December 15, 2023

Comments from University of California, San Francisco Program on Reproductive Health and the Environment on the Draft IRIS Toxicological Review of Inorganic Arsenic

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These comments are submitted on behalf of the University of California, San Francisco Program on Reproductive Health and the Environment. We declare collectively that we have no direct or indirect financial or fiduciary interest in any chemical or product that is the subject of these comments. Institutional affiliations are included for identification purposes only and do not imply institutional endorsement or support, unless indicated otherwise.

We appreciate the opportunity to provide written comments on the October 2023 External Review Draft *IRIS Toxicological Review of Inorganic Arsenic* ("Draft Toxicological Review"). This is an important assessment due to the significant health consequences of arsenic exposure and the significant advances in assessment methods and outputs used to evaluate arsenic toxicity. In particular, the IRIS program has incorporated for the first time a detailed dose-response assessment of multiple non-cancer health effects that supports estimation of risk at various levels of exposure currently experienced by the U.S. general population. The assessment includes dose-response functions for cardiovascular disease incidence, cardiovascular disease mortality, ischemic heart disease incidence, ischemic heart disease mortality, diabetes, and reduced birth weight. This assessment represents the best available science and will result in improved risk information for decision-makers, and improved quantification and monetization of regulatory benefits. It also provides a blueprint for future EPA dose-response assessments.

The significance of this dose-response assessment approach is demonstrated by EPA's recent proposed Lead and Copper Rule Improvements[1] and proposed drinking water standard for six per- and polyfluoroalkyl substances (PFAS).[2] For each of these proposed rules, reduced risks of cardiovascular disease accounted for a major proportion of the monetized benefits. For PFAS, the lower risk of reductions in birth weight were also a significant component of monetized benefits. The Draft Toxicological Review's dose-response analyses for cardiovascular disease, diabetes and reduced birth weight provide the necessary information to similarly quantify and monetize benefits for these effects in future EPA actions addressing arsenic exposure and will better inform decision makers regarding the public health consequences of the various regulatory options leading to better evidence-based decision making. It is therefore critical that these analyses, which implement important recommendations from the National Academy of Sciences, be retained and highlighted in the final version of the IRIS assessment.

[1] U.S. EPA. National Primary Drinking Water Regulations for Lead and Copper: Improvements (LCRI), Proposed rule, December 26, 2023. 88 FR 84878.

[2] U.S. EPA. PFAS National Primary Drinking Water Regulation Rulemaking, Proposed rule, March 29, 2023. 88 FR 18638.

EPA's current standard for arsenic in drinking water is 10 micrograms per liter. At this level of exposure, the Draft Toxicological Review's dose-response analysis indicates that mean and upper-bound estimated risks are as follows:[3]

- cardiovascular disease incidence: 208-in-10,000; 689-in-10,000
- cardiovascular disease mortality: 51-in-10,000; 153-in-10,000
- ischemic heart disease incidence: 178-in-10,000; 464-in-10,000
- ischemic heart disease mortality: 44-in-10,000; 122-in-10,000
- diabetes incidence: 179-in-10,000; 463-in-10,000
- bladder cancer: 8-in-10,000; 16-in-10,000
- lung cancer: 24-in-10,000; 59-in-10,000.

These extraordinary risks are far in excess of EPA's target range applied to protection from carcinogenic risks of 1-in-10,000 (10^{-4}) to 1-in-1,000,000 (10^{-6})[4] and indicate the urgency of promptly finalizing the Draft Toxicological Review so that this updated information regarding risks to people living in the United States can be used to inform regulatory revisions for arsenic in drinking water and in coal combustion waste, which is a major source contributor to arsenic in drinking water.

Our comments address the following main points:

1. **EPA's dose-response assessment for non-cancer effects of inorganic arsenic is a significant advance in the practice of risk assessment and provides a model for future EPA assessments.**

2. **EPA's proposed reference dose (RfD) for inorganic arsenic is not protective of public health and should be significantly revised.**
   a. **EPA should follow National Academy of Sciences guidance to specify a risk-specific dose in place of a traditional RfD.**
   b. **EPA's dose-response analysis demonstrates that the proposed RfD is not protective of public health for non-cancer effects.**
   c. **EPA choice of a 5% effect level as the point of departure for non-cancer health effects is too high and the resulting RfD demonstrates the deficiencies of the traditional RfD approach.**

We appreciate the opportunity to provide public input. Please do not hesitate to contact us with any questions regarding these comments.

Sincerely,

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[3] U.S. EPA. IRIS Toxicological Review of Inorganic Arsenic, External Review Draft, October 2023, Tables 4-10, 4-12, 4-3 and 4-5.

[4] U.S. EPA. Methylene Chloride; Regulation Under the Toxic Substances Control Act (TSCA), Proposed rule, May 3, 2023. 88 Fed. Reg. 28284, p. 28326.

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DETAILED COMMENTS

1. EPA's dose-response assessment for non-cancer effects of inorganic arsenic is a significant advance in the practice of risk assessment and provides a model for future EPA assessments.

The dose-response assessment in the Draft Toxicological Review implements improved approaches recommended in a series of authoritative reports from the National Academy of Sciences ("NAS").

In the 2009 report *Science and Decisions,* the NAS recommended that EPA revise its approach to estimating and characterizing the traditional reference dose (RfD) and that it instead quantify risks for non-cancer effects in the same way that it does for cancer:

> Separation of cancer and noncancer outcomes in dose-response analysis is artificial because noncancer end points can occur without a threshold or low-dose nonlinearity on the population level and in some cases on the individual level…quantification of risk (along with the attendant uncertainty) not only at the RfD but along the dose continuum is an important advance for risk benefit analysis.[5]

Science and Decisions recommended that EPA replace the traditional RfD with a more quantitative risk-specific dose:

> multiple risk-specific doses could be provided…in the various risk characterizations that EPA produces to aid environmental decision-making.[6]

> A Risk-Specific Reference Dose: For quantal effects, the RfD can be defined to be the dose that corresponds to a particular risk specified to be de minimis (for example, 1-in-100,000) at a defined confidence level (for example, 95%) for the toxicity end point of concern.[7]

In 2013, the NAS extended the *Science and Decisions* recommendations to the specific case of a new IRIS assessment of inorganic arsenic:

> The committee recommends that EPA develop risk estimates across the array of health effects on which there is adequate epidemiologic evidence and then derive risk-specific doses to address the needs of analyses that would typically use a reference dose (RfD). That approach would facilitate efforts to evaluate cumulative risks posed by exposure to multiple chemicals, conduct risk–benefit assessments, or to conduct other comparative analyses.[8]

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[5] National Research Council (2009). Science and decisions: Advancing risk assessment, pp. 177-178.
[6] National Research Council (2009). Science and decisions: Advancing risk assessment, p. 140.
[7] National Research Council (2009). Science and decisions: Advancing risk assessment, p. 140.
[8] National Research Council (2013). Critical aspects of EPA's IRIS assessment of inorganic arsenic: Interim report, pp. 6-7.

EPA responded to the 2013 report by developing proposed methods for dose-response assessment for cancer and non-cancer effects of arsenic, which were favorably reviewed by the NAS in 2019:

> EPA has implemented a sophisticated methodology that will allow it to use data from multiple epidemiological studies to determine the shape of the dose-response curve in the observed range. The majority of the committee supports this approach, and recommended clarifications on some of the procedures…The committee agrees with EPA's conversion of a variety of exposure metrics to a common intake value to facilitate including as many studies as possible in the dose-response analysis for each health end point considered.[9]

We strongly support EPA's decision to implement these recommendations in the Draft Toxicological Review with a thorough meta-regression methodology that integrates data from multiple epidemiologic studies for bladder cancer, lung cancer, cardiovascular disease incidence and mortality, ischemic heart disease incidence and mortality, and diabetes incidence. EPA has also estimated a dose-response function for reduced birth weight using different methods; the Draft Toxicological Review found that the meta-regression methodology could not be applied for this endpoint.

This is by far the most thorough and informative dose-response analysis for non-cancer effects ever conducted in an IRIS assessment. The dose-response functions will provide critical new information for EPA regulatory decisions affecting arsenic exposure and will enable a significant upgrade in quantification and monetization of health benefits in EPA benefit-cost analyses.

The strengths of EPA's meta-regression approach are manifold and include:

1) prior publication of methods in peer-reviewed journal articles;
2) application of Bayesian statistical modeling techniques;
3) selection of studies for inclusion in the meta-regression analysis using consistent criteria applied by two or more independent reviewers;
4) a focus on studies with low-to-moderate exposures most relevant to the U.S. general population;
5) integration of multiple studies from diverse locations (studies conducted in North America, South America, Asia, and Europe) that also include susceptible populations;
6) conversion of diverse exposure measures to a common metric across studies;
7) extensive sensitivity analysis including the separation of studies in cohorts with lower exposure levels;
8) estimation of risk at doses routinely experienced in the United States; and
9) inclusion of the dose-response functions necessary to calculate risks at any exposure level of interest.

The dose-response analysis methods used in the IRIS arsenic assessment should be applied to other IRIS assessments and EPA program office assessments for chemicals and pollutants with sufficient epidemiologic data. The meta-regression analysis applied to arsenic is extremely well

[9] National Academies of Sciences, Engineering, and Medicine (2019). Review of EPA's Updated Problem Formulation and Protocol for the Inorganic Arsenic IRIS Assessment, p. 2.

done, but this approach will not be necessary or feasible for every assessment. Even in the absence of an extensive evidence base that supports the meta-regression approach, all future IRIS assessments and risk assessments conducted by EPA program offices should include dose-response relationships for non-cancer effects at levels of exposure relevant for workers, consumers and the general public. The Draft Toxicological Review's approach to analysis of reduced birth weight is an excellent model for future IRIS dose-response assessments of epidemiological data. For IRIS assessments of non-cancer endpoints lacking suitable epidemiological data, the probabilistic methodology of the International Programme on Chemical Safety ("IPCS")[10] should be applied to derive risk-specific doses based on animal toxicology studies.

2. EPA's proposed reference dose (RfD) for inorganic arsenic is not protective of public health and should be significantly revised.

a. EPA should follow NAS guidance to specify a risk-specific dose in place of a traditional RfD.

As noted above, the NAS recommended in *Science and Decisions* that EPA reformulate the traditional RfD to make use of a probabilistic risk-specific dose. For example, a redefined RfD could be equal to the dose at which risks of a specified effect are no greater than 1-in-100,000 with 95% confidence.

EPA typically applies a target range for protection from carcinogenic risks of 1-in-10,000 (10^{-4}) to 1-in-1,000,000 (10^{-6}),[11] and this range should be applied for presentation of risk-specific doses for non-cancer effects of inorganic arsenic. The Draft Toxicological Review contains all of the analyses necessary to estimate risk-specific doses for multiple non-cancer endpoints, at multiple levels of risk (e.g. 1-in-10,000, 1-in-100,000, and 1-in-1,000,000). For the final version of the Toxicological Review, EPA should incorporate tables with risk-specific dose estimates for cardiovascular disease incidence and mortality, ischemic heart disease incidence and mortality, diabetes incidence, and low birth weight. EPA should then use these values, with adjustment for human variability beyond the variability that is captured in the underlying study populations, to select a risk-specific dose as the final RfD. We recommend that the RfD should be set at the dose for which upper bound risk of any health effect of is no more than 1-in-1,000,000.

b. EPA's dose-response analysis demonstrates that the proposed RfD is not protective of public health for non-cancer effects.

EPA has derived a traditional RfD of 0.031 μg/kg-d, based on cardiovascular disease incidence as the most sensitive endpoint. Calculations using the dose-response functions provided in the

[10] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition.

[11] U.S. EPA. Methylene Chloride; Regulation Under the Toxic Substances Control Act (TSCA), Proposed rule, May 3, 2023. 88 Fed. Reg. 28284, p. 28326.

Draft Toxicological Review demonstrate that the draft RfD is not health-protective. At the proposed RfD of 0.031 μg/kg-d, upper bound risks are:

- Greater than 1-in-100 for cardiovascular disease incidence (about 160 per 10,000)
- Greater than 1-in-100 for ischemic heart disease incidence (about 110 per 10,000)
- Greater than 1-in-100 for diabetes incidence (about 110 per 10,000)
- Greater than 1-in-1000 for cardiovascular disease mortality (about 35 per 10,000)
- Greater than 1-in-1000 for ischemic heart disease mortality (about 27 per 10,000).

Compared to EPA's typical target risk range of 1-in-10,000 (10^{-4}) to 1-in-1,000,000 (10^{-6}), EPA cannot interpret risks in excess of 1-in-100 for serious chronic diseases or risks in excess of 1-in-1000 for mortality as consistent with "likely to be without an appreciable increased risk"[12] and therefore should not issue a value of 0.031 μg/kg-d as the final RfD for inorganic arsenic.

c. EPA's choice of a 5% effect level as the point of departure for non-cancer health effects is too high and the resulting RfD demonstrates the deficiencies of the traditional RfD approach.

As discussed above, if EPA proceeds with establishing a traditional RfD rather than basing an RfD on a risk-specific dose as recommended by the NAS, it will result in an RfD that is not protective of public health. Part of the reason for this outcome is that EPA has selected a benchmark response ("BMR") level for RfD derivation of 5%, which represents a 1-in-20 risk level that is 50,000 times higher than the lower end of EPA's target risk range. Furthermore, division of a 5% effect level by the minimal uncertainty factors typically applied to epidemiological data will by definition yield a level with risk that is not substantially lower than 1-in-20.

EPA asserts that its choice of a 5% BMR is in line with the 2012 Benchmark Dose ("BMD") Technical Guidance,[13] saying that

> The effects under consideration, clinically diagnosed type II diabetes, CVD or IHD, which have a high, 40%, 70% and 40% probability of occurrence, respectively, within the U.S. population (see Section 4.3.4), are not frank effects and do not warrant a lower BMR on the basis of severity.[14]

EPA should not characterize chronic diseases that often require lifetime use of medication and frequent blood tests to be anything less than severe effects. Further, EPA's statement does not account for the severity of mortality and does not reflect EPA's BMD guidance regarding BMR selection for epidemiological data, which says:

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[12] U.S. EPA. IRIS Toxicological Review of Inorganic Arsenic, External Review Draft, October 2023, p. 4-66.
[13] U.S. EPA (2012). Benchmark Dose Technical Guidance.
[14] U.S. EPA. IRIS Toxicological Review of Inorganic Arsenic, External Review Draft, October 2023, pp.4-59 to 4-60.

> for epidemiological data…1% extra risk is often used as a BMR.[15]
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> a BMR of 1% has typically been used for quantal human data from epidemiology studies.[16]

EPA should follow the BMD guidance and generally use a BMR of 1% or lower, without trying to draw a conceptual line between adverse effects that are considered severe vs. those that are considered not severe.

EPA expresses concern about selecting a BMR at a level below the range of the observed data, but on this point the BMD Guidance states that:

> if one models below the observable range, one needs to be mindful that the degree of uncertainty in the estimates increases. In such cases, the BMD and BMDL can be compared for excessive divergence.[17]

In other words, the BMD guidance does not specifically require a POD to be within the range of the observed data, but to consider the extent of uncertainty at lower BMRs by comparing the BMD to the BMDL. EPA's Draft Toxicological Review does not discuss the extent of divergence between the BMD and BMDL. We examined this issue by calculating the ratio of BMD:BMDL for BMRs of 1% and 5%.

Ratio of BMD to BMDL for benchmark responses (BMR) of 1% and 5%: diseases of the cardiovascular system and diabetes in the Draft *IRIS Toxicological Review of Inorganic Arsenic*

Health outcome	BMD01	BMDL01	Ratio BMD01/ BMDL01	BMD05	BMDL05	Ratio BMD05/ BMDL05
CVD incidence	0.062	0.019	3.3	0.315	0.094	3.4
IHD incidence	0.073	0.028	2.6	0.362	0.140	2.6
Diabetes	0.073	0.028	2.6	0.36	0.140	2.6

Note: BMD and BMDL values were obtained from Table C-81, *IRIS Toxicological Review of Inorganic Arsenic: Supplemental Information*, External Review Draft, October 2023. Table C-81 does not indicate units, but they appear to be µg/kg-day. Table C-81 does not report BMD/BMDL values for CVD mortality and IHD mortality.

As shown in the table, the divergence between BMD and BMDL for a 1% response is similar to the divergence for a 5% response – with a ratio of approximately 3 for each BMR for all three endpoints, indicating stability in the dose-response rather than increasing divergence. Given this

[15] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 21.
[16] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 21.
[17] U.S. EPA (2012). Benchmark Dose Technical Guidance, p. 21.

finding, along with the BMD guidance statements that use of BMR=1% is typical for epidemiological data, EPA should use a BMR no greater than 1% as the point of departure ("POD").

Although an RfD derived from a 1% effect level would be more health-protective than one based on a 5% effect level, a BMR of 1% would also result in an RfD that is not protective of public health. The resulting RfD from a BMD_{01} would be 5-fold lower than EPA's proposed RfD, or 0.006 μg/kg-d. The upper-bound risks at this level would be in the range of 20-30 per 10,000 (i.e. greater than 1-in-1000) each for cardiovascular disease incidence, ischemic heart disease incidence, and diabetes incidence - as would be expected for an RfD based on a 1% effect level and minimal uncertainty factors - and around 5-7 per 10,000 (approaching 1-in-1000 risk) each for cardiovascular disease mortality and ischemic heart disease mortality. Thus, an RfD based on a BMR (effect level) of 1% would still result in a significant risk of chronic disease and mortality that should not be interpreted as "likely to be without an appreciable increased risk."

The Draft Toxicological Review is the first IRIS assessment to provide sufficient information to estimate risks of non-cancer effects at the level of an RfD. The risks of chronic disease and mortality at the level of the proposed RfD are significant. This reveals the substantial deficiencies in the RfD approach, which assumes that the value obtained by selecting a customary POD and dividing by customary uncertainty factors produces an exposure level that is likely to be without an appreciable risk of deleterious health effects during a lifetime. The Draft Toxicological Review's exceptional dose-response analysis of epidemiological data for inorganic arsenic demonstrates that, at least in this instance, the RfD approach does not result in a negligible risk level, highlighting the flaws of the RfD approach in general.

EPA should address the flaws of the traditional RfD approach by following the advice of the NAS in *Science and Decisions* to re-define the RfD as a risk-specific dose. Under this re-definition, RfDs could be calculated with either the methods used for analysis of epidemiological data in the Draft Toxicological Review, or the WHO/IPCS probabilistic methodology. With either approach, EPA should report risk-specific doses for multiple risk levels (e.g, 1-in-10,000, 1-in-100,000, and 1-in-1,000,000). Either approach will enable EPA to explicitly select the level of protection (e.g., 1-in-1,000,000) for each RfD, in contrast to the current approach, which assumes the RfD process produces a value of "no appreciable risk" without defining the level of risk it is meant to represent.