corresponding to an additional 0.045 µg/kg-day arsenic intake per µg/L arsenic in drinking water (assuming that drinking water as used for cooking in Bangladesh in the same manner as in Bengal.) Combining the intake estimates gives the results shown in Table C-75.

Table C-75. Arsenic dose estimates for critical water concentration in the Wasserman et al. (2004) cohort (µg/kg-day)

Water concentration	5 µg/L	10 µg/L	50 µg/L
Direct water arsenic	0.45	0.9	4.5
Indirect water arsenic	0.23	0.45	2.3
Total water arsenic	0.68	1.4	6.8
Dietary arsenic	1.0–1.3		
Total arsenic intake	1.7–2.0	2.4–2.7	7.8–8.1

These results suggest that the apparent LOAEL in the Wasserman et al. (2004) neurodevelopmental study (water arsenic = 50 µg/L) corresponds to approximately 8 µg/kg inorganic arsenic intake/day, with a wide range of variability.

Wasserman et al. (2014)

The other dataset available to the agency was provided by the authors of a cross-sectional study of IQ versus water arsenic concentrations in Maine school children (Wasserman et al., 2014). The authors recruited 272 elementary students in 3rd–5th grade, age 8–12 (average 9.67) from three school districts near Augusta, ME in 2006–2007. Families were contacted by mail, and 36% replied showing interest in participation. Exclusion criteria included the existence of conditions "with known adverse impact on intellectual functioning" and failure to reside at the current address for at least three years. Only a small number of students (2) were excluded owing to pre-existing conditions and 36 were excluded owing to short residential tenure. The other major reasons for lack of participation were inability to schedule an interview during the recruitment period or "loss of interest."

Home interviews were conducted to gather information related to covariates including parent's educational status and mother's IQ. Interviewers also assessed child rearing characteristics using the HOME Inventory. Water samples were taken at point of entry to the house and at point of use (kitchen sink, or at the outflow from any water treatment system that was present.) Toenail samples were taken from both of the children's feet for arsenic analysis. Water and toenail sample preparation and arsenic analysis were performed using well-validated methods, and with appropriately documented QA procedures.

Children's IQ was assessed by experienced testers using WISC-IV. Since the tests were conducted in subjects homes, examiners were probably not perfectly blinded to covariates including school district, HOME score, etc. Raw test results were apparently normed to the U.S. population and results are presented as Full Scale, Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed IQ scores. Mother's intelligence was assessed using the rapid WASI test. Data elements composing the HOME scores were imputed if fewer than 6 values were missing; if greater than six values were missing, HOME scores were classified as "missing."

Population characteristics and exposure metrics

Characteristics of the study population are shown in Table 1 of the original article. "Almost all" of the subjects were Caucasian and 53.3% of subjects were male. The average duration at the current residence was 7.3 years. While this represented the bulk of the children's lives, supporting the existing of long-term, relatively stable exposures, only 22% had lived in their current residence since the first year of life, suggesting that the bulk of the study population had not been exposed in utero to water from the same source. Residence prior to current addresses was not tracked, so full life exposure histories were not developed.

The population was generally well-education, with approximately 71% of fathers and 86% of mothers having at least "some college." The average maternal IQ was 114.8, above the national average. The study population was described as "mid-range" with regard to socioeconomic status. The authors did not measure blood lead levels or fluoride exposure, two variables known to affect

children's IQ; additional information is needed to decide if these coexposures could pose problems in this population. No information on the age of the housing stock or the geochemical regime sampled by the private wells was provided.

Approximately 10% of water arsenic measurements were less than the detection limit of 0.1 μg/L. The overall average water arsenic concentration was 9.88 ± 15.06 μg/L. The distribution was left-skewed, with a median of 4.6 μg/L, geometric mean of 2.6 μg/L and 5th and 95th percentile measurements of "ND" and 40.7 μg/L, respectively. Water concentrations were significantly different across the three school districts (see Table C-76), with the average exposure being significantly lower in District A than in the other two. The authors also note that District A had higher proportions of mothers with college degrees, higher average maternal IQ, and larger proportions of households with above-median HOME scores and water filtration or treatment systems.

Table C-76. Distributions of water arsenic in three school districts

School district	N	Minimum water arsenic	Maximum water arsenic, μg/L	Mean water arsenic, μg/L	Standard deviation
A	78	ND	50.5	6.6	9.8
B	51	ND	67.0	12.4*	17.3
C	143	ND	115	10.8*	16.4

Note: * Indicates significantly different from District A, $p \leq 0.05$, Mann-Whitney U test.

The authors compared IQ results across four strata of water arsenic concentration (see Table C-77). It can be seen that approximately 52% of subjects were in the referent (<5 μg/L) stratum.

Table C-77. Water arsenic concentrations in referent and exposed subjects

Water arsenic concentration range	Number of subjects	Water arsenic (mean ± std. dev.)
<5	141	1.24 ± 1.37
>5–10	46	7.37 ± 1.34
>10–20	52	14.80 ± 3.06
>20	33	42.55 ± 20.43

The average toenail arsenic concentration (from 248 of the 272 subjects) was 4.65 ± 4.60 μg/g, geometric mean = 3.37 μg/g, 5th and 95th percentile values 0.97 and 12.0 μg/g. Mean toenail arsenic concentrations were not significantly different across school districts.

Results

The authors report raw and covariate-adjusted decrements in Full-Scale IQ and in the specific domains noted above (Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed IQ) as a function of drinking water arsenic in the three exposed strata compared to the referent group with water arsenic <5 μg/L (see Table 2 in the article). The unadjusted means and standard deviations (calculated from the raw data) are shown in Table C-78.

Mean raw Full-Scale IQ scores were significantly reduced in the 2nd and 3rd exposure strata (>5–10 and >10–20 μg/L), but not in the >20 μg/L subjects. The reductions in raw Working Memory scores were significant in the 2nd and 4th strata, Perceptual Reasoning the 2nd and 3rd strata, and Verbal Comprehension only in the >5–10 μg/L group. Unadjusted Processing Speed scores were not significantly reduced compared to referents in any other group.

Table C-78. Unadjusted IQ scores in referent and exposed groups

Water arsenic concentration range	Full IQ	Working memory	Perceptual reasoning	Verbal comprehension	Processing speed
<5	112.9 ± 12.1	104.5 ± 12.9	111.3 ± 12.9	116.6 ± 15.7	103.1 ± 12.4
>5–10	106.0 ± 12.5**	99.3 ± 13.8*	105.4 ± 12.3**	109.1 ± 14.8**	101.7 ± 11.9
>10–20	108.4 ± 11.4*	102.0 ± 13.5	104.7 ± 12.8**	113.2 ± 14.7	102.4 ± 10.8
>20	108.3 ± 14.3#	98.0 ± 14.0*	107.4 ± 14.8	113.1 ± 17.5	103.1 ± 14.3

Note: * = $p < 0.05$, # = $p < 0.10$; ** indicates differences from referent significant at $p < 0.01$.

The authors employed multiple linear regression models to adjust for important covariates. Covariate were evaluated for inclusion based on "our prior work on child intelligence and lead and arsenic exposure." These included maternal intelligence and education levels, HOME score, and the number of children living in the household. Two HOME score variables were selected, one indicating a "low" (below median") score, and the other a variable indicating that six more items were "missing" from the HOME evaluation. Dummy variables for school district were also included in the model, given the observed correlation between district of residence, arsenic exposure, and several demographic and educational variables. The results of this analysis are summarized in Table C-79 (extracted from the Authors' Table 2.)

Table C-79. Adjusted IQ changes in exposed groups relative to referents

Arsenic exposure μg/L	Full IQ	Working memory	Perceptual reasoning	Verbal comprehension	Processing speed
>5–10	−6.09 ± 1.98**	−4.88 ± 2.24*	−4.97 ± 2.14*	−6.22 ± 2.49*	−1.74 ± 2.09
>10–20	−3.15 ± 1.91	−1.13 ± 2.16	−5.10 ± 2.06*	−1.86 ± 2.39	−1.15 ± 2.01
>20	−2.51 ± 2.29	−5.07 ± 2.59#	−2.29 ± 2.47	−0.82 ± 2.88	0.40 ± 2.42

Note: ** indicates differences from referent significant at $p < 0.01$, * = $p < 0.05$, # = $p < 0.10$.

After adjustment for covariates, the observed patterns of IQ change from the referent population are similar to that seen in the unadjusted data. For the first four metrics (Full IQ, Working Memory, Perceptual Reasoning, and Verbal Comprehension), the mean scores in subjects with water arsenic between 5 and 10 μg/L are again significantly lower than the referents. The magnitudes and statistical significance of the IQ reductions in the higher exposure strata are generally lower in the adjusted model, although the signs remain negative (for the four metrics just noted.) As in the unadjusted model, the differences in Processing Speed are not significantly different from referents in any exposed group.

Among the covariates, maternal IQ is the most consistently explanatory, having positive, highly significant coefficients for all the metrics except Processing Speed, where is it not significant. The coefficient representing maternal education (more than high school) is also positive across all the endpoints (even when maternal IQ is also included), and highly significant in the models for Full-Scale IQ and Verbal comprehension. Low HOME scores were not significant in any model but having a "missing" HOME score was negatively correlated with all the outcome metrics and significant two of them. When the other covariates were included in the regression model, being a resident of District A or B was not associated with a significant impact on IQ, except for Processing Speed, where the coefficient for living in District A was significantly negative.

Toenail arsenic concentrations were not found to be significantly correlated with any of the IQ metrics.

Dose-response considerations

While Wasserman et al. (2014) report covariate-adjusted changes in scores across exposure strata defined by water concentration ranges, they do not provide the results of exposure-response models where arsenic concentration is included as a continuous variable (see below.) One factor that increases the complexity of such an analysis is the apparent nonlinearity of the exposure-response relationship, even in log-linear space. It can be seen from Table C-79 that for all five IQ metrics, the greatest reduction relative to the referent group is observed in the 2nd exposure stratum (water arsenic 5–10 μg/L), with smaller reductions in the higher exposure groups. For all of the metrics except Processing Speed, the difference in IQ from the referent group remains negative, but the magnitudes are substantially smaller, and often lose statistical significance. The reasons for this are not clear, since the covariate distributions in the highest two exposure groups appear to be such as might contribute to even greater reductions in IQ compared to the referents. Maternal IQ is significantly lower in the highest two exposure groups, and maternal education and the frequency of "missing" HOME scores, which is also predictive of lower IQ scores, is again higher in subjects exposed to > 20 μg/L. A larger proportion of the subjects in the highest exposure stratum live in district B but removing school districts from the regression does not substantially change the overall shape of the exposure-response relationships shown in Table C-79. When exposure is entered as a dichotomous variable categorized as "referent" (< 5 μg/L) or "not referent" (all other subjects), the coefficients for "not referent" subjects having lower IQ are significant for

Full Scale IQ, Working Memory, and Perceptual Reasoning. The coefficient for Verbal Comprehension is negative but marginally significant (p = 0.79).

When drinking water arsenic is included in the Wasserman et al. (2014) regression as a continuous variable, only the coefficient for Working Memory achieves statistical significance at p = 0.05; Full-Scale IQ is marginally significant (p < 0.076), as shown in Table C-80.

Figure C-53 is a kernel-smoothed fit of Full-Scale IQ to drinking water arsenic concentration. The irregular shape of the relationship is evident, with a clear reduction in IQ in the at low arsenic exposure (where the bulk of the subjects are), with mild curvature upward in the higher exposure range. While the overall pattern of results from the regressions that include water arsenic as a continuous variable support the existence of a consistent relationship between arsenic exposure and IQ decrements, the marginal statistical significance of the arsenic coefficients and probably curvature in the exposure-response relationships suggests that using these models to estimate IQ loss across the full range of exposures would not be advisable.

Table C-80.Adjusted regression coefficients for (continuous) log water arsenic in Wasserman et al. (2014) model regression model

IQ metric	Adjusted β	Std. error	*p*-Value
Full IQ	−1.43	0.803	0.076
Working Memory	−1.75	0.890	0.050
Perceptual Reasoning	−1.11	0.859	0.197
Verbal Comprehension	−0.97	1.015	0.341
Processing Speed	−0.69	0.829	0.410

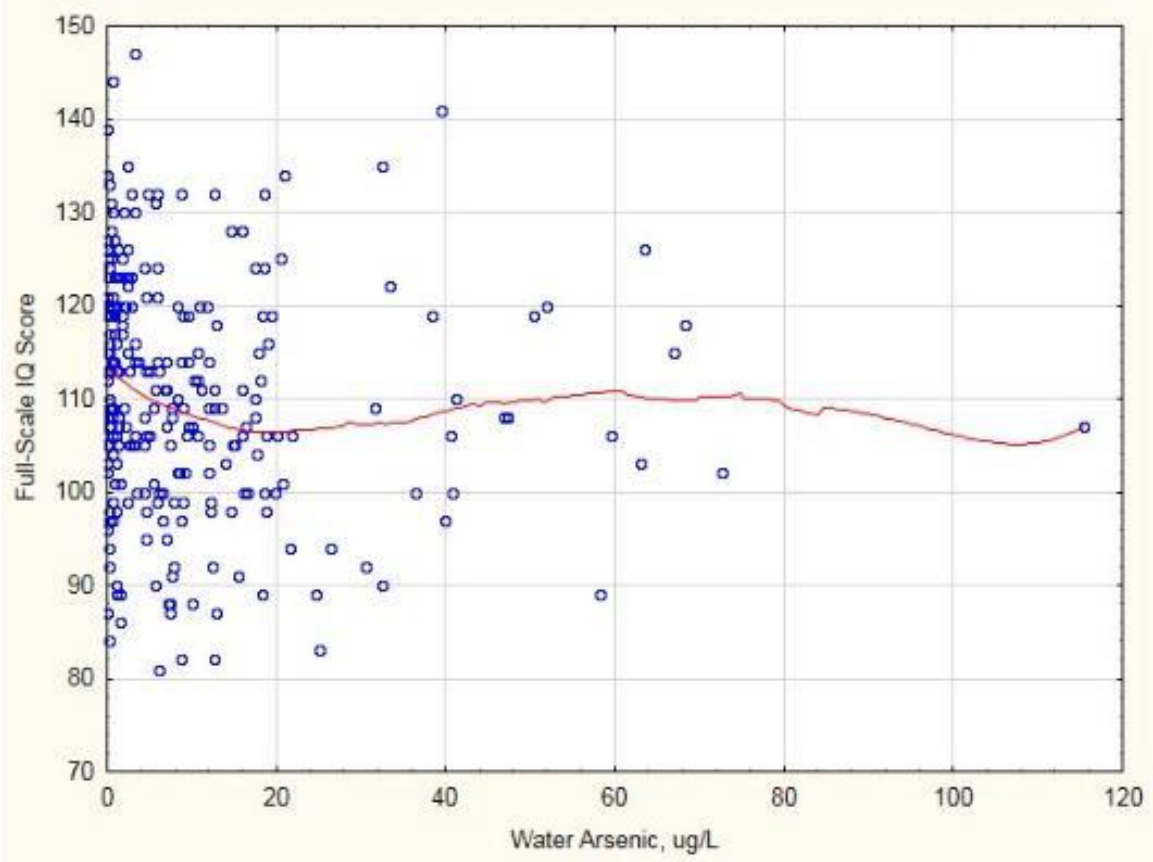


Figure C-53. Kernel smoothed fit of full-scale IQ to water arsenic concentration.

The other issues that need to be resolved in evaluating the Wasserman et al. (2014) data for use in dose-response are (1) estimating the inorganic arsenic dose associated with water intake and (2) evaluating the relative contribution of diet to total arsenic intake. EPA has estimated that mean water intake in U.S. children 6–11 years of age is approximately 0.014 L/kg-day, with a 95th percentile estimate of 0.043 L/kg-day (EFH 2011, Table 3-1). This implies each 1 µg/L increase in drinking water arsenic would be provide a dose of between 0.014 and 0.043 µg/kg-day inorganic arsenic. In this analysis, we assume that the arsenic concentrations measured in the Wasserman et al. (2014) study accurately represent the bulk of water consumed; to the extent that children's arsenic exposure is different outside the home, the dosimetric assumption will be inaccurate. Assuming this distribution of drinking water consumption implies that children with exposures greater than 5 µg/L received at least 0.07 µg/kg-day, and as much as approximately 0.22 µg/kg-day arsenic from water. The corresponding water arsenic intake ranges for the other exposure breakpoints are 0.14–0.43 µg/kg-day (10 µg/L) and 0.28–0.86 µg/kg-day (20 µg/L). Since the significant reductions in IQ metrics were observed in subjects exposed above 5 µg/L, the lowest of these estimates represent the potential "critical" dose of arsenic from drinking water associated with adverse neurodevelopmental effects.

The actual dietary intake of inorganic arsenic was not measured in this cohort, so other studies of U.S. dietary arsenic intake must provide estimates of arsenic intake. For this analysis, we rely on the study by Xue et al. (2010), who used food consumption data from NHANES and arsenic concentration data from FDA as inputs to the SHEDS simulation model, to estimate age-specific total and inorganic arsenic intake for the U.S. population. The average and 95th percentile inorganic arsenic intakes for 6–12-year-olds were 0.04 µg/kg-day and 0.13 µg/kg-day, respectively. Thus, the central tendency and 95th percentile dietary arsenic intake estimates are comparable to, but slightly less than the estimated arsenic intake associated with consuming 5 µg/L arsenic in drinking water for the same age group. Combining the two estimates (water at 5 µg/L and national average dietary intake) indicates that Maine schoolchildren receiving more than approximately 0.11 (central tendency) to 0.35 (upper end) µg/kg-day inorganic arsenic experienced statistically significant reductions in several IQ metrics. Based on the presented analyses and data, these values may be considered LOAELS for this population.

C.3. $BMDL_{01}$, $BMDL_{05}$, AND $BMDL_{10}$ ESTIMATIONS FOR DCS AND DIABETES TOXICITY VALUES

The modeling approach used for diabetes and DCS is discussed in this section. Briefly, after applying the meta-regression approach, BMDs and BMDLs were estimated for diabetes and the two non-fatal DCS health outcomes as:

$$BMD = \frac{\ln\left(odds\ at\ P(d) \Big/ odds\ at\ P(0)\right)}{\beta\ mean}$$

and

$$BMDL = \frac{\ln\left(odds\ at\ P(d) \Big/ odds\ at\ P(0)\right)}{95^{th} upper\ bound\ on\ \beta\ mean}$$

where P(d) is the probability associated with either 1%, 5% or 10% extra risk, P(0) is the probability associated with 0% extra risk, and β_mean_{95} is the 95% (one-sided) upper bound on the mean(β_mean) estimated in the meta-regressions for the Logistic model slope.

Table C-81. $BMDL_{01}$ $BMDL_{05}$ and $BMDL_{10}$ estimations for DCS and diabetes toxicity values[a]

Health outcome	BMD_{01}	$BMDL_{01}$	BMD_{05}	$BMDL_{05}$	BMD_{10}	$BMDL_{10}$
CVD incidence	0.062	0.019	0.315	0.094	0.641	0.190
IHD incidence	0.073	0.028	0.362	0.140	0.717	0.277
Diabetes	0.073	0.028	0.360	0.140	0.713	0.278

[a] $BMDL = \frac{\ln\left(\text{odds at } P(d) / \text{odds at } P(0)\right)}{95^{th}\text{upper bound on mean}(\beta\ \text{mean})}$, 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.

APPENDIX D. INFORMATION IN SUPPORT OF HAZARD IDENTIFICATION AND DOSE-RESPONSE ANALYSIS

D.1. TOXICOKINETICS

D.1.1. Absorption

Water-soluble forms of inorganic arsenic (both trivalent and pentavalent) are readily absorbed from the GI tract in experimental animal models [about 80–90% 0.62 mg/kg of sodium arsenate (Freeman et al., 1995)] as well as humans [Pomroy et al. (1980) who recovered 62% of a 0.06 ng dose of arsenic in seven days]. Monomethyl arsonic acid (MMA^V) and dimethylarsinic acid (DMA^V) also appear to be well absorbed (75–85%) in humans and experimental animals (Hughes et al., 2005; Yamauchi and Yamamura, 1984; Buchet et al., 1981; Stevens et al., 1977). Using an in vivo swine test, however, Juhasz et al. (2006) determined that MMA (oxidation state not specified) and DMA (oxidation state not specified) were poorly absorbed, with only 16.7% and 33.3%, respectively, bioavailable.

Laparra et al. (2006) used a Caco-2 permeability model, which measured transport through a monolayer of human intestinal cells, to examine the intestinal permeability of As^{III}. A decrease in the apical to basolateral permeability with increasing dose was found, indicating the presence of a saturable intestinal transport system. The data also indicated that Caco-2 cells have a secretory system for As^{III}. In an earlier study, Laparra et al. (2005b) demonstrated that the retention and transport of As^{III} in Caco-2 cells was more efficient than that of As^V. However, this could have been due to the presence of phosphate in the culture medium, which would compete with arsenate for transport across the membrane.

Gastrointestinal absorption of low-solubility arsenic compounds such as arsenic trisulfide, lead arsenate, arsenic selenide, gallium arsenide (Yamauchi et al., 1986; Webb et al., 1984; Mappes, 1977), and arsenic-contaminated soil (Freeman et al., 1995) is much less efficient than that of soluble inorganic arsenic compounds. The degree of absorption of arsenic from soil was found to be dependent on the arsenic species present in the soil and on the type of soil. Juhasz et al. (2007) performed in vivo bioavailability studies in swine and determined that the bioavailability of total arsenic in soils was highly variable, with a range of 6.9% to 74.7% depending on the soil type. They also determined that a simplified bioaccessibility extraction test (SBET; a rapid in vitro chemical extraction method) had results highly correlated with the in vivo results. Therefore, they concluded that the less expensive in vitro test was just as effective for determining bioavailability.

There is little information concerning the bioavailability of inorganic arsenic from various types of food (NRC, 2001, 1999). However, there have been studies examining the bioaccessibility of arsenic from rice (Juhasz et al., 2006; Laparra et al., 2005a). Laparra et al. (2005a) determined that while cooking rice (they tested several types but did not specify them) in deionized water caused no change in arsenic content compared to the raw form, cooking in water contaminated with 0.5 µg/mL of As^{V} increased the inorganic arsenic content 5- to 17-fold over the raw rice. Laparra et al. (2005a) subjected the rice samples (10 grams) to an in vitro simulated digestion process. They measured levels of soluble arsenic to determine bioaccessibility. The results demonstrated that large amounts of the arsenic (i.e., 63%–99%), mainly in the pentavalent form, were bioaccessible for intestinal absorption. Ackerman et al. (2005) also found 89%–105% bioaccessible arsenic in different samples of white and brown rice cooked in water containing As^{V}.

Juhasz et al. (2006) examined the bioavailability of arsenic from rice (mainly white rice samples) using an in vivo swine assay. Quest rice was grown in arsenic-contaminated water and cooked in arsenic-free water. This caused the rice to contain arsenic, mainly in the form of DMA. Administration of the cooked rice to swine demonstrated a bioavailability similar to that observed after a single oral administration of DMA in water (i.e., 33.3%). Basmati white rice cooked in water contaminated with 1,000 ppb of As^{V}, which contained entirely inorganic arsenic as a result of the arsenate in the cooking water, had a bioavailability of 89.4%.

Although there have been no studies performed on the rate of inorganic arsenic absorption through intact human skin, systemic toxicity due to high dermal occupational exposure to aqueous inorganic arsenic solutions indicates that the skin may be a significant exposure route (Hostýnek et al., 1993). The systemic absorption via the skin from less concentrated solutions, however, appears to be low (NRC, 1999). An in vivo study by Wester et al. (1993) demonstrated that 2% to 6% of radiolabeled arsenate (as a water solution) was absorbed by rhesus monkey skin over a 24-hour period. Results demonstrated that the lower dose (0.000024 µg/cm^2) was absorbed at a greater rate (6%) than the higher arsenic exposure (2.1 µg/cm^2; 2%), but the difference did not reach statistical significance. Wester et al. (2004) performed another in vivo dermal absorption study using female rhesus monkeys. Using the levels excreted in the urine and the applied dose, they calculated that 0.6% to 4.4% was absorbed in the three monkeys tested, which was similar to their previous results. In vitro results on human skin (from donors) demonstrated a 24-hour absorption of 1.9% (Wester et al., 1993). Mouse dorsal skin was demonstrated to absorb 30% to 60% of applied arsenic (Rahman et al., 1994) using similar in vitro testing, with 60% to 90% of the absorbed arsenic being retained in the skin. NRC (1999) suggests this indicates that inorganic arsenic binds significantly to skin and hair. Lowney et al. (2007) found that dermal absorption of arsenic from soils was negligible in an in vivo study in rhesus monkeys.

Harrington et al. (1978) compared arsenic metabolite levels in the urine from a group of people in Fairbanks, Alaska, who had arsenic-contaminated water (345 ppb) in their home, but drank only bottled water, with the levels measured in a group of people who drank home water

containing less than 50 ppb. The results demonstrated that the group with high arsenic in their water had close to the same average concentration of total arsenic metabolites in their urine (i.e., 43 µg/L) as the group who drank home water with less than 50 ppb arsenic (i.e., 38 µg/L in urine), indicating possible dermal absorption via bathing or other exposure sources. Levels of arsenic in the bottled water, however, were not measured. Possible exposure through using contaminated water for cooking also was not examined.

D.1.2. Distribution

The retention and distribution patterns of arsenic species are strongly dependent on their chemical properties. While both As^{III} and As^{V} bind to sulfhydryl groups, As^{III} has approximately a 5- to 10-fold greater affinity for sulfhydryl groups than As^{V} (Jacobson-Kram and Montalbano, 1985). Cellular uptake rates and resulting tissue concentrations are substantially lower for the pentavalent than for the trivalent forms of arsenic. DMA (an important metabolite of inorganic arsenic) appears to be more readily excreted than MMA (NRC, 2001). Liu et al. (2002) found arsenite to be transported into cells by aquaglycoporins (AQP7 and AQP9), whose usual substrates are water and glycerol. Liu et al. (2006b) also detected transport of monomethylarsonous acid (MMA^{III}) by AQP9. MMA^{III} was transported at a rate nearly 3 times faster than As^{III}. A hydrophobic residue at position 64 was required for the transport of both species, suggesting that both species are transported by AQP9 using the same translocation pathway. As^{V}, however, has been suggested to be transported by the phosphate transporter (Huang and Lee, 1996). Retention of arsenic can vary not only with its form, but also with tissue (Thomas et al., 2001). Other factors that affect the retention and distribution of arsenic include the chemical species, dose level, methylation capacity, valence state, and route of administration.

D.1.3. Transport in Blood

Once arsenic is absorbed, it is transported in the blood throughout the body. In the blood, inorganic arsenic species are generally bound to sulfhydryl groups of proteins and low-molecular-weight compounds such as glutathione (GSH) and cysteine (NRC, 1999). Binding of As^{III} to GSH has been demonstrated by several investigators (Delnomdedieu et al., 1994a; Delnomdedieu et al., 1994b; Scott et al., 1993; Anundi et al., 1982). Because of the different binding and transport characteristics of various arsenic compounds, the persistence in the blood varies across species. Inorganic arsenic elimination in humans has been observed to be triphasic, with first-order half-lives for elimination of 1 hour, 30 hours, and 200 hours (Mealey et al., 1959) used AsIII; (Pomroy et al., 1980) used AsV. A single intravenous (iv) dose of 5.8 µg As/kg body weight (in the form of $73As^{V}$) administered to two male chimpanzees had a half-life plasma elimination rate of 1.2 hours and a half-life elimination rate from red blood cells (RBCs) of about 5 hours (Vahter et al., 1995b).

Rats retain arsenic in the blood considerably longer than other species because dimethylarsenous acid (DMA^{III}) and DMA^{V} accumulate in RBCs, apparently bound to hemoglobin (Vahter et al., 1984; Lerman and Clarkson, 1983; Vahter, 1983; Odanaka et al., 1980).

Naranmandura et al. (2007) found that 75% of an oral dose of arsenite accumulated in rat RBCs mainly in the form of DMA^{III}; however, less than 0.8% of the same dose to hamsters was found in their RBCs. Rats maintained this level in their RBCs for at least 7 days whereas the treated hamsters had levels equivalent to those in controls by 3 days after the administered dose. Stevens et al. (1977) calculated an elimination half-life for inorganic arsenic of 90 days in rat whole blood after a single oral dose of 200 mg/kg. Lanz et al. (1950) also reported a high retention of arsenic in the blood of cats, although less than in the rat. However, they did not determine if the retained arsenic was in the form of DMA.

The relative concentration of arsenic in human plasma and RBCs apparently differs depending on exposure levels and the health status of the exposed individuals. Heydorn (1970) reported that healthy people in Denmark with low arsenic exposures had similar arsenic concentrations in their plasma and RBCs (2.4 µg/L and 2.7 µg/L, respectively; the RBC:plasma ratio was 1.1). However, normal healthy Taiwanese exposed to arsenic-contaminated water had plasma levels of 15.4 µg/L and RBCs levels of 32.7 µg/L (RBC:plasma ratio 2.1). Blackfoot disease (BFD) patients and their unaffected family members had 38.1 µg/L and 93 µg/L of arsenic species in their plasma and RBCs, respectively (RBC:plasma ratio 2.4). These results indicate a different distribution between the RBCs and the plasma depending on exposure levels. However, examining the BFD patients and their families, who presumably have the same exposure levels, demonstrates a different distribution, possibly due to disease state. BFD patients had a ratio of 3.3 (106 µg/L in RBCs and 32.3 µg/L in plasma) compared to 1.8 (81 µg/L in RBCs and 45.2 µg/L in plasma) in family members without BFD. This indicates that accumulation of arsenic in the RBCs is greater as exposure increases and possibly even greater when health is compromised. The ratio between plasma and RBC arsenic concentrations may also depend on the exposure form of arsenic (NRC, 1999).

D.1.4. Tissue Distribution

Once arsenic compounds enter the blood, they are transported and taken up by other tissues and organs, with a large proportion of ingested material being subject to "first pass" processing through the liver. Uptake varies with arsenic species, dose, and organ. The observed uptake of inorganic arsenic (mainly As^{III}) in the skin, hair, oral mucosa, and esophagus is most likely due to the binding of inorganic arsenic species with sulfhydryl groups of keratins in these organs. In studies using rabbits and mice, where the transfer of methyl groups from Sadenosylmethionine- (SAM; a proposed major reaction during arsenic metabolism; see Section 3.3) was chemically inhibited, the concentration of arsenic in most tissues (especially the skin) was found to be increased (Marafante and Vahter, 1984). The important role of chemical binding of arsenic species also is supported by the observed tissue distribution in the marmoset monkey, which does not methylate inorganic arsenic (Vahter et al., 1982).

Human subjects also have demonstrated high concentrations of arsenic in tissues containing a high content of cysteine-containing proteins, including the hair, nails, skin, and lungs.

Total arsenic concentrations in these tissues of human subjects exposed to background levels of arsenic ranged from 0.01 to 1.0 mg/kg of dry weight (Cross et al., 1979; Liebscher and Smith, 1968). Benign and malignant skin lesions from 14 patients, with a minimum of 4 years of exposure to inorganic arsenical medication, had higher arsenic levels (0.8 to 8.9 ppm) than six subjects with no history of arsenic intake (0.4 to 1.0 ppm) (Scott, 1958). In West Bengal, India, where the average arsenic concentration in the drinking water ranges from 193 to 737 ppb, arsenic concentrations in the skin, hair, and nails were 1.6–5.5, 3.6–9.6, and 6.1–22.9 mg/kg dry weight, respectively (Das et al., 1995). Mandal et al. (2004) measured different arsenic species in the hair and fingernails of 41 subjects in West Bengal, India, who were drinking arsenic-contaminated water and in blood from 25 individuals who had stopped drinking contaminated water 2 years earlier. Results were: fingernail contained As^{III} (62.4%), As^{V} (20.2%), MMA^{V} (5.7%), DMA^{III} (8.9%), and DMA^{V} (2.8%); hair contained As^{III} (58.9%), As^{V} (34.8%), MMA^{V} (2.9%), and DMA^{V} (3.4%); RBCs contained arsenobetaine (22.5%) and DMA^{V} (77.5%); and blood plasma contained arsenobetaine (16.7%), As^{III} (21.1%), MMA^{V} (27.1%), and DMA^{V} (35.1). However, the amount of arsenic in these tissues resulting from other exposure pathways (e.g., dermal exposure) was not determined.

The longest retention of inorganic arsenic in mammalian tissues during experimental studies has been observed in the skin (Marafante and Vahter, 1984), hair, squamous epithelium of the upper GI tract (oral cavity, tongue, esophagus, and stomach wall), epididymis, thyroid, skeleton, and the lens of the eye (Lindgren et al., 1982). Although the study authors measured radioactive arsenic (^{74}As) in the various tissues, they did not differentiate between the different species of arsenic and could not determine if accumulation was due to the originally administered compound or metabolites. Arsenic levels in all these tissues, with the exception of the skeleton, were greater in mice administered As^{III} than in mice administered As^{V}. This could indicate that As^{III} is taken up more efficiently than As^{V} and that less was found in the tissues of As^{V}-treated mice due to the initial reduction to As^{III}. The calcified areas of the skeleton in mice administered As^{V} accumulated and retained more arsenic than mice administered As^{III}, most likely due to the similarities between As^{V} and phosphate, causing a substitution of phosphate by As^{V} in the apatite crystals in bone. Marmoset monkeys were found not to accumulate arsenic in the ocular lens or the thyroid (Vahter et al., 1982) following intraperitoneal injection of arsenite; however, intravenous administration of ^{74}As-labelled DMA to mice resulted in accumulation of DMA in the ocular lens and the thyroid. Marmoset monkeys do not methylate arsenic, and DMA was found to accumulate in the ocular lens and thyroid of mice; this suggests that only the methylated species are retained in these organs. Mouse tissues with the largest retention of DMA were the lens of the eyes, thyroid, lungs, and intestinal mucosa (Vahter et al., 1984). Methylated arsenic species (DMA), in general, have a shorter tissue retention time in mice than rats (i.e., more than 99% of the administered dose was eliminated in mice within 3 days as compared to 50% in rats due to accumulation in blood) (Vahter et al., 1984).

Hughes et al. (2003) estimated that a steady-state, whole-body arsenic balance was established after nine repeated oral daily doses of 0.5 mg As/kg as radioactive As^{V} in adult female

B6C3F1 mice. Twenty-four hours after the last dose, the whole-body burden of arsenic was about twice that observed after a single dose. The rate of elimination was slower following repeated doses. Accumulation of radioactivity was highest in the bladder, kidney, and skin, while the loss of radioactivity was greatest from the lungs and slowest from the skin. Atomic absorption spectrometry was used to characterize the organ distribution of arsenic species. MMA was detected in all tissues except the bladder. DMA was found at the highest levels in the bladder and lung after a single oral exposure, with increases after repeated exposures. Inorganic arsenic was predominantly found in the kidney. After a single oral exposure of As^{V} (0.5 mg As/kg), DMA was the predominant form of arsenic in the liver, but after nine repeat exposures, the proportion of DMA decreased while the proportion of inorganic arsenic increased (this could indicate metabolic saturation or GSH depletion; see Section 3.3 for more details). A trimethylated form of arsenic also was detected in the liver.

Kenyon et al. (2005) examined the time course of tissue distribution of different arsenic species after a single oral dose of 0, 10, or 100 µmole As/kg as sodium arsenate to adult female B6C3F1 mice. The concentrations of all forms of arsenic were lower in the blood than in other organs across all doses and time points. The concentration of inorganic arsenic measured in the liver was similar to that measured in the kidney at both dose levels, with peak concentrations observed 1 hour after dosing. For the first 1 to 2 hours, inorganic arsenic was the predominant form in both the liver and kidney, regardless of dose. At the later times, DMA became the predominant form. Kidney measurements 1 hour after dosing demonstrated that MMA levels were 3 to 4 times higher than in other tissues. DMA concentrations in the kidney reached their peak 2 hours after dosing. DMA was the predominant form measured in the lungs at all time points following exposure to 10 µmole As/kg as As^{V}. DMA concentrations in the lung were greater than or equal to those of the other tissues beginning at four hours. The study did not distinguish the different valence states of the MMA or DMA compounds.

In a follow-up study by Kenyon et al. (2008), adult female C57BL/6 mice were administered 0, 0.5, 2, 10, or 50 ppm of arsenic as sodium arsenate in the drinking water for 12 weeks. The average daily intakes were estimated to be 0, 0.083, 0.35, 1.89, and 7.02 mg As/kg/day, respectively. After 12 weeks of exposure, the tissue distributions were as follows: kidney > lung > urinary bladder > skin > blood > liver. In the kidney, MMA was the predominant form measured, while DMA was more prominent in the lungs and blood. The skin and urinary bladder had nearly equal levels of both inorganic arsenic and DMA and the liver had equal proportions of all three species.

Naranmandura et al. (2007) characterized the tissue distribution in rats and hamsters administered a single oral dose of As^{III} (5.0 mg As/kg body weight, or BW). In rats, the highest concentrations were found in RBCs. Because hamsters did not accumulate arsenic species in their RBCs, they exhibited a more uniform tissue distribution. While the quantity of arsenic in the liver and kidneys of the hamster were significantly greater than those observed in the rat, arsenic

accumulated more and was retained longer in the kidneys than the liver in both species. The hamster had greater levels of MMA^{III} bound to protein in the kidney than rats.

As^{III} and As^{V}, as well as methylated metabolites, cross the placenta at all stages of gestation in mice, marmoset monkeys, and hamsters (Jin et al., 2006; Hood et al., 1987; Lindgren et al., 1984; Hanlon and Ferm, 1977), with tissue distribution of arsenic similar between the mother and the fetus in late gestation. Jin et al. (2006) found increased levels of inorganic arsenic and DMA in the livers and brains of newborn mice from dams administered either As^{III} or As^{V} in their drinking water throughout gestation and lactation. The levels of total arsenic in the mothers' livers increased in a dose-dependent manner and were greater than those observed in the mothers' brains or in the newborns' brains or livers. The levels of total arsenic in the livers and brains of newborn mice, however, were greater than those observed in the mothers' brains, suggesting easier passage through the placenta than through a mature blood-brain barrier. Because the levels of inorganic arsenic in the newborn livers and brains were nearly identical, it appears that there was no difficulty in passing through an immature blood-brain barrier. In addition, the nearly 2:1 ratio of DMA in the brains compared to the livers of newborns indicates either a preferential distribution of DMA in the newborns' brains or an increased distribution of inorganic arsenic to the brain that is subsequently metabolized. The marmoset monkey (known to not methylate arsenic) displayed somewhat less placental transfer after administration of As^{III} than was seen in mice (Lindgren et al., 1984).

The arsenic concentration in the cord blood (11 µg/L) was similar to that observed in maternal blood (an average of 9 µg/L) in pregnant women living in a village in northwestern Argentina, where the arsenic concentration in the drinking water was approximately 200 ppb (Concha et al., 1998b). Hall et al. (2007) also found a strong association between maternal (11.9 µg/L) and cord blood levels (15.7 µg/L) in Matlab, Bangladesh (arsenic exposure ranged from 0.1 to 661 ppb in drinking water). They also measured arsenic metabolite levels and found that the association also was observed for the metabolites MMA and DMA. Elevated arsenic concentrations also were noted in pregnant women living in cities with low dust fall (i.e., low arsenic inhalation exposures), where an average of 3 µg/L was measured in the maternal blood and 2 µg/L in cord blood (Kagey et al., 1977). Women living near smelters also have been observed to have an increased concentration of placental arsenic (Tabacova et al., 1994). Although the human fetus is exposed to arsenic, it may be more in the form of DMA (at least in late gestation) because 90% or more of the arsenic in the urine and plasma of newborns and mothers (at time of delivery) was DMA.

D.1.5. Cellular Uptake, Distribution, and Transport

Cellular uptake of inorganic arsenic compounds also depends on oxidation state, with As^{III} generally being taken up at a much greater rate than arsenate (Cohen et al., 2006). In Chinese hamster ovary (CHO) cells, the rate of uptake was $DMA^{III} > MMA^{III} > As^{III}$ (Dopp et al., 2004), with the pentavalent forms being taken up much more slowly than the trivalent forms. Delnomdedieu et

al. (1995) demonstrated that As^{III} is taken up more readily than As^{V}, MMA^{V}, or DMA^{V} by RBCs in rabbits. Drobna et al. (2005) found that MMA^{III} and DMA^{III} were taken up by modified UROtsa cells expressing arsenic methyltransferase (this is a human urothelial cell line that normally does not methylate inorganic arsenic) at an order of magnitude faster than As^{III}. Because arsenate uptake is inhibited in a dose-dependent manner by phosphate (Huang and Lee, 1996), it has been suggested that a common transport system is responsible for the cellular uptake for both compounds. As^{III} uptake, however, is not affected by phosphate; therefore, Huang and Lee (1996) suggested that cellular uptake of As^{III} occurs through simple diffusion. (Liu et al., 2006a; 2002), however, suggested that transport of As^{III} and MMA^{III} across the cellular membrane may be mediated by AQP7 and AQP9 with MMA^{III} transported at a higher rate. Lu et al. (2006) found that inorganic arsenic (both pentavalent and trivalent oxidation states) can be transported by organic anion transporting polypeptide-C (OATP-C; which was transfected into cells of a human embryonic kidney cell line), but not MMA^{V} or DMA^{V}. In a cell line resistant to arsenic (R15), Lee et al. (2006) found little AQP7 or AQP9 messenger RNA (mRNA) and only half the AQP3 mRNA expression compared to the parental cell line (CL3, a human lung adenocarcinoma cell line). Suppressing the AQP3 expression in CL3 cells caused less arsenic to accumulate in these cells. Over-expression of AQP3 in a 293 cell line (a human embryonic kidney cell line) resulted in an increase in arsenic accumulation in the cells. Hexose permease transporters (HXT) also have been suggested as another influx pathway for As^{III} (Thomas, 2007).

Shiobara et al. (2001) demonstrated that the uptake of DMA in RBCs was dependent on not only the chemical form (or oxidation state), but animal species. DMA^{III} and DMA^{V} were incubated with rat, hamster, mouse, and human RBCs. DMA^{V} was only minimally absorbed by RBCs, and the cellular uptake was very slow in all animal species tested. DMA^{III}, on the other hand, was efficiently taken up by the RBCs in the following order: rats > hamsters > humans. Mouse RBCs were less efficient at the uptake of DMA^{III} than any of the other species. Rat RBCs retained the DMA^{III} throughout the 4 hours of the experiment, but hamster RBCs were found to excrete the arsenic absorbed as DMA^{III} in the form of DMA^{V}. Human RBCs also excreted DMA^{III} as DMA^{V}, though the rate of uptake of DMA^{III} and efflux of DMA^{V} was much slower than in hamster RBCs.

Cellular excretion of arsenic species also depends on oxidation state and the degree of methylation. Leslie et al. (2004), using membrane vesicles from a multi-drug resistant human lung cancer cell line (H69AR), found that a multi-drug resistance protein (MRP) called MRP1 transports As^{III} in the presence of GSH but did not transport As^{V} under any conditions. This suggests that As^{V} must be reduced to As^{III} before being excreted from the cell. Further, the MRP1 transport was more efficient with arsenic triglutathione (ATG) as the substrate. This finding, along with the observation that As^{III} transport is more efficient at neutral or low pH where ATG is more readily formed and more stable, suggests that ATG is formed prior to transport. (Leslie et al., 2004) also suggest that the formation of the conjugate is catalyzed by the glutathione-S-transferase P1-1 (GSTP1-1) enzyme. MRP2 may also be involved in the efflux of arsenic species from cells (Thomas, 2007).

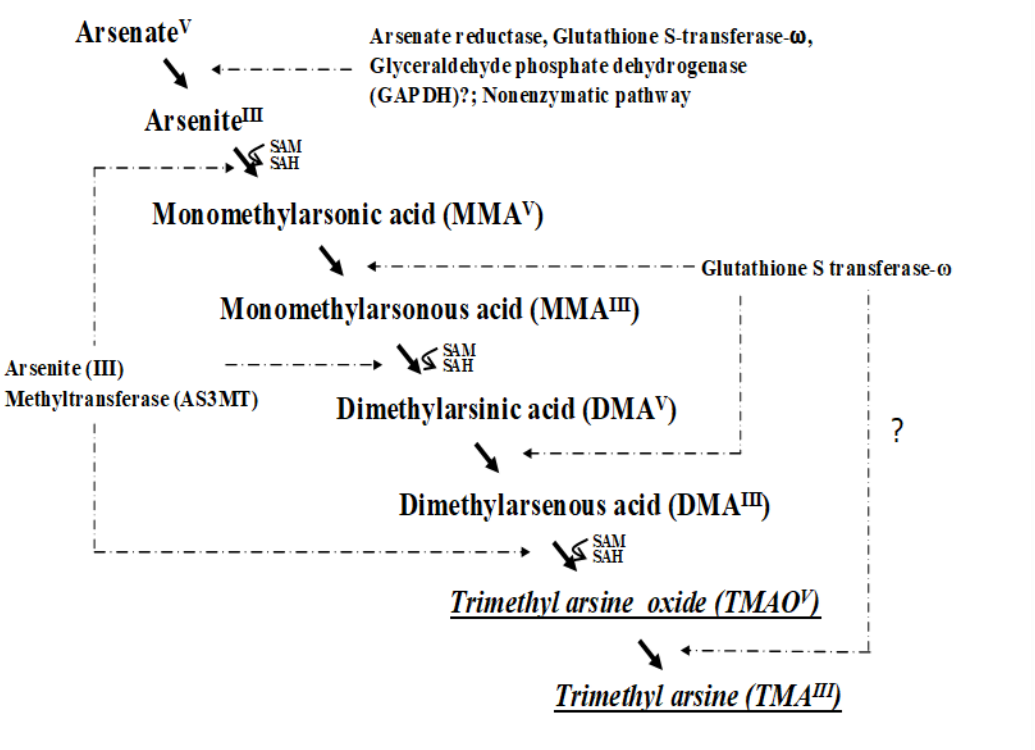
MRP2 expression was found to be five times higher in arsenic-resistant (R15) cells compared to the parent cell line (CL3). However, expression levels of MRP1 and MRP3 were similar to levels in parent cells (Lee et al., 2006). Suppressing the multi-drug resistant transporters reduced the efflux of arsenic from R15 cells.

In a study of rabbits and mice exposed to radio-labeled As^{III}, the majority of the arsenic was found in the nuclear and soluble fractions of liver, kidney, and lung cells (Marafante and Vahter, 1984; Marafante et al., 1981). The marmoset monkey had a different intracellular distribution, with approximately 50% of the arsenic dose found in the microsomal fraction in the liver (Vahter and Marafante, 1985; Vahter et al., 1982). Chemical inhibition of arsenic methylation in rabbits did not alter the intracellular distribution of arsenic (Marafante et al., 1985; Marafante and Vahter, 1984).

Increases in tissue arsenic concentration (especially in the liver) have been found to be associated with increased arsenic concentrations in the microsomal fraction of the liver in rabbits fed diets containing low concentrations of methionine, choline, or proteins, which leads to decreased arsenic methylation (Vahter and Marafante, 1987). The levels of arsenic in the microsomal fraction of the liver in these rabbits were similar to those observed in the marmoset monkey (Vahter et al., 1982), indicating that nutritional factors may play a role in determining the subcellular distribution of arsenic.

D.1.6. Metabolism

After entering the body, As^{V} can be reduced to As^{III}, which can then proceed through a series of methylation and conjugation reactions, some of which involve re-oxidation of arsenic to As^{V}. The traditional metabolic pathways proposed for arsenic are shown in Figure D-1. In this metabolic scheme, less toxic species (i.e., As^{V}, MMA^{V}, and DMA^{V}) can be converted to more toxic species (i.e., As^{III}, MMA^{III}, and DMA^{III}). The trivalent species have been found to be more cytotoxic, genotoxic, and more potent inhibitors of enzyme activity (Thomas et al., 2001). While the final metabolite in humans is predominantly DMA^{V}, as this is the form most highly excreted, some animal species further metabolize DMA^{V} through DMA^{III} to trimethylarsine oxide (TMAO).



Source: Sams et al. (2007).

Figure D-1. Traditional metabolic pathway for inorganic arsenic in humans.

Hayakawa et al. (2005) suggested a possible alternate metabolic pathway for inorganic arsenic (see Figure D-2). As in the previously described model, the first step involves reduction of As^{V} to As^{III}. A major difference, however, is that Hayakawa et al. (2005) suggest that arsenic-glutathione complexes are important intermediates in the metabolism of arsenic and are the primary substrates for arsenic methyltransferases. The proposed model was based on the observation that more DMA^{V} is produced from As^{III} than from MMA^{V}. This should not be the case if the reactions depicted in Figure D-1 are the primary arsenic metabolic pathways. Their data suggest that arsenite, in the presence of GSH, non-enzymatically reacts to form ATG. In support of this mechanism, they observed a dose-dependent increase in concentration of ATG with increasing doses of GSH, up to 4 mM. Monomethyl and dimethyl arsenic species were generated by the transfer of a methyl group from SAM in the presence of human recombinant arsenic (+3 oxidation state) methyltransferase (AS3MT), and only occurred when ATG or monomethylarsonic diglutathione (MADG) was present. At concentrations of glutathione of 2.0 mM or greater, there was a dose-dependent increase in DMA^{V} levels, accompanied by a dose-dependent decrease in As^{V}.

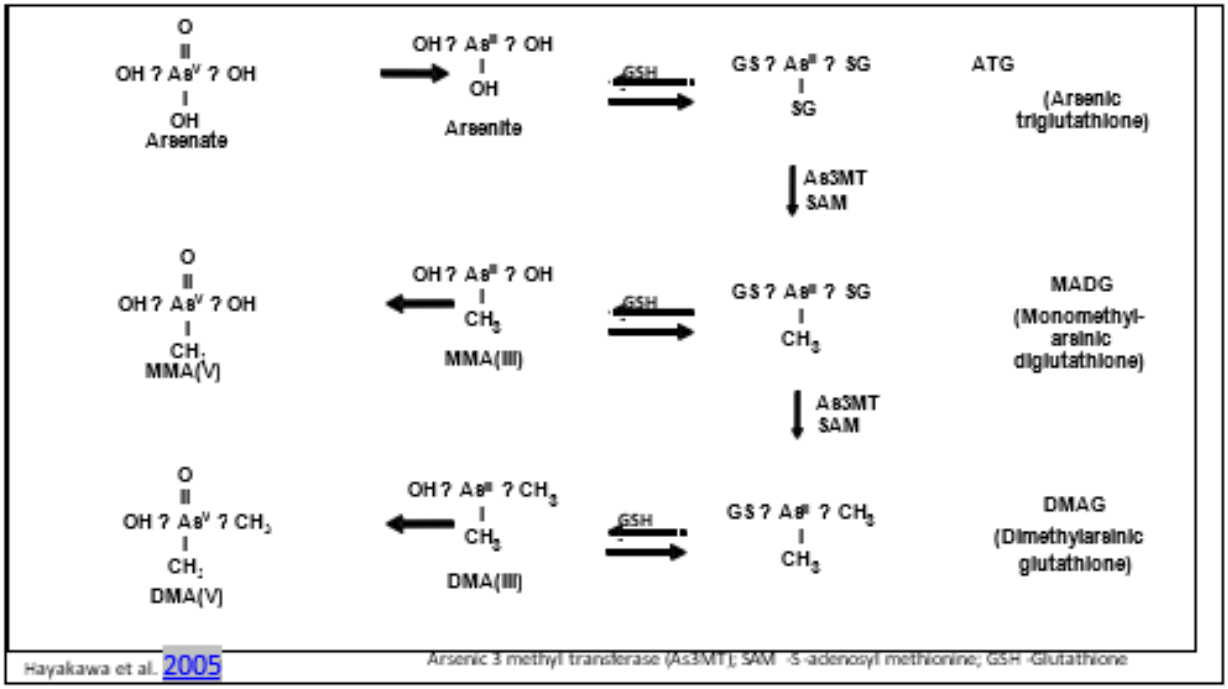


Figure D-2. Alternative metabolic pathway for inorganic arsenic in humans proposed by Hayakawa et al. (2005).

In summary, the proposed metabolic model of Hayakawa et al. (2005) suggests that As^{V} is first reduced to As^{III}, which then reacts (non-enzymatically) with GSH (producing ATG). In the presence of AS3MT (specified as cyt19 in the Hayakawa article),[35] ATG is methylated to MADG if the GSH concentration is sufficient, which then comes to equilibrium with MMA^{III} (GSH concentrations lower than 1 mM caused MADG to be unstable in solution and was readily hydrolyzed and oxidized to MMA^{V}). While some of the MMA^{III} is oxidized to MMA^{V}, some of the MADG is methylated by AS3MT to dimethylarsinic glutathione (DMAG), which, like MADG, is in equilibrium with its trivalent form and can be oxidized to its pentavalent form. This more recently proposed pathway leads to higher proportions of less toxic final species than the original proposed metabolic pathway (see Figure D-1).

Results reported by Hughes et al. (2005) may provide support for the Hayakawa et al. (2005) revised pathway. B6C3F1 mice administered MMA^{V} by oral gavage demonstrated its rapid absorption, distribution, and excretion, with 80% of the dose eliminated within 8 hours. Very little of the absorbed dose, however, was methylated to DMA and/or TMAO. Less than 10% of the dose

[35]Arsenic (+3 oxidative state) methyltransferase (AS3MT) has been referred to by many investigators as cyt19 in their references. According to Thomas et al. (2007), the Human Genome Nomenclature Committee (http://www.gene.ucl.ac.uk/cgi-bin/nomenclature/searchgenes.pl) recommends that this protein be systematically named AS3MT. In this document, references to cyt19 it has been changed to AS3MT to avoid confusion and for uniform consistency.

excreted in urine and 25% or less of the dose measured in the tissues were in the form of DMA. In contrast, in MMA^{III}-treated mice, more than 90% of the excreted dose and more than 75% of the arsenic measured in the tissues was identified as DMA. This discrepancy between the two forms of MMA is not expected if the generally accepted metabolic pathway (see Figure D-1) is followed. However, if MMA^{III} is the form methylated to DMA while MMA^{V} is an end product, as is suggested by Hayakawa et al. (2005), then it would be expected that a greater proportion of MMA^{III} would be methylated to DMA than MMA^{V}. There are, however, factors that may limit the in vivo methylation of MMA^{V} that are unrelated to the metabolic pathway proposed by Hayakawa et al. (2005). First, MMA^{V} does not appear to be taken up well by the liver (Hughes et al., 2005), a major site of inorganic arsenic metabolism (Thomas et al., 2001). In fact, pentavalent species of arsenic are not taken up by cells as readily as trivalent arsenicals (Dopp et al., 2004). In addition, in the generally accepted metabolic pathway (see Figure D-1), MMA^{V} needs to be reduced to MMA^{III} in order to be methylated. Therefore, if very little is taken up into cells, very little can be methylated.

Aposhian and Aposhian (2006) suggest that it is too early to accept AS3MT as the primary methyltransferase responsible for arsenic methylation in humans because it has only been observed in experiments involving deoxyribonucleic acid (DNA) recombinant technology and because there is no indication that the enzyme is expressed in human liver. Although AS3MT has been detected in human liver cell lines (Zakharyan et al., 1999), it has not been isolated from surgically removed liver tissue. Thomas (2007) also states the evidence supports the conclusion that arsenic methylation catalyzed by AS3MT is not strictly dependent on the presence of GSH, which would suggest that other pathways may be involved in addition to those included in Hayakawa et al. (2005) model. GSH depletion would likely occur at high arsenic exposures under Hayakawa et al. (2005) proposed pathway. Therefore, it is possible that both pathways work in conjunction, or one is predominant over the other depending on the concentration of arsenic. Hayakawa et al. (2005) found that levels of MMA^{V} were not dependent on GSH level (from 2 to 5 mM), suggesting that this indicated possible further methylation to DMA^{V}. Since this is not part of the proposed Hayakawa et al. (2005) pathway, at least some of the MMA^{V} may be methylated through the classic pathway.

D.1.7. Reduction

A substantial fraction of absorbed As^{V} is rapidly reduced to As^{III} in most species studied; in mice, rabbits, and marmoset monkeys, the reduction apparently occurs mainly in the blood (Marafante et al., 1985; Vahter and Marafante, 1985; Vahter and Envall, 1983). Reduction also may occur in the stomach or intestines prior to absorption, but quantitative experimental data are not available to determine the importance of this GI reduction. In addition to the reduction of inorganic As^{V}, as shown in Figure D-1, methylated As^{V} species also may be reduced by different enzymes.

GSH may play a role in the reduction of As^{V}, but is not the only cofactor, as cysteine and dithiothreitol (DTT) also have been found to reduce As^{V} to As^{III} in vitro (Németi and Gregus, 2002; NRC, 1999; Zakharyan et al., 1995). Inorganic phosphate inhibits the formation of As^{III} from As^{V} in

intact RBCs (Németi and Gregus, 2004), probably by competing with the phosphate transporter for the uptake into cells.

Arsenate reductase enzymes have been detected in the human liver (Radabaugh and Aposhian, 2000). At least one of these enzymes has been characterized as a purine nucleoside phosphorylase (PNP) (Gregus and Németi, 2002; Radabaugh et al., 2002). This enzyme requires a thiol and a heat-stable cofactor for activation. According to Radabaugh et al. (2002), dihydrolipoic acid (DHLP) is the most active naturally occurring thiol in mammalian systems and appears to be required for the enzymatic reduction of As^{V} to As^{III}. PNP, however, did not catalyze the reduction of MMA^{V} to MMA^{III}. An MMA^{V} reductase has been detected in rabbit liver (Zakharyan and Aposhian, 1999), hamster tissues (Sampayo-Reyes et al., 2000), and human liver (Zakharyan et al., 2001). In humans, this reductase is human glutathione-S-transferase ω (hGST-O1), which is a member of the glutathione-S-transferase (GST) superfamily (Aposhian and Aposhian, 2006).

Although PNP has been determined to reduce As^{V} to As^{III}, Nemeti et al. (2003) observed this reduction only in vitro. PNP did not appear to be a major player in the reduction of As^{V} to As^{III} in either human erythrocytes or in rats in vivo. Németi and Gregus (2004) and Németi and Gregus (2005) further demonstrated that human erythrocytes exhibit a PNP-independent As^{V}-reducing pathway that requires GSH, nicotinamide adenine dinucleotide (NAD), and a substrate for either one or both of the following enzymes: glyceraldehyde-3-phosphate dehydrogenase (GAPDH) or phosphoglycerate kinase (PGK). This mechanism of reduction also was demonstrated in rat liver cytosol (Németi and Gregus, 2005). In addition, another unidentified enzyme in the liver cytosol had the capacity to reduce As^{V}. A further study (Gregus and Németi, 2005) demonstrated that GAPDH exhibited As^{V} reductase activity, but that PGK served as an auxiliary enzyme when 3-phosphoglycerate was the glycolic substrate.

The reduction of pentavalent arsenicals also has been observed to be catalyzed by AS3MT (Waters et al., 2004b). According to Waters et al. (2004a), AS3MT may possess both As^{III} methyltransferase and As^{V} reductase activities. In the presence of an exogenous or physiological reductant, AS3MT was found to catalyze the entire sequence converting arsenite to all of its methylated metabolites through both methylation and reduction steps (see Figure D-1). Thomas (2007) also suggest that thioredoxin (Trx, isolated from E. coli) is necessary, possibly reducing some critical cysteine residue in AS3MT as a step in the methyltransferase reaction. Cohen et al. (2006) suggest that Trx, thioredoxin reductase (TrxR), and nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) are the primary reducing agents involved in the conversion of MMA^{V} to DMA^{V}, but they are orders of magnitude less effective than the arsenic methyltransferase isolated from rabbit liver (i.e., AS3MT). Zakharyan and Aposhian (1999) found that MMA^{V}-reductase was the rate-limiting enzyme in arsenic biotransformation in rabbit livers. Jin et al. (2006) also suggest that As^{V} reduction is possibly a rate-limiting step in arsenic metabolism at low concentrations. At higher concentrations, saturation or methylation inhibition may cause other reactions to become rate-limiting.

D.1.8. Arsenic Methylation

Methylation is an important factor affecting arsenic tissue distribution and excretion. Humans and most experimental animal models methylate inorganic arsenic to MMA and DMA, with the amounts differing across species, as determined by analysis of urinary metabolites. The methylated metabolites in and of themselves have historically been considered less acutely toxic, less reactive with tissue constituents, less cytotoxic, and more readily excreted in the urine than inorganic arsenic (Hughes and Kenyon, 1998; Sakurai et al., 1998; Moore et al., 1997; Rasmussen and Menzel, 1997; Marafante et al., 1987; Vahter et al., 1984; Yamauchi and Yamamura, 1984; Vahter and Marafante, 1983). The trivalent species MMA^{III} and DMA^{III}, however, have been demonstrated to be more cytotoxic in a human liver cell line called Chang cells (Petrick et al., 2001; Petrick et al., 2000), CHO (Dopp et al., 2004), and cultured primary rat hepatocytes (Styblo et al., 2000; Styblo et al., 1999) than As^{III}, As^{V}, MMA^{V}, or DMA^{V}.

Although the kinetics of arsenic methylation in vivo are not fully understood, it is believed the liver may be the primary site of arsenic methylation. However, the testes, kidney, and lung also have been observed to have a high methylating capacity (Cohen et al., 2006). Marafante et al. (1985) found that DMA appeared in the liver prior to any other tissue in rabbits exposed to inorganic As. It also has been demonstrated oral administration of inorganic arsenic favors methylation more than either subcutaneous or intravenous administration (Buchet et al., 1984; Vahter, 1981; Charbonneau et al., 1979), presumably because the arsenic will pass through the liver first after oral administration. However, liver disease (i.e., alcoholic, post-necrotic or biliary cirrhosis, chronic hepatitis, hemochromatosis, and steatosis) can be associated with increased ratios of DMA to MMA in the urine following a single injection of sodium arsenite (Geubel et al., 1988; Buchet et al., 1984). This appears to indicate that efficient methylation of arsenic continues in the presence of liver damage, possibly indicating that a different organ is responsible for methylation under these circumstances. In addition, the site of methylation may depend on the rate of reduction of As^{V} to As^{III}. Isolated rat hepatocytes readily absorbed and methylated As^{III}, but not As^{V} (Lerman et al., 1983). Kidney slices, on the other hand, produced five times more DMA from As^{V} than As^{III} (Lerman and Clarkson, 1983). Therefore, it is likely that any As^{V} not initially reduced can be efficiently methylated in the kidney for subsequent urinary excretion.

Identifying the main organs responsible for methylation of arsenic in vivo has not been straightforward because in vitro results do not necessarily reflect in vivo methylation patterns (NRC, 1999). Buchet and Lauwerys (1985) identified the rat liver as the main organ for methylation, with the methylating capacities in the RBCs, brain, lung, intestine, and kidneys being insignificant in comparison. Assays of arsenite methyltransferases from mouse tissues demonstrated the testes had the highest methylating activity, followed by the kidney, lung, and liver (Healy et al., 1998). Aposhian (1997) determined that the amount of methyltransferases vary in the liver of different animal species. Arsenite bound to components of tissue can be methylated and released (Vahter and Marafante, 1983; Marafante et al., 1981). This may explain the initial rapid

phase (immediate methylation and excretion) followed by a slow elimination phase (continuous release of bound arsenite through methylation) (NRC, 1999), as described in Section 3.4.

It has been demonstrated that inhibition of arsenic methylation results in increased tissue concentrations of arsenic (Marafante et al., 1985; Marafante and Vahter, 1984). Loffredo et al. (2003) suggest that the second methylation step is inducible and that the inducibility is possibly polymorphic (i.e., more than one enzyme or enzyme form may be involved, depending on the individual). This suggestion is based on observations that human urinary DMA concentrations in high-exposure groups were higher and more variable than urinary MMA levels, and because urinary DMA levels appeared to have a bimodal distribution in a population from Mexico, regardless of exposure status. Others have suggested that the second methylation step may be saturable, which would be consistent with the decreasing excretion of DMA with increasing arsenic exposures (Ahsan et al., 2007). Cysteine, GSH, and DTT have been shown to increase the activity of arsenite methyltransferase and MMA methyltransferase (both later identified as AS3MT) (Lin et al., 2002) in purified rabbit liver enzyme preparations (Zakharyan et al., 1995). Dithiols (e.g., reduced lipoic acid) have also been found to enhance arsenite methylation by MMA^{III} methyltransferase (Zakharyan et al., 1999). Glutathione-S-transferase omega 1 (GSTO1) has also been associated with arsenic biotransformation (Meza et al., 2007). Although humans have been observed to methylate arsenic, no arsenic methyltransferase has yet been isolated from human tissues (Aposhian and Aposhian, 2006).

In vitro studies using rat liver preparations indicate that the methylating activity is localized in the cytosol, with SAM being the main methyl donor for As^{III} methylation (Styblo et al., 1996; Styblo et al., 1995; Zakharyan et al., 1995; Buchet and Lauwerys, 1985; Marafante et al., 1985; Marafante and Vahter, 1984). AS3MT catalyzes the transfer of the methyl group from SAM to the arsenic substrates (Thomas, 2007; Lin et al., 2002). Expressing AS3MT in UROtsa (human urothelial cells that do not normally methylate inorganic arsenic) caused the cells to effectively methylate arsenite (Drobna et al., 2005). High concentrations of As^{III} or MMA^{III} in the culture caused an inhibition in the formation of DMA but had little effect on the formation of MMA. The inhibition of DMA production resulted in MMA accumulation in cells. Drobna et al. (2006) demonstrated that AS3MT was the major enzyme for arsenic methylation in human hepatocellular carcinoma (HepG2) cells but reducing it by 88% (protein levels) only accounted for a 70% reduction in methylation capacity, suggesting that there is another methylation process that is independent of AS3MT.

The addition of GSH has been found to increase the yield of mono- and dimethylated arsenicals but suppressed the production of TMAO in the presence of rat AS3MT (Waters et al., 2004b), indicating that GSH suppresses the third methylation reaction but not the first two (Thomas, 2007). Thomas et al. (2004) discovered a similar arsenic methyltransferase in the rat liver, which they designated cyt19 because an orthologous cyt19 gene encodes an arsenic methyltransferase in the mouse and human genome. It has subsequently been concluded that this methyltransferase was the same as AS3MT.

GSH alone does not support recombinant rat AS3MT catalytic function, but when added to a reaction mixture containing other reductants, the rate of arsenic methylation increases (Waters et al., 2004a). GSH alone (5mM) does not support the catalytic activity of AS3MT, but stimulates the methylation rate in the presence of the reductant tris(2-carboxylethyl)phosphine (TCEP; 1 mM) (Thomas, 2007). GSH (5 mM) did not have any effect on DTT (1 mM)-induced arsenic methylation. Drobna et al. (2004) linked the genetic polymorphism of AS3MT with other cellular factors and to the inter-individual variability in the capacity of primary human hepatocytes to retain and metabolize As^{III} (see Section 4.7).

The main products of arsenic methylation in humans are MMA^{V} and DMA^{V}, which are readily excreted in the urine (Marcus and Rispin, 1988). MMA^{III} and DMA^{III} have recently been detected in human urine (NRC, 2001); however, most studies do not differentiate the valence state of mono- or dimethylated arsenic species detected in urine or tissue samples. Le et al. (2000a), Le et al. (2000b) and Del Razo et al. (2001) noted that the concentration of trivalent metabolites in the urine may be underestimated because they are easily oxidized after collection. Le et al. (2000b) found 43 to 227 µg/L of MMA^{III} in the urine of populations from Inner Mongolia, China, who were exposed to 510–660 ppb (0.46 µM) of arsenic via the drinking water.

A small percentage of DMA^{III} may further be methylated to TMAO in mice and hamsters (see (Kenyon and Hughes, 2001) for a review). A single human volunteer ingesting DMA excreted 3.5% of the dose as TMAO (Kenyon and Hughes, 2001). TMAO can be detected in urine following DMA exposure, but has not been detected in the blood or tissues of mice exposed intravenously to DMA (Hughes et al., 2000) or in the urine of mammals orally exposed to inorganic As. This may be due to rapid clearance of DMA and MMA from cells (Styblo et al., 1999) however, most analytical methods are not optimized for the detection of TMAO that could have been present but not detected.

D.1.9. Species Differences in the Methylation of Arsenic

There is considerable variation in the patterns of inorganic arsenic methylation among mammalian species (NRC, 1999). Humans, rats, mice, dogs, rabbits, and hamsters have been shown to efficiently methylate inorganic arsenic to MMA and/or DMA. Rats and hamsters appear to methylate administered DMA into TMAO more efficiently than other species (NRC, 1999; Yamauchi and Yamamura, 1984). About 40% of urinary arsenic was present as TMAO 1 week after exposure to DMA in the drinking water, while 24% was present as TMAO after 7 months of exposure (100 mg/L) in male rats (Yoshida et al., 1998).

Humans (mainly exposed to background levels or exposed at work) have been estimated through a number of studies to excrete 10% to 30% of the arsenic in its inorganic form, 10% to 20% as MMA, and 55% to 75% as DMA (see Vahter (1999a) for a review). In contrast, a study of urinary arsenic metabolites in a population from northern Argentina exposed to arsenic via drinking water demonstrated an average of only 2% MMA in the urine (Concha et al., 1998a; Vahter et al., 1995a). This may indicate variations in methylation activity depending on the route of exposure, level of exposure, and possible nutritional or genetic factors. Although humans are

considered efficient at arsenic methylation, they are less efficient than many animal models, as indicated by the larger proportion of MMA^V excreted in the urine (Vahter, 1999a). This is important because it may explain why humans are more susceptible to cancer from arsenic exposures, and why no adult animal model for inorganic-arsenic-induced cancers has yet been identified (Tseng et al., 2005).

The rabbit (Maiorino and Aposhian, 1985; Vahter and Marafante, 1983; Marafante et al., 1981) and hamster (Marafante and Vahter, 1987; Yamauchi and Yamamura, 1984; Charbonneau et al., 1980) appear to be more comparable to humans with respect to arsenic methylation than other experimental animals (NRC, 1999). However, rabbits and hamsters, in general, excrete more DMA and less MMA than humans. In contrast, Flemish giant rabbits (De Kimpe et al., 1996) excrete MMA in amounts similar to humans. Mice and dogs, efficient methylators of arsenic, excrete more than 80% of a single arsenic dose administered as DMA within a few days (Vahter, 1981; Charbonneau et al., 1979). Guinea pigs (Healy et al., 1997), marmoset monkeys (Vahter and Marafante, 1985; Vahter et al., 1982), and chimpanzees (Vahter et al., 1995b), on the other hand, do not appear to appreciably methylate inorganic arsenic. In addition, no methyltransferase activity was detected in these species (Vahter, 1999a; Healy et al., 1997; Zakharyan et al., 1996; Zakharyan et al., 1995). Li et al. (2005) identified a frameshift mutation in the chimpanzee AS3MT gene that resulted in the production of an inactive truncated protein, possibly explaining the lack of methylation activity in that species.

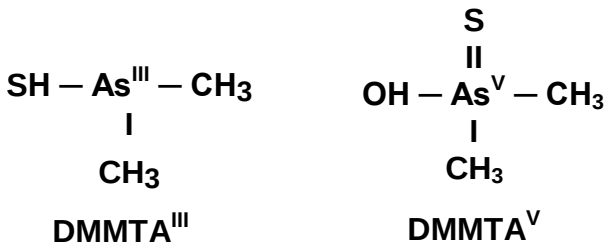
AS3MT homolog proteins with five fully conserved cysteine residues have been observed in the genome of numerous species (Thomas, 2007). Chimpanzees were found to differ from other species studied in that their AS3MT protein was shorter and lacked the 5th cysteine (Thomas, 2007). Healy et al. (1999) identified marked variations in the activity of methyltransferases, while Vahter (1999b) characterized differences in methylation efficiency among different human populations. The observed variations in methyltransferase activity and methylation efficiency are probably the underlying reason for the cross-species variability in methylation ability, as all the species had ample arsenate reductase activity (NRC, 2001; Vahter, 1999a).

Although arsenic methylation is generally believed to take place in order to enhance excretion, there are several species (guinea pigs, marmoset monkeys, and chimpanzees) that do not methylate arsenic, but still efficiently excrete it. In fact, these animals do not retain arsenic any longer than species that methylate arsenic (Cohen et al., 2006), indicating that factors other than methylation also affect arsenic excretion rates. Supporting this is the fact that inorganic arsenic is found in the urine of even the most efficient methylators (Vahter, 1994).

D.1.10. Thioarsenical Metabolites

In 2004, Hansen et al. (2004) reported the detection of unusual arsenic-containing metabolites in the urine of sheep exposed to arsenic-contaminated vegetation. The metabolite was tentatively identified as dimethylmonothioarsinic acid ($DMMTA^{III}$), a sulfur-containing derivative of DMA^{III} as shown in Figure D-3. Because the exposed sheep consumed algae known to contain

arsenosugars, some of which contain sulfur, the relevance of this finding to human exposures was not initially clear. Subsequently, Raml et al. (2006) detected the presence of $DMMTA^{III}$ in the urine of Japanese men, but again, consumption of arsenosugars was suspected as a source of the observed arsenic containing species.



Source: Hansen et al. (2004).

Figure D-3. Thioarsenical structures.

In experiments addressing this issue, Adair et al. (2007) and Naranmandura et al. (2007) found substantial concentrations of thioarsenical metabolites in arsenic-exposed experimental animals. Adair et al. (2007) administered drinking water containing 100 ppm As^{V} or up to 200 ppm DMA^{III} to female Fisher 344 rats for 14 days. During analysis of the urine (collected during the last 24 hours of exposure) for metabolites, they found high levels of $DMMTA^{III}$ and trimethylarsine sulfide (another sulfur-containing metabolite) in the urine of rats treated with DMA^{III}. Lower levels of the sulfur-containing metabolites were detected in the urine of arsenate-treated animals. They proposed a mechanism whereby the reaction of DMA^{III} and DMA^{V} with hydrogen sulfide resulted in the observed metabolites.

Naranmandura et al. (2007) administered single doses of 5.0 mg/kg As^{III} to Syrian hamsters and Wistar rats by gavage and measured the levels of sulfur-containing arsenic metabolites in urine. Both $DMMTA^{III}$ and dimethylmonothioarsonic acid ($DMMTA^{V}$) were found at appreciable levels in urine from hamsters, but only the latter metabolite was found in rat urine. A previously uncharacterized metabolite, monomethylmonothioarsonic acid, was also found in urine from both species.

These studies suggest that the generation of sulfur-containing arsenic metabolites does not depend on exposures to arsenosugars, at least in rodents, but can occur during the metabolism of inorganic arsenic compounds. In 2007, Raml et al. (2007) presented evidence that this pathway was also significant in humans. $DMMTA^{III}$ was detected in the urine of 44% (33 of 75) women exposed to inorganic arsenic-contaminated drinking water in Bangladesh. The metabolite was present in urine samples at concentrations between "trace" amounts and 24 µg/L, with total arsenic concentrations ranging from 8 to 1034 µg/L. It was suggested that thioarsenical metabolites may

have been present in urine from other epidemiological studies of arsenic-exposed populations but may have not been detected due to analytical difficulties.

D.2. ELIMINATION

The major route of excretion for most arsenic compounds by humans is via urine (Buchet et al., 1981; Pomroy et al., 1980; Tam et al., 1979; Yamauchi and Yamamura, 1979). Six human subjects who ingested 0.01 µg of radio-labeled $^{74}As^{V}$ excreted an average of 38% of the administered dose in the urine within 48 hours and 58% within 5 days (Tam et al., 1979). Inorganic arsenic elimination in humans has been observed to be triphasic, with first-order half-lives for elimination of 1 hour, 30 hours, and 200 hours (Mealey et al., 1959) used AsIII (Pomroy et al., 1980) used AsV.

As mentioned in the preceding section, MMA and DMA are metabolites generated after exposure to inorganic arsenic. These methylated metabolites are excreted in the urine faster than inorganic arsenic. In humans orally exposed to MMA or DMA in aqueous solution, about 78% of MMA and 75% of DMA were excreted in the urine within 4 days of ingestion (Buchet et al., 1981). In mice, the half-time of MMA and DMA excretion was found to be about 2 hours following iv administration (Hughes and Kenyon, 1998).

Kenyon et al. (2008) administered 0, 0.5, 2, 10, or 50 ppm of arsenic as sodium arsenate to adult C57Bl/6 female mice in the drinking water for 12 weeks. The average daily intakes were estimated to be 0, 0.083, 0.35, 1.89, and 7.02 mg As/kg-day, respectively. Levels of MMA^{III}, DMA^{III}, DMA^{V}, and TMAO in the urine collected at the end of treatment increased in a linear manner with dose, but As^{V} and MMA^{V} did not.

Rats excrete DMA slowly compared to other species (Vahter et al., 1984), even though they are efficient at methylating inorganic arsenic to DMA. The slow excretion is believed to be associated with retention of a significant portion of the DMA in erythrocytes (Vahter et al., 1984; Lerman and Clarkson, 1983; Vahter, 1983; Odanaka et al., 1980). The biliary excretion of inorganic arsenic by rats is about 800 times greater than observed in dogs and 37 times that of rabbits, as proportion of administered dose. Hughes et al. (2005) found that in mice the level of MMA^{V} excreted in the urine compared to the bile was related to dose, with fecal excretion increasing at higher doses. Cui et al. (2004) also found that rat biliary excretion rates varied with dose, but found it was also related to route of administration and chemical form. After oral administration of inorganic arsenic (either form) to male Sprague-Dawley rats, MADG and DMA^{V} (likely present due to dissociation of DMAG) were the predominant forms in the bile. MADG was found at a higher level after a higher (i.e., 100 ppm) dose, while DMA^{V} was more prevalent at the lower dose (i.e., 10 ppm). Kala et al. (2000) found that the secretion of arsenic into the bile of rats was dependent on the multi-drug resistance-associated protein 2 transporter (MPR2/cMOAT) and that GSH is necessary for the transport, as arsenic-glutathione complexes accounted for the majority of arsenic found in the bile.

Although absorbed arsenic is removed from the body mainly via the urine, small amounts of arsenic are excreted through other routes (e.g., skin, sweat, hair, breast milk). While arsenic has been detected at low levels in the breast milk of women in northwestern Argentina (i.e., 2 µg/kg), breastfeeding was associated with lower concentrations of arsenic in the urine of newborn children (Concha et al., 1998c) than formula feeding, owing to the use of arsenic contaminated water in formula preparation. Parr et al. (1991) measured arsenic (as well as other elements) in the breast milk from three groups of mothers from four countries (Guatemala, Hungary, Nigeria, and the Philippines), and one to two groups from Sweden and Zaire. The breast milk was collected 3 months after birth. Levels of arsenic in the breast milk from women in the Philippines were higher than other regions with levels about 19 µg/kg. Women from Nigeria had levels similar to those observed by Concha et al. (1998c). Women from all the other areas measured had levels of 0.24 to 0.55 µg/kg.

The average concentration of arsenic in sweat induced in a hot and humid environment was 1.5 µg/L, with an hourly loss rate of 2.1 µg (Vellar, 1969). Based on an average arsenic concentration in the skin of 0.18 mg/kg, Molin and Wester (1976) estimated that the daily loss of arsenic through desquamation was 0.1 to 0.2 µg in males with no known exposure to arsenic.

D.2.1. Physiologically Based Pharmacokinetic Models

Physiologically based pharmacokinetic (PBPK) models for inorganic arsenic are important for developing a biologically based dose-response (BBDR) model. The development of useful BBDR models has proved to be challenging because inorganic arsenic appears to mediate its toxicity through a range of metabolites, and their roles with regard to specific adverse effects are not clear (Clewell et al., 2007).

A PBPK model for exposure to inorganic arsenic (orally, intravenously, and intratracheally) was developed in hamsters and rabbits by Mann et al. (1996a). The model includes tissue compartments for lung (nasopharynx, tracheobronchial, pulmonary), plasma, RBCs, liver, GI tract, skin, kidney, keratin, and combined other tissues. Oral absorption of As^{III}, As^{V}, and DMA (pooled III and V oxidation states) was modeled as a first-order transport process directly from the GI contents into the liver. Distribution to tissues was diffusion-limited, with transfer rates estimated based upon literature values for capillary thickness and pore sizes for each tissue. Reductive metabolism of As^{V} to As^{III} was modeled as a first-order process occurring in the plasma. Oxidative metabolism of As^{III} to As^{V} was modeled as first-order processes in the plasma and kidneys. Methylation of inorganic arsenic species to MMA (pooled III and V oxidation states) and then to DMA were modeled as saturable Michaelis-Menten processes taking place in the liver. Urinary, biliary, and fecal excretion of As^{III}, As^{V}, MMA, and DMA also are modeled as first-order processes. Parameters for absorption, tissue partition, metabolism, and biliary excretion were estimated by fitting the model to literature data on the urinary and fecal excretion of total arsenic from rabbits and hamsters administered various arsenic compounds by iv, oral gavage, or intratracheal instillation (Marafante et al., 1987; Marafante et al., 1985; Yamauchi and Yamamura, 1984; Charbonneau et al.,

1980). The model was found to accurately simulate the excretion of arsenic metabolites in the urine of rabbits and hamsters and to produce reasonable fits to liver, kidney, and skin concentrations in rabbits and hamsters (Marafante and Vahter, 1987; Marafante et al., 1985; Yamauchi and Yamamura, 1984).

Mann et al. (1996b) extended their PBPK model for use in humans by adjusting physiological parameters (organ weights, blood flows) and re-estimating absorption and metabolic rate constants. The model was fit to literature data on the urinary excretion of total arsenic following a single oral dose of As^{III} or As^{V} in human volunteers (Buchet et al., 1981; Tam et al., 1979). The extended human model was further tested against empirical data on the urinary excretion of the different metabolites of inorganic arsenic following oral intake of As^{III}, intake of inorganic arsenic via drinking water, and occupational exposure to arsenic trioxide (ATO) (Vahter et al., 1986; Buchet et al., 1981; Valentine et al., 1979; Harrington et al., 1978). The model predicted a slight decrease (about 10%) in the percentage of DMA in urine with increasing single-dose exposure (highest dose of arsenic at 15 μg/kg of body weight), especially following exposure to As^{III}, and an almost corresponding increase in the percentage of MMA. The model predicted that adults' drinking water containing 50 ppb would excrete more arsenic in urine than an occupational inhalation exposure of 10 $\mu g/m^3$ (Mann et al., 1996b).

Yu (1999) also developed a PBPK model for arsenic in humans that includes tissue compartments for lung, skin, fat, muscle, combined kidney and richly perfused tissues, liver, intestine, GI and stomach contents, and bile. Oral absorption of As^{III}, As^{V}, and DMA (pooled III and V oxidation states) was modeled as first-order transport from the GI contents into the intestinal tissue. Distribution to tissues was modeled as perfusion-limited. Reductive metabolism of As^{V} to As^{III} was modeled as a first-order, GSH-dependent process taking place in the intestinal tissue, skin, liver, and kidney/rich tissues. Oxidative metabolism of As^{III} to As^{V} was not modeled. Methylation of inorganic arsenic species to MMA (pooled III and V oxidation states) and then to DMA was modeled as saturable Michaelis-Menten processes occurring in the liver and kidney. Urinary, biliary, and fecal excretion of As^{III}, As^{V}, MMA, and DMA were modeled as first-order processes. Parameters for absorption, tissue partition, metabolism, and biliary excretion were estimated by fitting the model to literature data on tissue concentrations of total arsenic from a fatal human poisoning (Saady et al., 1989), and blood, urine, and fecal elimination of total arsenic following oral administration (Odanaka et al., 1980; Pomroy et al., 1980). The model was not tested further against external data, and fits to the data sets used for parameter estimation were not provided.

Gentry et al. (2004) adapted the model proposed by Mann et al. (1996a) to different mouse strains by adjusting physiological parameters (organ weights and perfusion rates). The absorption, partition, and metabolic rate constants were re-estimated by fitting the model to literature data on urinary excretion of various arsenic species following iv administration of MMA to B6C3F1 mice (Hughes and Kenyon, 1998) or single oral administration of As^{III} or As^{V} to mice (Hughes et al., 1999; Kenyon et al., 1997). Additionally, the description of methylation in the model was refined to

include the uncompetitive inhibition of the conversion of MMA to DMA by As^{III}. The PBPK model was then validated using data from a single oral administration of As^{V} (Hughes et al., 1999) and a 26-week drinking water exposure of As^{III} to C57Black mice (Moser et al., 2000). These data were found to adequately fit the model without further parameter adjustment. Ng et al. (1999) had found arsenic-induced tumors in C57Bl/6J mice, while numerous other mouse strains (Swiss CR:NIH[S], C57Bl/6p53[+/−], C57Bl/6p53[+/+], and Swiss CD-1) had not experienced a significant increase in arsenic-induced tumors. The Gentry et al. (2004) model was unable to explain the different outcomes in the mouse bioassay on the basis of predicted target organ doses.

The Mann et al. (1996b), Mann et al. (1996a) and Gentry et al. (2004) models are well documented, were validated against external data, and appear to capture the salient features of arsenic toxicokinetics in rodents and humans. The information provided by these models may help explain the MOAs involved in carcinogenesis along with possible reasons that humans are apparently more susceptible to the carcinogenic effects of arsenic.

Clewell et al. (2007) noted that the then-available PBPK models did not incorporate the most recent available information on arsenic methylation kinetics and suggested several steps for improving the PBPK models. Kenyon et al. (2008) have developed a PBPK model incorporating some of the improvements suggested by Clewell et al. (2007) (although not the simulation of changes in gene expression). The model predicts the levels of inorganic arsenic and its metabolites in human tissues and urine following oral exposure of As^{V}, As^{III}, and for oral exposure to organoarsenical pesticides. The model consists of interconnecting submodels for inorganic arsenic (As^{III} and As^{V}), MMA^{V}, and DMA^{V}. Reduction of MMA^{V} and DMA^{V} to their trivalent forms is also modeled. The submodels include the GI tract (lumen and tissue), lung, liver, kidney, muscle, skin, heart, and brain, with reduction of MMA^{V} and DMA^{V} to their trivalent forms modeled as occurring in the lung, liver, and kidney. The model also incorporates the inhibitory effects of As^{III} on the methylation of MMA^{III} to DMA and MMA^{III} on the methylation of As^{III} to MMA into consideration, modeled as noncompetitive inhibition. This model differs from the other models described above because it provides an updated description of metabolism using recent biochemical data on the mechanism of arsenic methylation. In addition, it uses in vitro studies to estimate most of the model parameters (statistically optimizing those that are sensitive to urinary excretion levels to avoid problems with parameter identifiability) and can predict the formation and excretion of trivalent methylated arsenicals. The partition coefficients estimated in the model are comparable to those developed by Yu (1999). The performance of the model was tested against limited human data on urinary excretion; the model needs to be evaluated for its ability to predict the tissue and urinary concentrations of arsenicals in large numbers of subjects. This model is an improvement over previous models because it can quantitatively assess impacts of parameter variability arising from genetic polymorphism.

D.3. PBPK MODEL EVALUATION SUMMARY

See Section 4 of the Updated Problem Formulation and Protocol for the Inorganic Arsenic IRIS Assessment.

APPENDIX E. QUALITY ASSURANCE FOR THE IRIS TOXICOLOGICAL REVIEW OF INORGANIC ARSENIC

This assessment is prepared under the auspices of the U.S. Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS) Program. The IRIS Program is housed within the Office of Research and Development (ORD) in the Center for Public Health and Environmental Assessment (CPHEA). EPA has an agency-wide quality assurance (QA) policy that is outlined in the *EPA Quality Manual for Environmental Programs* (see CIO 2105-P-01.3) and follows the specifications outlined in EPA Order CIO 2105.3.

As required by CIO 2105.1, ORD maintains a Quality Management Program, which is documented in an internal Quality Management Plan (QMP). The latest version was developed in 2013 using Guidance for Developing Quality Systems for Environmental Programs (QA/G-1). An NCEA/CPHEA-specific QMP was also developed in 2013 as an appendix to the ORD QMP. Quality assurance for products developed within CPHEA is managed under the ORD QMP and applicable appendices.

The IRIS Toxicological Review of Inorganic Arsenic is designated as Highly Influential Scientific Information (HISA)/Influential Scientific Information (ISI) and is classified as QA Category A. Category A designations require reporting of all critical QA activities, including audits. The development of IRIS assessments is done through a seven-step process. Documentation of this process is available on the IRIS website: https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#process.

Specific management of quality assurance within the IRIS Program is documented in a Programmatic Quality Assurance Project Plan (PQAPP). A PQAPP is developed using the EPA Guidance for Quality Assurance Project Plans (QA/G-5), and the latest approved version is dated April 2021. All IRIS assessments follow the IRIS PQAPP, and all assessment leads and team members are required to receive QA training on the IRIS PQAPP. During assessment development, additional QAPPs may be applied for quality assurance management. They include:

Title	Document number	Date
Program Quality Assurance Project Plan (PQAPP) for the Integrated Risk Information System (IRIS) Program	L-CPAD-0030729-QP-1-6	June 2023
An Umbrella Quality Assurance Project Plan (QAPP) for Dosimetry	L-CPAD-0032188-QP-1-3	June 2023

Title	Document number	Date
and Mechanism-Based Models (PBPK)		
Quality Assurance Project Plan (QAPP) for Enhancements to Benchmark Dose Software (BMDS)	L-HEEAD-0032189-QP-1-3	July 2023
ICF-General Support of CPHEA Human Health Assessment Activities QAPP	L-CPAD-0031961-QP-1-5	September 2022

During assessment development, this project undergoes four quality audits during assessment development including:

Date	Type of audit	Major findings	Actions taken
August 2020	Technical system audit	None	None
July 2021	Technical system audit	None	None
August 2022	Technical system audit	None	None
June 2023	Technical system audit	None	Note

APPENDIX F. RESPONSE TO EXTERNAL COMMENTS

APPENDIX G. SUMMARY OF OTHER AGENCY CONCLUSIONS

In addition to EPA (McGeer et al., 2004; U.S. EPA, 2002, 1993), other national and international health agencies have also assessed inorganic arsenic. Toxicity information on inorganic arsenic has been evaluated by the Agency for Toxic Substances and Disease Registry (ATSDR, 2016, 2007), the World Health Organization (WHO, 2011a, b; IARC, 2004a; WHO, 2000), National Institute for Occupational Safety and Health (NIOSH, 2005), Occupational Safety and Health Administration (OSHA, 2005), Food and Drug Administration (CFSAN, 2023; FDA, 2020, 2005), Health Canada (Health Canada, 2006), Dutch National Institute for Public Health and the Environment (RIVM, 2001), and the International Agency for Research on Cancer (IARC, 2012), and the National Toxicology Program (NTP, 2016). EPA used these assessments to ensure that the literature search captured pertinent studies and to identify key issues and health outcomes that have been previously evaluated. Toxicity values and their bases from these assessments are presented in Table G-1. It is important to recognize that these assessments may have been prepared at different times, for different purposes, using different guidelines and methods. In addition, newer studies may be included in the IRIS assessment.

Table G-1. Health assessments and regulatory limits by other national and international health agencies for inorganic arsenic

Organization	Toxicity value
Agency for Toxic Substances and Disease Registry (ATSDR, 2016, 2007)	Acute-duration oral MRL of 0.0005 mg/kg-d Chronic-duration oral MRL of 0.0003 mg/kg-d
Dutch National Institute for Public Health and the Environment (RIVM, 2001)	TDI of 1.0 µg/kg/d for chronic oral exposures and 1.0 µg/m^3 for chronic inhalation exposures
Food and Drug Administration (CFSAN, 2023; FDA, 2020, 2005)	Bottled drinking water level of 0.01 mg/L "action level" of 10 µg/L in apple juice "action level" of 100 µg/L in rice and rice products
Health Canada (Health Canada, 2006)	MAC of 0.01 mg/L
International Agency for Research on Cancer (IARC, 2012)	Carcinogenic to humans (Group 1)
National Institute of Occupational Safety and Health (NIOSH, 2005)	REL (15 min ceiling limit) of 0.002 mg/m^3 IDLH of 5 mg/m^3

Organization	Toxicity value
National Toxicology Program (NTP, 2016)	Known to be a human carcinogen
Occupational Safety and Health Administration (OSHA, 2005)	PEL (8-hr TWA) of 10 µg/m^3
U.S. Environmental Protection Agency	RfD of 0.0003 mg/kg/d U.S. EPA (1993) Cancer slope factor of 1.5 mg/kg/d U.S. EPA (1993) Inhalation unit risk of 0.0043 µg/m^3 U.S. EPA (1993) DWEL of 0.01 mg/L McGeer et al. (2004) MCLG of zero U.S. EPA (2002) MCL of 0.01 mg/L U.S. EPA (2002)
World Health Organization (WHO, 2011b; IARC, 2004b; WHO, 2000)	Air quality guidelines of 1.5 × 10^{-3}-unit risk Drinking water quality guidelines of 0.01 mg/L

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