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August 15, 2010

Angela Nugent, PhD nugent.angela@EPA.gov
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Designated Federal Officer
Science Advisory Board, USEPA
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Re: Graphic Representation of Sensitivity Analysis (Page 140)
Toxicological Review of Inorganic Arsenic in Support of
Summary Information on the Integrated Risk Information System (IRIS)
February 2010

Dear Drs. Sams, Ramasamy, Faustman, and Nugent,

It was clear at the meeting of the SAB panel on arsenic both their and your desire to clarify the findings for the reader. I focus my attention on Section 5.3.8.5. Figure 5-2 (page 140) has been designed to visually present the information from Table 5-11, but does so in a way not helpful to the reader.

In once more reviewing the Toxicological Review on Inorganic Arsenic (February 2010), I find that the graph (Figure 5-2) on page 140 gives a false representation of the results shown in Table 5.11. I have revised (see below) Figure 5-2 using the data from Table 5-11 in a manner that, I think, is more informative. Figure 5-2 is in error in that it presents "Zero; 0.0" as the reference value for a relative risk where, by definition, the reference value for the relative risk is "one; 1.0". We have corrected it in our Figure 5-2a.

EPA states (Page 138) that "Figure 5-2 summarizes the impact of alternative modeling assumptions, showing the ratios of estimated cancer risks to the base case estimates for changes in input variables having a substantial (>20%) effect on the risk estimates." Figure 5-2 does not show that; Figure 5-2 (Linear/Logarithmic) do. This is highlighted by including lines for +/- 20% effect on the risk estimates. This is being submitted to the public record and may be used and modified.

EPA states (Sec 5.3.8.5 - Page 137) that it "examined several aspects of the cancer risk modeling through single-value sensitivity analysis." These are the results that are shown figuratively in Figure 5.2. EPA's sensitivity analysis is in response to the recommendations of NRC (2001) and SAB (2007) that "the impacts of different modeling assumptions and input parameter values be investigated in the risk assessment for arsenic in drinking water."

Additionally, we have added vertical lines to separate out the findings for each change in model parameter and each change in model assumption. We have also presented the findings both graphed linearly (which is easier on the reader) and logarithmic (which is more appropriate for the relative risk function).

There are a few observations I would make from Figure 5-2 (modified).

Model input parameter values -

(1) As the cancer rates and arsenic medians are already established for each village, varying the quantitative value of the generic exposure input parameter will directly vary the unit risk value, often substantially, depending upon the magnitude of shift from baseline. The bases for the values used as the parametric choices need to be sourced. They are not self-evident, particularly when the effects are substantial.

(2) Exposure input parameter values seem to more strongly affect female bladder cancer risk than those of the other cancer groups.

Model Assumptions -

(1) The cancer risk estimates are consistently and substantially decreased when either village well arsenic maxima are used as the village metric rather than medians (average 28% decrease) or the SW Taiwan reference population is not included in the model (average 67% decrease).

The current sensitivity analysis is limited to single value sensitivity. Since that analysis shows that the cancer risk estimate was substantially affected by either use of village maxima or non-use of reference population, the sensitivity analysis should be further extended to consider the effect of both alternative assumptions simultaneously.

We would suggest that changes in model input parameter values and changes in model assumptions are quite different conceptually in sensitivity analyses and should be handled separately both analytically (appendix) and graphically.

We respectfully submit these graphic clarifications.

Cordially, and Respectfully,

[Signature]

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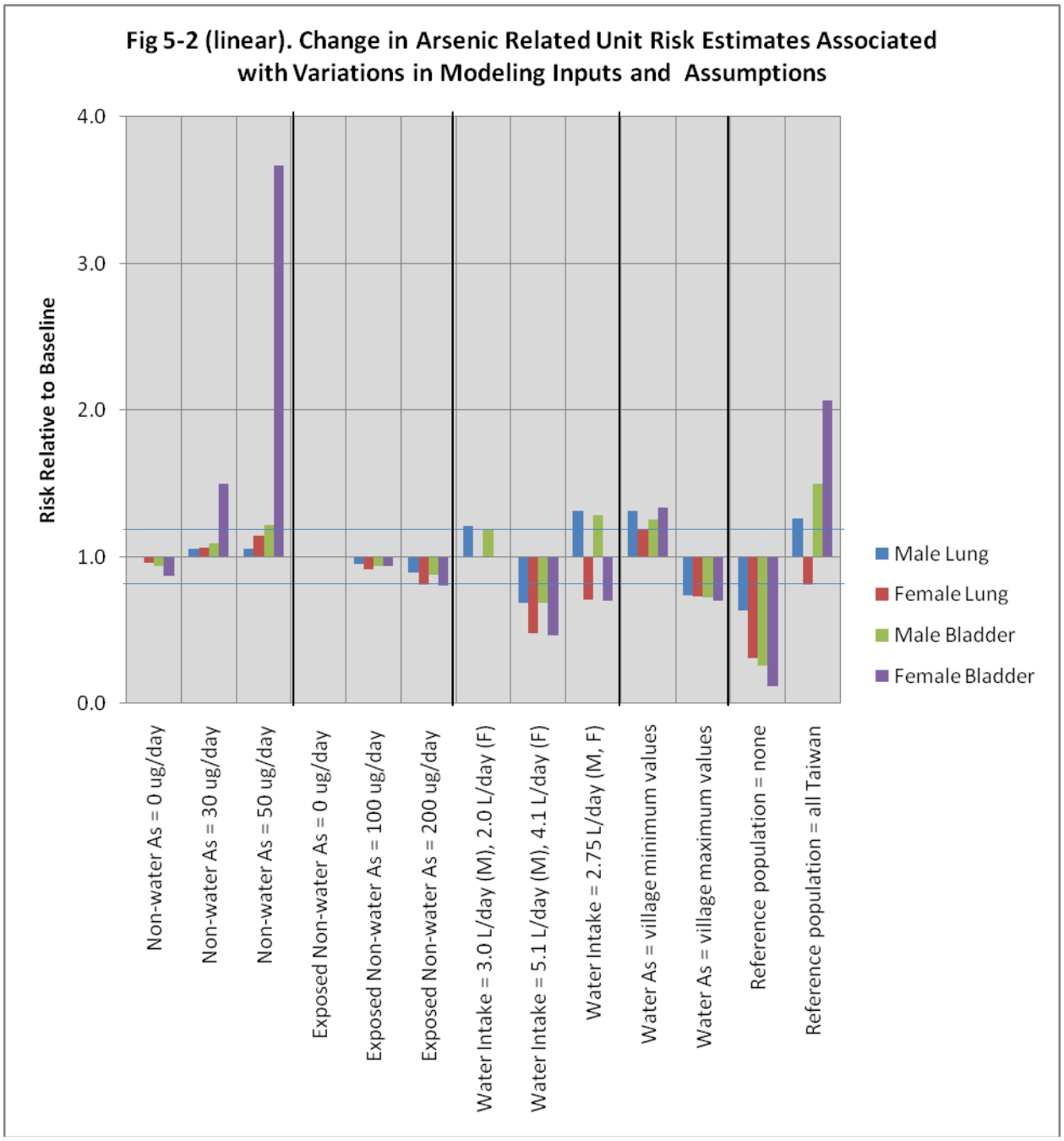
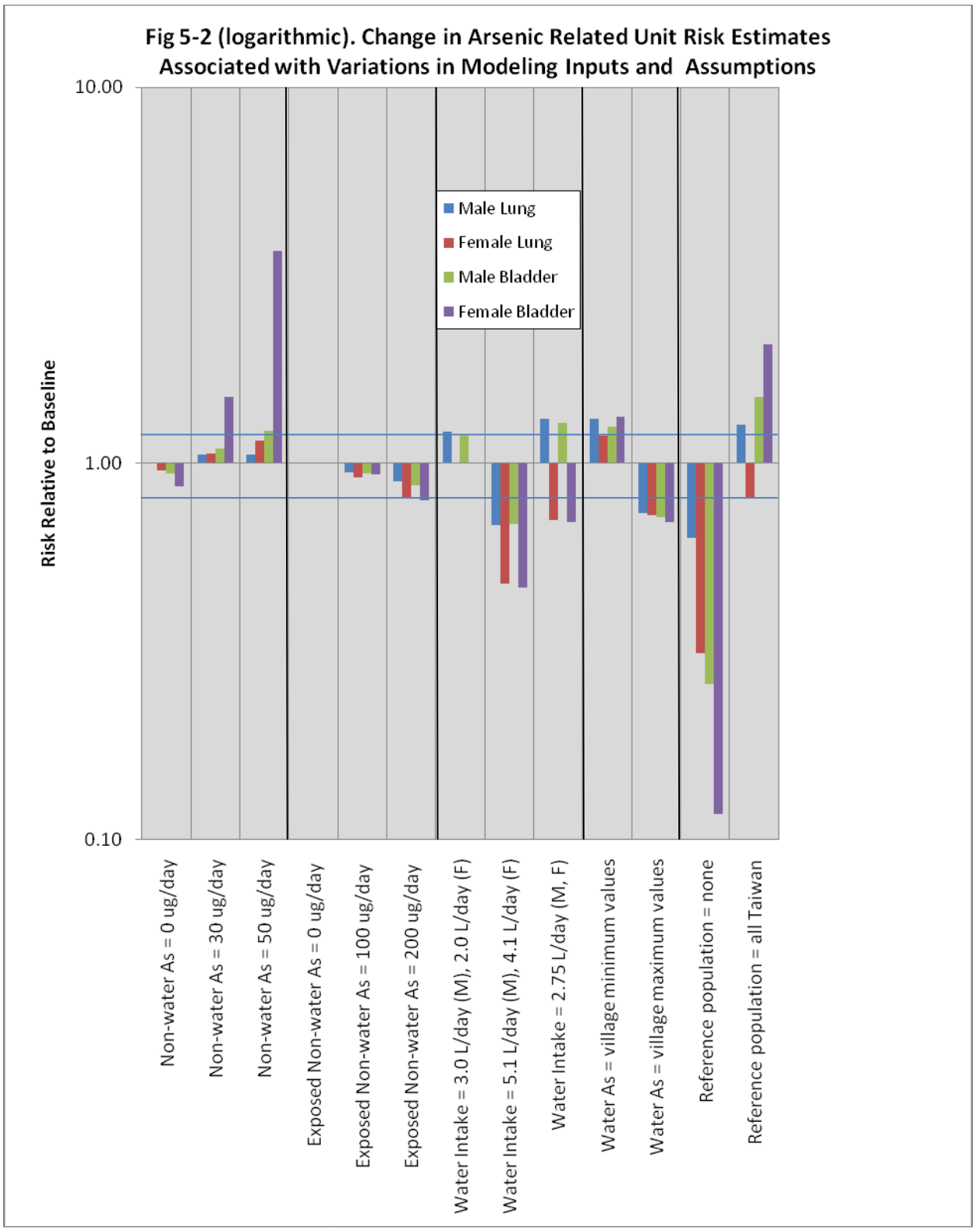
CC: Dr. Reeder Sams, Dr. Santhini Ramasamy, Dr. Elaine Faustman



Horizontal lines represent +/- 20%, the indication of substantial effect on the risk estimate.



Horizontal lines represent +/- 20%, the indication of substantial effect on the risk estimate.

Appendix (August 9, 2010)

Modeling Input Parameter Values (Quantitative)

1. Non-water daily arsenic intake –
    a. Decreasing it from 10 ug/day to 0 ug/day has no substantial effect on the cancer risk estimate
    b. Increasing it from 10 ug/day to 30 ug/day increases the risk estimates, substantially for female bladder (+50%).
    c. Increasing it further to 50 ug/day increases the risks, substantially for male bladder (+22%) and quite substantially for female bladder cancer (+267%).
2. Non-water daily arsenic intake for exposed (study) populations –
    a. Decreasing from 10 ug/day to 0 ug/day has no effect.
    b. Increasing from 10 ug/day to 100 ug/day decreases the risk estimates, but non-substantially.
    c. Increasing it further to 200 ug/day further decreases the risks, now to borderline substantiality for females (Lung -19%; Bladder -20%).
3. Daily water intake –
    a. Males – Increasing the assumed volume from 3.5 L/day to 5.1 L/day substantially decreases the risk estimate (Male Lung -32%; Male Bladder -31%). Decreasing the assumed volume from 3.5 L/day to 3.0 L/day yields increased risks of borderline substantiality (Male Lung +21%; Male Bladder +19%) and while reducing it to 2.75 L/day yields risks that are substantially increased (Male Lung +32%; Male Bladder +28%).
    b. Females – Increasing the assumed volume from 2.0 L/day to 2.75 L/day yields substantially decreased risks (Female Lung -29%; Female Bladder -30%) – and increasing it further to 4.1 L/day decreases the risk estimates substantially further (Female Lung -52%; Female Bladder -53%).

Modeling Assumptions (Qualitative)

1. Village Well Arsenic Summary Metric -
    a. Minimum – Using the minimum village arsenic level as the village metric instead of the median village arsenic level increases the risk estimate, generally substantially, all in the range of a 19-33% increase (Male Lung +32%; Female Lung +19%; Male Bladder +25%; Female Bladder +33%).
    b. Maximum – Using the maximum village arsenic level as the village metric instead of the median village arsenic level decreases the risk estimate substantially, all in the range of a 26-30% decrease, (Male Lung -26%; Female Lung -27%; Male Bladder -28%; Female Bladder -30%).
2. Reference Population –
    a. None – Using no reference population instead of using the SW Taiwan data as a reference population leads to a substantial decrease in the risk estimate for all four groups (Male Lung -37%; Female Lung -69%; Male Bladder -74%; and Female Bladder -88%).
    b. All-Taiwan – Using the total Taiwan population as the reference population instead of using the SW Taiwan data as the reference population increases the risk estimate substantially for three of the four groups (Male Lung +26%: Male Bladder +50%; Female Bladder +107%) while the risk for female lung cancers is decreased (-19%).