Comments on **Risk of Bias Analysis** aspect of Draft Documentation for EPA/IRIS Tox Review

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Considerations

1. This is intended to be a hazard identification document with a dose-response analysis. It specifically excludes exposure assessment, which must be critical to a dose-response analysis.

2. NRC request that the review begin with a clear statement of the research question. This is not evident. NRC proposed [chapter 3, box 4] – **What is the dose-relationship between arsenic and** [outcome of concern] ***throughout the range of arsenic exposure that is relevant for human populations***. The draft document deals with the first part of that question but not with its qualifier.

3 EPA makes the assumption that study exposures up to two orders of magnitude above population exposure levels are relevant. That is an assumption that should be examined.

Considerations 2

4. NRC proposed that study data be separated into that for arsenic exposures below 100 ug/L and that for arsenic exposures greater than 100 ug/L. The draft document has not followed up on that critical request. It should.

5. The exposure metric includes an assumption of the mechanism or mode of action or of the pattern of risk. Beware that it may narrow your options.

6. The term "Risk of Bias" may be meaningful for regulatory purposes, but from the outside it appears offensive. Consider as an alternative term – "Sources of Uncertainty". Further, allow a process for the primary investigator to assist the Agency.

Examination of an Example

Study:

Ferreccio et al. Arsenic, Tobacco Smoke, and Occupation – Associations of Multiple Agents with Lung and Bladder Cancer *Epidemiology*, Nov 2013; 24(6):898-905 plus Supplementary Tables 1-9

Concept:

Ferreccio et al. (2013b) is a case/control study of 2007-2010 lung cancer cases (n = 306) and controls (538) from Northern Chile specifically designed to also account for tobacco smoking and occupation.

Assessment of Risk of Bias

Risk of Bias Overview (page 4-34)

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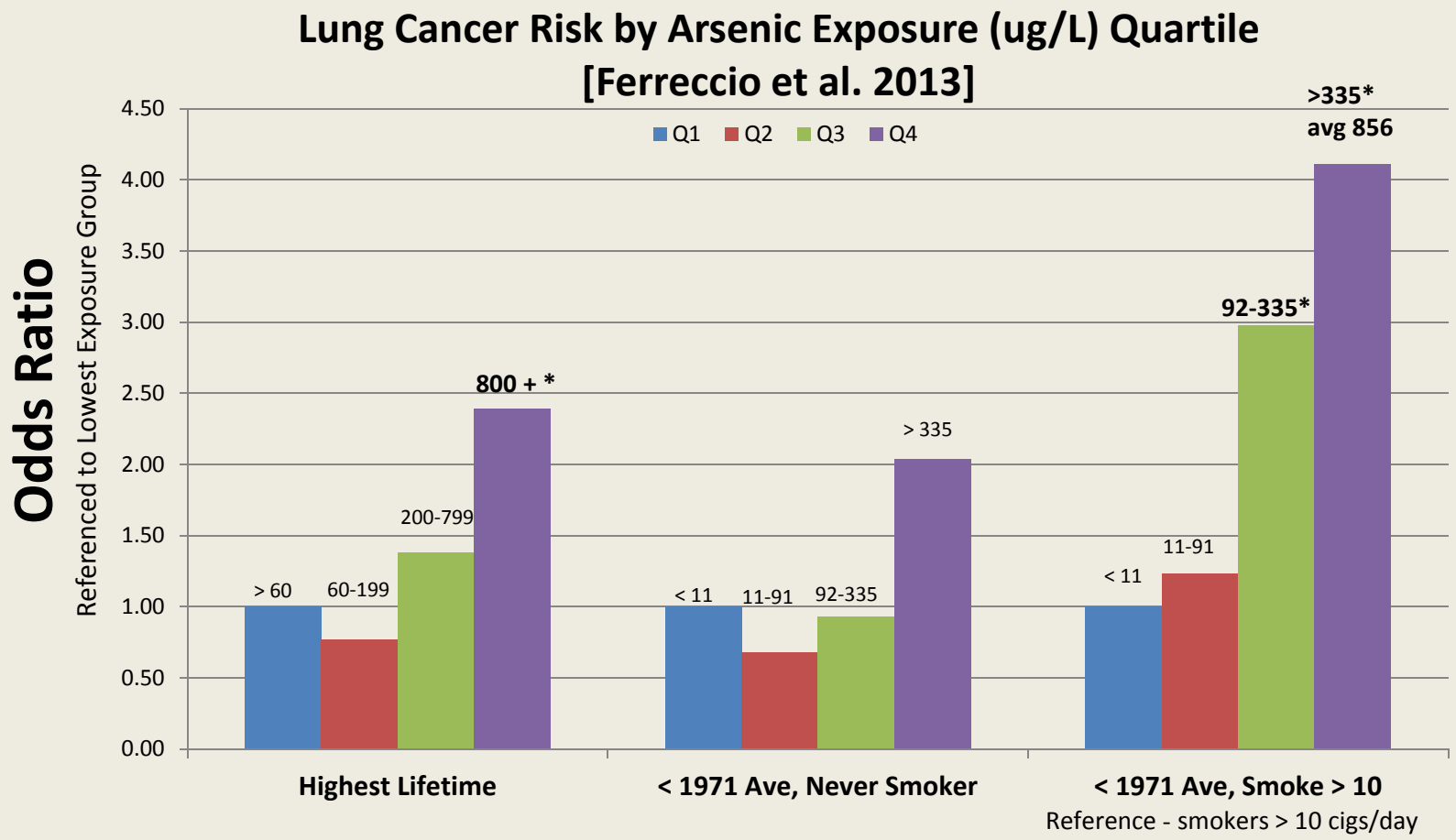
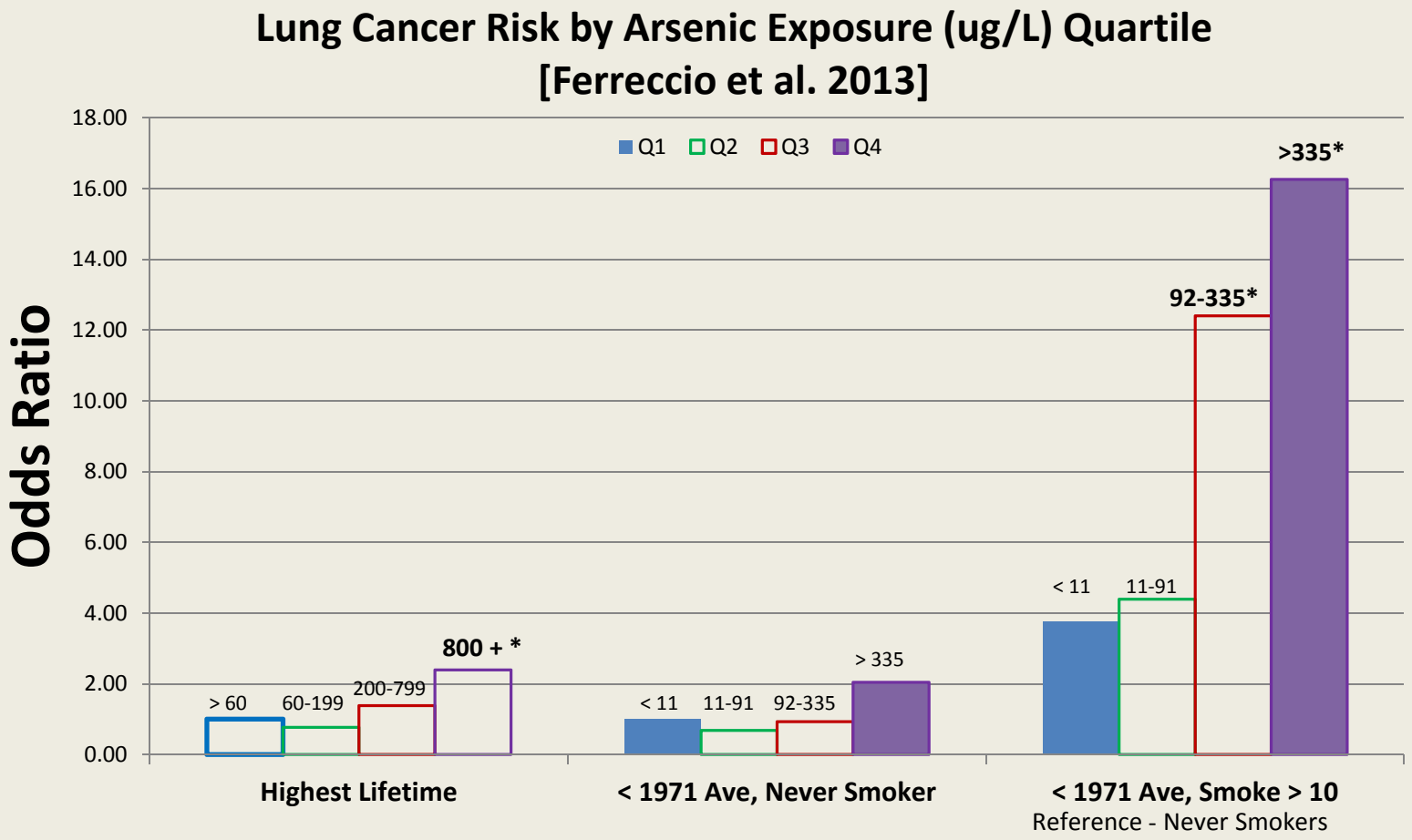
Comparison Group	1	Protocol Deviations		Confounding (Analysis)	2b
Confounding (Design)	2a	Missing Outcome Data		Exposure Characterization	4
Unintended Exposure	3	Blinding (Outcome Assessment)			
Outcome Assessment	5	Outcome Reporting			
Internal Validity	6				

Tiered Assessment – Either "**Low Risk of Bias**" or "**Probably High Risk of Bias**"

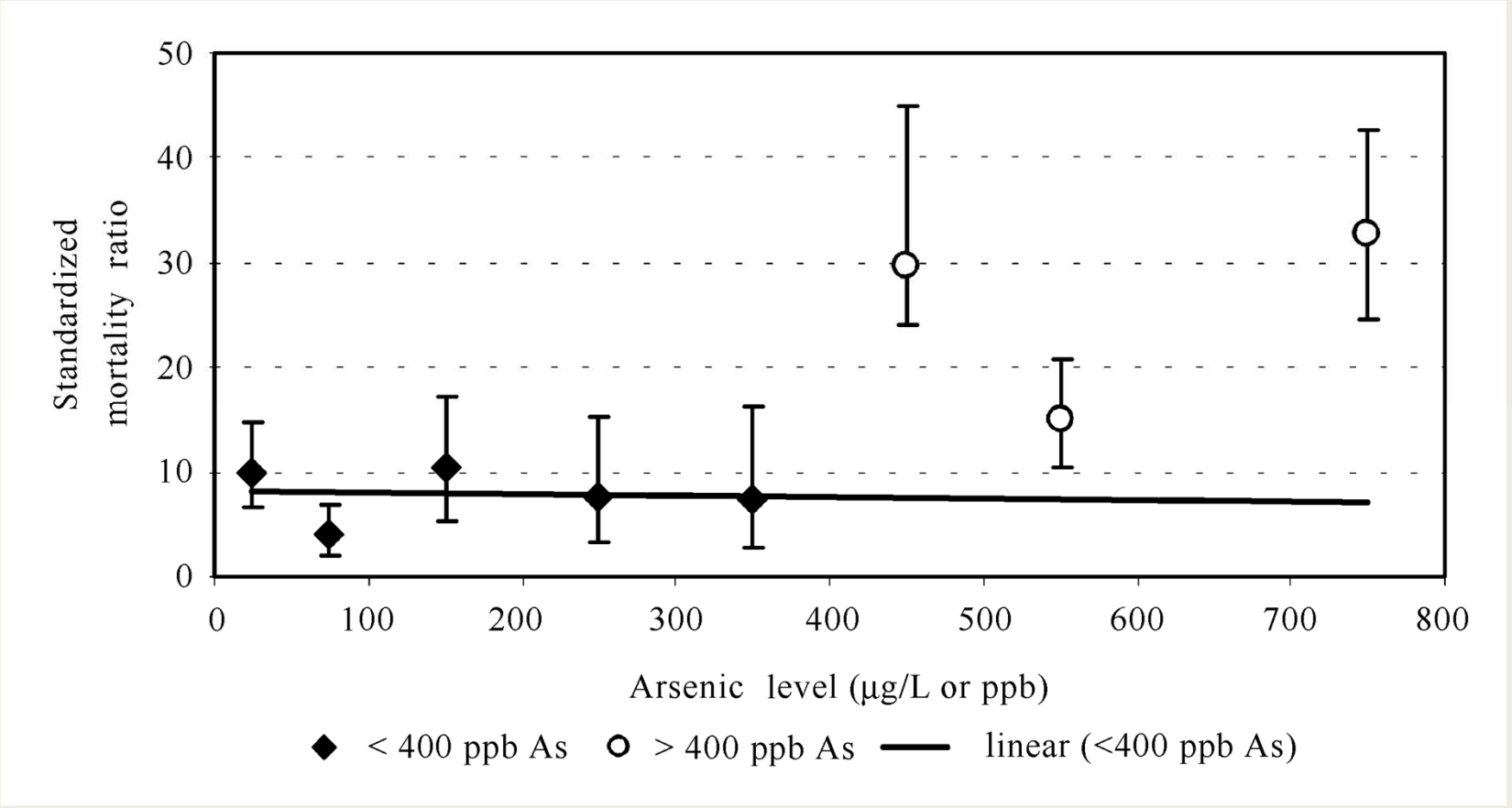
Ferreccio et al. 2013



April 2014 Data Report

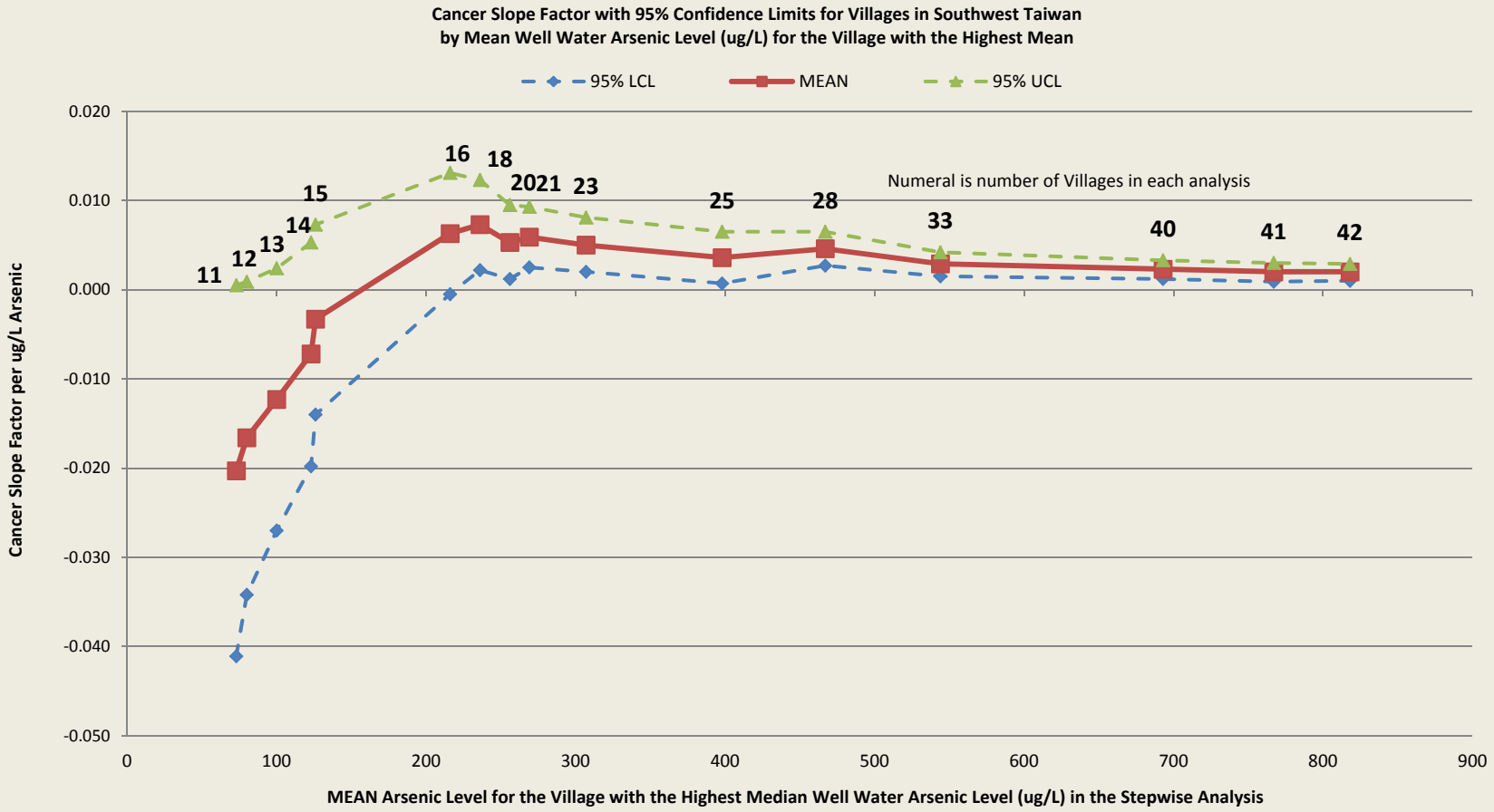


Methods to Separate out High Exposure Outcomes - SMR

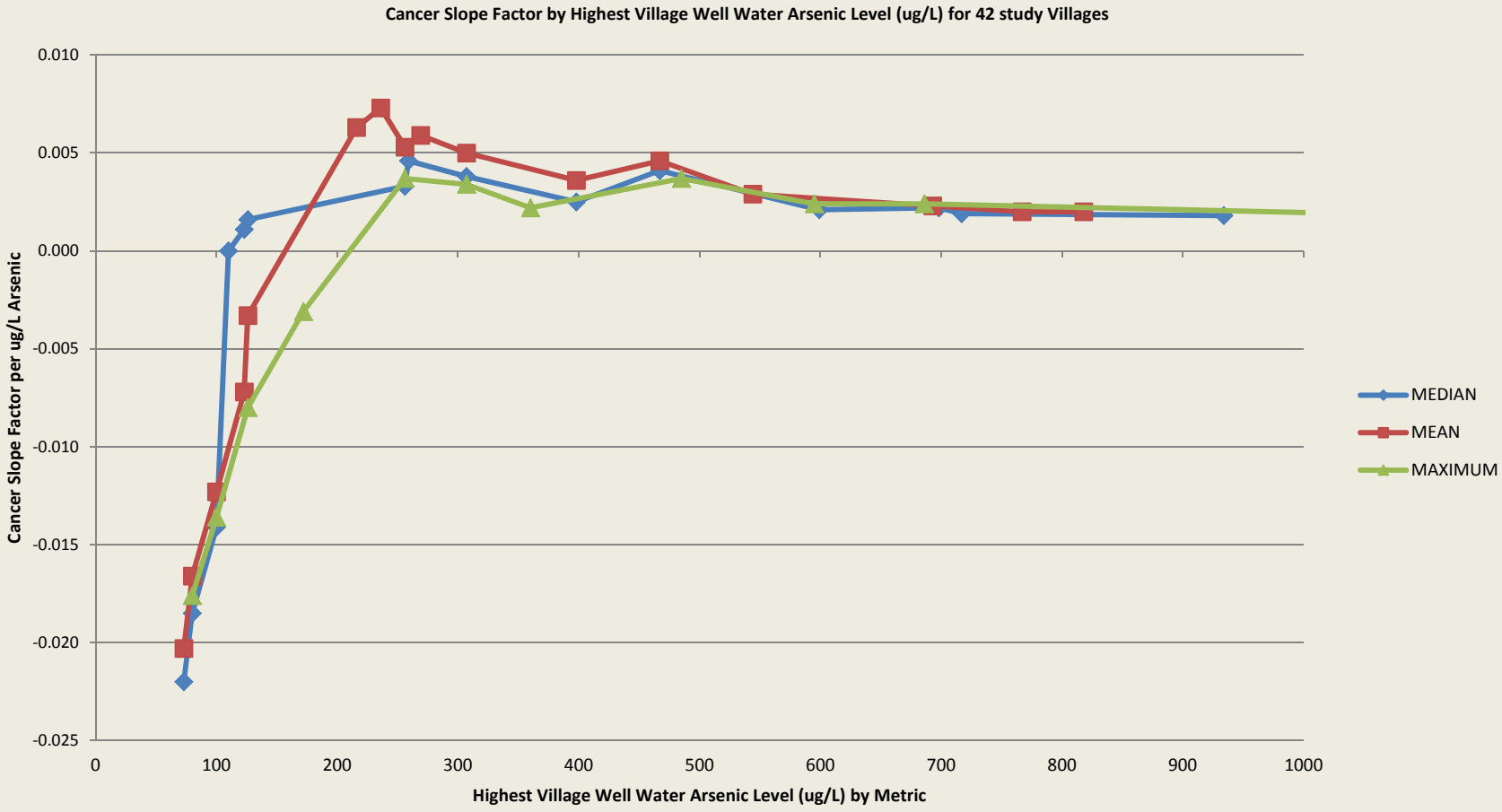


Bladder Cancer Mortality (Data from Morales, 2000)

Methods to Separate out High Exposure Outcomes – Reiterative Poisson



Comparison of Metrics



Acknowledgments:
Nana Ama Afari-Dwamena, Hamid, and the Appalachian Research Initiative for Environmental Sciences (ARIES)

Thank You

Appendix to comments – Steven H. Lamm, MD

Ferreccio et al. (2013) includes a study of306 lung cancer cases and their controls in Northern Chile for cases diagnosed between October 2007 and December 2010. The evidence extracted from this study and presented in Summary Table 5-15 [page 5-227 or page 468] is a biased presentation of the findings in this paper. It is unclear how the Risk of Bias analysis picks up this type of source of bias.

The important findings in this paper are presented in Table 1 (which gives the drinking water arsenic levels in the various time periods) and Table 2 (which give the primary dose-response analysis).

Table 2: Lung Cancer Odds Ratios by Arsenic Exposure

Exposure	N	Percent	OR	95% CI
0-59 ug/L	48	(16%)	1.00	
60-199 ug/L	52	(17%)	0.77	(0.49-1.21)
200-799 ug/L	69	(23%)	1.38	(0.89-2.13)
>= 800 ug/L	**138**	**(45%)**	**2.39**	**(1.61-3.54)**

Table 2 shows that there is no significant increased risk of lung cancer until the category of exposure >= 800 ug/L is reached. It is important to note that the exposure metric used is that of the "highest single year exposure throughout the subject's entire lifetime from birth to diagnosis, … based on the concentrations in the four largest cities in the study area: Arica, Iquique, Calama, and Antofagasts"). Review of the data in Table 1 (see below) will show that the >= 800 ug/L group is 860 ug/L for the residents of Antofagasta and Mejillones during the period 1958-1970. It is important to note that the analysis in Table 2 includes all the study subjects.

Table 1: Historic Arsenic Concentrations in Drinking Water (ug/L) by Location and Year

Exposure Strata	Location	Population	Time Period	Average As
➢ 800 ug/L	**Antofagasta**	**270,184**	**1958-1970**	**860 ug/L**
	Mejillones	**7,660**	**1958-1970**	**860 ug/L**
➢ 600 ug/L	**Tocopilla**	**21,827**	**1971-1977**	**636 ug/L**
	Maria Elena	**6,852**	**1971-1977**	**636 ug/L**
	San Pedro	**4,522**	**1930-1995+**	**600 ug/L**
➢ 200 ug/L	**Calama**	**125,946**	**1971-1977**	**287 ug/L**
	Tocopilla	21,827	1930-1970	250 ug/L
	Maria Elena	6,852	1930-1977	250 ug/L
➢ 100 ug/L	Calama	125,946	1930-1970	150 ug/L
	Antofagasto	270,184	1971-1979	110 ug/L
	Mejillones	7,660	1971-1979	110 ug/L
	Calama	125,946	1978-1987	110 ug/L
	Maria Elena	6,850	1978-1987	110 ug/L
➢ 59 ug/L	Antofagasta	270,184	1930-1957	90 ug/L
	Mejillones	7,660	1930-1987	90 ug/L
	Antofagasta	270,184	1980-1987	70 ug/L
	Mejillones	7,660	1980-1987	70 ug/L
	Iquique	**196,941**	**1930-1994**	**60 ug/L**
	Taltal	**10,101**	**1930-1995+**	**60 ug/L**

Highest <= 59 ug/L	**Pozo Almonte**	**9,855**	**1930-1995+**	**40 ug/L**
	Huara	**2,365**	**1930-1995+**	**30 ug/L**
	Arica	**168,594**	**1930-1994**	**10 ug/L**

The draft document cites as the critical data the findings from Supplementary Table 2 where a partial stratified analysis on smoking behavior is given. The smoking strata could be (a) Non-smoker; (b) 1-10 cigs/day smoker; (c) 11-20 cigs/day smoker; and > 20 cigs/day smoker; the exposure strata are (A) < 11 ug/L; (B) 11-91 ug/L; (C) 92-335 ug/L; and (D) > 335 ug/L.

The analysis presented compares for smoking strata the non-smoker [strata (a)] and the > 10 cigs/day smoker [strata (c) and (d) together]. The subjects in smoking strata (b) are absent from this analysis. The analysis presented compares for arsenic strata those with < 11 ug/L [strata A] with those having > 335 ug/L [strata D]. The subjects in arsenic strata B and arsenic strata C are absent from this analysis. In contrast, the analysis in Table 2 above had included all subjects in the study.

Further, the exposure metric in Supplementary Table 2 is not the highest exposure experienced but is the average exposure prior to 1971. The effect of the change in the exposure metric is to move locations into different exposure strata. The 28,000 residents of Tocopilla and Maria Elana are moved from the third strata to the fourth strata, suggesting their risk is from exposure at 250 ug/L rather than at 636 ug/L. Their high exposure occurred after 1970, which is the cut-off date for Supplementary Table 2.

My purpose in presenting this detailed analysis of a particular study is as an example of bias that exists in the report but not in the underlying study. It is not clear how the risk of such biases is brought in consideration in the procedures outlined.

The analyses below might be the type of analysis that should be considered for assessment of risk in the arsenic exposure range of interest.

Ferrecio et al. (2013)

Mantel-Haenszel Odds Ratios for (11-90 vs. < 11 ug/L)

Odds Ratios for elevated Arsenic

Non-Smokers	0.94	(0.43-2.03)	p = 1.00
> 20 cig/day	1.93	(0.72-5.19)	p = 0.22
M-H (As)	1.23	(0.67-2.65)	p = 0.60

Mantel-Haenszel Odds Ratios for (11-90 vs. < 11 ug/L)

Odds Ratios for elevated Arsenic

Non-Smokers	0.94	(0.43-2.03)	p = 1.00
> 10 cig/day	1.23	(0.65-2.34)	p = 0.62
M-H (As)	1.10	(0.67-1.80)	p = 0.80

June 20, 2014

EPA/IRIS Bimonthly Public Science Meeting
On Inorganic Arsenic –Science issue 2: Risk-of-Bias Approach.

To whom it my concern:

There are a few points I would like to bring to attention in the discussion of the assessment of the "Risk of Bias".

1. The term "Risk of Bias" is offensive. It is the "Redskins" term in the systematic review of the literature. The items that go into relate to issues of uncertainty in the risk assessment of various studies and to what the reviewers do not know of a study, rather than of what they do. It makes the assumption that all there is to know about a study is contained in its published version. Such a position is fatuous, as any author can relate. The published paper may well be an extraction from a larger report, publishing that aspect that is considered of interest to the readers, the reviewers, and the editors of the Journal. The purpose of the publication is not necessarily the same as the purpose of the regulatory reviewers. Thus, their information needs may differ. What the reviewer may see as evidence of the "risk of bias" may rather be lack of evidence or "sources of uncertainty" with respect to the reviewers and their tasks.

   Further, I recommend that whenever an assessment is made of a particular study that that assessment be shared with the primary authors for their input. Furthermore, in doing so, please call it a process to identify "sources of uncertainty" in the understanding of the study, not an assessment of the "Risk of Bias". That may be a term of art for the regulatory agency, but it is pejorative to the scientific investigator. After all, it challenges one's primary value that of being "scientific researchers", with all the positive values that that term includes. Our system is supposed to be built on the concept of "presumed innocent, until proven guilty". The term "Risk of Bias" assessment does not imply that. A goal of identifying and reducing "sources of uncertainty" is one that a scientist will co-operate with. A goal of identifying the "Risk of Bias" sounds like it should call forth the institutions lawyer. The purpose of the process should be to bring the scientists in to better the assessment.

2. The major concept under consideration in the assessment of the cancer risk from the ingestion (and inhalation) of inorganic arsenic is whether the dose-response relationship follows a linear model, a hockey-stick model, or something in between. Is there a threshold level above which it appears that cancer risk is related to arsenic dosage and below which it is not (or not significantly so). The "Causal Determination Framework" proposes [Table 1-5, page 1-33 or page 46] that a causal relationship has been demonstrated when "evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposure (i.e., doses or exposures generally within one to two orders of magnitude of current levels). This is a definition that might be appropriate for definition of a hazardous substance, but not of a substance of risk at the exposures experienced.

   This definition completely obliterates the question at hand. There is no doubt that ingestion of inorganic arsenic at 500 ug/L for some period of time can cause skin, bladder, or lung cancer. It does not follow that this demonstrates evidence that ingestion of inorganic arsenic at 5 ug/L for some period of time can cause skin, bladder, or lung cancer. The evidence as it has been developing over the past decade is that it does not. In our own studies, we showed for skin

cancer a threshold of 122 ug/L in the Inner Mongolia study (Lamm et al., 2007), a threshold of 100-200 ug/L for bladder and lung cancer in the southwest Taiwan BDF-endemic area study (Lamm et al., 2006), and no increased risk over the range of 3-60 ug/L for male bladder cancer in the US (Lamm et al., 2004) or for lung cancer (Lamm et al., 2014, under review). Furthermore, Tsuji et al. (2014) showed the absence of increased risk of bladder cancer among non-smokers in a meta-analysis of the literature. Similarly, Dissen et al. (2014) presented at SOT (2014) a systematic review of lung cancer and low-level arsenic ingestion showing no increased risk below 100 ug/L.

3. Greater attention should focus on the exposure assessments, bringing in the skills deep within the Agency. I follow with a number of examples on inorganic arsenic from my experiences:

    a. For years the exposure assessment of the southwest Taiwan study derived from the Kuo (1968) report has been accepted as absolute with no impending uncertainty. Only about half the exposure data found in the NRC (1999) report could be found in the Kuo (1968) report. The issue as to whether the data taken in 1961-1964 was inclusive of the wells extant in 1959 before piped water arrived has not been discussed. Whether the median is the better measure of central tendency rather than the mean or whether the maximum should be considered instead has been discussed outside of the Agency but not apparently inside.
    b. I have appended an analysis of the section in the report extracting the analyses from Ferreccio et al. (2013) on lung cancer and arsenic ingestion in Northern Chile. That demonstrates that the choice of exposure metric heavily affects the risk analysis. In that case, a number of subjects were classified on the basis of their exposures through1970 when their greater exposures occurred following 1970 and 30-40 years before their diagnoses.
    c. In the section dealing with risk of lung cancer from inhalation of arsenic at the Anaconda copper smelter two classifications of the exposure categories have been published in the literature but no such discussion comes into this document.

    I speak so far on the studies that I personally know well. I would like to see the Agency give greater attention to the exposure assessments.

I bring these matters to your attention as they have occurred to me in my first reading of the report. I hope these concepts can be incorporated into the next draft.

Cordially,

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