Expert External Peer Review of Section 4.2, Carcinogenic Potential, of the Development Support Document for Arsenic and Inorganic Arsenic Compounds

Peer Review organized by
Toxicology Excellence for Risk Assessment (*TERA*)
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Introduction

The Toxicology Division of the Chief Engineer's Office, Texas Commission on Environmental Quality (TCEQ) has prepared a draft Development Support Document (DSD) that outlines the hazard assessment and dose-response processes used to derive Effects Screening Levels (ESLs), Reference Values (ReV), and a Unit Risk Factor (URF) for arsenic. The toxicity values were developed using RG-442 *Guidelines to Develop Effects Screening Levels, Reference Values, and Unit Risk Factors* (TCEQ, 2006). ESLs are chemical-specific air concentrations set to protect human health and welfare. Short-term ESLs are based on data concerning acute health effects, odor potential, and vegetative effects, while long-term ESLs are generally based on data concerning chronic noncarcinogenic and/or carcinogenic health effects. ESLs are used in the evaluation of air permit applications as well as proposed rules and regulation (e.g. Permits by Rule). ReVs and URFs, used as the basis of ESLs, are used in the evaluation of air monitoring data and in the development of Protective Concentration Levels for remediation sites.

TERA is supporting the Texas Commission on Environmental Quality (TCEQ) in conducting an expert external peer review of Section 4.2, Carcinogenic Potential, of the *Development Support Document for Arsenic and Inorganic Arsenic Compounds*. The review materials, including draft document, charge to reviewers, and key references (available at http://www.tera.org/Peer/arseniccarc/index.html) were distributed to the panel in May 2010. Panel members reviewed Section 4.2 of the DSD and submitted written comments that addressed the charge questions in July 2010. These written comments are presented in Part A of this report and the Peer Review Charge is attached as Appendix A.

On August 26, 2010, TERA facilitated a follow-up conference call between the panel and TCEQ. Conference call materials (available at the above website), including a focused charge, attached as Appendix B, and the reviewer comments in Part A, were distributed prior to the call; members of the public were allowed to listen to the call. The purpose of this call was to allow TCEQ to ask the panel questions regarding their written comments and to allow the panel members to discuss issues on which there were divergent opinions in the written comments. A TERA staff member took notes during the call to create a record of the panel's discussion and recommendation. This report of the conference call is presented in Part B of this report. Therefore, the written comments submitted by the panel and the report of the follow-up conference call comprise the complete peer review of Section 4.2 of the arsenic DSD.

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Part A: Panel Written Comments

General Issues
Please consider all aspects of Section 4.2, Carcinogenic Potential, of the DSD and evaluate strengths and weaknesses of the procedures used to develop the URF and chronic ESL for cancer, based on the specific questions described below. Where possible, try to put the strengths and weaknesses in perspective by indicating their relative magnitude. Please try to avoid emphasizing minor technical details or making tutorial comments. Reviewers should identify scientific uncertainties and suggest ways to reduce or eliminate those uncertainties.

- **Were procedures outlined in the ESL Guidelines followed by the TCEQ to perform arsenic's carcinogenic toxicity assessment? If references to accepted procedures in federal, state, or other appropriate guidance documents were made in the ESL Guidelines, were those accepted procedures followed?**

  Reviewer 1: TCEQ followed their guidelines correctly. In addition TCEQ referenced others' guidelines as appropriate.

  Reviewer 2: The TCEQ Guidelines to Develop Effects Screening Levels, Reference Values, and Unit Risk Factors (RG-442, November 2006) were <u>not</u> followed. In Section 1.5.2 of that document, it clearly states that the Unit Risk Factor (URF) for linear dose-response effects is an <u>upper bound</u> estimate of the risk as a function of dose. The TCEQ Development Support Document (DSD) <u>incorrectly</u> used a central estimate of the URF.

  The central estimate of the URF was appropriately calculated as the weighted average of the central estimates of the URF_i from four (i=1,2,3,4) human studies of arsenic exposures, as shown on page 52, lines 4 and 5,

  $$\text{Central URF} = \sum w_i \cdot URF_i / \sum w_i = 2.09\text{E-}04 \text{ per } \mu g/m^3, \qquad \text{(eq. 1)}$$

  where w_i is the person-years for the ith study.

  However, an upper bound estimate of the URF is needed. Since averages tend to be normally distributed, the 95% upper confidence limit (95% UCL) for the URF is

  Central URF + 1.645 x [standard error (se) of the estimate of the Central URF].

  The variance, $(se)^2$, of the sum of independent variables is the sum of their variances. Hence, for the Central URF defined by eq.(1), the variance is

  $$\{se(\text{Central URF})\}^2 = \Sigma \{se(w_i \cdot URF_i / \Sigma w_i)\}^2. \qquad \text{(eq. 2)}$$

  The standard error of a constant ($w_i / \Sigma w_i$) times a variable (URF_i) is the

constant times the standard error of the variable. Hence,

$$se(w_i \cdot URF_i / \Sigma w_i) = w_i \cdot se(URF_i) / \Sigma w_i .$$

Substituting this result into (eq. 2) gives the standard error for the weighted average as

$$se(\text{ Central URF }) = \sqrt{ [\sum w_i^2 \cdot \{se(URF_i)\}^2 / (\sum w_i)^2] } . \qquad \text{(eq. 3)}$$

The standard error for each URF_i readily can be obtained from the results in Table 19,

$$se(\ URF_i\ ) = [\ \beta_i\ (95\%\ UCL) - \beta_i\ (MLE)\ ] / 1.645. \qquad \text{(eq. 4)}$$

Hence, $se(\ URF_1\ ) = [\ 2.12E\text{-}04 - 1.19E\text{-}04\ ] / 1.645 = 0.57E\text{-}04$ per $\mu g/m^3$, similarly
$se(\ URF_2\ ) = 0.61E\text{-}04$ per $\mu g/m^3$,
$se(\ URF_3\ ) = 0.62E\text{-}04$ per $\mu g/m^3$,
$se(\ URF_4\ ) = 5.26E\text{-}04$ per $\mu g/m^3$.

Entering these values into (eq. 3) gives se(Central URF) = 0.519.

Then, the 95% UCL is
$URF = 2.09 + (1.645 \times 0.519) = 2.94E\text{-}04$ per $\mu g/m^3$. (eq. 5)

Hence, using weights of person-years, the

95% UCL for lung cancer risk = 0.000294 x ($\mu g/m^3$ of airborne arsenic).

With weights of person-years, the <u>correct</u> airborne arsenic screening level (ESL) following TCEQ ESL Guidelines associated with a 95% UCL lifetime lung cancer risk of 10^{-5} is

$$ESL = 10^{-5} / 0.000294 = 0.034\ \mu g/m^3.$$

Reviewer 3: NA

Reviewer 4: NA

- **Does the arsenic DSD clearly describe the approaches used by TCEQ to perform the toxicity assessment (i.e., hazard identification and dose-response assessment)?**

Reviewer 1: Clarity could be improved in the text. For example, TCEQ could put summary language in front of each study description to allow non-math-oriented

folks to get a sense of what they are about to read. Appendix A includes an example of how TCEQ might do this.

Reviewer 2: The TCEQ Development Support Document (DSD) is well-written and contains adequate information and discussion to justify the use of the four arsenic exposure studies in humans, calculate estimates of arsenic exposures in workers, and derive exposure-response (lung or respiratory cancer) models for estimating cancer risk as a function of airborne arsenic exposure.

Reviewer 3: NA

Reviewer 4: NA

- **Please identify any relevant studies or data that have not been cited. Explain how they may impact the assessment.**

Reviewer 1: We ran an additional literature search and found several studies, many of which we do not think will affect the overall results (see attachment). However, TCEQ should read at least the abstracts of the following two studies for possible use:

Parvez, F., Y. Chen, et al. 2010. "A prospective study of respiratory symptoms associated with chronic arsenic exposure in Bangladesh: findings from the Health Effects of Arsenic Longitudinal Study (HEALS)." Thorax 65(6): 528-33.

Sakuma, A. M., E. M. De Capitani, et al. "Arsenic exposure assessment of children living in a lead mining area in Southeastern Brazil." Cad Saude Publica 26(2): 391-8.

Reviewer 2: I am not aware of additional studies or data.

Reviewer 3: Rather that mention ATSDR and nothing else, there are some good reviews that fairly summarize large amounts of detailed and sometimes conflicting data. Why not cite some of them here:

M. Hughes, Kitchin KT, in: K. Singh (Ed.), Oxidative stress, disease and cancer, Imperial College Press, London, 2006

Kitchin, K. T. and Conolly, R., Arsenic induced carcinogenesis– oxidative stress as a possible mode of action and future research needs for more biologically based risk assessment. Chem Res Toxicol. 23(2):327-35 2010.

Much of the literature you cite here is very old. You have omitted lots of good studies and reviews among them:

A. Basu, J. Mahata, S. Gupta, A.K. Giri, Mutation research, vol. 488, 2001, pp. 171-194.

A.D. Kligerman, C.L. Doerr, A.H. Tennant, K. Harrington-Brock, J.W. Allen, E. Winkfield, P. Poorman-Allen, B. Kundu, K. Funasaka, B.C. Roop, M.J. Mass, D.M. DeMarini, Environ Mol Mutagen, vol. 42, 2003, pp. 192-205.

E Dopp, A.D. Kligerman and R.A. Diaz-Bone
Chapter 7 Organarseicals. Uptake, metabolism and toxicity
Pages 231-265
In Metal Ions in Life Sciences
Editors A Sigel, H Siegel and R.K.O. Siegal
Volume 7 Organmetallics in Environemtn and Toxicology, 2010
RSCPublishing
ISBN 978-84755-177-1

In addition, there are so many good books and review articles on arsenic carcinogenesis that it is surprising that some of them are barely or not at all mentioned in your document. Ones to add include:

N.R.C., in: N.A. Press (Ed.), Arsenic in Drinking Water, National Academy Press, Washington DC, 1999, pp. 194-196 or whole book.

N.R.C., National Academy Press, Washington, DC, 2001, pp. 1-225.

IARC Journal 84 (2004) Pages.

WHO, vol. Environmental health criteria document 224, 2001, pp. 1-405.

K.T. Kitchin, Toxicol Appl Pharmacol, vol. 172, 2001, pp. 249-261.
General discussion of MOA and serious proposals for MOA

M.P. Waalkes, J. Liu, H. Chen, Y. Xie, W.E. Achanzar, Y.S. Zhou, M.L. Cheng, B.A. Diwan, J Natl Cancer Inst, vol. 96, 2004, pp. 466-474.
Best summary of gestational carcinogenesis by arsenic

Reviewer 4: NA

Cancer Weight of Evidence and Unit Risk Factor (URF)

The arsenic DSD describes the approaches used to evaluate carcinogenicity and derive the URF and chronic ESL for cancer. Please review the key decisions made by TCEQ in deriving these values. For each decision, please comment on the consistency of the decision with TCEQ's ESL guidelines, the scientific appropriateness of the decision, and any additional approaches or additional information that would improve that decision. The key decisions and some specific issues to consider are listed below. Please discuss

other issues specific to developing URFs for carcinogenic effects that have not been adequately addressed in the document.

- **Was the proper weight of evidence (WOE) classification, using the USEPA (2005) guidelines for carcinogen risk assessment, given to arsenic compounds? If not, what WOE classification should be given to arsenic compounds, specifically inorganic arsenic?**

  Reviewer 1: TCEQ made the correct designation for arsenic's WOE. Arsenic is a known human carcinogen.

  Reviewer 2: The proper WOE classification was assigned to arsenic compounds.

  Reviewer 3: I and many other experimental biologists do not agree with this opinion that animal models are significantly limited in respect to carcinogenesis. Rather epi studies are "significantly limited" because they do not isolate a single cause and generally have poor exposure characterization data. In experimental animals there are usable arsenic induced cancer model in lungs, urinary bladder, liver and skin. Only the kidney is lacking a current model of arsenic induced carcinogenesis.

  TCEQ stated "Further, humans differ from animals in the pattern of metabolism as they excrete significantly more methylated forms of arsenic when compared to other mammalian species (with the mouse and rabbit may be an exception)." No this statement is not true except in the most biased of views. In all methylating mammals, arsenic methylation is fairly similar. The big metabolism differences are that certain species are nonmethylators (e. g. guinea pigs and some primates like chimpanzees) and that humans excrete a lot more MMM(V) than other species do.

  It is worth mentioning that there is no doubt that inorganic arsenic is carcinogenic to humans if the exposure is via drinking water. Lungs respond to arsenic exposure with carcinogenesis, both oral and respiratory routes are carcinogenic.

  Reviewer 4: Yes.

- **Is the epidemiological evidence in Enterline et al (1995), Lubin et al (2000 and 2008), Jarup et al (1989) and Viren and Silvers (1994) properly used in the characterization of chronic cancer risks? Is use of these four studies for calculating URFs justified?**

  Reviewer 1: TCEQ described the epidemiology quite nicely (although it would be helpful if summary information is made available (as attached). The use of 4 studies, rather than just one, is reasonable and more scientifically appropriate.

Reviewer 2: Adequate information and discussion is supplied to justify the use of these four studies to provide estimates of arsenic exposures and the associated lung or respiratory cancer risks.

Reviewer 3: In the era in which these studies were done it is possible that only total arsenic was measured in urine. Dietary arsenic particularly from seafood (e. g. arsenobetaine) can confound the available human urinary data. Nowadays arsenobetaine and other arsenicals would probably be separated quantified so the inhaled inorganic arsenic could be better estimated.

Reviewer 4: It is not clear to me why Enterline et al. (1987b) was excluded from this analysis. I do not have the original but the abstract indicates that the authors had data on smoking and quantitative exposure estimates.

I do not believe the study by Jones et al. should be included. The only exposure metric which shows an effect is one which is 'weighted' by age and time since first exposure, which seems rather arbitrary; the implication is that there is some kind of interaction (effect modification) with age and time since first exposure, which is not well defined in what is presented (also the text notes that risk decreased with time since exposure, a strange phenomenon for a cancer with latency). In addition there are co-exposures which may act as confounders (there is some evidence that lead, for example, is a lung carcinogen), and there are no exposure data for exposures before 1972, introducing uncertainty.

- **Were the statistical and modeling approaches used for calculating URFs appropriate?**

Reviewer 1: Although this is not my area of expertise, the statistical and modeling approaches seem reasonable.

Reviewer 2: Statistical and modeling approaches were appropriate for calculating URFs from individual studies and for obtaining a weighted average (central estimate) URF from the four studies. As discussed above in the answer to the first charge question, an upper bound estimate for the weighted average URF was not derived and needs to be added.

Reviewer 3: NA

Reviewer 4: The use of an excess relative risk model (ERR), or multiplicative linear RR model, seems appropriate but it is not clear why it is not consistently tested against the common log linear model (also referred to in the text as a linear-exponential model), where the log RR is a linear function of exposure. It is noted for 2 of the 4 studies that the log linear model was fit, but no data are given on which model fits better, nor was the log RR model apparently fit for 2 other studies. While the log RR model is not strictly linear in the low dose region, it is close to linear, and this can be dealt with by using a point of departure. For example on page 31 it is said

only that the beta for the linear-exponential model was lower and therefore more conservative, not which model fit better. By this argument one would always choose the model with the highest beta regardless of how well the model fit.

A second question regarding modeling is why only models linear in exposure are used. For data where risk attenuates at higher exposures a two piece linear model is a nice alternative for example. Granted only summary data (with a few categorical points) are available, limiting model possibilities, but nonetheless it might be possible to try other models (square root transformation, two piece linear, etc). A simple graph of the categorical points might help the reader be more convinced that a linear model is a good one.

Adjusting for time at hire, as is done in 2/4 studies, seems questionable to me for two reasons. First, I can't see any data to indicate the time since hire is significantly associated with outcome (is the coefficient significant, is it a potential confounder?), although I suspect it is, as lung cancer rates have changed over time. Second, time at hire may often serve as a surrogate for exposure and hence should not be controlled a priori. Time at hire may be associated with lung cancer rates because of changing smoking rates over time, but the use of an intercept term to adjust background rates is supposedly capturing differences between working cohorts and general population referent groups (see below).

There seems to be some problem in the modeling of differences between background referent rates and cohort rates independent of an exposure effect, for example in the estimation of 'alpha'. We know that smoking differences between working cohorts and external referents can produce SMRs between 1.1 and 1.4, with the more common situation being about 1.2. Other factors which might drive up cohort rates would be use of inappropriate national rates rather than state or local rates which might be higher, although such differences are usually not great, on the order also of 20%. (no data are given on what referent rates are used in these studies). Yet here we find 'alphas' of 1.5-2.5 in Tables 8 and 14, much higher than can be explained by smoking differences (no 'alphas' are presented for Montana cohort analyzed by Lubin et all; why - it would appear to be small or even negative as per data in Table 10? The alpha for the Jones et al cohort is a more reasonable 1.2-1.3. These estimates of alpha are likely driven by the lowest exposure category, which have high SMRs in the Tacoma and Swedish cohorts (see Tables 7 and 13, SMRs of 1.54 and 2.71, compared to SMRs of 0.84 and 1.25 for Montana and English cohorts).

The use of these high (and ostensibly implausible) 'alphas' for two cohorts biases exposure-response coefficients downward, I believe. I can think of two possible solutions. First, use a priori an alpha of 1.2 (based on known likely effects of confounding by smoking) and perhaps take a Bayesian approach where this is an a priori parameter with a distribution. Second, and the course I recommend, is to do a meta-analysis rather than analyze each study separately. This will provide a different a more reasonable estimated 'alpha', given that the Montana (Lubin et al.) study is the largest study and likely has the lowest alpha.

In general I believe a meta-analysis would be preferable to the current approach. Note the meta-analysis done by Crump et al. (2003) in a similar analysis of SMR data for dioxin studies, which incidentally estimated alpha as 1.17. Instead of weighting the individual slopes at the end, instead one estimates a common slope in the meta-analysis, potentially avoiding the problem of the aberrant alphas. Of course one would also be able to test heterogeneity in the different slopes of each study, and various functional forms besides linear, with potentially more power due to more data.

While there appears to be some smoking data in at least two studies (Lubin et al, Jarup et al), it is not used. Further discussion of the data on this key potential confounder should be provided. Why did Welch et al. and Higgins et al. in the early 1980s conclude that smoking was not likely to be a confounder in the Montana cohort? In the Jarup et al. data it is said there is an interaction between arsenic and smoking. Generally such interactions are hard to ascertain and usually non-significant due to the rarity of lung cancer among non smokers. On the other hand, smoking (as noted above) is often a confounder between worker and general populations, as workers smoke more. If data were available on smoking rates in the exposed and referent populations, even if not known for the entire cohort, an adjustment to the SMRs can be made (eg, Steenland and Greenland AJE 2006).

Minor points. Page 20 the author should explain the difference between added risk and extra risk (perhaps the latter is (R1-R0)/R0?). P 22. "supports the good fit of the Enterline data"? I narrow confidence intervals says the exposure term is important and well estimated, but says little about how well that particular model fits the data, compared to other possible models. I would modify this language. Same language is used elsewhere, a on p 38 for example for the Jarup et al. data.

- **Was the dose metric selected (mg/m^3-years) the most relevant and appropriate choice?**

Reviewer 1: TCEQ made the correct choice for arsenic's dose metric, especially since several of the studies only list the chosen dose metric in this fashion.

Reviewer 2: For the exposure data available from past airborne exposures of arsenic to workers, the dose metric (mg/m^3-years) is relevant and appropriate.

Reviewer 3: NA

Reviewer 4: Yes. However, Jarup et al found an effect of exposure intensity but not duration. Some further explanation should be provided why Texas should calculate an exposure-response using cumulative exposure. Ie, it is the metric used in the other studies and it is significantly related to lung cancer, presumably because it is correlated with average intensity.

- **Is use of total arsenic for the four studies justified given the purpose of the URF and carcinogenic ESL?**

  Reviewer 1: TCEQ made the correct choice of total arsenic for its carcinogenic form, especially since multiple arsenic forms are likely the basis of the epidemiology exposures and arsenic, per se and not its multiple forms, is listed as a known human carcinogen. Although I did not see any arsenic form-specific data, such data, if available, might allow another designation.

  Reviewer 2: The discussions in the DSD support the use of total arsenic exposure for calculation of the URF and carcinogenic ESL.

  Reviewer 3: NA

  Reviewer 4: Yes.

- **Are the most appropriate URFs from each study used to calculate the final URF?**

  Reviewer 1: TCEQ appeared to make the correct choice URFs from each study. However, in at least one study, the slopes are different among concentrations over time. For example, see Lubin et al. (2008) Figure 1 (page 31 of appendices). If this is true of other epidemiology studies, why should TCEQ settle for one slope per study? Alternatively, why not pick the slope associated with the lowest concentration, since this is the one most likely to be appropriate for low dose extrapolation?

  Reviewer 2: Considerable effort was devoted to calculating various URFs for the studies. It appears that appropriate URFs were selected for the four studies.

  Reviewer 3: NA

  Reviewer 4: I don't think the correct slope factor (beta) was used for the Lubin study. Lubin et al. found an interaction with, or effect modification by concentration, the beta for cumulative exposure being much higher for higher average exposures. Since the environmental exposures of interest to Texas are clearly in this low range, it would seem appropriate to use the coefficient for the low average exposure group.

- **Is use of the central estimate URFs appropriate? Does the DSD provide adequate support for the decision to use the central estimate URFs?**

  Reviewer 1: TCEQ made the correct selection of the central estimate in order to average the URLs of multiple studies. Other approaches for averaging are not scientifically reasonable.

Reviewer 2: In order to obtain an unbiased central estimate of the overall mean URF, unbiased central estimates of the individual URFs from the four studies must be used, as was done by the TCEQ in the DSD, in calculating the weighted average. As was discussed above in the response to the first charge question, since the TCEQ guidelines to develop ESLs specify that an upper bound for the URF is to be used, it is then necessary to perform a second step to derive an upper bound estimate of the URF. This second step was not performed in the DSD and needs to be added before a proper ESL can be derived, as discussed above in response to the first charge question.

Reviewer 3: NA

Reviewer 4: I have worked on EPA risk assessments where the standard procedure was to use the upper confidence limit (90%) of the beta to derive the level which corresponds to a 1 in 100,000 extra risk. Here the beta itself is used, I am not sure why.

- **Was cancer endpoint selected as the basis of the potency estimates (lung cancer) the most appropriate and relevant choice?**

  Reviewer 1: Absolutely. It is not surprising that the lung is affected first after inhalation exposures due to one of more MOAs at the portal of entry. This is a common occurrence with many inhaled toxicants. Arsenic is not exceptional in this regards.

  Reviewer 2: Lung cancer appears to be an appropriate and relevant choice.

  Reviewer 3: NA

  Reviewer 4: Yes.

- **Are respiratory cancer data from Enterline et al (1995) and Lubin et al (2000; 2008) a reasonable surrogate for lung cancer for reasons discussed in the DSD?**

  Reviewer 1: TCEQ discussion here was convincing. I agree with it.

  Reviewer 2: Outside my area of expertise. The data seem to support the use of respiratory cancer.

  Reviewer 3: NA

  Reviewer 4: Yes.

- **Are lung cancer incidence and mortality sufficiently similar as to be comparable for purposes of this assessment for reasons discussed in the DSD?**

Reviewer 1: TCEQ discussion here was also convincing. I also agree with it.

Reviewer 2: The data indicate adequate similarity of lung cancer incidence and mortality.

Reviewer 3: NA

Reviewer 4: Yes.

- **Is the URF weighting procedure used to calculate the final URF reasonable and justified?**

Reviewer 1: Each of the available epidemiology studies has one or more complications, making reliance on any one study more susceptible to critique. Often it is the case that one study is clearly superior. However, in this case, the available studies are all reasonably close in results and in conduct. Thus, TCEQ made a logical and scientifically defensible choice in their weighting system. I wish more groups would do this.

Reviewer 2: Use of person-years to provide weights for the four studies is reasonable. As discussed above, an upper bound estimate for the URF is required by the TCEQ ESL guidelines.

An alternative weighting procedure based on the standard errors of the individual URFs takes into account the both the person-years and the spacing of measures of exposures in estimating the slopes (URFs) of the exposure-responses for each of the four studies. The best unbiased estimate of the URF, i.e., the weighting procedure that minimizes the standard error of the weighted average estimate, is to weight each individual central URF by the reciprocal of its variance, where variance it the square of its standard error. This best linear unbiased estimate weighting scheme that produces the smallest standard error for a weighted average estimate is discussed in many basic applied statistics texts.

From the results presented in the DSD, the best linear unbiased estimate of the Central URF based on weights of the reciprocals of the squares of the URFs standard errors is: weighted Central URF = 1.51E-04 per $\mu g/m^3$. Using the procedure to estimate the standard error of the weighted average as described in the response to the first charge question, for this best estimate of the Central URF the standard error = 0.345 $\mu g/m^3$.

The upper bound estimate for the URF = 1.51E-04 + (1.645 x 0.345E-04) = 2.08E-04 $\mu g/m^3$. For an upper bound lifetime cancer risk of 10^{-5}, based on the best weighting scheme, the

$$ESL = 10^{-5} / 2.08E\text{-}04 = 0.048\ \mu g/m^3.$$

It is coincidental that this equals the value that was incorrectly derived by the TCEQ in the DSD.

Reviewer 3: NA

Reviewer 4: It would seem, if the betas are to be combined via weighting, that one would weight them by the inverse of their variance rather than the person years in the study, as per page 52 (although this should give similar results). However, as noted above, I believe a meta-analysis is the preferred way to approach these data.

- **Is the decision not to apply age-dependent adjustment factors (ADAFs) to the URF to account for potential increased sensitivity of children justified and properly considered?**

Reviewer 1: I am quite comfortable with TCEQ's decision. Arsenic does not appear to be causing tumors exclusively by a genotoxic MOA, which is one of the criteria for ADAF use in EPA's 2005 guidelines. In fact, the overall tumor endpoint might exhibit a threshold as TCEQ notes in its MOA section. Furthermore, studies of populations including several generations, such as in Taiwan indicate that adverse effects occur late in life, not in childhood, suggesting that arsenic is affecting late stages of the carcinogenic process. In such cases children are not more at risk than adults.

Reviewer 2: It is agreed that an ADAF for children is not needed.

Reviewer 3: TCEQ stated "Arsenic has not been identified by USEPA as having a mutagenic MOA (USEPA 2005b), and data are not sufficient to determine the carcinogenic MOA." However, Arsenic is usually thought of as being highly clastogenic, but to have low or zero inherent mutagenicity. In 32-P post labeling experiments done at the US EPA (unpublished), arsenic does not incorporate into DNA. However arsenic is "genotoxic" in many assays systems even if the word mutagenic does not apply to it very well.

There is GREAT evidence (not just some) indicating transplacental arsenic carcinogenesis in mice exposed to 85 ppm arsenite in their drinking water. For a mouse 85 ppm arsenite is NOT A HIGH DOSE, because mice can methylate and excrete arsenic at amazing rates. Humans cannot do this. Mice can be exposed to 250 ppm arsenite in their drinking water and not show many biological changes. No mice died in a 30 day drinking water exposure to arsenite at 250 ppm (Chilakapati and Kitchin, unpublished results except in SOT abstract form).

Reviewer 4: Yes.

- **Does the uncertainty section adequately discuss main areas of uncertainty in the development of the URF?**

  Reviewer 1: The overall uncertainties associated with the specific TCEQ analysis seem well described. However, the authors should note that EPA (2005) cancer guidelines (page 3-22) state:

  > "If there are multiple modes of action at a single tumor site, one linear and another nonlinear, then both approaches are used to decouple and consider the respective contributions of each mode of action in different dose ranges. For example, an agent can act predominantly through cytotoxicity at high doses and through mutagenicity at lower doses where cytotoxicity does not occur."

  Thus, TCEQ is not limited to the consideration of only one MOA and may elect to consider different MOAs at different parts of the dose response curve. An example of this for acrylamide is found in Dourson M., Hertzberg, R., Allen, B., Haber, L., Parker, A., Kroner, O., Maier, A. and Kohrman, M. 2008. Evidence-Based Dose Response Assessment for Thyroid Tumorigenesis from Acrylamide. Regulatory Toxicology and Pharmacology 52 (2008) 264–289.

  In addition, perhaps I am confused but I was perplexed by the authors citing older EPA (1984) text on MOA (page 10). EPA (2005) would let TCEQ approach the dose response assessment in several ways, including linear, or linear with an upper bound determined by a threshold. I can step TCEQ through the latter approach if this is desired. Or you could refer to EPA (1998) where this is described for thyroid tumors. See: EPA. 1998. ASSESSMENT OF THYROID FOLLICULAR CELL TUMORS. EPA/630/R-97/002. March.

  Furthermore, the differences in the URFs calculated by the TCEQ and USEPA (1986) were shown on page 23 and elsewhere. It would be helpful if TCEQ put an approximately quantitative value on these differences, especially since the values are so very far apart. I would be especially interested in the last difference, "the use of 2005 Texas-specific lung cancer mortality rates and survival probabilities compared to USEPA (1984) use of US 1976 lung cancer mortality rates and survival probabilities," since other folks might want to use more generalized data, or data from their location.

  Finally, I attach a slightly annotated text that has a few questions in the margin (some of which I describe in these comments). Please feel free to use these as needed.

  Reviewer 2: As discussed above, the DSD fails to consider the uncertainty in the URF as measured by an upper bound on the URF.

  Reviewer 3: NA

Reviewer 4: It would seem that the section on exposure measurement error could be expanded. This is probably the main source of uncertainty in estimating the exposure-response. For example Lubin assumed a protective factor due to personal protective equipment, only for the high exposed, and multiplied their exposures by 0.1. This would seem to introduce huge uncertainty.

Appendix A: Example of Summary Language for Quantitative Estimates

Summary text for epidemiology studies used to develop URFs

Enterline et al. 1995: The Asarco smelter in Tacoma, Washington

- Respiratory cancer mortality (lung, bronchus, trachea, etc.)
- Slope parameter estimates (β)
    - Fitted equation indicates a curvilinear response:

$$SMR = 100 + 10.5\ (\text{cumulative response})^{0.279}$$

        - The intercept (100) was set, not calculated, for persons with 0 cumulative exposure since background is expected to be an SMR of 1 (or 1 x 100 for this study) – This could drive some of the curvilinearity. Lubin et al. (2000) also suggest Enterline's use of a power model is driving the curvilinear response.
        - Viren and Silvers (1999) extended the Enterline analysis with updated results. They used 3 multiplicative and 3 additive models to assess non-linearity (nonlinear, linear with set intercept, and linear without set intercept)
            - The nonlinear model "fit" the data approximately as well as the linear model without a set intercept, but due to extra uncertainties (due to addition of parameters) in the curvilinear model, the AIC values indicate that the linear (without a set intercept) model is more appropriate for this data.
            - Curvilinearity was evident only among workers hired prior to 1940, and probably because of the artifactually low lung cancer mortality rates observed in those workers.
            - The linear model with a SET intercept at and SMR of 1 (aka 100) did not fit the data. This indicates that the cohort of workers, even at 0 cumulative years of exposure, may have an increased baseline of risk
    - TCEQ determined that the slope estimate derived by this study (Enterline et al. 1995) is not appropriate for use and instead suggest a variation of the 2-parameter multiplicative linear model (the linear model without a set slope): Expected # lung cancer = differences in lung cancer rates X expected # of background lung cancer X (1 + slope X cumulative exposure)

NOTE: There is an adjustment for time of hire, where the above equation is multiplied by 1 for workers hired before 1940 or an "estimate" for workers hired after

Lubin et al. 2000, 2008: Anaconda smelter in Montana

- Respiratory cancer mortality (lung, bronchus, trachea, etc.)
- Lubin et al. 2000 – slope of RR vs Duration of exposure increases with increased exposure (categorized by heavy, medium, and light + unknown). The authors assumed that unknown = lowest exposure is health protective.
    - Fitted model = RR = 1 + β(continuous exposure)^k, where k=1 (a power model converted to a "linear excess relative risk" model)

      (NOTE: They, like Enterline 1995 set the intercept to 1. Verin and Silvers indicate this may not provide the most accurate fit if there is increased background response at 0 mg/m3-year))
    - Additive (absolute excess risk) models provided a worse fit than the linear excess risk model
    - (See Figure 2) Most estimated RRs fall in the 0-25 mg/m3-year range. Only one lies further out at > 150 mg/m3-year. If this point is included, the associated regression line is slightly curvilinear. Removal of this point (aka down-weighting of work areas with heavy exposures, due to the use of protective equipment, for example) results in a much steeper, linear slope. The down-weighted line is more consistent with the data. The authors suggest that the curvilinear relation is driven by overweighting areas of heavy exposure.
- Lubin et al. 2008
    - ERRs for a fixed cumulative exposure are greater when the exposure is from short durations at high concentrations than from long exposures to low concentrations – This indicates that concentrations may be an effect modifier and may need to be controlled for in the model.
    - Fixed model: RR = 1 + β x concentration$^{(\text{effect of concentration on cumulative exposure})}$ x cumulative exposure
        - The authors divided the data into concentration categories, all of which were consistent with linearity. However, estimates of the slope parameter increased with concentration, suggesting effect modification (the test for homogeneity of slope is significant; p = 0.02. The visual fit shows an obvious difference with the lowest

concentration, but less so among higher concentrations. See Fig 1 of Lubin et al. (2008)).

Jarup et al. 1989; Viren and Silvers 1994: Ronnskar Copper Smelter in Sweden

- Lung cancer mortality
- Jarup et al. 1989
  - *NOTE: we were not able to get full copy of this Jarup study.*
  - *Suggest that arsenic concentration influences the outcome more than duration in the combined metric of per years. This is in line with Lubin's idea that concentration is an effect modifier.*
- Viren and Silvers 1994
  - Used summary data from Jarup et al. 1989; used an absolute risk model, but didn't provide enough info. TCEQ took the summary data and calculated their own β estimates using poisson regression and a multiplicative model.
    - Note: the summary data did not provide average concentrations. Viren and Silvers used the midpoint of each range to fit the models
  - Adjusted slope for year of hire when appropriate
  - Results are VERY similar to the Tacoma cohort (Enterline 1995 and Viren and Silvers 1999)

Binks et al. 2005; Jones et al. 2007: UK tin smelter

- Lung cancer mortality
- Jones et al. 2007
  - Results suggested there was no significant association between lung cancer mortality and cumulative exposure to either lead, antimony, arsenic, cadmium, or radioactivity. Cumulative exposures to arsenic, antimony and lead became significant after weighting cumulative exposure by time since exposure and attained age (ERR "diminishes" with increasing time since exposure and attained age)
  - Used poisson regression with weighted average of dose metric to diminish the risk of lung cancer with the time since exposure and age of the worker.

- Used a multiplicative model with an additive intercept where: expected # deaths = expected # of background deaths x (multiplicative factor accounting for differences in background + slope of risk vs. cumulative exposure x cumulative exposure)
    - "The multiplicative factor that accounts for differences in background" just means that they let the model pick the best intercept (or background).

Other details of interest

- TCEQ chose to use a linear multiplicative risk model to obtain MLEs (maximum likelihood estimates) of βs (aka parameter slopes) for the studies without survival data (e.g., Enterline et al. 1995 and Jarup et al. 1989 only provide summary data). TCEQ chose the linear multiplicative model over an additive risk model because assumptions of risk sharply increasing with age are better model with the multiplicative model (which increases background rates of disease multiplicatively rather than additively).
    - In non-math speak: As you age, your risk for cancers increases naturally. This "multiplicative" model captures the steepness of a biologically relevant slope better than an "additive" would use.
- Children may be susceptible due to early-life exposures – if age is an effect modifier, then this could explain why Jones et al. 2007 observed a decrease in mortality rates with increased age of exposure in workers. However, this decrease in mortality could also be associated with a decrease in duration of employment, assuming older workers do not work as long as younger workers.

Appendix B: Reviewer 1 Extra Arsenic References

Bruske-Hohlfeld, I. (2009). "Environmental and occupational risk factors for lung cancer." Methods Mol Biol **472**: 3-23.

Lung cancer is the world's leading cause of cancer death. It is primarily due to the inhalation of carcinogens and highly accessible to prevention by diminishing exposures to lung carcinogens. Most important will be the complete cessation of exposure to cigarette smoke (first and second hand) and to asbestos. Two environmental exposures--radon in homes and arsenic in drinking water--cannot be totally avoided, but people in certain geographical regions would greatly benefit from a reduction in exposure magnitude. And last but not least, workers all over the world deserve that preventive measures at the workplace are observed with regard to exposures, such as arsenic, beryllium, bis-chloromethyl ether (BCME), cadmium, chromium, polycyclic aromatic hydrocarbons (PAHs), and nickel.

d'Errico, A., S. Pasian, et al. (2009). "A case-control study on occupational risk factors for sino-nasal cancer." Occup Environ Med **66**(7): 448-55.

OBJECTIVES: Sino-nasal cancer has been consistently associated with exposure to wood dust, leather dust, nickel and chromium compounds; for other occupational hazards, the findings are somewhat mixed. The aim of this study was to investigate the risk of sino-nasal epithelial cancer (SNEC) by histological type with prior exposure to suspected occupational risk factors and, in particular, those in metalworking. METHODS: Between 1996 and 2000, incident cases were collected on a monthly basis from hospitals throughout the Piedmont region of Italy by the regional Sino-nasal Cancer Registry. A questionnaire on occupational history, completed by 113 cases and 336 hospital controls, was used to assign exposure to occupational hazards. The relationship between SNEC and cumulative exposure to these hazards was explored using unconditional logistic regression to statistically adjust for age, sex, smoking and co-exposures, allowing for a 10-year latency period. RESULTS: The risk of adenocarcinoma was significantly increased with ever-exposure to wood dust (odds ratio; OR = 58.6), and to leather dust (OR = 32.8) and organic solvents (OR = 4.3) after controlling for wood dust, whereas ever-exposure to welding fumes (OR = 3.7) and arsenic (OR = 4.4) significantly increased the risk for squamous cell carcinoma. For each of these hazards, a significant increasing trend in risk across ordered cumulative exposure categories was found and, except for arsenic, a significantly increased risk with ever-exposure at low intensity. Treating cumulative exposure on a continuous scale, a significant effect of textile dusts was also observed for adenocarcinoma. For a mixed group of other histological types, a significant association was found with wood dust and organic solvents. CONCLUSIONS: Some occupational risk factors for SNEC were confirmed, and dose-response relationships were observed for other hazards that merit further investigation. The high risk for adenocarcinoma with low-intensity exposure to wood dust lends support for a reduction in the occupational threshold value.

Fox, M., F. Curriero, et al. "Evaluating the community health legacy of WWI chemical weapons testing." J Community Health **35**(1): 93-103.

Han, Y. H., H. J. Moon, et al. (2009). "The effect of MAPK inhibitors on arsenic trioxide-treated Calu-6 lung cells in relation to cell death, ROS and GSH levels." Anticancer Res **29**(10): 3837-44.

Arsenic trioxide (ATO) can regulate many biological functions such as apoptosis and differentiation. We recently demonstrated that ATO-induced apoptosis in Calu-6 lung cancer cells is correlated with glutathione (GSH) content. Here, the effects of ATO and/or mitogen-activated protein kinase (MAPK) inhibitors on Calu-6 cells were investigated in relation to cell growth, cell death, reactive oxygen species (ROS) and GSH levels. Treatment with ATO inhibited the growth of the Calu-6 cells at 72 hours. ATO induced apoptosis, which was accompanied by the loss of mitochondrial membrane potential (MMP; DeltaPsi(m)). While general nonspecific ROS decreased in the ATO-treated Calu-6 cells, the intracellular superoxide anion (O(2)(-)) level including mitochondrial O(2)(-) increased. ATO also induced GSH depletion in the Calu-6 cells. The treatment with MAP

kinase kinase (MEK), c-Jun N-terminal kinase (JNK) and p38 inhibitors intensified the cell growth inhibition, cell death, MMP (DeltaPsi(m)) loss, and GSH depletion in the ATO-treated Calu-6 cells. In addition, the JNK and p38 inhibitors significantly increased the ROS levels including O(2)(-) in the ATO-treated Calu-6 cells. In conclusion, all the MAPK inhibitors slightly intensify cell death in the ATO-treated Calu-6 cells and the changes of ROS and GSH brought about by ATO and/or MAPK inhibitor treatment partially influence cell growth and death in Calu-6 cells.

Hughes, M. F. (2009). "Arsenic methylation, oxidative stress and cancer--is there a link?" J Natl Cancer Inst **101**(24): 1660-1.

Kaletin, G. I., N. A. Pavlovskaia, et al. (2009). "[Unidirectionality of elemental state disorders in workers contacting arsenic compounds and in oncologic patients]." Med Tr Prom Ekol(10): 7-13.

The authors determined concentrations of 24 elements in hair of workers contacting arsenic high concentrations in workplace air, of individuals suffering from malignancies variable in localization, and of general population residing in places with environmentally high level of arsenic. Individuals with high hair content of arsenic and certain elemental dysbalance (sharp decrease of elements ratio Si/Hg, Zn/Hg, Se/Hg, P/Hg, Ni/Hg and Nb/Hg, if compared to control group) were assigned to high risk group for malignancies development.

Lencinas, A., D. M. Broka, et al. "Arsenic exposure perturbs epithelial-mesenchymal cell transition and gene expression in a collagen gel assay." Toxicol Sci **116**(1): 273-85.

Arsenic is a naturally occurring metalloid and environmental contaminant. Arsenic exposure in drinking water is reported to cause cancer of the liver, kidneys, lung, bladder, and skin as well as birth defects, including neural tube, facial, and vasculogenic defects. The early embryonic period most sensitive to arsenic includes a variety of cellular processes. One key cellular process is epithelial-mesenchymal transition (EMT) where epithelial sheets develop into three-dimensional structures. An embryonic prototype of EMT is found in the atrioventricular (AV) canal of the developing heart, where endothelia differentiate to form heart valves. Effects of arsenic on this cellular process were examined by collagen gel invasion assay (EMT assay) using explanted AV canals from chicken embryo hearts. AV canals treated with 12.5-500 ppb arsenic showed a loss of mesenchyme at 12.5 ppb, and mesenchyme formation was completely inhibited at 500 ppb. Altered gene expression in arsenic-treated explants was investigated by microarray analysis. Genes whose expression was altered consistently at exposure levels of 10, 25, and 100 ppb were identified, and results showed that 25 ppb in vitro was particularly effective. Three hundred and eighty two genes were significantly altered at this exposure level. Cytoscape analysis of the microarray data using the chicken interactome identified four clusters of altered genes based on published relationships and pathways. This analysis identified cytoskeleton and cell adhesion-related genes whose disruption is consistent with an altered ability to undergo EMT. These studies show that EMT is sensitive to arsenic and that an interactome-based approach can be useful in identifying targets.

Parvez, F., Y. Chen, et al. 2010. "A prospective study of respiratory symptoms associated with chronic arsenic exposure in Bangladesh: findings from the Health Effects of Arsenic Longitudinal Study (HEALS)." Thorax 65(6): 528-33.

Background and aims A prospective cohort study was conducted to evaluate the effect of arsenic (As) exposure from drinking water on respiratory symptoms using data from the Health Effects of Arsenic Exposure Longitudinal Study (HEALS), a large prospective cohort study established in Ariahazar, Bangladesh in 2000-2002. A total of 7.31, 9.95 and 2.03% of the 11 746 participants completing 4 years of active follow-up reported having a chronic cough, breathing problem or blood in their sputum, respectively, as assessed by trained physicians. Methods Cox regression models were used to estimate HRs for respiratory symptoms during the

follow-up period in relation to levels of chronic As exposure assessed at baseline, adjusting for age, gender, smoking, body mass index, education and arsenic-related skin lesion status. Results Significant positive associations were found between As exposure and respiratory symptoms. As compared with those with the lowest quintile of water As level (</=7 mug/l), the HRs for having respiratory symptoms were 1.27 (95% CI 1.09 to 1.48), 1.39 (95% CI 1.19 to 1.63), 1.43 (95% CI 1.23 to 1.68) and 1.43 (95% CI 1.22 to 1.68) for the second to fifth quintiles of baseline water As concentrations (7-40, 40-90, 90-178 and >178 mug/l), respectively. Similarly, the corresponding HRs in relation to the second to fifth quintiles of urinary arsenic were 1.10 (95% CI 0.94 to 1.27), 1.11 (95% CI 0.95 to 1.29), 1.29 (95% CI 1.11 to 1.49) and 1.35 (95% CI 1.16 to 1.56), respectively. These associations did not differ appreciably by cigarette smoking status. Conclusions This prospective cohort study found a dose-response relationship between As exposure and clinical symptoms of respiratory diseases in Bangladesh. In particular, these adverse respiratory effects of As were clearly evident in the low to moderate dose range, suggesting that a large proportion of the country's population may be at risk of developing serious lung diseases in the future.

Qu, G. P., Q. Y. Xiu, et al. (2009). "Arsenic trioxide inhibits the growth of human lung cancer cell lines via cell cycle arrest and induction of apoptosis at both normoxia and hypoxia." Toxicol Ind Health **25**(8): 505-15.

Arsenic trioxide (As(2)O(3)) has been established to be an effective agent for treating acute promyleocytic leukemia. Laboratory data suggest that As(2)O(3) induces apoptosis of several solid tumor cells including lung cancer cells. Regions of tissue hypoxia often arise in aggressive solid tumors, and hypoxic tumors exhibit augmented invasiveness and metastatic ability in several malignancies. Furthermore, hypoxia may impair the treatment efficiency; therefore, we studied the cytotoxic effect of As(2)O(3) on human lung adenocarcinoma cell lines A549 and A549/R (resistant to vincristine, adriamycin and mitomycin etc.) grown under normoxic and hypoxic (1% oxygen) conditions. At both normoxia and hypoxia, 5, 10 and 15 microM As(2)O(3) induced evident growth inhibition and apoptosis in A549 cells as well as A549/R cells after 48 hours of exposure. In contrast, the conventional chemotherapeutic drug vincristine showed lowered efficiency in hypoxic A549 cells. As(2)O(3) induced G(2)/M cell cycle arrest in both normoxic and hypoxic A549 cells. As(2)O(3) significantly decreased the messenger RNA (mRNA) levels of Cyclin B(1) and survivin and the protein levels of Cyclin B(1), phospho-CDC(2) (Thr 161) and survivin in both normoxic and hypoxic A549 cells. Together, our findings indicated that As(2)O(3) significantly inhibited the proliferation of lung cancer cells via G(2)/M cell cycle arrest and induction of apoptosis at both normoxia and hypoxia, and the induction of apoptosis was associated with down regulation of survivin.

Rushton, L., S. Bagga, et al. "Occupation and cancer in Britain." Br J Cancer **102**(9): 1428-37.

BACKGROUND: Prioritising control measures for occupationally related cancers should be evidence based. We estimated the current burden of cancer in Britain attributable to past occupational exposures for International Agency for Research on Cancer (IARC) group 1 (established) and 2A (probable) carcinogens. METHODS: We calculated attributable fractions and numbers for cancer mortality and incidence using risk estimates from the literature and national data sources to estimate proportions exposed. RESULTS: 5.3% (8019) cancer deaths were attributable to occupation in 2005 (men, 8.2% (6362); women, 2.3% (1657)). Attributable incidence estimates are 13 679 (4.0%) cancer registrations (men, 10 063 (5.7%); women, 3616 (2.2%)). Occupational attributable fractions are over 2% for mesothelioma, sinonasal, lung, nasopharynx, breast, non-melanoma skin cancer, bladder, oesophagus, soft tissue sarcoma, larynx and stomach cancers. Asbestos, shift work, mineral oils, solar radiation, silica, diesel engine exhaust, coal tars and pitches, occupation as a painter or welder, dioxins, environmental tobacco smoke, radon, tetrachloroethylene, arsenic and strong inorganic mists each contribute 100 or more registrations. Industries and occupations with high cancer registrations

include construction, metal working, personal and household services, mining, land transport, printing/publishing, retail/hotels/restaurants, public administration/defence, farming and several manufacturing sectors. 56% of cancer registrations in men are attributable to work in the construction industry (mainly mesotheliomas, lung, stomach, bladder and non-melanoma skin cancers) and 54% of cancer registrations in women are attributable to shift work (breast cancer). CONCLUSION: This project is the first to quantify in detail the burden of cancer and mortality due to occupation specifically for Britain. It highlights the impact of occupational exposures, together with the occupational circumstances and industrial areas where exposures to carcinogenic agents occurred in the past, on population cancer morbidity and mortality; this can be compared with the impact of other causes of cancer. Risk reduction strategies should focus on those workplaces where such exposures are still occurring.

Sakuma, A. M., E. M. De Capitani, et al. "Arsenic exposure assessment of children living in a lead mining area in Southeastern Brazil." Cad Saude Publica 26(2): 391-8.

Environmental contamination by arsenic compounds in the Ribeira River Valley, Sao Paulo, Brazil has already been observed. Lead mining and refining activities had been carried on since late colonial times and finished recently, at the end of 1995. The source of As in the region is known to be mainly from arsenopirite geological presence in the lead ore. Chronic exposure to arsenic compounds may cause peripheral vascular disorders, hyperpigmentation, hiperkeratosis and cancer of the skin, bladder, lung, liver and other internal organs. The purpose of this study was to assess children exposure to arsenic from environmental sources in the region. Urine samples from children between 7 to 14 years old were collected at the following localities: Cerro Azul (Parana); urban areas of Ribeira (Sao Paulo) and Adrianopolis (Parana); Vila Mota neighborhood (rural area of Adrianopolis) and Serra neighborhood (Iporanga, Sao Paulo), identified as groups 1, 2, 3 and 4, respectively. Group 1 was considered as non-exposed control group. Toxicologically relevant forms of As were determined by atomic absorption spectrometry with hydride generation system. The median values of urine arsenic levels obtained in groups 1, 2, 3 and 4 were respectively: 3.60, 6.30, 6.41 e 8.94 microg/L.

Sorahan, T. "Cadmium, arsenic and lung cancer: the bigger picture." Occup Med (Lond) **60**(3): 236.

Tajima, H., T. Yoshida, et al. "Pulmonary injury and antioxidant response in mice exposed to arsenate and hexavalent chromium and their combination." Toxicology **267**(1-3): 118-24.

Chromated copper arsenate, which is used worldwide as a wood preservative, can adversely affect human health. Accumulating evidence suggests that chromium (Cr) and arsenic (As) can potentially disrupt the redox balance and cause respiratory diseases and cancer in humans. The present study was designed to determine the combined toxic effects of these metals in the lungs and to clarify the specific molecules that are stimulated by combined exposure to both metals. Male C57BL/6J mice were intratracheally instilled with arsenate [As(V)], hexavalent chromium [Cr(VI)], or a combination of both metals. Mice were sacrificed 2 days after treatment to collect bronchoalveolar lavage fluid and lung tissue samples. Inflammation, cytotoxicity, apoptosis, and oxidative stress markers were measured. Our results indicated that administration of Cr(VI) alone or in combination with As(V) induced neutrophil-dominant inflammation as well as phosphorylation of mitogen-activated protein kinases; effects of treatment with As(V) alone were comparatively less potent. By analyzing the production of interleukin-6 and activity of lactate dehydrogenase and caspase, we confirmed that co-treatment intensified pulmonary injury and that it was accompanied by oxidative stress, as confirmed by marked increases in the production of reactive oxygen species, reduced glutathione content, and thioredoxin reductase (TRXRD) activity. Expressed mRNA levels

of heme oxygenase-1, glutamylcysteine ligase, glutathione peroxidase 2, thioredoxin (TRX) 1, and TRXRD1 were also enhanced by co-treatment, whereas treatment with As(V) alone reduced the mRNA expression level of TRX2. Our data suggest that co-treatment with As(V) exacerbated Cr(VI)-induced pulmonary injury and that this effect may be exerted through a disruption in the balance among several antioxidant genes.

Ueda, K., S. Nagai, et al. "Arsenic-induced pericardial and pleural effusion without acute promyelocytic leukemia differentiation syndrome." Leuk Res **34**(1): e25-6.

Walsh, L., A. Tschense, et al. "The influence of radon exposures on lung cancer mortality in German uranium miners, 1946-2003." Radiat Res **173**(1): 79-90.

Extensive uranium extraction took place from 1946 until 1990 at the former Wismut mining company in East Germany. A total of 58,987 male former employees of this company form the largest single uranium miners cohort that has been followed up for causes of mortality occurring from the beginning of 1946 to the end of 2003. The purpose of this study was to investigate and evaluate different forms of models for the radon exposure-related lung cancer mortality risk based on 3,016 lung cancer deaths and 2 million person years. Other exposure covariables such as occupational exposure to external gamma radiation, long-lived radionuclides, arsenic, fine dust and silica dust are available. The standardized mortality ratio for lung cancer is 2.03 (95% CI: 1.96; 2.10). The simple cohort excess relative risk (ERR/WLM) for lung cancer is estimated as 0.0019 (95% CI: 0.0016; 0.0022). The BEIR VI model produced risks similar to those obtained with a selected mathematically continuous ERR model for lung cancer. The continuous model is linear in radon exposure with exponential effect modifiers that depend on the whole range of age at median exposure, time since median exposure, and radon exposure rate. In this model the central estimate of ERR/WLM is 0.0054 (95% CI: 0.0040; 0.0068) for an age at median exposure of 30 years, a time since median exposure of 20 years, and a mean exposure rate of 3 WL. The ERR decreases by 5% for each unit of exposure-rate increase. The ERR decreases by 28% with each decade increase in age at median exposure and also decreases by 51% with each decade increase in time since median exposure. The method of determination of radon exposure (i.e., whether the exposures were estimated or measured) did not play an important role in the determination of the ERR. The other exposure covariables were found to have only minor confounding influences on the ERR/WLM for the finally selected continuous model when included in an additive way.

Wang, F., Y. Shi, et al. "p52-Bcl3 complex promotes cyclin D1 expression in BEAS-2B cells in response to low concentration arsenite." Toxicology **273**(1-3): 12-8.

Arsenic is a well-recognized human carcinogen that causes a number of malignant diseases, including lung cancer. Previous studies have indicated that cyclin D1 is frequently over-expressed in many cancer types. It is also known that arsenite exposure enhances cyclin D1 expression, which involves NF-kappaB activation. However, the mechanism between cyclin D1 and the NF-kappaB pathway has not been well studied. This study was designed to characterize the underlying mechanism of induced cell growth and cyclin D1 expression in response to low concentration sodium arsenic (NaAsO(2)) exposure through the NF-kappaB pathway. Cultured human bronchial epithelial cells, BEAS-2B, were exposed to low concentration sodium arsenite for the indicated durations, and cytotoxicity, gene expression, and protein activity were assessed. To profile the canonical and non-canonical NF-kappaB pathways involved in cell growth and cyclin D1 expression induced by low concentration arsenite, the NF-kappaB-specific inhibitor-phenethyl caffeate (CAPE) and NF-kappaB2 mRNA target sequences were used, and cyclin D1 expression in BEAS-2B cells was assessed. Our results demonstrated that exposure to low concentration arsenite enhanced BEAS-2B cells growth and cyclin D1 mRNA and protein expression. Activation and nuclear localization of p52 and Bcl3 in response to low concentration arsenite indicated that the non-canonical NF-kappaB pathway was involved in arsenite-induced cyclin D1

expression. Moreover, we further demonstrated that p52/Bcl3 complex formation enhanced cyclin D1 expression through the cyclin D1 gene promoter via its kappaB site. The up-regulation of cyclin D1 mediated by the p52-Bcl3 complex in response to low concentration arsenite might be important in assessing the health risk of low concentration arsenite and understanding the mechanisms of the harmful effects of arsenite.

Zhang, H., G. H. Huang, et al. (2009). "Health risks from arsenic-contaminated soil in Flin Flon-Creighton, Canada: integrating geostatistical simulation and dose-response model." Environ Pollut 157(8-9): 2413-20.

Elevated concentrations of arsenic were detected in surface soils adjacent to a smelting complex in northern Canada. We evaluated the cancer risks caused by exposure to arsenic in two communities through combining geostatistical simulation with demographic data and dose-response models in a framework. Distribution of arsenic was first estimated using geostatistical circulant-embedding simulation method. We then evaluated the exposures from inadvertent ingestion, inhalation and dermal contact. Risks of skin cancer and three internal cancers were estimated at both grid scale and census-unit scale using parametric dose-response models. Results indicated that local residents could face non-negligible cancer risks (skin cancer and liver cancer mainly). Uncertainties of risk estimates were discussed from the aspects of arsenic concentrations, exposed population and dose-response model. Reducing uncertainties would require additional soil sampling, epidemic records as well as complementary studies on land use, demographic variation, outdoor activities and bioavailability of arsenic.

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Part B: Report from Follow-Up Conference Call

On August 26, 2010, TERA facilitated a follow-up conference call between the panel and TCEQ. Conference call materials (available at http://www.tera.org/Peer/arseniccarc/index.html), including a focused charge, attached as Appendix B, and the reviewer comments in Part A, were distributed prior to the call; members of the public were allowed to listen to the call. The purpose of this call was to allow TCEQ to ask the panel questions regarding their written comments and to allow the panel members to discuss issues on which there were divergent opinions in the written comments.

1. In general, the panel agreed with the weight of evidence (WOE) classification that TCEQ assigned to arsenic compounds. Please discuss the qualitative descriptions of the weight of animal evidence compared to human evidence that TCEQ used in the overall WOE classification.

One reviewer opened by commenting that the document relies too heavily on the human data when animal data also support the weight of evidence conclusions. This reviewer noted that the human and animal models for arsenic carcinogenicity have more in common than we think. For arsenic, the animal models are good for skin and bladder cancers but are weaker for lung cancers.

The panel members discussed their understanding that animal studies appear to be negative for lung cancer, which would mean that they are not good models for humans, who primarily get lung cancer following exposure. One reviewer explained that the animal studies that observe lung cancer are new and response is weak. Also, these studies are all done with drinking water exposure, not inhalation. Another reviewer also explained that the animals in these studies died before they could develop lung tumors. Another panel member agreed that the animal studies are better models for arsenic carcinogenesis than was originally thought, still believes that the WOE statement should be primarily based on the human data.

The panel reached consensus that they agreed with overall WOE as developed by TCEQ, but recommended that TCEQ add more discussion regarding the support that the animal studies provide to the WOE statement.

2. In general, the panel agreed that using multiple studies is an appropriate

approach for calculating the URFs, and that the epidemiological evidence in Enterline et al (1995), Lubin et al (2000 and 2008), Jarup et al (1989) and Viren and Silvers (1994) was properly characterized. Please comment on which studies are most appropriate for calculating the URFs.

3. Is the epidemiological evidence in the Jones et al. 2007 study appropriate for calculating a URF?

(Note, the panel discussed both questions 2 and 3 together, so the meeting report combines the discussion of these 2 charge questions)

Reviewer 4 began the discussion by indicating that he retracts his written comments regarding Enterline 1987b. On further review, he discovered this study is an earlier version of Enterline 1995.

One reviewer expressed concerns about including the data from Jones et al (2007) study in the calculations for the URF. This reviewer noted that the study was confounded by co-exposure to other carcinogens in work place. In addition, Jones et al (2007) did not find a significant association between lung cancer and arsenic exposure unless the cumulative exposures were weighted according to time since exposure and attained age (described on page 38 of the DSD). Therefore, the reviewer questions the findings of the study. Another reviewer asked whether the data from Jones et al (2007) that is presented in Table 16 (page 47 of the DSD) demonstrate an exposure response relationship. The first reviewer responded that no, weighting by latency does not seem appropriate and that, typically, age is usually addressed as a confounder, not by changing the exposure metric.

TCEQ stated that page 42 of the DSD outlined the approach Jones et al (2007) used for modeling. TCEQ noted that this approach is very similar to weighting of cumulative exposure used by other study authors (for example Lubin and the BIER VI report) in which cumulative exposure is considered to be a function of age and time since exposure. One panel member asked why TCEQ did not do a separate analysis instead of weighting cumulative exposure by age. TCEQ replied that, unfortunately, Jones et al (2007) did not report the observed and expected number of deaths by cumulative exposure, just by weighted cumulative exposure, and they could not go back to original data.

Another reviewer asked TCEQ how they have adjusted the URF to make it comparable with other groups. TCEQ replied that they adjusted program to compute dose using age and time since exposure. The first panel member

explained that, although he needs to look at BIER VI, the coefficients used on p 42 of the DSD look random. The reason for weighting the cumulative exposure by age is not clear; if there is an age effect, the different age groups should just be analyzed separately. Therefore, this reviewer is still not convinced that the Jones et al (2007) study is comparable with others because it appears to be outlier. Therefore, inclusion of Jones et al (2007) is still questionable. Other reviewers agreed that Jones appears to be an outlier. TCEQ noted that Jones et al (2007) has 35,000 person years, which is the smallest number of person-years of all of the studies used to generate the URF; so will carry less weight overall compared with the other studies.

A different panel member stated that, in any epidemiological evaluation of inhalation risk, there is a high degree of uncertainty so it is better to be inclusive rather than exclusive. By including more studies it enables risk assessors to look for commonality and maybe do a meta-analysis or meta-interpretation. Other reviewers agree that use of multiple studies is an appropriate approach that addresses more of the uncertainties. A different reviewer agreed with the concept of using multiple studies, but questioned how Jones et al (2007) derived their slope. This reviewer indicated that it appears as if they adjusted the dose metric till they got a dose-response because there is no dose-response without adjustment for age and time.

The Chair noted that the panel might not be able to reach consensus on the utility of the Jones et al (2007) until the panel does more work to understand the weighting adjustments conducted by Jones et al (2007). Therefore, a panel member agreed to review Jones et al (2007) as well as the BIER VI report and Lubin et al. (2000, 2008) to understand why the adjustment was done. After further evaluation of the Jones et al (2007) study

The panel reach consensus that Enterline et al (1995), Lubin et al (2000 and 2008), Jarup et al (1989) and Viren and Silvers (1994) are all appropriate to use in calculating the URF and are all properly characterized. The panel agreed that using multiple studies provides a better characterization of the data than any single study. However, the panel agreed that, in order for this dose response to be believable, TCEQ needs to explain the weighting approach more completely. The panel decided to postpone a recommendation regarding the Jones et al (2007) study until the additional review was completed.

4. Please discuss alternative statistical and modeling approaches that could be used and the dose-response modeling characteristics that warrant such alternative approaches along with any MOA justification.

The reviewers noted that since the MOA for arsenic is unclear, the issue of linearity vs nonlinearity for dose response is an ongoing issue; there is evidence both for and against linearity as the low-dose extrapolation assumption. The evidence supporting linearity includes clastogenicity and strand breaks. Following inhalation exposure, there is evidence for cytotoxicity, which supports nonlinearity. In addition, the epidemiology studies support nonlinearity; however, the epidemiology studies have significant error away from the center tendencies of the dose-response line. Therefore, while there is a slightly better fit for non-linear model, a linear model also fits pretty well.

One reviewer mentioned decisions made by other risk assessment agencies. For example, RIVM considered arsenic to be a threshold carcinogen. This reviewer also consulted with a genetic toxicologist from FDA who indicated that arsenic is mutagenic, so it is not realistic to eliminate the mutagenic component of the MOA. However, the shape of mutation dose response curve over entire dose range is not linear.

One reviewer suggested that a better, alternate approach would be to combine the data from all four of the critical studies, and model them all together. This approach would allow TCEQ to look at potential attenuation of the dose-response slope at higher exposures, because there are insufficient data to conduct this analysis for each separate study. This approach also addresses problems with estimation of background rate, or "alpha", for each separate study.

The reviewers discussed the shape of the dose response curve in the epidemiology studies. One reviewer explained that the curve has a high slope at lower exposures but flattens out at higher exposures. This dose response curve is typical for occupational studies and could be due misclassification of high exposures, or loss of subjects, for example. Another reviewer observed that the Lubin study seems to have different slopes based on concentration/exposure, and asked if this observation was related to the process just mentioned for occupational studies. The first reviewer explained that the effect observed in the Lubin study is more related to dose rate, rather than cumulative exposure, which is a combination of duration and average intensity. The Lubin paper separates those components and sees an effect of duration vs intensity. This is interesting, but not directly relevant to risk assessment.

One reviewer stated that he did not recommend any alternative approaches to the dose-response modeling; he was satisfied with the approach TCEQ used. This reviewer noted that there are dozens of models that could be used, which might change the URF estimate 10-20%. Practically, using different models will not result in a significantly different URF value. In risk assessment, our concern is about low dose exposures to general population. Arsenic exposure to the general population is probably down in the linear part of the dose response curve, so using a low dose linear approach is probably reasonable. Other reviewers agreed, noting that we do not have data on the MOA for arsenic in general, much less on the specific MOA that might be relevant in different dose ranges. Therefore, the best choice in face of uncertainty is to be linear.

The panel then discussed using a meta analytic approach. One reviewer commented that a single analysis of combined data points from all studies will give a better answer. Another reviewer indicated that he was comfortable with the approach that TCEQ used, but could also agree with the suggestion to do a meta analysis. In this case, the reviewer suggested weighting by variance rather than person-years (see additional discussion on this issue below for #9). This reviewer also noted that, since the weighted approach used by TCEQ is a form of meta analysis, conducting a meta analysis would not result in a significantly different value for the URF.

TCEQ asked about approaches for dealing with problems that arise when trying to combine data points from different studies including different dose metrics, populations from different countries with different expected responses, and different background rates. The panel explained that treatment of these issues should be no different than what TCEQ did for combining the URFs at the end anyway. In addition, one reviewer explained that, as demonstrated by the Crump 2003 analysis of dioxin, doing a meta analysis reveals more about the shape of dose-response curve, provides more power than analyzing each study separately.

In summary, the panel agreed that a linear approach is appropriate given the lack of information on MOA. The panel suggested that TCEQ consider conducting meta analysis to improve the quantitative estimate if it can be done for minimal effort. However, the panel suggested that a meta analysis should be presented in addition to TCEQ's existing analysis, but should not replace what has been done already.

5. Please discuss the rationale for making restrictions (i.e., fixing the background hazard rates for unexposed workers) to dose-response models.

TCEQ opened this discussion by referring reviewers to the supplemental information/graphs that were provided before the conference call and explaining that the intercepts all vary and are not all at 1. Therefore, TCEQ would like the panel's recommendation on whether those graphs should have all been done with the intercept fixed at the same number. If so, what should that number be?

One reviewer noted that the alphas represent the difference between the workers with low or no levels of exposure and the background population used for referent rates. Typically the exposed population is composed of workers in one or more plants, while the referent population is the national population, composed of workers and non-workers. These differences are very unlikely to be large, almost certainly less than 1.5, because lung cancer rates do not differ markedly between local populations and national populations within the same country, and because smoking differences between workers and the national population have been shown to typically result in rate ratios of 1.1.-1.3. Therefore, an intercept of 2 does not make sense. Conducting a meta analysis, would result in a common alpha and address this issue. However, another reviewer disagreed noting that even if doing a meta analysis, it would be more appropriate to use four separate alphas than to force the data into a common alpha. Finally, another reviewer suggested that if TCEQ does conduct a meta analysis, they should use both approaches and discuss any differences that are observed.

A different reviewer suggested another approach for fixing the background rate - rather than selecting an "average" for alpha, TCEQ could define criteria for alpha and adjust the intercept from a study only if the alpha from that study is outside the acceptable range. The panel agreed with this recommendation, noting, however, that practically, this will not make much difference in actual final value.

6. Please discuss how should a meta-analysis that combines the data before modeling can reflect heterogeneity in data sets due to different epidemiological settings, differences in co-exposures, differences in dose characterization, differences in dose-metric, differences in follow up.

One panel member suggested that using variables in the regression model could help address these questions. However, this reviewer also noted that TCEQ is already combining four sets of data without addressing these issues, so combining

the data sets first should not cause any additional concern for these issues. TCEQ explained that if they combined all of the points, such an analysis would be criticized for not looking at the differences between the studies. However, TCEQ scientists also noted the utility of doing this as a sensitivity analysis.

The panel recommended that TCEQ conduct a simple meta analysis first, and noted that some of these issues have already been addressed in the process of combining URFs from these studies.

7. Please discuss TCEQ's choice of slope (beta) from the Lubin (2008) study that was used to calculate the final URF and suggest alternate approaches.

Generally, the panel agreed that the approach and the URF value rounded to 2.2E-4 per $\mu g/m^3$ used by TCEQ was reasonable, because the value was not inconsistent with other studies and it was develop as an average among different dose groups. As a caveat, one panel member stated that since Lubin (2008) shows that the slope in the low dose group is clearly different, then perhaps combining slopes from different doses is not appropriate, especially since it is the slope in the low dose region that is of interest.

However, the panel did not recommend that TCEQ take a different approach.

8. In general, the panel suggested that TCEQ should present an upper bound estimate in addition to the central estimate of URFs. Please discuss the importance of and approaches for calculating the upper bound estimate.

The panel started this discussion by noting that, in general, risk assessment always includes an upper limit. In addition both the TCEQ and EPA guidelines require an upper bound. One reviewer did observe that there are occasions when EPA has used a best estimate instead of an upper bound. In fact, the arsenic assessment on IRIS used the best estimate rather than upper bound. This reviewer indicated that the EPA guidelines indicate that "generally" use of the upper bound is recommended, but EPA has often used a best estimate when the risk value is based on human data. This reviewer also noted that the TCEQ guidelines mention EPA guidelines and allow for the possibility of a best estimate when the URF is based on human epidemiology data. This reviewer observed

that the ESL guidelines have a list of analysis points to guide the decision on when to use the best estimate compared to the upper bound; this reviewer asked TCEQ if it conducted this analysis before determining that it was appropriate to use the MLE. TCEQ indicated that they did conduct the analysis, but they did not include it in the DSD. They indicated that they will add this discussion and will also add an upper bound value for a comparison.

There was some discussion regarding whether the central estimate is a conservative value. One reviewer noted that, although the four critical studies are good quality, the upper bound value is still 50% higher than MLE estimate and that should not be ignored. In addition, use of the upper bound value helps to address statistical variation, which is present regardless of study quality.

Therefore, while the panel all agreed that TCEQ should include upper bound estimate calculations in the DSD, two panel members felt strongly that the upper bound value should be the basis of the regulatory value.

9. Please discuss alternate approaches for the weighting procedure used to calculate the final URF.

One reviewer began the discussion by stating that the best statistical weight is the inverse of the variance of the risk factor estimate. Making this change in weighting procedure would result in approximately a 50% change in the UCL and tighter confidence intervals, but the URF would remain the same. This reviewer also emphasized that this weighting procedure does not provide much weight to Jones et al. (2007), incorporates person-years, and results in the statistic with the lowest upper bound. Another panelist requested clarification on evaluating the weighting system and directed the other reviewers to look at Table 19, on page 51, of the TCEQ report. The first panelist confirmed that a study with a smaller difference between its UCL and MLE will have a greater weight.

TCEQ asked if using both variance and person-years to weight the studies would result in a more robust weighting scheme. One reviewer stated that it may not be possible to weight both simultaneously. Another reviewer re-emphasized that the inverse variance weighting procedure is the standard and also incorporates person-years. All reviewers agreed that, although there are exceptions, weighting by the standard of inverse variance is the best option in this case. All panelists agreed that weighting by both person-years and variance would not improve the document.

The panel reached consensus that TCEQ should weight their studies by the

inverse of study variance, since the measurement is more standard and is appropriate for this dataset. They determined that no additional weighting approaches were necessary.

10. Please discuss additional areas of uncertainty that should be included in the document.

One reviewer suggested that, in the uncertainty discussion, TCEQ should address uncertainty in exposure measurement more completely. Another reviewer suggested that TCEQ expand the comparison of its URF with EPA's value cancer assessment. Specifically, this reviewer suggested that TCEQ should add specific discussion on the approaches that TCEQ used that differ from EPA's approach and describe the quantitative effect these different approaches have.

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Appendix A - Peer Review Charge

Scientific Peer-Review of the
Carcinogenic Sections of the Arsenic Development Support Document
Charge to Peer Reviewers

The Toxicology Division of the Chief Engineer's Office, Texas Commission on Environmental Quality (TCEQ) has prepared a draft Development Support Document (DSD) that outlines the hazard assessment and dose-response processes used to derive a Unit Risk Factor (URF) and carcinogenic-based Effects Screening Levels (ESL) for arsenic. The toxicity values were developed using RG-442 *Guidelines to Develop Effects Screening Levels, Reference Values, and Unit Risk Factors* (TCEQ 2006). ESLs are chemical-specific air concentrations set to protect human health and welfare. Short-term ESLs are based on data concerning acute health effects, odor potential, and vegetative effects, while long-term ESLs are generally based on data concerning chronic noncarcinogenic and/or carcinogenic health effects. ESLs are used in the evaluation of air permit applications as well as proposed rules and regulation (e.g. Permits by Rule). ReVs and URFs, used as the basis of ESLs, are used in the evaluation of air monitoring data and in the development of Protective Concentration Levels for remediation sites.

The toxicity values will be used to evaluate emissions from facilities during the air permit review process, for evaluation of ambient air monitoring data, and as toxicity factors in the Texas Risk Reduction Program remediation program. Because the arsenic concentrations in air from these processes are measured as total arsenic, not as individual arsenic species, the cancer ESL derived for arsenic must be health protective for total arsenic without being overly conservative.

We are asking you to provide a review of the scientific approaches used by TCEQ in developing the toxicity values that are described in this draft document. The DSD is a summary document and does not provide a detailed description of every aspect of the toxicity assessment for a chemical. References to appropriate papers or documents are provided if more detailed information is needed. TCEQ relies on toxicity assessments conducted by other federal, state, and international agencies that have undergone a peer-review process as a starting point in their toxicity assessments, because of time and resource constraints. However, TCEQ obtains copies of key studies and supporting studies and critically reviews these studies. The toxicity assessments conducted by others are critically reviewed.

There are a number of policy decisions the TCEQ has made and included in this assessment that the agency does not seek comment on. These risk management goals were approved by the Commissioners and Executive Director of the TCEQ and are consistent with other TCEQ programs. ESLs developed in accordance with these no significant risk levels are intended to prevent adverse effects potentially associated with cumulative and aggregate exposures as defined in Section 1.2 of RG-442 ESL Guidelines (TCEQ 2006). Therefore, please do not spend your time commenting on the following policy decisions:

- The use of a target excess cancer risk level of 1 in 100,000 (1E-05) for the arsenic carcinogenic-based ESL.
- Assumption of a lifetime exposure of 70 years.

General Issues

Please consider all aspects of Section 4.2, Carcinogenic Potential, of the DSD and evaluate strengths and weaknesses of the procedures used to develop the URF and chronic ESL for cancer, based on the specific questions described below. Where possible, try to put the strengths and weaknesses in perspective by indicating their relative magnitude. Please try to avoid emphasizing minor technical details or making tutorial comments. Reviewers should identify scientific uncertainties and suggest ways to reduce or eliminate those uncertainties.

- Were procedures outlined in the ESL Guidelines followed by the TCEQ to perform arsenic's carcinogenic toxicity assessment? If references to accepted procedures in federal, state, or other appropriate guidance documents were made in the ESL Guidelines, were those accepted procedures followed?
- Does the arsenic DSD clearly describe the approaches used by TCEQ to perform the toxicity assessment (i.e., hazard identification and dose-response assessment)?
- Please identify any relevant studies or data that have not been cited. Explain how they may impact the assessment.

Cancer Weight of Evidence and Unit Risk Factor (URF)

The arsenic DSD describes the approaches used to evaluate carcinogenicity and derive the URF and chronic ESL for cancer. Please review the key decisions made by TCEQ in deriving these values. For each decision, please comment on the consistency of the decision with TCEQ's ESL guidelines, the scientific appropriateness of the decision, and any additional approaches or additional information that would improve that decision. The key decisions and some specific issues to consider are listed below. Please discuss other issues specific to developing URFs for carcinogenic effects that have not been adequately addressed in the document.

- Was the proper weight of evidence (WOE) classification, using the USEPA (2005) guidelines for carcinogen risk assessment, given to arsenic compounds? If not, what WOE classification should be given to arsenic compounds, specifically inorganic arsenic?

- Is the epidemiological evidence in Enterline et al (1995), Lubin et al (2000 and 2008), Jarup et al (1989) and Viren and Silvers (1994) properly used in the characterization of chronic cancer risks? Is use of these four studies for calculating URFs justified?

- Were the statistical and modeling approaches used for calculating URFs appropriate?

- Was the dose metric selected (mg/m^3-years) the most relevant and appropriate choice?
- Is use of total arsenic for the four studies justified given the purpose of the URF and carcinogenic ESL?
- Are the most appropriate URFs from each study used to calculate the final URF?
- Is use of the central estimate URFs appropriate? Does the DSD provide adequate support for the decision to use the central estimate URFs?
- Was cancer endpoint selected as the basis of the potency estimates (lung cancer) the most appropriate and relevant choice?
- Are respiratory cancer data from Enterline et al (1995) and Lubin et al (2000;2008) a reasonable surrogate for lung cancer for reasons discussed in the DSD?
- Are lung cancer incidence and mortality sufficiently similar as to be comparable for purposes of this assessment for reasons discussed in the DSD?
- Is the URF weighting procedure used to calculate the final URF reasonable and justified?
- Is the decision not to apply age-dependent adjustment factors (ADAFs) to the URF to account for potential increased sensitivity of children justified and properly considered?
- Does the uncertainty section adequately discuss main areas of uncertainty in the development of the URF?

Appendix B – Conference Call Charge

Scientific Peer-Review of the
Carcinogenic Sections of the Arsenic Development Support Document
Focused Charge for Conference Call

The Toxicology Division of the Chief Engineer's Office, Texas Commission on Environmental Quality (TCEQ) has prepared a draft Development Support Document (DSD) that outlines the hazard assessment and dose-response processes used to derive a Unit Risk Factor (URF) and carcinogenic-based Effects Screening Levels (ESL) for arsenic. The toxicity values were developed using RG-442 *Guidelines to Develop Effects Screening Levels, Reference Values, and Unit Risk Factors* (TCEQ 2006). ESLs are chemical-specific air concentrations set to protect human health and welfare. Short-term ESLs are based on data concerning acute health effects, odor potential, and vegetative effects, while long-term ESLs are generally based on data concerning chronic noncarcinogenic and/or carcinogenic health effects. ESLs are used in the evaluation of air permit applications as well as proposed rules and regulation (e.g. Permits by Rule). ReVs and URFs, used as the basis of ESLs, are used in the evaluation of air monitoring data and in the development of Protective Concentration Levels for remediation sites.

The toxicity values will be used to evaluate emissions from facilities during the air permit review process, for evaluation of ambient air monitoring data, and as toxicity factors in the Texas Risk Reduction Program remediation program. Because the arsenic concentrations in air from these processes are measured as total arsenic, not as individual arsenic species, the cancer ESL derived for arsenic must be health protective for total arsenic without being overly conservative.

We are asking you to provide a review of the scientific approaches used by TCEQ in developing the toxicity values that are described in this draft document. The DSD is a summary document and does not provide a detailed description of every aspect of the toxicity assessment for a chemical. References to appropriate papers or documents are provided if more detailed information is needed. TCEQ relies on toxicity assessments conducted by other federal, state, and international agencies that have undergone a peer-review process as a starting point in their toxicity assessments, because of time and resource constraints. However, TCEQ obtains copies of key studies and supporting studies and critically reviews these studies. The toxicity assessments conducted by others are critically reviewed.

There are a number of policy decisions the TCEQ has made and included in this assessment that the agency does not seek comment on. These risk management goals were approved by the Commissioners and Executive Director of the TCEQ and are consistent with other TCEQ programs. ESLs developed in accordance with these no significant risk levels are intended to prevent adverse effects potentially associated with cumulative and aggregate exposures as defined in Section 1.2 of RG-442 ESL Guidelines (TCEQ 2006). Therefore, please do not spend your time commenting on the following policy decisions:

- The use of a target excess cancer risk level of 1 in 100,000 (1E-05) for the arsenic

carcinogenic-based ESL.
- Assumption of a lifetime exposure of 70 years.

Cancer Weight of Evidence and Unit Risk Factor (URF)

The arsenic DSD describes the approaches used to evaluate carcinogenicity and derive the URF and chronic ESL for cancer. In their written comments, the panel reviewed the key decisions made by TCEQ in deriving these values and made comments regarding issues specific to developing URFs for arsenic carcinogenic effects that were not adequately addressed in the document. TERA reviewed the panel's written comments noting areas of disagreement or issues that warranted further discussion. These areas are included as discussion questions, below. In addition, TCEQ also reviewed the panel's written comments and included clarifying questions that will help them better respond to the panel's recommendations.

1. In general, the panel agreed with the weight of evidence (WOE) classification that TCEQ assigned to arsenic compounds. Please discuss the qualitative descriptions of the weight of animal evidence compared to human evidence that TCEQ used in the overall WOE classification.

2. In general, the panel agreed that using multiple studies is an appropriate approach for calculating the URFs, and that the epidemiological evidence in Enterline et al (1995), Lubin et al (2000 and 2008), Jarup et al (1989) and Viren and Silvers (1994) was properly characterized. Please comment on which studies are most appropriate for calculating the URFs.

3. Is the epidemiological evidence in the Jones et al. 2007 study appropriate for calculating a URF?

4. Please discuss alternative statistical and modeling approaches that could be used and the dose-response modeling characteristics that warrant such alternative approaches along with any MOA justification.

5. Please discuss the rationale for making ad-hoc restrictions (i.e., fixing the background hazard rates for unexposed workers) to dose-response models.

6. Please discuss how should a meta-analysis that combines the data before modeling can reflect heterogeneity in data sets due to different epidemiological settings, differences in co-exposures, differences in dose characterization, differences in dose-metric, differences in follow up.

7. Please discuss TCEQ's choice of slope (beta) from the Lubin (2008) study that was used to calculate the final URF and suggest alternate approaches.

8. In general, the panel suggested that TCEQ should present an upper bound estimate in addition to the central estimate of URFs. Please discuss the importance of and approaches for calculating the upper bound estimate.

9. Please discuss alternate approaches for the weighting procedure used to calculate the final URF.

10. Please discuss additional areas of uncertainty that should be included in the document.

Appendix C – Panel Information

Conflict of Interest

An essential part of an independent expert review is the identification of conflicts of interest and biases that might interfere with a candidate's objectivity and be reason to disqualify a candidate, as well as the identification of situations which may appear to be a conflict or bias. TERA was selected by TCEQ to independently organize and conduct this expert panel review and is solely responsible for the selection of the panel. TCEQ has had no influence on the selection of the panel or implementation of the process. Prior to being selected to conduct this expert review, TERA provided information to TCEQ regarding its past and current relevant work, in order to assure TERA's corporate independence to organize and conduct this review for TCEQ. TERA has experience in risk assessment and toxicity of metals, including arsenic, from project work that has been done for a variety of public and private sponsors in the past; however, there are no currently ongoing projects that could be considered a conflict of interest. TERA has not participated in the development or preparation of the document that is the subject of this meeting. TERA has an ongoing contract with TCEQ to organize peer reviews and is being paid for its level of effort from funds in this contract.

The evaluation of real and perceived bias or conflict of interest is an important consideration in panel selection to ensure that the public and others can have confidence that the peer reviewers do not have financial or other interests that would interfere with their ability to carry out their duties objectively. TERA follows the U.S. National Academy of Sciences (NAS) guidance on selection of panel members to create panels that have a balance of scientific viewpoints on the issues to be discussed. As a result, the expert panels have a broad and diverse range of knowledge, experience, and perspective, including diversity of scientific expertise and affiliation. Panel members serve as *individuals*, representing their own personal scientific opinions. They do not serve as representatives of their companies, agencies, funding organizations, or other entities with which they are associated. Their opinions should not be construed to represent the opinions of their employers or those with whom they are affiliated.

Prior to selection, the candidates completed a questionnaire, which TERA used to determine whether their activities, financial holdings, or affiliations could pose a real or perceived conflict of interest or bias. TERA asked each promising candidate to report on his or her financial and other relationships with TCEQ, and with Texas companies that have reported releases of arsenic on the Toxic Release Inventory. The completed questionnaires were reviewed by TERA staff and discussed further with panel candidates as needed. (See www.tera.org/peer/COI.html for TERA conflict of interest and bias policy and procedures for panelist selection.)

TERA has determined that the selected panel members have no conflicts of interest and are able to objectively participate in this peer consultation. None of the panel members has a financial or other interest that would interfere with his or her abilities to objectively participate on the panel. None of the panel members is employed by TCEQ, or Texas companies releasing arsenic. Nor do the panel members have any financial interests in

these organizations or in the outcome of the review. None of the panel members was involved in the preparation of the document.

A brief biographical sketch of each panel member is provided below. To promote transparency, a short statement describing situations which might appear to present a conflict of interest or bias are included, as appropriate.

Biographical Sketches of Panel Members

Dr. Michael L. Dourson. Dr. Michael Dourson is the President of Toxicology Excellence for Risk Assessment (*TERA*), a nonprofit corporation dedicated to the best use of toxicity data in risk assessment. Before founding *TERA* in 1995, Dr. Dourson held leadership roles in the U.S. Environmental Protection Agency as chair of EPA's Reference Dose (RfD) Work Group, as a charter member of the EPA's Risk Assessment Forum and as chief of the group that helped create the Integrated Risk Information System (IRIS). Dr. Dourson received his Ph.D. in Toxicology from the University of Cincinnati. Dr. Dourson has served on or chaired numerous expert panels, including peer review panels for EPA IRIS assessments, EPA's Risk Assessment Forum, *TERA* International Toxicity Estimates for Risk (*ITER*) independent peer reviews and consultations, FDA's Science Board Subcommittee on Toxicology, the NSF International's Health Advisory Board, and SOT's harmonization of cancer and non-cancer risk assessment. Dr. Dourson has organized numerous symposia on a variety of topics, including: risk communication; chromium; information resources for toxicology and environmental health; risk assessment of essential trace elements; risk characterization; EPA's IRIS; uncertainty in risk assessment techniques; statistical and dose response models in risk assessment; benchmark dose methodology; basics of risk assessment; improvements in quantitative noncancer risk assessment; and neurotoxicity risk assessment. Dr. Dourson is a Diplomate of the American Board of Toxicology and a Fellow of the Academy of Toxicological Sciences. In 2003, Dr. Dourson was awarded the Arnold J. Lehman award for major contributions that improve the scientific basis of risk assessment by the Society of Toxicology (SOT). He has been elected to multiple officer positions in the American Board of Toxicology, SOT, and the Society for Risk Analysis. He is also a media resource specialist in risk assessment for the SOT, member of the editorial board of three journals, and vice chair of the NSF International Health Advisory Board. Dr. Dourson has chaired dozens of expert panels reviewing risk assessments. Dr. Dourson was selected for this panel for his expertise in dose-response assessment, metals toxicology, mode of action analysis, and familiarity with U.S. EPA's carcinogen risk assessment guidelines. In addition, Dr. Dourson has extensive experience effectively chairing panels of expert scientists in review of risk assessments.

Dr. David Gaylor. Dr. Gaylor, whose expertise is in the fields of biometry, statistics, and health risk assessment retired from the National Center for Toxicological Research (NCTR), FDA, where he served as the principal advisor to the NCTR Director/FDA Associate Commissioner for Science on matters related to the planning, development, implementation and administration of health risk assessment policies reaching across a wide range of FDA's activities. In a prior position with the NCTR, he was Director of the Biometry and Risk Assessment Division where he was responsible for the administration and scientific direction of the Biometry and Risk Assessment program. In that position, he developed experimental protocols and provided statistical analyses of experiments in carcinogenesis, teratogenesis, mutagenesis, and neurotoxicity, and developed techniques to advance the science of quantitative health risk assessment. Currently, he is a consultant

in the area of quantitative health risk assessment. Dr. Gaylor also serves as an Adjunct Professor of Statistics at the University of Arkansas for Medical Sciences, Little Rock. Dr. Gaylor obtained a Ph.D. in Statistics from North Carolina State University; he is a Fellow of the American Statistical Association, the Society for Risk Analysis, and Academy of Toxicological Sciences. He is a member of the Biometric Society, Society for Regulatory Toxicology and Pharmacology, and the Teratology Society. Dr. Gaylor has served on more than 80 national and international work groups and committees on many aspects of biometry, toxicology, and risk assessment. He is currently a member of the editorial board of: Risk Analysis, Human and Ecological Risk Assessment, Toxicology and Industrial Health, and Regulatory Toxicology and Pharmacology. Dr. Gaylor has also authored or coauthored more than 180 journal articles, 25 book chapters, and made over 100 presentations at scientific conferences. Dr. Gaylor has served on more than 70 national and international committees on aspects of biometry, toxicology, and risk assessment for the FDA, U.S. EPA, CDC, World Health Organization, Health Canada, International Life Sciences Institute, and the National Research Council. Dr Gaylor was selected for this panel for his expertise in biostatistics, dose-response assessment, and for his experience in serving on panels of expert scientists in review of risk assessments.

Dr. Kirk Kitchin. Dr. Kirk Kitchin. Dr. Kirk Kitchin is a Research Toxicologist in the genetic and Cellular Toxicology Branch, Integrated Systems Toxicology Division, National Health and Environmental Effects Research Laboratory, Office of Research and Development at the U.S. EPA in Research Triangle Park, NC. Dr. Kitchin received his BA in Chemistry and his PhD in Toxicology from the University of Rochester. His research interests include the design and conduct of mode of action studies and dose-response studies in experimental animals and/or biological systems (elaborate dose-response studies include arsenic, 1,2-dimethylhydrazine, 1,2-dibromoethane and TCDD) in order to generate data used in risk assessments to refine mathematical models and allow the consideration of alternative extrapolation methods below the dose range in which meaningful observations are possible. Dr. Kitchin served as the coordinator of arsenic research for U.S. EPA's Environmental Carcinogenesis Division for many years. He was also a member of the team that prepared U.S. EPA's Research Plan for Arsenic in Drinking Water document (EPA/600/R-98/042) and served as a reviewer for U.S. EPA's Arsenic Health Assessment. Dr. Kitchin is a Diplomate of the American Board of Toxicology. He is a member of the Society of Toxicology where he has served as a Councilor, Vice-president, and President of the Metal Specialty Section, and he is Chairman of the International Society for the Study of Xenobiotics' Committee on Regulatory Affairs. Dr Kitchin has been a member of the Editorial Board for the journal Toxicology and Toxicology Letters; he has numerous publications and invited presentations in the areas of mechanisms of carcinogenicity and arsenic carcinogenicity. Dr. Kitchin was selected for this panel for his expertise in metals carcinogenicity, and cancer mode of action research.

Dr. Kyle Steenland. Dr. Steenland is a Professor of Epidemiology in the Department of Environmental and Occupational Health at Emory University's Rollins School of Public

Health. Prior to joining Emory University, Dr. Steenland served as an Epidemiologist for the National Institute for Occupational Safety and Health and for the International Agency for Research on Cancer. Dr. Steenland received his BA in History from Stanford University, a PhD in history from the University of New York at Buffalo, a PhD in Epidemiology from the University of Pennsylvania and a Masters in Mathematics from the University of Cincinnati. Dr. Steenland has been an investigator in epidemiological studies to evaluate the relationship between risk of disease and occupational exposure to numerous chemicals, including dioxin, polychlorinated biphenyls, silica, lead, ethylene oxide, and pesticides. His current research interests include Alzheimer's and Parkinson's disease, as well as a comprehensive cohort study on the health effects of Perfluoroctanoate. Dr. Steenland has served on Federal Advisory Committees, including the National Toxicology Program's work group evaluating lead carcinogenicity, and an EPA committee to develop a criteria document on lead carcinogenicity. He is a Fellow of the American College of Epidemiology, a member of the International Congress on Occupational Health, and Editor of the journals *Epidemiology* and *American. Journal of Industrial Medicine*. Dr. Steenland has numerous peer reviewed publications on epidemiological methods and chemical-specific epidemiology studies, and he has edited two books on occupational and environmental epidemiology. Dr. Steenland was selected for this panel for his expertise in epidemiology and dose-response assessment using epidemiological data sets.

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Appendix D - List of Conference Call Registrants

Scientific Peer-Review of the
Carcinogenic Sections of the Arsenic Development Support Document
Participant List

Panel Members

Dr. Michael Dourson
Toxicology Excellence for Risk Assessment (TERA)

Dr. Kirk Kitchin
U.S. EPA

Dr. Dave Gaylor
Gaylor Associates

Dr. Kyle Steenland
Emory University

Observers

Lea Aurelius
Parsons

Alejandro Nava-Ocampo
Ontario Ministry of the Environment

Andrew Chiu
Ontario Ministry of the Environment

Tania Onica
Ontario Ministry of the Environment

Dr. David A. Fowler
CDC/ATSDR

Dr. Julie Schroeder
Ontario Ministry of the Environment

Dr. Grazyna Kalabis
Ontario Ministry of the Environment

Dr. Akos Szakolcai
Ontario Ministry of the Environment

Carol McSweeney
Air Matters Limited

Appendix E: Post-Conference Communications from Panel Members

From: Steenland, Kyle [mailto:nsteenl@emory.edu]
Sent: Sunday, August 29, 2010 6:35 PM
To: Joan Strawson; Mike Dourson; David Gaylor; Kitchin.Kirk@epamail.epa.gov
Cc: Roberta Grant
Subject: RE: Materials for next weeks Arsenic conference call

I said I would check into the Jones et al. study and their weighting scheme, which lowers exposure at older ages and longer latency, as per BiER VI.

The assumption of Jones et al. is that arsenic carcinogencity follows the pattern of radiation carcinogenicity (for which there is more abundant data), and therefore the weighting scheme used for radiation should be used for arsenic. I think this is a big assumption, and also makes the dose metric in the Jones et al. study not comparable to the other three studies. My conclusion is that it would be best to drop the Jones et al. study.

For fun I also fit a regression line to the combined points of the Enterline, Lubin, and Jarup studies (attached Excel spreadsheet and SAS program), after weighting each point by the observed number of lung cancer deaths. The observed SMRs are in blue and the predicted are in red. The predicted slope is 0.000069, higher than the inverse-variance weighted average of the three reported betas for these three studies (which I show as 0.000039, see spreadsheet). The linear model provides a good fit to the data, there is no evidence of attenuation here. The R-square is 0.78, residuals are reasonably normal, albeit based on small sample size. The intercept is now a reasonable SMR of 1.28. There is heterogeneity as expected between the intercepts for each study and some evidence of heterogeneity of slopes between the studies, both of which up to now have been ignored in the risk assessment – which I think in fact should continue to be ignored.

The method of analysis used here (linear regression), and the weighting, are probably not optimal, as Poisson regression may be preferred (as was done in the risk assessment), which does not need to be weighted (or which is inherently weighted). But you do get a flavor for the combined analysis approach.

Kyle

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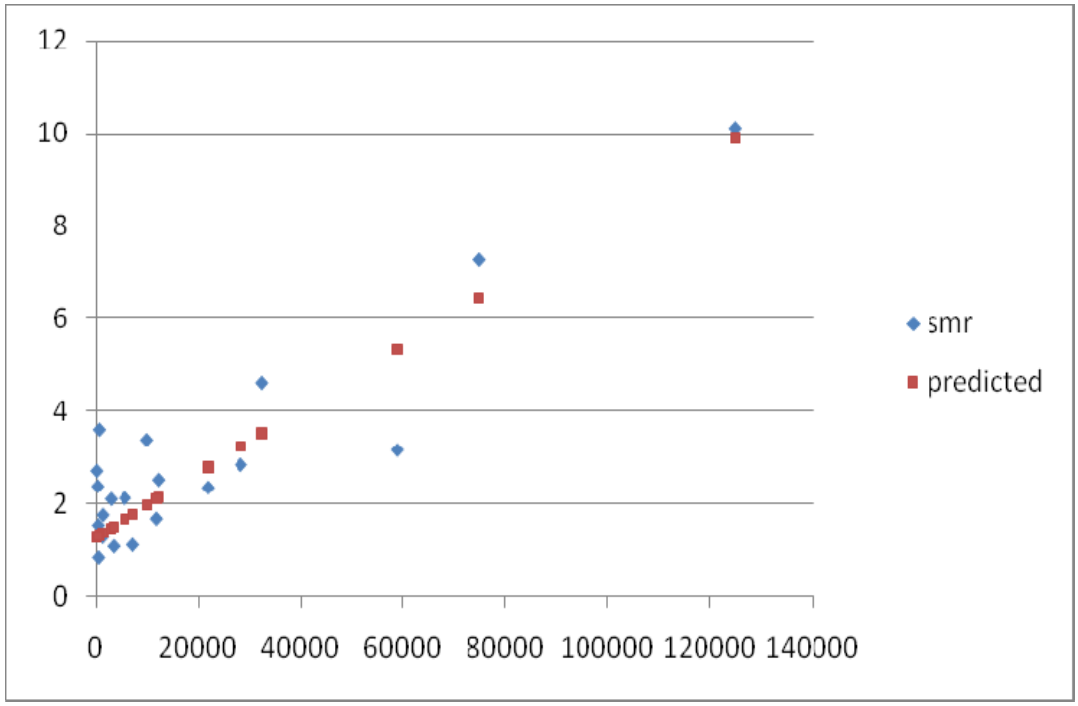
				dose	smr	predicted	obs	exp
Enterline				405	1.54	1.30	22	14.3
				1305	1.76	1.37	30	17.1
				2925	2.1	1.48	36	17.2
				5708	2.12	1.67	36	17
				12334	2.52	2.13	39	15.5
				28336	2.84	3.23	20	7
				58957	3.16	5.34	5	1.6
Lubin				470	0.84	1.31	62	73.4
				1240	1.28	1.36	96	75
				3430	1.08	1.51	74	69
				7270	1.11	1.78	83	75
				11900	1.68	2.10	84	50
				21900	2.35	2.79	47	20
Jarup				125	2.71	1.28	14	5.2
				625	3.6	1.32	13	3.6
				300	2.38	1.30	17	7.1
				10000	3.38	1.97	15	4.4
				32500	4.61	3.52	29	6.3
				75000	7.28	6.45	6	0.8
				125000	10.11	9.90	12	1.1




```
*arsenic.texas.aug29.2010;
*analyzes data from enterline, lubin, jarup, for lung cancer;
data one;
input cumdose smr obs exp study;
if study=1 then do; study2=0; study3=0; end;
if study=2 then do; study2=1; study3=0; end;
if study=3 then do; study2=0; study3=1; end;
*1 is Enterline, 2 is Lubin, 3 is Jarup;
inter1=study2*cumdose;
inter2=study3*cumdose;
cumdosesq=cumdose*cumdose;
lncumdose=log(cumdose);
lnsmr=log(smr);
cards;
405         1.54  22    14.3   1
1305        1.76  30    17.1   1
2925        2.1   36    17.2   1
5708        2.12  36    17     1
12334       2.52  39    15.5   1
28336       2.84  20    7      1
58957       3.16  5     1.6    1
470         0.84  62    73.4   2
1240        1.28  96    75     2
3430        1.08  74    69     2
7270        1.11  83    75     2
11900       1.68  84    50     2
```

```
21900       2.35  47    20     2
125         2.71  14    5.2    3
625         3.6   13    3.6    3
300         2.38  17    7.1    3
10000       3.38  15    4.4    3
32500       4.61  29    6.3    3
75000       7.28  6     0.8    3
125000      10.11 12    1.1    3
;
proc reg ;weight obs;  model smr=cumdose;  run;

proc reg ;weight obs;  model lnsmr=cumdose;  run;
proc reg ;weight obs;  model smr=sqrtcumdose;  run;
proc reg ;weight obs;  model smr=lncumdose;  run;
proc reg ;weight obs;  model smr=cumdose;  run;
output out=new residual=resid;
proc univariate normal plot data=new; var resid; run;
proc reg ;weight obs;  model smr=cumdose  study2 study3 inter1 inter2;
run;
```

From: David Gaylor [mailto:davidgaylor@earthlink.net]
Sent: Monday, August 30, 2010 7:59 PM
To: Steenland, Kyle; Joan Strawson; Mike Dourson; Kitchin.Kirk@epamail.epa.gov
Cc: Roberta Grant
Subject: Re: Materials for next weeks Arsenic conference call

Based on the comments by Dr. Steenland, it appears reasonable to drop the Jones et al. study.

David Gaylor

From: Michael Dourson [mailto:dourson@tera.org]
Sent: Friday, September 03, 2010 6:40 PM
To: Steenland, Kyle; Joan Strawson; David Gaylor; Kitchin.Kirk@epamail.epa.gov
Cc: Roberta Grant
Subject: Re: Materials for next weeks Arsenic conference call

Dr. Steenland

Thanks so much for doing this extra work. I have no inherent problem with dropping the Jones et al work, especially since it seems at odds with the other studies. However, I apologize for a naïve question: how do your beta values related to the information found in Table 19 on page 51 of the TCEQ text?

Cheers!

Michael Dourson

Toxicology Excellence for Risk Assessment (TERA),
leader in educating diverse groups on risk assessment issues. See www.tera.org/global/training

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From: Steenland, Kyle [mailto:nsteenl@emory.edu]
Sent: Tuesday, September 07, 2010 5:31 PM
To: Mike Dourson; Joan Strawson; David Gaylor; Kitchin.Kirk@epamail.epa.gov
Cc: Roberta Grant
Subject: RE: Materials for next weeks Arsenic conference call

My beta value for the combined data is a kind of weighted average of the exposure response coefficients for each individual study , found in Tables 8, 11, and 14. The betas in these tables are used in the document to obtain three separate URLs, and in the document these URLs (actually four of them, as the Jones et al study is included) are what is weighted to obtain an average URL in Table 19 on page 51.

The beta value (exposure response coefficient) I obtained from the combined data is not the same as a simple inverse variance weighted average of the three study specific betas (which is given in my spreadsheet) but similar to that.

Hope this helps

Kyle

From: Mike Dourson
Sent: Monday, September 20, 2010 2:00 PM
To: Steenland, Kyle
Cc: Roberta Grant; Joan Strawson; David Gaylor; Kitchin.Kirk@epamail.epa.gov
Subject: Re: Materials for next weeks Arsenic conference call

Dear Kyle

I apologize for my lengthy pause between emails. I was fishing in Northern Minnesota.

Thanks for your explanation. I now agree that the Jones et al. study should be dropped and that our TCEQ colleagues should recalculate their combined URF in a manner consistent with only 3 studies. The TCEQ folks should also probably estimate the combined URF as you suggest, if only for an alternate analysis.

Cheers!

Michael

Toxicology Excellence for Risk Assessment (TERA),
Dose Response Boot Camp..... Risk Assessment from 0 to 100 in 5 days! Check it out at www.tera.org/global/training

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From: Kitchin.Kirk@epamail.epa.gov [mailto:Kitchin.Kirk@epamail.epa.gov]
Sent: Wednesday, September 22, 2010 7:04 AM
To: Joan Strawson
Subject: Re: FW: Materials for next weeks Arsenic conference call

It is OK with me. There are weakness in all the human epi data sets. I wish the author had been contacted (Dr. Jones) to see what his/her opinion was and if something could be done to make the standard and format of x axis dosimetry match that of the other included epi studies.

Best wishes,

Kirk T. Kitchin, PhD., DABT
NHEERL, US EPA
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27711, USA

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email kitchin.kirk@epa.gov