Summary of Public Comments Received on IRIS Inorganic Arsenic Protocol for Transmittal to NAS Committee

This table provides a comprehensive summary of public comments received through the EPA docket (https://www.regulations.gov/document?D=EPA-HQ-ORD-2012-0830-0040), where the full set of comments as submitted are available. Comments are organized by broad topic areas and are mapped to Committee Charge Questions, where possible, for convenience. A legend of Commenters is available at the end of this document.

GENERAL	**Commenter (page)**	**Relevant Charge Question(s)**
1. Don't extrapolate low dose risk from use high dose epidemiology studies. Focus primarily on studies that evaluate health effects of low dose exposures, including human, animal, and mechanistic studies.	ASTF (1) EPRI (3)	#4, #5
2. Don't ignore MOA, which supports a dose-response threshold for cancer and noncancer effects of iAs.	ASTF (1) SC (1) EPRI (3)	#3
3. Consider animal studies, not just epidemiology (ASTF), particularly for health outcomes for which the human health effects literature is not as extensive or conclusive (EPRI).	ASTF (1) EPRI (3, 10)	#2
4. Indicate how the adequacy of epidemiological evidence for characterizing the dose-response in a way that is consistent with the MOA will be assessed.	ASTF (2)	#3
5. Consideration should be given to the role of digestive tract microbiome in the dosimetry/toxicity of As in the assessment.	DoD (1)	
6. Discuss absorption mechanisms in the assessment.	DoD (1)	
7. Evaluate further to see if the comparison between smoking exposure and the RfD can be expanded in the full review.	DoD (1)	
8. "Since IRIS reviews are both intended to be comprehensive and are used for multiple purposes by States and Federal agencies they should include a discussion of all scientifically supported alternatives that have been published."	DoD (2)	
9. Difference between "support," "agree" and "recommend" in the Section 2.3 bullets is not clear. "Suggest all be changed to "support" or that EPA indicate why certain conclusions and recommendations were determined to be "agree."	DoD (3)	
10. Change the Abhyankar et al. (2012) reference (which is the French version) to the full, original English version. Make Lynch et al. (2017) the main article.	DoD (3)	
11. WHO, IARC, and NCR, do not assess cancer risk. Thus, the statement "The carcinogenic risk to humans has been established by..." should be changed to "The potential for arsenic to cause cancer in people has been established by...".	DoD (5)	
12. "Bearing in mind that human exposure is about 15 µg/L iAs. In animal studies, there is a very large (x1000-fold) discrepancy between the doses (or exposures listed in Table A.3 with those in the realistic range (Goggin et al., 2012; 50 ppb) lumped together with unrealistically high concentrations (Suzuki and Nohara, 2013; 50 ppm). If possible, we suggest ranking the importance of animal and in vitro studies based on how well the doses or exposures approximate the measurable levels of iAs in blood or urine. Otherwise studies that exposure animals to levels x1000-fold greater than that found in well water will be treated the same as other more realistic efforts."	DoD (16)	
13. "Please clarify if the NRC will in fact review the final draft EPA IRIS Toxicological Review of Inorganic Arsenic. This will most likely add another 12 months to the already extensive internal EPA and interagency review processes."	DoD (17)	

GENERAL	Commenter (page)	Relevant Charge Question(s)
14. "TCEQ applauds EPA for identifying and characterizing data in a more transparent, efficient and systemized manner."	TCEQ (1)	#2
15. "TCEQ supports EPA's intentions to apply MOA data in a more global manner throughout the assessment, particularly to inform model systems chosen, modeling assumptions selected, and coding mathematical expressions used to inform dose-response relationships."	TCEQ (1)	#3
16. Figures 4-2, A-1 and E-2 are blurry in the pdf version of the document. Higher resolution figures should be considered.	TCEQ (3)	
17. Is the MIE box in Figure A-2 supposed to have more bullets (e.g., bullet point in front of increase in oxidative stress)?	TCEQ (3)	
18. "The focus of the current scoping is unclear as to whether it includes oral exposure only or oral and inhalation exposure. EPRI recommends that clarification of this issue be provided in the document… It is unclear how inhalation estimates would be developed based on the approaches presented and the focus of the literature search (e.g., exclusion of arsenic trioxide, which is the arsenic compound of concern for inhalation exposure)."	EPRI (3) EPRI (13)	#2
19. "It is unclear based on the information presented in the Updated Arsenic Review Protocol how USEPA will use the dose-response modeling results to make risk-based decisions at background concentrations. Considering that the Problem Formulation "frames scientific questions that will be the focus of systematic review conducted as part of assessment development", the USEPA needs to describe how they plan to evaluate risks associated with background exposures and apply the results to site-based risk assessments. For instance, are risks associated with background going to be considered acceptable or will they be considered unacceptable? Or will USEPA consider some level of exposure above background acceptable? If so, what procedures will be used to determine that level? Moreover, given that natural background exposures vary substantially across the United States, how will USEPA establish background concentrations of inorganic arsenic in relevant environmental media?"	SIM (3)	#5

GENERAL	Commenter (page)	Relevant Charge Question(s)
20. "It appears that the USEPA opened a docket for the submission of public comments for its 2015 Assessment Development Plan for the IRIS Toxicological Review of Inorganic Arsenic; however, this docket does not appear to have been well-advertised (USEPA, 2015a). According to an internal memorandum authorizing the posting of the 2015 document to Regulations.gov for public access, the docket for public comment was open from November 20, 2015 to December 31, 2016 (USEPA, 2015b). Yet, only two public comments were received during the entire year-long public comment period (USEPA, 2019b). Furthermore, there was only brief mention of Bayesian approaches and no mention of using advanced modeling techniques, such as polynomial approximations or an RRE20 value (RRE20 = exposure that increases relative risk by 20%) to derive a relative risk to background exposure (RRB) value. Given the complexity of these approaches and a lack of their description in the 2015 document, the 30-day public comment period associated with the current Problem Formulation document (USEPA, 2019a) and the materials provided are insufficient for stakeholders to meaningfully review USEPA's current Updated Arsenic Review Protocol. In addition, USEPA's RRB analysis was already performed and results are described in the 2019 document without the opportunity for the public to review methods, input data, or provide comments. The RRB analysis is not routine, nor has guidance been published by USEPA outlining its use. Because the results of the RRB analysis "were used to inform the selection of studies and data sets for further dose-response analysis," an unreviewed, novel approach has the potential to affect the USEPA's ultimate selection of reference toxicity values for arsenic (USEPA, 2019a). USEPA's Updated Arsenic Review Protocol should include an additional Appendix that details the methods, input data, and modeling results that were used to develop the *Initial Screening Analyses* (Section 5.1). Additionally, the comment period for the Updated Arsenic Review Protocol (USEPA, 2019a) should be extended to allow time for the public to review and comment on this new information."	SIM (7)	#2
21. "If this next revision of the EPA assessment is to succeed, it needs to explicitly, forthrightly, and credibly address the basis for asserting any conclusions about the potential for low exposures to iAs to cause health impacts, rather than simply relying on "upper bound" projections from effects at much higher exposures."	RGC (1)	
22. "There are enough studies with enough low-exposure dose points to show that, as one goes upward in exposure from low doses, there are no apparent effects and no real evidence of upward trends in cancer risks until exposures get higher than those resulting from water concentrations of over 100 µg/L."	RGC (1, 3)	
23. "…low-dose exposures estimated from iAs levels in drinking water do not account for other sources of iAs (*e.g.*, from the diet) and, therefore, may be underestimating total iAs exposure."	RGC (1)	

MOA	Commenter (page)	Relevant Charge Question(s)
1. Focusing on human studies "…essentially ignores large bodies of evidence that can inform the potential for health effects in the low-concentration region (<200 µg/L or ppb ingested) for which there is limited epidemiological evidence as noted by NRC (2013)…animal and *in vitro* data should be used to support dose-response evaluation, especially in the low concentration region, as recommended by NRC (2013). These data play a key role in determining mode of action of iAs toxicity and the shape of the dose-response curve, including the potential presence of a threshold for health effects (e.g., Tsuji et al., 2019; Cohen et al., 2013). "…the NRC recommendations to the EPA for its further iAs evaluation include a clear call to examine low dose issues in terms of modes of action and not simply to extrapolate from high doses in epidemiology studies. Other reviews of earlier EPA assessments…also make this point." EPA's plan to rely on epidemiology data would "…would flout the reviewing NRC committee's call for real consideration of mode-of-action arguments and the evaluation of the basis for inferences about any potential for cancer risks at low iAs doses… We see it as a mistake to assert that a mode-of-action argument needs to be definitive and exclusionary of any alternative approach before it can be presented as an informative analysis… and a lack of definitive proof should not be used as an excuse to invoke an unsupported linear projection from high doses."	EPRI (3) SC (1) ASTF (1) RGC (2-3, 5)	#3
2. "The only mode of action that can produce a linear extrapolation from high to low dose is DNA reactivity, and this is the only one for which a non-threshold approach is possibly appropriate. Nesnow et al. (2002), among others, showed that inorganic arsenic and all of its metabolites are anions and therefore cannot react with DNA in mammalian organisms, including humans. This means that the only mode of action that can produce a linear dose-response is not relevant to arsenic. All of the multiple possible modes of action proposed for arsenic have thresholds."	SC (2)	#3
3. "It is widely accepted that the biological effects of arsenicals are due to a reaction of trivalent forms with sulfhydryl groups (Kitchin and Wallace, 2005; 2008; Cohen et al., 2006; 2013)…[such] protein reactions involve a threshold… biological effects require a level adequate to affect the functionality of the protein… This mode of action has a threshold."	SC (3) RGC (2, 5)	#3
4. "Cytotoxicity and regeneration have been demonstrated as the mode of action for dimethylarsinic acid-induced bladder cancer, in rats, with a clearly documented threshold (Cohen et al., 2006), and similar changes have been identified following oral administration of inorganic arsenic." Commenter cites Cohen et al. (2013) and Tsuji et al. (2019) for more detail.	SC (3) RGC (5)	#3
5. "Details of the bladder cancer case study should be provided in the protocol (or elsewhere) for transparency."	EPRI (5)	#3
6. "High concentrations of arsenic in food can also be a confounding factor in human [as well as animal] studies when attempting to assess the potential health effects resulting from exposure to inorganic arsenic in drinking water. The contribution of concentrations from food would need to be determined for either type of study to understand overall exposure."	EPRI (4)	#3

MOA	Commenter (page)	Relevant Charge Question(s)
7. The statement, "The EPA Cancer Guideline recommendations for MOA analyses are typically applied for chemicals for which human evidence is insufficient or human relevance needs to be established" is not accurate. It requires either a reference or an analysis of data to support the sentence. If not, it should be deleted, or the sentence modified to more accurately state that in the past most MOA analyses were based on animal studies but as human studies have been more frequently used, MOA information has been used to inform them.	DoD (4)	#3
8. The statement "a MOA analysis to address potential differences in response across human populations was not considered essential" is not correct and contrary to NRC (2013) recommendations. It should be deleted unless EPA proposes using another method for elucidating differences in responses in human populations.	DoD (4)	#3
9. "The major purpose for a MOA analysis for carcinogenicity, i.e., to determine the appropriate method for extrapolation to low doses should be added to this [first] paragraph [of Section 2.3.2]. Its absence significantly misrepresents EPA's 2005 cancer guidelines on an issue of importance for inorganic arsenic. As discussed in further comments, the assumption that MOA analyses are only for interspecies extrapolation could be interpreted as an underlying bias in the analyses presented in this document."	DoD (5)	#3
10. The sentence "Concern over not using MOA analyses in dose-response analysis is offset by ..." assumes the procedures listed are more accurate than information from MOA. They are complementary and should be used together. If the results are consistent, then confidence is increased… EPA should not only present its analysis in an appendix, but also demonstrate in the main text how its results/conclusions would differ if MOA were used… By rejecting MOA before presenting the potential effects, EPA does not allow an independent reviewer to draw conclusions as to the validity or effect of these decisions without substantial additional scientific analyses -- which many reviewers do not have the resources to perform.	DoD (6)	#3
11. The text in Section 2.3.2 paragraph 1, "or any toxicity within hypothesized MOAs," is not accurate and should be deleted.	DoD (5)	#3
12. On Page A-16, A.2.4. Hypothesized Mode of Action (MOA): Epigenetics Relevant Health Effects: Bladder Cancer, Skin Cancer, Skin Lesions does not include lung cancer. This may well be appropriate but a statement as why it is not included would be useful. It is the only high priority outcome that is not included. Problem formulation should include integration of lines of evidence regarding the MOAs and what is contradictory information.	CEOH (6)	#3
13. EPA's protocol ignores the 2005 Cancer Guidelines and NRC (2013) recommendations to work through the evaluation of mode-of-action possibilities for each endpoint associated with exposure.	ASTF (2) EPRI (6)	#3
14. Epidemiology studies for which "no increased risk for cancers … is detected when exposures in the drinking water are at or below 100 μg/L" support the existence of a threshold. EPA's protocol ignores "the wealth of currently existing data that strongly points to a threshold."	ASTF (2-3)	#3
15. Uncertainty due to multiple MOAs is not justification for relying on epidemiology data because "all the possible modes of action lead to the same conclusion that the dose-response has a threshold."	ASTF (3) EPRI (6)	#3

MOA	Commenter (page)	Relevant Charge Question(s)
"…studies have been conducted that elucidate the dose-response for the key events associated with the iAs MOA and show a potential threshold below which effects do not occur." EPRI cites and summarizes Clewell et al. (2018) as support. "NRC recommends on page 73 of its report "[i]f after execution of a mode-of-action framework analysis a cohesive mode of action is not apparent, or it is clear that multiple modes of action may be involved, a mode-of-action summary statement should indicate that while elaborating the data and hypotheses assessed" (NRC, 2013)."	RGC (5)	
16. Epidemiological evidence relies on exposures greater than 100 ppb, but "there is strong evidence from mechanistic studies that the dose-response for the carcinogenicity is highly nonlinear with a threshold for activity at drinking water concentrations below 100 ppb (Yager et al., 2013; Efremenko et al., 2015; Gentry et al., 2014; Tsuji et al., 2019)."	ASTF (3)	#3
17. Mechanistic studies indicate that "…the effects of inorganic arsenic result from chemical interactions with thiols in key cellular signaling proteins, disrupting control of oxidative stress, inflammation, DNA repair and replication, not from mutagenicity (Snow et al., 2005; Kitchen and Wallace, 2008; Clewell et al., 2018), so data in the range of observation is not informative for the dose-response below."	ASTF (6-7)	#3
18. "A recurring theme in this document is that mode-of-action analysis is either not needed or too complex to be useful. This is inconsistent with the NRC analysis, including the full chapter devoted to this topic. EPA may disagree with the NRC report, since this document cite NRC as an authority when consistent with EPA, for clarity, transparency, and impartiality, the document should also state where NRC differs with EPA. In the absence of such information, the logical inference is that NRC either agreed with, or offered no opinion on, those issues."	DoD (14)	#3
19. Appendix A – Not all of the recommendations of the NRC re: the use of MOA are given. One that is not given is using MOA to elucidate "biologic plausibility or mechanisms of arsenic causation of effects observed in epidemiologic studies and interpretation of low-dose effects". "By listing only one of several recommendation made by NRC, EPA is neither clear nor transparent about the wide range of uses the NRC envisioned for MOA to enhance understanding of and predictions for arsenic toxicity and carcinogenicity. Please be more complete and clear regarding NRC recommendations."	DoD (15)	#3
20. Regarding the statement "A MOA analysis was considered less effective for hazard characterization given the abundance of epidemiological evidence, including at low levels of exposure," the commenter stated that "While EPA may prefer ATSDR's opinion, we note that ATSDR's document significantly predates NRC's. Moreover, the NRC was specifically charged with analyzing EPA's approach. At a minimum, EPA should present both opinions and their sources."	DoD (15)	#3
21. Appendix A – "In the list of MOAs discussed, there is no mention of the growth stimulatory effect of iAs, although regenerative proliferation is used frequently. At low levels iAs may have an inverted dose response curve, indicating an adoptive or protective response. Even some epidemiological studies show that those with low levels of As in drinking water may be at lower risk than controls. Please consider addressing this in the full profile for iAs."	DoD (16)	#3

MOA	Commenter (page)	Relevant Charge Question(s)
22. Appendix A reflects a comprehensive, useful and transparent review of the MOA literature. However, it is unclear how these MOA parameters and conclusions will be integrated into modeling exercises and/or assumptions.	TCEQ (3)	#3
23. "Clewell et al. (2018) proposed an iAs MOA related to disruption of cellular signaling following binding to vicinal dithiols in cellular proteins leading to disruption of inflammatory and oxidative stress signaling with inhibition of DNA damage responses. Clewell et al. (2018) proposes the related key events for the MOA along with dose-response data for each key event. This information should be considered and used to expand the information reported in Appendix A."	EPRI (14)	#3
24. "As noted above, Gentry et al. (2010) published a comprehensive review of literature related to gene expression changes following exposure to iAs compounds. The available in vitro iAs gene expression data provide evidence of a carcinogenic MOA involving interactions with critical proteins, along with a background of chemical stress, including proteotoxicity and depletion of nonprotein sulfhydryl which lead to the inhibition of DNA repair and inability of cells to maintain DNA integrity. These results support the conclusion that iAs does not produce a direct genotoxic effect."	EPRI (15)	#3
25. "A cross reference of the primary literature identified in the Gentry et al. (2010) article was performed against the mode of action literature (Appendix A) in the protocol document. Only a small percentage of the 35 primary studies listed as important to the characterization of the dose response by Gentry et al. (2010) were referenced by USEPA. It is not clear why other MOA studies were excluded."	EPRI (15)	#3
26. "Given that much of the debate to date has focused on arsenic's cancer mode of action (i.e., arsenic potentially having a non-linear cancer MOA with a threshold), the USEPA does not allocate enough consideration to this point nor do they discuss the method/approach they will use to identify which type of reference toxicity value (i.e., a cancer slope factor or a reference dose) is most appropriate for evaluating arsenic's cancer risks. The USEPA's Updated Arsenic Review Protocol needs to describe the method/approach that will be used to identify which type of reference toxicity value (i.e., a cancer slope factor or a reference dose) is most appropriate for evaluating arsenic's cancer risks."	SIM (4)	#3
27. "Similar approaches should be used for non-cancer and cancer effects…The mode of action of the non-cancer epithelial endpoints is toxicity involving persistent increased cell proliferation, which results in a non-cancer lesion, e.g., skin arseniasis. For non-DNA reactive carcinogens, the non-cancer lesion is a precursor of a cancer endpoint, and of course cancer will not occur if the precursor lesion does not occur. Thus, the level that is determined to be protective for the noncancer precursor lesion will also be protective for cancer."	SC (3)	#3
28. "The discussion on epigenetics fails to indicate that these are threshold phenomena, and that such effects occur in cells even with normal biological functions, such as eating. Their indication that methylation of arsenicals could deplete S-adenosylmethionine (SAM) does not take into account the fact that arsenicals are present at micromolar or lower concentrations, and that SAM is present in cells at millimolar concentrations and is being constantly replenished."	SC (3)	#3

MOA	Commenter (page)	Relevant Charge Question(s)
29. "The section on endocrine disruption does not take into account that the evidence for such effects in humans is limited and weak. Animal models of such effects are limited and that at high doses the findings in vitro have generally not been replicated in vivo. Moreover, such effects will involve a threshold."	SC (3)	#3
30. "A large number of publications have examined possible modes of action of the carcinogenic effects of iAs and their expected low-dose behaviors. In evaluating these, it is important to consider the dose-range over which the effects occur."	RGC (2)	#3
31. "We recognize that species differences in arsenic metabolism complicate the use of animal studies in probing mode of action. But existing pharmacokinetic models provide a basis for adjusting considerations of tissue-level dosimetry, and the biological impacts invoked in mode-of-action arguments are expected to be quite generally operative across species, such that useful analyses can and should be made."	RGC (3, 6)	#3

Systematic Review/Literature Search/PECO/Risk of Bias	Commenter (page)	Relevant Charge Question(s)
1. "We applaud the use of systematic review to evaluate the base of relevant studies in identifying endpoints to evaluate… it may be useful to consider how the TSCA assessment process is implementing its legislative mandates to use weight of evidence and the best-available science in its evaluations."	RGC (3)	#2
2. "The Agency does not provide sufficient information on how these [robust, moderate or slight] classifications were assigned, including how USEPA's systematic reviews were performed. It is also unclear whether the evidence only pertains to the epidemiological evidence or to animal evidence as well."	EPRI (4)	#2
3. "…for Tier 1 outcomes, USEPA relies primarily on reviews from other agencies or other reviews in the peer-reviewed literature. For other outcomes, USEPA notes that a systematic review process was conducted…Therefore, it appears that the evidence analysis will not be conducted evenly across health outcomes."	EPRI (5) EPRI (8)	#1
4. "EPRI is particularly concerned with how risk of bias is evaluated across the body of scientific evidence, particularly when USEPA may be relying solely on other agency reviews." "It is unclear from the protocol if risk of bias evaluation will be conducted for all epidemiological studies for all outcomes or only for Tier 2 and Tier 3 outcomes"	EPRI (5) EPRI (10)	#2
5. "While most of the criteria [for risk of bias; Appendix C] are suitable for the different types of human studies, several criteria appear to be copied from a bisphenol A (BPA) evaluation (see exposure characterization criteria on pages C-16-C-18) and these criteria should be updated to be specific to iAs and not BPA."	EPRI (10)	#1, #2
6. "In order for this process to achieve transparency, each of these systematic reviews [for each health outcome] would need to have associated problem formulation documents and systematic review results available for public review and comment."	EPRI (5)	#2
7. The reference list is "almost bare" of ecological studies despite them being addressed in Appendix C. "It appears as if a decision has been made somewhere that the information gleaned from ecological studies is irrelevant for the assessment of risk. If this is so, it is an egregious error… ecological studies be included among the information sources of the risk assessment."	CEOH (1)	#2
8. Tables and graphs (e.g., Lamm et al., 2015) are provided as evidence that ecological studies provide similar linear-quadratic dose-response fits as other types of epidemiology studies.	CEOH (2-3)	#2
9. A list of relevant ecological studies is provided.	CEOH (4)	#2
10. Part II PECO Table 3-1 has no indication that co-variates are subsumed within the category of exposures.	CEOH (5)	#2
11. We recommend that PECO become PECCO, where the first "C" is for "Co-Variates."	CEOH (5)	#2
12. "PECO criteria are used as inclusion criteria, but these criteria are too vague to be useful. For example: the comparator is "comparison or reference population with no detectable exposure or exposure to lower levels of iAs"; however, USEPA does not specify how one can confirm no exposure or what it considers to be a low level of exposure."	EPRI (8)	#2

Systematic Review/Literature Search/PECO/Risk of Bias	Commenter (page)	Relevant Charge Question(s)
13. EPRI objects to the fact that "animal and mechanistic data are considered to be "supplemental material" and not PECO relevant."	EPRI (8)	#2
14. "Since PBPK models that are not traditional PECO elements were added to Table 3-1 … it is not clear why other elements that are also becoming more important in IRIS reviews were not also added to Table 3-1, such as ADME."	DoD (7)	#2
15. Section 3.3 states that "The literature search will be updated during the assessment to identify literature published during the review. The last literature search update will occur within a year before the planned release of the draft document for public comment and peer review." We commend the plan to keep the literature search open as long as feasible and yet permitting the risk assessment to be brought to completion.	CEOH (5)	#2
16. EPA's position expressed in item 3.5 re: Non-Peer reviewed data " is "…commendable. Science should not be truncated by an artificial timeline if it is relevant and feasible and can be assessed for reliability."	CEOH (5)	#2
17. CEOH noted that since EPA's 2013 literature review (Table 5-3), "…three prostate cancer epidemiological studies have been published (Garcia-Equinas et al., 2013; Burka et al., 2016; and Roh et al., 2017) that should be given consideration. Additionally, we recently presented our analysis of the dose-response relationship of prostate cancer incidence to drinking water arsenic levels for U.S. counties which we presented at SOT 2019 [see attached poster] which should be published by the time the literature search window is closed. These studies suggest that the level of evidence for prostate cancer might be raised from slight to moderate." DoD suggested that absence of the Roh et al. (2017) study "…indicates an issue with the systematic review."	CEOH (6) DoD (6)	#1, #2
18. Section 3.4 (starting on p. 16), "several articles in the HERO database that would appear to be important for this analysis were neither used nor in the Reference section" (e.g., Gamboa-Loira et al., 2017 and Tseng, 2009). "The decisions as to which studies were included, and in particular why studies such as the ones listed here were excluded, are not apparent from the process outlined in this section. Suggest that, especially as the use of machine learning and other techniques are relatively new, conventional processes that rely on experts be used to spot check that potentially critical data was not excluded from the analyses," and that "…all of the relevant articles in HERO be reconsidered with regard to relevance for the issues discussed in this report, rather than the more limited PECO criteria."	DoD (6-7, 8)	#2
19. "IRIS states that a "pilot phase" was used "to calibrate screening guidance." More information is needed to determine how IRIS assessed this pilot program for success. No public input was obtained for evaluating the success of this "pilot" to screen literature for inclusion into the arsenic assessment."	ASTF (4)	#2
20. "More information on DRAGON is needed and should be made publicly available. Specifically, is DRAGON a proprietary tool used by EPA and was it appropriately peer-reviewed?" "The results of this [DRAGON] process should be made available for public review." "…Section 3.1 indicates a list of data abstraction elements should be presented in Section 3.3; however, no such list appears in Section 3.3. It is also unclear which studies will be considered for data extraction, i.e., only studies rated high after risk of bias evaluation?"	ASTF (4) EPRI (10)	#2

Systematic Review/Literature Search/PECO/Risk of Bias	Commenter (page)	Relevant Charge Question(s)
21. "Study quality and type of study should be taken into consideration before the risk of bias evaluation is conducted. Studies with adequate methods and quality should be considered more important for determining primary studies than studies with the lowest risk of bias." "The protocol fails to outline how study quality will be addressed. For example, the protocol mentions that the mouse in utero model has multiple tumor sites as reported by Waalkes and colleagues (Waalkes et al., 2014; Tokar et al., 2011; 2012). However, the lack of reproducibility of the findings in most of the tissues and the limitations of the mouse lung as a target is ignored. The publication by Nohara et al. (2012) from a Japanese laboratory failed to reproduce the lung findings and is not cited in the IRIS document. See Garry et al. (2015) for a critique of this model. Importantly, even if this model is valid, it is a high dose phenomenon, with positive results only at doses in the ppm, not ppb range."	EPRI (10) SC (3)	#1, #2
22. "In addition, risk of bias only addresses internal validity. Additional consideration should be given to external validity issues. For example, some epidemiological studies may not be generalizable if the study population is significantly different from the US population. This is particularly important for iAs, as factors such as nutritional status can impact susceptibility of population subgroups to iAs exposure."	EPRI (10)	#2
23. "We question the automatic exclusion of "Records that do not contain original data, such as scientific literature reviews". Some such as Tseng (2009, in HERO) integrate data on multiple confounders and issues that might not be apparent from individual papers or, though titled reviews, contain new analyses in Discussions or Conclusions. Moreover, all of the secondary sources on which this document appears to rely, e.g., NRC, ATSDR, IARC, NTP, WHO, NIOSH, OSHA, and OEHHA, should be excluded by this criterion. Whether the meta-analytic papers should also be excluded because they do not include "original data", only original analyses, is unclear."	DoD (7-8)	#2
24. "To be as clear and transparent as possible [for evaluation of bias, Section 3.9], EPA should provide more information as to its guidance for weighting and combining all of these factors. Since this process presumably affects selection of critical studies for the quantitative evaluations, it should be as comprehensive as possible."	DoD (8)	#2
25. "Several recent publications – several supported by EPRI - of in vivo and in vitro analyses have provided new data with which to elucidate effects at low concentrations. EPRI recommends that these be integrated with the epidemiological evidence for the IRIS assessment." Cited references are Tsuji et al. (2019), Gentry et al. (2014a), Gentry et al. (2014b), Efremenko et al. (2015), Yager et al. (2013), Cohen et al. (2013) and Gentry et al. (2010).	EPRI (7-8)	#2
26. "It is unclear why the search strings presented in Appendix B, Table B-1 contain both inorganic and organic forms of arsenic when this review focuses on the toxicological effects of iAs. Was this to capture data regarding arsenic metabolites? It is also unclear why arsenic trioxide, a form of iAs, was specifically excluded in the literature search strings provided (i.e., NOT "arsenic trioxide")."	EPRI (9)	#2
27. "USEPA notes that 3,715 studies were identified from the reference clustering; however, this number does not appear in the Literature Flow diagram (Figure 3-1) or in the HERO database flow diagram."	EPRI (9)	#2

Systematic Review/Literature Search/PECO/Risk of Bias	Commenter (page)	Relevant Charge Question(s)
28. EPRI could not reproduce the PubMed search using the search string information presented in Table B-1 and limiting the search to publications through June 2018. "…searches should be reproducible based on the information provided in the protocol document."	EPRI (9)	#2
29. "Web of Science requires significant fees to use. The lack of free access of this search engine to the general public will limit the ability of all reviewers to duplicate the literature searching process, limiting the transparency of the results."	EPRI (9)	#2
30. "EPRI recommends that USEPA's use of machine learning/clustering methodology be explained in more and clearer detail…For transparency, the criteria used to determine the inclusion or exclusion of the 900 "seed" studies used to identify relevant hazard identification data should be provided. In addition, a more in-depth discussion of the software and how it works is warranted, including reporting of all parameters used."	EPRI (9)	#2
31. "Different labels are given to the strength of the evidence (robust, moderate, slight), symbols used for the risk of bias evaluation (++,+, -, - -), and final conclusions regarding carcinogenicity (carcinogenic, likely, suggestive, etc.). It appears that USEPA is attempting to blend multiple ways to assess the evidence based on OHAT, GRADE, and EPA guidance. The analysis would be clearer and less convoluted if one "grading" or classification scheme were adopted. Alternatively, USEPA should provide clearer definitions and a roadmap for the overall assessment, with clear indication of the classification scheme at each level of the analysis."	EPRI (11-12)	#2
32. "…a brief literature search returned three peer-reviewed publications that describe incidental arsenic trioxide exposure in humans that may be of relevance to the USEPA's review of arsenic (Benramdane et al., 1999; Farmer and Johnson ,1990; Pinto et al., 1977). Given that non-therapeutic exposure to arsenic trioxide has been documented in the human population, USEPA's Updated Arsenic Review Protocol should provide specific rationale and detailed justification for excluding studies that evaluated arsenicals, primarily arsenic trioxide and Fowler's solution. Absent this justification, USEPA would need to include and evaluate this information in the arsenic IRIS assessment."	SIM (2)	#2

PBPK	Commenter (page)	Relevant Charge Question(s)
1. "We take no issue with selection of the [El-Masri and Kenyon, 2008] model. However, to be both clear and transparent, a disclaimer should be added somewhere in this section which notes the chosen model was developed by EPA scientists as part of their work for that agency. Furthermore, one of the authors is also an author of this document."	DoD (8-9)	
2. "The El-Masri and Kenyon (2008) PBPK model is a human male model and is for the oral route of exposure only. Revisions to the model will be necessary to evaluate exposure in different subpopulations and to evaluate inhalation exposure for development of an RfC or IUR."	EPRI (11)	
3. "USEPA notes that a systematic sensitivity and uncertainty analysis is needed for each parameter in the model. This is not a minor issue and this analysis is needed to understand the most sensitive parameters in the model and whether adequate data are available to support the parameter values used in the model. This is particularly important if the model will be modified to evaluate the pharmacokinetics of iAs or its metabolites in different subpopulations."	EPRI (11)	
4. "The El-Masri and Kenyon (2008) model was developed for a human male and does not account for a fetal compartment in the case of female pregnancy. However, pregnancy outcomes, including fetal and infant morbidity, fetal loss, stillbirth, and neonatal mortality, are listed as health outcomes that will be evaluated in the dose-response assessment. The El-Masri and Kenyon (2008) PBPK model will be used to obtain a common exposure metric for use in dose-response meta-analyses, and yet sex differences in the disposition and excretion of metals have been documented in the scientific literature (Lindberg et al., 2008; Vahter et al., 2007). Given the evidence for such differences, the application of a male PBPK model indiscriminately across male and female datasets will likely inaccurately predict exposure metrics in some cases…The Updated Arsenic Review Protocol would be improved if USEPA's approach for addressing this limitation was described. If USEPA has not developed or researched an approach for addressing this limitation, then the USEPA needs to demonstrate that the literature searches described in the Updated Review Protocol captured relevant information needed to address this data gap. Alternatively, the USEPA should state that a targeted literature search needs to be performed to address this data gap and will be included in the IRIS assessment."	SIM (3)	

Selection of Studies for Dose-Response Analyses	Commenter (page)	Relevant Charge Question(s)
1. The "biological judgments" described by EPA as part of the process of selecting studies for use in dose-response analyses "must be part of the public record and must have a public review. When will this information be published?"	ASTF (4)	#2
2. "The evaluation of moderate evidence is based on lack of either consistency or protection from bias in the available studies: it is not clear how studies with such limitations can be used with confidence for dose-response analyses."	ASTF (4)	#4
3. ASTF - "It is difficult to see how some of the listed considerations [Table 5-1] for prioritizing data sets will be applied in a transparent and consistent manner. For example, what defines exposure histories that are "inadequately ascertained or reported"? What are the specific criteria used here? How is "sufficient number of subjects" specifically defined and how does that relate to standard study designs for subchronic or chronic exposure? (For example, animal subchronic studies use 10 animals, five of each sex, in an acceptable design)…All these evaluations must be transparent, published and available for public review." TCEQ – "This table would benefit from being broken into more columns to provide greater clarity for readers and users regarding study quality criteria. Further, if this rating system is based on the development of a score or other numerical system, it should be communicated to make it clear what the end product from this exercise should be."	ASTF (5) TCEQ (1)	#4
4. "…the analysis presented does not reference the analyses that conclude that the epidemiological data support a threshold for cancer and non-cancer effects." At least 1 such analyses (Sidhu et al., 2015) is neither in the document's reference list nor in EPA's HERO database: Another (Haque et al., 2003) is in HERO but not cited in this document.	DoD (13)	#2

RRB Method	Commenter (page)	Relevant Charge Question(s)
1. "…provide details about how benchmark dose modeling was used to obtain a study-specific estimate of the exposure level associated with a given relative risk."	EPRI (11)	
2. Table 5-1 needs clarification. "For example, for exposure ascertainment…it is not clear what is preferred; individual measurements should be preferred over large group averages. Other criteria are similarly unclear as to preference, including exposure reporting, adjustment for covariates, number of subjects and cases reported, and exposure timing and duration"	EPRI (11)	
3. "Only studies that have been rated as high quality with low chance of bias across all criteria should be considered for dose-response assessment."	EPRI (12)	
4. Limit the RRB analysis to "studies that only assess lower doses."	EPRI (12)	
5. "…prioritize studies that provide better estimates of exposure, rather than attempting to estimate exposures from incomplete or uncertain estimates (top of page 49)."	EPRI (12)	
6. "…due to significant differences across study populations that can impact susceptibility to iAs (e.g., nutritional status), USEPA should prioritize studies of western populations."	EPRI (12)	
7. "USEPA presents a number of different analytical approaches…USEPA should specify the preferred approach and the criteria for deciding on an approach given data availability (e.g., the number of studies required to consider a certain approach). USEPA should note that several recent studies have employed the approaches that USEPA has specified, and these could be used as examples of viable approaches (e.g., Tsuji et al., 2019; Lynch et al., 2017a, 2017b)."	EPRI (12)	
8. Additional information that was relied upon for endpoint and study selection should be provided, including List of published studies considered; Specific reasons for a study to be excluded; Publications used and the 250 datasets derived from those publications that were used in the screening analysis; How datasets were categorized into the groups (vertical classes) and categories (colored dataset indicators) in Figure 5-1; Details from Figure 5.1 specifically, RDD20 and RRD20 need to be defined); Details on benchmark dose modeling for the screening analysis; Specific background values used to determine RRBs that were plotted in Figure 5-1; and How these background values were determined."	EPRI (12)	
9. "....published relative risk [RR] estimates are necessary for the RRB analysis" Does this mean that studies that determined odds ratios are eliminated? Contrast the analysis by Lynch et al. (2017) "We also extracted quantitative information on RRs, such as risk ratios, ORs, hazard ratios, and standardized incidence ratios, and their 95% CIs"	DoD (9)	
10. "While we understand that there may be a "large number of datasets" we are unclear as to why analyzing all of these datasets is "problematic"…This reanalysis has lasted approximately a decade… Suggest that, to be clear, transparent, and accurate, EPA evaluate all high-quality epidemiological data. As indicated in additional comments on a partial analysis of the selection process given, additional selection criteria could be interpreted as biasing the outcome. This is especially of concern since EPA has already modeled 250 data sets and, presumably, examined the results."	DoD (9)	

RRB Method	Commenter (page)	Relevant Charge Question(s)
11. "Please provide a reference or a rationale for dividing the estimated exposure (RRE) by the background exposure…we are unclear as to how this would provide a value that could be used to estimate a toxicity value independent of the background level."	DoD (9-10)	
12. "One of the additional criteria applied to the datasets for dose response is "whether sufficient number of subjects were included in the analysis (it is desirable to have five cases/exposure group)"… If a criteria for selection among epidemiological datasets is being determined by the IRIS program, it should be generic, not chemical specific. Suggest the preference for 5 cases be justified."	DoD (10)	
13. "What is the justification for using a cutoff of a 20% increase in relative risk for determining points of departure to derive the RRB? This is not meant to be a "clinically significant" endpoints so it is unclear how this relates to the use of human data in a defensible manner."	ASTF (5)	
14. "…selection of the effect level has significant consequences not discussed…that which appears to be the lower ratio at 20% effect may be the higher ratio at, for example, 10% effect. Since the effects measured the various epidemiological studies are likely to be different and the uncertainties also variable by power of the study, selection of the effect level for such a ratio should be based on a biological interpretation… Using a ratio of exposures hides that dietary intake is being compared to urinary excretion, but does not make the comparison valid. Suggest reconsideration and/or present the consequences and trade-offs associated with this procedure. It produces values that can be compared across studies, but given the issues mentioned (as well as others that could be), such a comparison has no accurate toxicological interpretation. It appears to be an uninformed analogy to EPA's relative potency factors that require biological and mathematical considerations similar to those mentioned above. These are discussed in EPA's 1986 guidelines and 2000 guidance on risk assessment for mixtures."	DoD (10-11)	
15. "The "necessary quantitative data for modeling" depends on the models being used. Even the more generic examples provided in the parenthesis have not always been required by EPA, for example, the non-cancer toxicity value for dioxin. This appears to be specific for inorganic arsenic, and therefore may be biased by the data sets already reviewed. If EPA is going to establish criteria for quantitative analysis of epidemiological data, the process should undergo a rigorous, independent peer review."	DoD (11)	
16. "EPA is to be complimented for laying out precisely in Table 5-2 … their baseline exposure assumptions for the general population. Presumably body weight is found elsewhere."	CEOH (5)	
17. It would be helpful to note that some categories of disease (e.g., diseases of the circulatory system) refer to a wide range of different diseases and not to a single disease, such as bladder cancer or lung cancer. See, Figure 5-1."	CEOH (5)	

Bayesian Meta-regression Method	Commenter (page)	Relevant Charge Question(s)
1. USEPA should not conduct dose-response analyses for outcome relationships in the absence of understanding a potential MOA. Biological plausibility is key for supporting a causal association, especially when relying solely on epidemiological studies.	EPRI (5) SC (1) ASTF (1) TCEQ (1)	#3, #4
2. "Extrapolation below the experimentally observed range should not solely be inferred by modeling of epidemiological data due to the large uncertainties involved and the tendency of exposure error to bias the dose-response evaluation (Crump, 2006; Rhomberg et al., 2011)."	EPRI (6) RGC (2)	#5
3. "The text of this section, specifically that the expected results for carcinogenicity will be either an OSF or IUR, assumes that MOA for carcinogenicity will not have a threshold… we note that EPA's 2005 cancer guidelines require the use of RfD/C for all nonlinear dose-response functions even when no threshold has been established… If the dose-response function is nonlinear in the range where cancer potency is being assessed, a slope factor cannot be estimated…Therefore, the text in the paragraph beginning, "For priority cancer health outcomes" does not seem internally consistent nor consistent with EPA's cancer guidelines. If this reading of the text is not correct, then the text needs to be clarified significantly."	DoD (11-12)	#3, #5
4. EPA states that linear relationships will be provided if the dose-response is deemed "sufficiently linear." What does this mean, specifically? How will this determination be made?	ASTF (5) DoD (12)	#5
5. Relationship at low doses is greatly affected by the relationship at high doses. "Any use of epidemiology to estimate low-dose cancer risks consists of projecting effects seen at high doses using the ability to hypothesize low-dose risks that are small enough to appear difficult to distinguish from the observed low-dose patterns of lack of risk. This is true even when "flexible" dose-response models that do not impose linearity are used." Lynch et al. (2017) is cited as showing "…that populations with relatively high iAs exposures appeared to drive the pooled cancer risk estimates." Other studies cited in support of 100 ug/L threshold are (Begum et al., 2015; Saint-Jacques et al., 2014; Tsuji et al., 2014; Mink et al., 2008; Chu and Crawford-Brown, 2006).	EXP (2) RGC (1, 2, 4)	#5
6. "Please see Tsuji et al. (2014a,b; 2015; 2019) for more detailed information on specific studies and issues." EPA "…should consider the approach recommended by Tsuji et al. (2019)."	EXP (2) EPRI (6)	#4, #5
7. Time-averaged dose that includes a short period of high-dose exposure is not toxicologically equivalent to a more constant average dose	EXP (3)	#4a
8. "Case-control studies or studies in which drinking water intake is self-reported are more prone to bias because those with the disease (or their relatives for decedents) may be more likely to recall drinking greater quantities of water than those without the disease…Converting to ug/kg-day introduces bias from self-reported water intake rates, particularly in certain studies (Baris et al. (2016) is cited as a "troubling" example where no association is found with arsenic water concentration but a positive association is found with self-reported intake rates). "Because of this potential bias, EPA should convert the water concentrations to arsenic intake using a standard drinking water intake for all participants"	EXP (3)	#4a

Bayesian Meta-regression Method	Commenter (page)	Relevant Charge Question(s)
9. In foreign subsistence populations, average drinking water intake is greater than that in U.S.	EXP (4)	#4a
10. Assessment of arsenic exposure based on biomarkers (e.g., levels in urine, blood, or nails) is complicated by the metabolism of inorganic arsenic to methylated forms, some of which are also contributed by dietary sources of other arsenic forms	EXP (4-6)	#4a
11. Low-resource populations have greater susceptibility to arsenic toxicity due to nutritional deficiencies, such as folate, that are not relevant to the general U.S. population	EXP (6)	#4
12. TCEQ supports the use of models that do not confine the shape of the dose-response curve to "conventional monotonic forms." Section 5.5 may benefit from an expanded discussion of modeling approaches that can increase model flexibility to capture possible nonmonotonic curves or references to studies where these approaches have been used in comparable cancer assessments. TCEQ encourages EPA to be vigilante in ensuring that the data, rather than the modeling assumptions, inform the final dose-response model.	TCEQ (2)	#5
13. A Bayesian meta-regression is "highly susceptible to unintended bias associated with the selection of dose-response models and the definition of quasi-informative prior distributions for model parameters."	ASTF (5)	#4
14. A Bayesian meta-analysis will inappropriately reinforce biases such as "selection bias, and bias arising from the failure to include unknown, unpublished studies (the so-called publication bias), as well as various other biases that can arise from imperfect study designs and variable study quality."	TBS (3)	#4
15. "Given the biases discussed in the [ASTF] comments on Section 5.2, extrapolating an order of magnitude further below the lowest available study data is not biologically supportable."	ASTF (6)	#5
16. The Bayesian meta-analysis as described does not address study heterogeneity across studies, the "inappropriate comparison of apples with oranges."	TBS (3) ASTF (6)	#4
17. "There is also the problem of possible confounding by uncontrolled exposures to other substances that may also cause or at least be correlated with the effect of interest."	TBS (3)	#4a
18. "Furthermore, numerous unsupported assumptions are required by the analyses, including those related to specification of the prior distributions of parameters to be estimated… To avoid or at least minimize this problem, non-informative, or "flat", prior distributions should be included as an alternatives to other "non-flat" priors that are going to be considered (Babapulle and Joseph, 2004; Jansen et al., 2008)."	TBS (3)	#4
19. USEPA must thoroughly discuss these limitations of its proposed approach and, in fact, "bend over backwards" to demonstrate that their preferred prior distributions, analyses, and inferences are at least as, if not possibly more, credible than those of other alternatives.	TBS (3)	#4
20. "The use of fractional polynomial models is an interesting approach to the curve-fitting of non-linear relationships, but it is also essentially ad hoc and completely lacking of any truly scientific basis… extrapolations outside the range of the fitted observations have no reliability whatsoever."	TBS (4)	#5

Bayesian Meta-regression Method	Commenter (page)	Relevant Charge Question(s)
21. "True, the same criticism can be leveled against ordinary polynomials, but the extraordinary success of even simple linear covariate models in describing widely varied real world phenomena over limited ranges provides strong support for their continued use, at least for interpolation over the range of the observations."	TBS (4)	#5
22. According to USEPA, fractional polynomials can even describe threshold behavior, but I, for one, am not persuaded that this is the case unless it arises from a rightward shift in the origin of a covariate.	TBS (4)	#5
23. It is not possible to prove a negative and threshold response models "cannot be proven to logically exist. That said, there are still situations in which a response minimum can be demonstrated at a non-zero exposure level." Copper studies by U. of Ottawa were cited as an example.		#5
24. "In the case of inorganic arsenic, the epidemiologic data are not informative regarding the mechanisms by which this substance causes adverse human health effects. However, there is a large experimental animal database, reviewed very recently by Tsuji et al. (2019), that USEPA needs to carefully and thoroughly consider in selecting a priori which mathematical dose-response models to include in its Bayesian meta-regression analyses of the human data."		#3
25. Meta-analyses have a "tendency toward linearization of the apparent dose-response (Crump, 2006; Rhomberg et al., 2011)"	ASTF (5) RGC (2)	#4
26. Section 5.5 is not very detailed. If a systematic review of modeling approaches was conducted it should be discussed. If various models were considered, the justification for the models and approaches chosen should be documented. For the sake of transparency and scientific documentation, TCEQ recommends expanding the Section 5.5 discussion, perhaps into a separate Appendix.	TCEQ (2)	#2, #4
27. The proposed Bayesian MR approach is an "…unproven approach with a high susceptibility to manipulation and bias through the selection of quasi-informative priors. Instead, USEPA should utilize MOA information to inform the shape of the dose-response curve at low doses… The nature of the true dose-response for iAs below the range of observation in epidemiological studies can only be determined from animal and *in vitro* studies that inform the mode of action at low concentrations."	EPRI (13)	#3, #4, #5
28. "If routes of exposure other than well water are to be evaluated, additional equations for determining dose estimates should be provided."	EPRI (13)	#4a
29. "In the one dose equation provided, LE (low-end water concentration) is not defined."	EPRI (13)	#4a
30. "USEPA indicates that a Monte Carlo analysis will be used to characterize uncertainty in the dose but does not indicate which variable will be varied nor the source of the information to develop the distributions of the parameter values if this information is not provided in the individual study being evaluated."	EPRI (13)	#4a
31. EPA states that a determination will be made on whether an adjustment in estimated dose-response behavior in the US population is warranted. The protocol should "specify both how the determination will be made to adjust, and how the adjustment will be performed."	EPRI (14)	#5

Bayesian Meta-regression Method	Commenter (page)	Relevant Charge Question(s)
32. "Additional information is needed to understand how consideration of covariates, such as cigarette smoking, will be considered in the probabilistic dose conversions, and if other covariates will be considered."	EPRI (14)	#4
33. "USEPA is casting a wide net through this experimental approach to dose-response and uncertainty modeling. It is unclear that including a wide variety of approaches will be advantageous, and likely more importantly, the criteria for selecting the single, appropriate approach once results have been obtained from multiple approaches have not been adequately described. Selecting a final reference toxicity value from a long list of possible reference toxicity values has the potential to erode the public's confidence in USEPA's methods for IRIS assessment if a decision framework for model selection is not described ahead of time in the problem formulation document."	SIM (5)	#5
34. "While we commend the USEPA for showing a strong motivation to develop and use cutting-edge and advanced modeling techniques to inform IRIS assessments, doing so for IRIS's inorganic arsenic assessment without first developing guidance or a decision framework for those advanced modeling techniques will confound the outcome of the reassessment of inorganic arsenic with the effect of the advanced modeling techniques. That is likely to result in an assessment that suffers from a lack of transparency and whose objectivity and credibility will be questioned. The USEPA needs to develop guidance on how to appropriately use and evaluate the soundness of these cutting edge and advanced modeling techniques before applying them to the IRIS evaluation for inorganic arsenic."	SIM (5)	#4
35. "The USEPA states that, "in the cases of non-linear dose-response relationships, flexible polynomial approximations will be provided." Arcadis is not aware of any other instance where USEPA has used this model for IRIS dose-response assessments… USEPA has not provided guidance for how to parameterize these models nor are there common tools or best practices with which reviewers can independently reproduce or verify the modeling results... we are concerned that this may lead USEPA to simply select the lowest modeled reference toxicity value without additional toxicological considerations."	SIM (5)	#5

Comments on Charge Questions	Commenter (page)	Relevant Charge Question(s)
1. Charge Question #2 - "Some of the language used in the charge questions could be interpreted to set a low bar for quality, e.g., "appropriateness" and "adequately". Please revise Question 2 to ask the NRC to comment on the accuracy of the systematic review and whether the approach comprehensively addresses the potential health effects."	DoD (17)	#2
2. Charge Question #3 - "The EPA document contains a considerable amount of material on MOA. Charge question 3 attempts to address this in the context of the MOA template. Would it be more appropriate to ask the committee to weigh in on the limitations of the in vitro MOA approach (immortal cell lines, short duration unreasonably high exposures, etc) which cannot link up adequately with the findings of epidemiology studies, rather than asking about additional MOA analysis? Please consider rephrasing question 3 regarding an assessment of the MOA approach and its limitations compared to evidence from epidemiological studies. Suggest revising to: "..levels of arsenic exposure. Please comment on the MOA approach, its utility and limitations. If additional...."	DoD (17)	#3

Commenter Key

ASTF: Arsenic Task Force comments 06272019 ORD-2012-0830 ASTF-1.pdf
CEOH: Comments 06262019 ORD-2012-0830 CEOH-2.pdf
DoD: DoD Comments Arsenic Prob_Form and Protocol 2019.docx
EPRI: Comments on Updated Protocol for Inorganic Arsenic IRIS Assessment-062619-Final.pdf
EXP: Exponent Comments 06272019 ORD-2012-0830 Exponent-1.pdf
RGC: Rhomberg Goodman Cohen Inorganic Arsenic Problem Formulation Comments 062719.pdf
SC: Sam Cohen Comments to Docket Re IRIS 06_27_19.pdf
SIM: Simplot 6-27-2019--Ltr_to_EPA_IRIS_As_Comments.pdf
TBS: Associates Comments 06272019 ORD-2012-0830 TBS Associates-1.pdf
TCEQ: Texas CEQ EPAComments_06272019.pdf