**Comments on CPSC's analysis of cancer risk to children from contact with CCA-treated wood products**

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**About the author.** Ph.D. in statistics from Johns Hopkins University. Numerous publications on statistics and applications to risk assessment. With regard to arsenic, served on committees (NRC/NAS subcommittee on arsenic in drinking water, Arsenic Task Force of the Society for Environmental Geochemistry and Health), workshops on research needs (NCI/NIEHS/EPA, American Water Works Association), drafted the position paper of the American Council on Science and Health, presented invited and contributed papers at numerous conferences, co-authored 12 articles - 5 in conference proceedings, 7 in refereed journals (2 invited). Research supported by U.S. EPA, industry, and trade associations (e.g., American Water Works Association).

**Introduction.** The CPSC claims that it has dealt with sources of uncertainty and variability, but that is not quite accurate. They have considered a range of values for some of their parameters (such as concentration of arsenic on children's hands, hand-to-mouth transfer, exposure frequency, and bioavailability), which is commendable, but they have not considered the uncertainty in their methodology or the risk estimates of cancer from arsenic in drinking water taken from the National Research Council (NRC) and U. S. Environmental Protection Agency (EPA) reports. "Uncertainty refers to lack of knowledge in the underlying science" (NRC1, p.109), and uncertainties require assumptions, either implicitly or explicitly, to derive numerical values of risk. The credibility of the assumptions affects the extent to which the CPSC claim of excess lifetime risk of lung and bladder cancer of two to 100 per million for children who play on CCA-treated playground structures is warranted (or to what is referred to as "an approximation of reasonable 'worst' and 'best' cases", ranging from 0.2 per million to 5,000 per million across their range of parameters, is warranted).

Two critical assumptions are discussed below, the first related to CPSC's technical approach and the second related to the Taiwan data used in the NRC and EPA risk assessments for arsenic in

drinking water. In the first case, the assumption is due to insufficient information about the mode-of-action of arsenic carcinogenicity, a biological consideration. In the second case, the assumption is because the exposure data in the principal study used for risk assessment of arsenic in drinking water is highly aggregated, instead of specific to individuals, a statistical consideration (technically refered to as ecological exposure data, and thus making statistical inference subject to what epidemiologists refer to as the "ecological fallacy"). Both assumptions are the result of genuine limitations of the science or the available data, and both are important to warranting CPSC's estimates of the cancer risk.

The premise in the discussion that follows is that conclusions from risk analysis for health effects should be as strong as warranted, but not stronger. Just how strong is warranted depends on statistical characteristics, such as the quality and level of detail of the available data and the appropriateness of the statistical methodology, and on consistency of the data analysis with biological expectations. In short, claims based on data analysis for health effects are warranted by both statistical and biological considerations.

**Assumption 1**. Excess cancer risk from arsenic ingested from CCA-wood products at two to six years of age is the same as if that total arsenic intake were distributed evenly over a lifetime.

The CPSC analysis begins with the lifetime risk estimates of bladder and lung cancer from the NRC and EPA. Both were determined from the same data in southwestern Taiwan, which is discussed next, and the comments of this section apply equally to either the NRC or EPA data. The CPSC calculated a lifetime average daily dose (LADD) that it multiples by a cancer potency factor (Q), where Q is described as the "[lifetime] cancer risk per unit of daily [arsenic] exposure" (CPSC, p.306). CPSC staff calculated a value for Q of 0.023 $(\mu g/kg/day)^{-1}$ (CPSC, p. 22) from the NRC analysis and a range of about 0.00041 to 0.0037 $(\mu g/kg/day)^{-1}$ (CPSC, p.22) from the EPA analysis. The lifetime daily dose is the estimated daily intake if the total arsenic consumed by a child from contact with CCA-wood products during the ages of two to six inclusive were spread evenly over a lifetime of average duration. That implies that lifetime risk (1) increases linearly with duration (number of days or years) of exposure, and (2) is determined

by cumulative arsenic intake without regard to exposure regimen, such as the ages at which exposure begins and terminates, and whether exposure is continuous or intermittent.

With regard to (1), NRC2 statistical models for cancer risk from lifetime exposure (NRC2, Table 5.4), all include the effect of duration (the same as age in those data) as quadratic rather than linear, i.e., the effect of duration of exposure increases disproportionately to dose. This suggests that the CPSC formula probably produces estimates that are too high. The formula is being used an approximation to the NRC2 model that was chosen (or the EPA model in the case of the EPA estimates). The formula could be checked by calculating lifetime cancer risks for an array of exposure levels (units of arsenic per day) and exposure durations (number of years) and the values compared with the outcomes that would be obtained using the NRC and EPA models from which the values of Q were determined. That could not be done for this review because more technical detail is needed than has been published in the relevant reports. If the CPSC formula is not a good approximation for continuous lifetime exposure, then it could not be expected to apply to partial lifetime exposure as experienced by children exposed to CCA.

With regard to (2), cancer risk from arsenic exposure for a limited time-period, e.g., five years, can depend on factors such as the age exposure begins, the time since exposure ended, and whether exposure was intermittent or continuous, all of which are related to the biology of the relevant cancer mechanism(s). The issue of intermittent versus continuous exposure is related to whether periods of no exposure provide some opportunity for recovery/regeneration from the effects of exposure. Other factors of interest are whether arsenic is a complete or incomplete carcinogen, whether late or early stages, or both, of cancer development are affected, etc. Unfortunately, research on the mechanism(s) of arsenic carcinogenicity has been hampered somewhat by the difficulty of inducing cancer in experimental animals from exposure to arsenic.

There are few substances with enough epidemiological data to address such issues of partial lifetime exposure, although tobacco smoking is an exception. Tobacco smoke is known to contain a large number of human carcinogens, so its biological mechanisms are probably a mix of possibilities. The risk of lung cancer appears to be higher for people who started smoking at a

younger age, but risk decreases with time since smoking cessation, which has been interpreted as suggesting both initiation and promotion capabilities of tobacco smoke components (U.S. EPA, 1992, Sec. 4.2.2). One cannot draw conclusions about arsenic based on the example of tobacco smoke, but it demonstrates the importance of maintaining a biological perspective.

**Conclusion 1.** The CPSC accepts the results of NRC2 but its approach to modify risk estimates to apply to arsenic intake from CCA is inconsistent with the NRC2 analysis. If one accepts the NRC2 cancer risk estimates (to be discussed next), then CPSC probably overestimates risk from CCA. Implicit biological assumptions are introduced about the mechanism(s) of arsenic carcinogenicity that may not apply. CPSC's claim of excess cancer risk, and the numerical estimates, from CCA-treated wood are unwarranted on either statistical or biological grounds.

**Assumption 2.** The risk analyses of cancer from arsenic in drinking water based on the southwestern Taiwan data assume that all persons from the same village in the southwestern Taiwan study area were exposed to the same arsenic concentration in drinking water, namely the median value of the wells tested in the village.

The two NRC reports mention several sources of uncertainty, but only one, the potential for misclassification of human exposure to arsenic in the data from southwestern Taiwan, is discussed here. By way of background, the exposure data consists of well tests for arsenic in villages made prior to about 1970, while the data for bladder and lung cancer were taken from mortality records for the period 1973-1986 that included the cause of death and the village of residence. Thus, individual mortality records for bladder cancer deaths connect an individual to a village, but not to a specific well(s) within the village. The assumption made in the NRC reports is that persons from the same village were exposed to the same level of arsenic concentration in drinking water, specifically the median value of the wells tested within the village. Wells within the same village, however, often differed markedly in arsenic concentrations. Figure 1, showing the arsenic concentrations by village, for villages with more than one well, was constructed from Table A10-1 of NRC1. The same data were analyzed more fully by Morales et al. (2000), that was cited heavily in NRC2 and in the EPA report.

The first village listed in Figure 1, O-G, had a relatively large number of cancer occurrences. There were five wells with arsenic concentration test results of 10, 10, 30, 259, and 770 μg/L. There was a total of 10,000 person-years for the village with 11 bladder or lung cancer deaths. The analyses of the two NRC reports, and EPA, treat the village the same as if there were one well with arsenic concentration of 30 μg/L, effectively assuming that all 11 cancer deaths occurred at an arsenic concentration of 30 μg/L. The range of well tests is not so extreme across all villages, but it is readily apparent from the figure that the example just described is not an isolated case. The potential for serious exposure misclassification is obviously high. The data contain only one well test for 20 of the 42 villages. The effect of such data on risk estimation is apparent in a diagram in which different dose-response models were fit to the data. First, however, it may be useful to see an example of a model fit to good dose-response data.

The data in Figure 2 are from mortality of rats exposed to hydrogen sulfide, and are used here strictly for illustration, with a logistic model fit to the data. A statistical measure of the goodness of fit, or something such as the Akaike Information Criteria (AIC) used by the NRC to compare different alternatives, is not adequate by itself; it is necessary to graphically examine the fit of the data. In this case, it is apparent graphically that the model describes the data well – the data are close to the curve and predicted values calculated from the curve should be reasonable. Another model might fit the data about equally well, but to do so it is clear that it would have to be very close to the current curve. Thus one can have some level of comfort in using the fitted curve to estimate risk at arbitrary exposure values that may not have been actually observed.

By contrast, several different models were statistically fit to the Taiwan data, with disagreement between EPA's Science Advisory Board and the NRC2 subcommittee on whether the dose-response analysis should include no external comparison group, or a comparison group consisting of either a southwestern region of Taiwan or all of Taiwan (NRC2, Ch. 5). The results for the three alternatives, and selected model choices, are displayed in Figure 3, which appeared in Morales et al. (2000) and NRC2 (Lifetime risk of death from bladder cancer for males plotted against U.S. equivalent arsenic concentration in μg/L of drinking water). It is clear that the data

are so variable that none of the models provide a good fit to the data. One point near the center of the exposure range is exceedingly high, suggesting that it might be an outlier. More than one model has about the same AIC value, indicating that they cannot be distinguished on a statistical measure of fit (the AIC provides a relative comparison of fits – no statistical measure of fit was found). As one can see graphically, the estimated risks very close to the origin vary widely for different models, so there is considerable model sensitivity (as noted in NRC2 and Morales et al.). Nevertheless, NRC2 settled on one of the models linear in dose, using the southwestern Taiwanese region as the comparison group, and concluded that it is a "biologically plausible model that provides a satisfactory fit to the epidemiological data and represents a reasonable model choice for use in arsenic risk assessment" (NRC2, Ch. 5, Summary).

In light of Figure 3, it is hard to see how that statement could be justified even if the data were valid and reliable. Considering the high exposure misclassification expected from treating individuals within a village as all drinking water with the same arsenic concentration (the median-concentration well in the village), there would be little basis for much credence in any model fit to the data (Figure 1). The validity and reliability of the data and the appropriateness of the statistical model are both questionable. Regarding biological plausibility, NRC1 (Ch. 7.) notes that the mode-of-action of carcinogenicity has not been established, and that it is prudent not to rule out the possibility of a linear response. However, it also states that the several modes-of-action that are considered plausible (namely, indirect mechanisms of mutagenicity) would lead to a sublinear dose-response curve at some point below the point at which a significant increase in tumors is observed (i.e., less than linear response at sufficiently low arsenic concentrations). Thus, the NRC2 model choice with linear dose is not the most biologically plausible option, nor does it appear to be among those with superior statistical fit. According to NRC2 (Ch. 5), "statistically superior fits were produced using models that included a log or square-root transformation of dose (Morales, 2000), despite the fact that those models are not as biologically plausible as other ones." When the biological information and the statistical outcomes collide, something is fundamentally wrong, and in this case one can find "probable cause" in the misclassification of study subjects to arsenic.

**Conclusion 2.** The NRC2 claim that chronic exposure to arsenic causes cancer is supported, but conclusions regarding the magnitude of risk at specific exposure levels, based on statistical modeling of the southwestern Taiwan data, are beyond the level of detail warranted by the data. Furthermore, the statistical analysis is not consistent with the most biologically plausible mode-of-action(s) of arsenic carcinogenicity

**Summary Conclusion.** Of the two sources of uncertainty described above, the first addressed an assumption that CPSC made to extrapolate cancer risk estimates based on chronic exposure to intermittent childhood exposure from contact with CCA-treated wood products, given that the NRC2 estimates for chronic exposure to low arsenic concentrations in drinking water are valid and reliable. The second source of uncertainty questioned the validity and reliability of the NRC2 estimates of risk. It is clear from the data of southwestern Taiwan and elsewhere that lifetime exposure to arsenic concentrations in drinking water of several hundred μg/L produces detrimental health effects, including cancer of the bladder and other organs. Claims that these detrimental effects also occur at small arsenic intakes, e.g., 10μ/L (10-20 μg/day), and that quantitative estimates of risk determined from the available data are valid and reliable, is more speculation than science. The implications for the CPSC analysis is that they are trying to ferret out cancer risks at extremely small arsenic intakes for which it is not at all clear that there even is a cancer risk.

**Addendum: Are the NRC1, Morales et al., and NRC2 concerned about the southwest Taiwan database?**

This is not a full and complete discussion, which would be much too lengthy, and one could argue against quoting text from these sources out of context. It describes the impression of the current author, with some supporting quotations.

NRC1 sends a mixed message. It seems to be concerned about the quality of the southwestern Taiwan data, but draws some rather strong conclusions anyway. Within the body of the report, NRC1 provides some instruction on dose-response analysis and an analysis of the bladder cancer data with the proviso that, "it is important to emphasize again that the results are not to be

interpreted as a formal risk assessment, or as an endorsement of these data for the use of risk assessment" (NRC1, p. 273). This is consistent with the preface that states: "EPA did not request, nor did the subcommittee endeavor to provide, a formal risk assessment for arsenic in drinking water" (NRC1, p. 2); and the recommendation that, "Additional epidemiological evaluations are needed to characterize the dose-response relationship for arsenic-associated cancer and non-cancer endpoints, especially at low doses. *Such studies are of critical importance for improving the scientific validity of risk assessment*." [emphasis added] (NRC1, p.3)

The executive summary of NRC1, however, then proceeds with risk assessment estimates, specifically a bladder-cancer risk of one to 1.5 per 1,000, with speculation that the combined risk with lung cancer included could be on the order of one per 100, and concludes that EPA's MCL for arsenic of 50 μg/L requires downward revision as promptly as possible. Those are pretty strong conclusions based on data explicitly stated as not being endorsed for the use of risk assessment. The lung cancer data from the Taiwan data had not been analyzed at all, and the risk from lung cancer was based on the claim that, "some studies have shown that excess lung cancer deaths attributed to arsenic are 2-5 fold greater than the excess bladder cancer deaths" (NRC1, p.8). The supporting statement in the body of the report appears to be that studies in Chile (Smith et al., 1998) and Argentina (Hopenhayn-Rich et al., 1996, 1998) "observed risks of lung and bladder cancer of the same magnitude as those reported in the studies in Taiwan at comparable levels of exposure." (NC1, p.292) The current author is not aware of any analyses to support that statement, however, and in the opinion of the second NRC committee, exposure levels were not sufficiently well quantified in those studies to support a quantitative dose-response analysis (NRC2, Ch. 5).

The article by Morales et al. (2000) that analyzed the southwestern Taiwan data in considerable detail—employing a number of different models and addressing cancer risk of bladder, lung, and liver—appeared after NRC1 and was influential to the subsequent EPA analysis and to NRC2. The article expresses concerns about the Taiwan data; but, like NRC1, doesn't let it interfere with drawing some substantive conclusions about the risk of arsenic. Results were reported to depend

highly on the choice of model, as well as whether or not a comparison population was used in the analysis. It is noted that exposure is measured at the village level, and that there appears to be variability in the exposure assessment, causing high variability in the risk estimates. The article concludes, however, that, *in spite of that*, and other factors that may affect risk but could not be evaluated quantitatively, the current standard of 50 μg/L of arsenic in drinking water is associated with a substantial increased risk of cancer. It is a little difficult to see how the "in spite of" part of the conclusion is justified, without extensive simulations or something else for support.

NRC2 makes almost no mention of treating individuals within a village as if they were all exposed at the same arsenic concentration, even though the well concentrations in a village may cover a wide range. Instead, reference is made to measurement error, which refers to error on the dose scale. An exercise is included in Chapter 5 in which the exposure data in southwestern Taiwan is addressed using theory of measurement error in nonlinear models. Further assumptions are required, however, that appear questionable, and it is concluded that "The analysis reported here is based on strong assumptions and should not be over interpreted as an actual assessment of the measurement error." NRC2 (Ch. 5) Further exploration of the issue is recommended (NRC2, Ch. 5). The executive summary, however, simply notes that statistical analyses were conducted to investigate the sensitivity of the risk estimates to measurement error, as if the issue (Assumption 2) had been addressed satisfactorily. It is not clear to the current author, however, that measurement error is an appropriate approach (aside from the strong assumptions required), because the problem is not being able to match individuals to a specific well(s). Nonetheless, the executive summary concludes that, “There is a sound database on the carcinogenic effects of arsenic in humans that is adequate for the purposes of a risk assessment,” and that, "The human data from southwestern Taiwan used by EPA in its risk assessment remain the most appropriate for determining quantitative lifetime cancer risk estimates." NRC2 also analyzed the data from a small case-control study of lung cancer in Chile that had an issue regarding the selection of controls. NRC2, however, appears to be concluding that the Taiwan data are a sound database for use in risk assessment which, based on Figure 1 alone, is not statistically warranted.

## References

**EPA**. U. S. Environmental Protection Agency, "40 CFR Parts 9, 141, and 142, Final Rule: National Primary Drinking Water Regulations; Arsenic and Clarifications to Compliance and New Source Contaminants Monitoring," Code of Federal Regulations, 66(14), January 22, 2001.

**EPA**. U. S. Environmental Protection Agency, *Respiratory Health Effects of Passive Smoking: Lung Cancer and other Disorders*. EPA/600/6-900/006F, 1992: Washington, DC. U. S. EPA.

**Morales**, K.H., L. Ryan, T.L Kuo, M.M. Wu, and C.J. Chen, "Risk of Internal Cancers from Arsenic in Drinking Water," *Environmental Health Perspectives*, vol. 108, no. 7, 2000. pp. 655-661.

**NRC1**. National Research Council, *Arsenic in Drinking Water*. 1999: Washington, DC. National Academy Press.

**NRC2**. National Research Council, *Arsenic in Drinking Water: 2001 Update*. 2001: Washington, DC. National Academy Press.

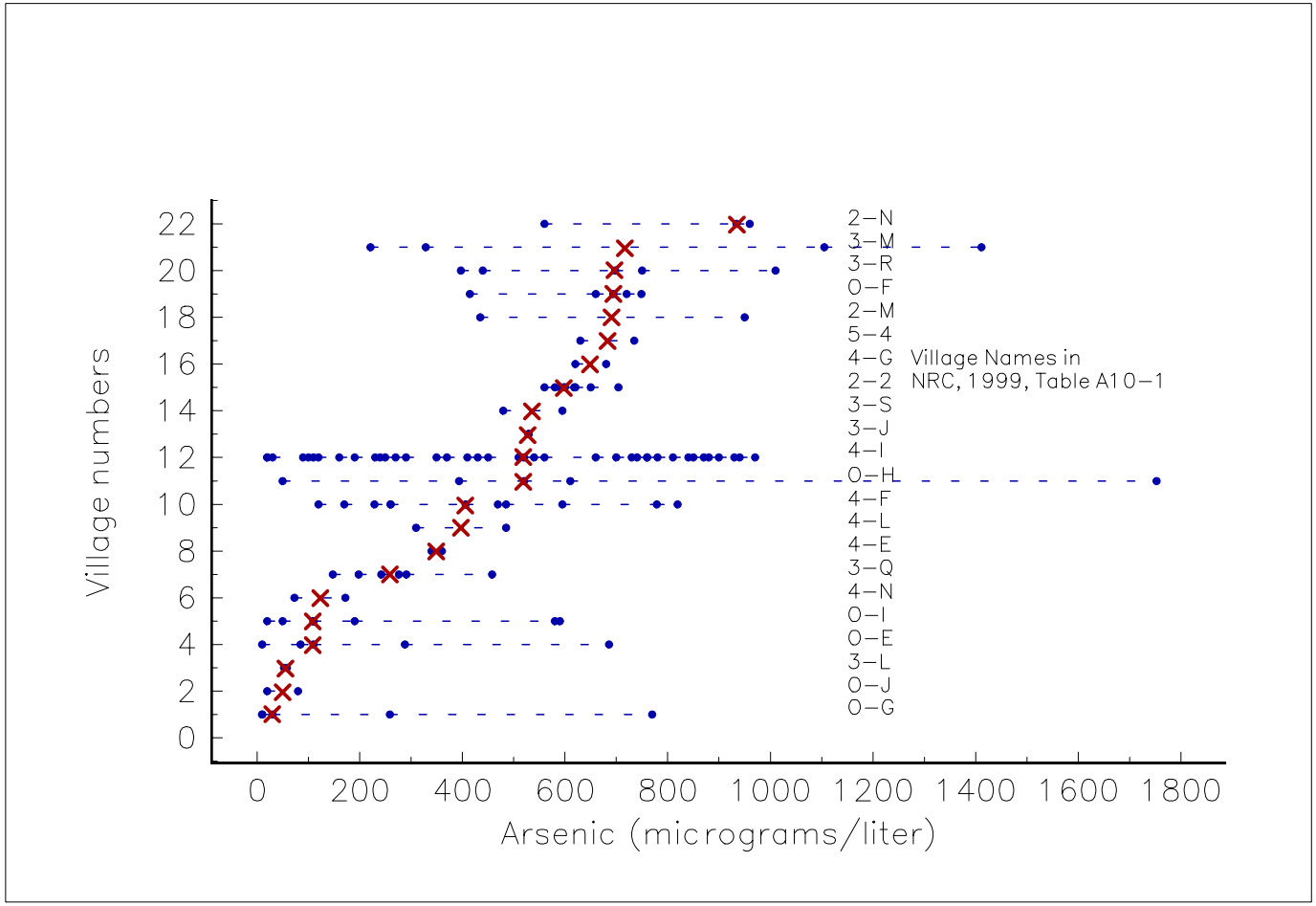


**Figure 1.** Arsenic well tests from villages with multiple wells in southwestern Taiwan database (NRC1, A10-1)

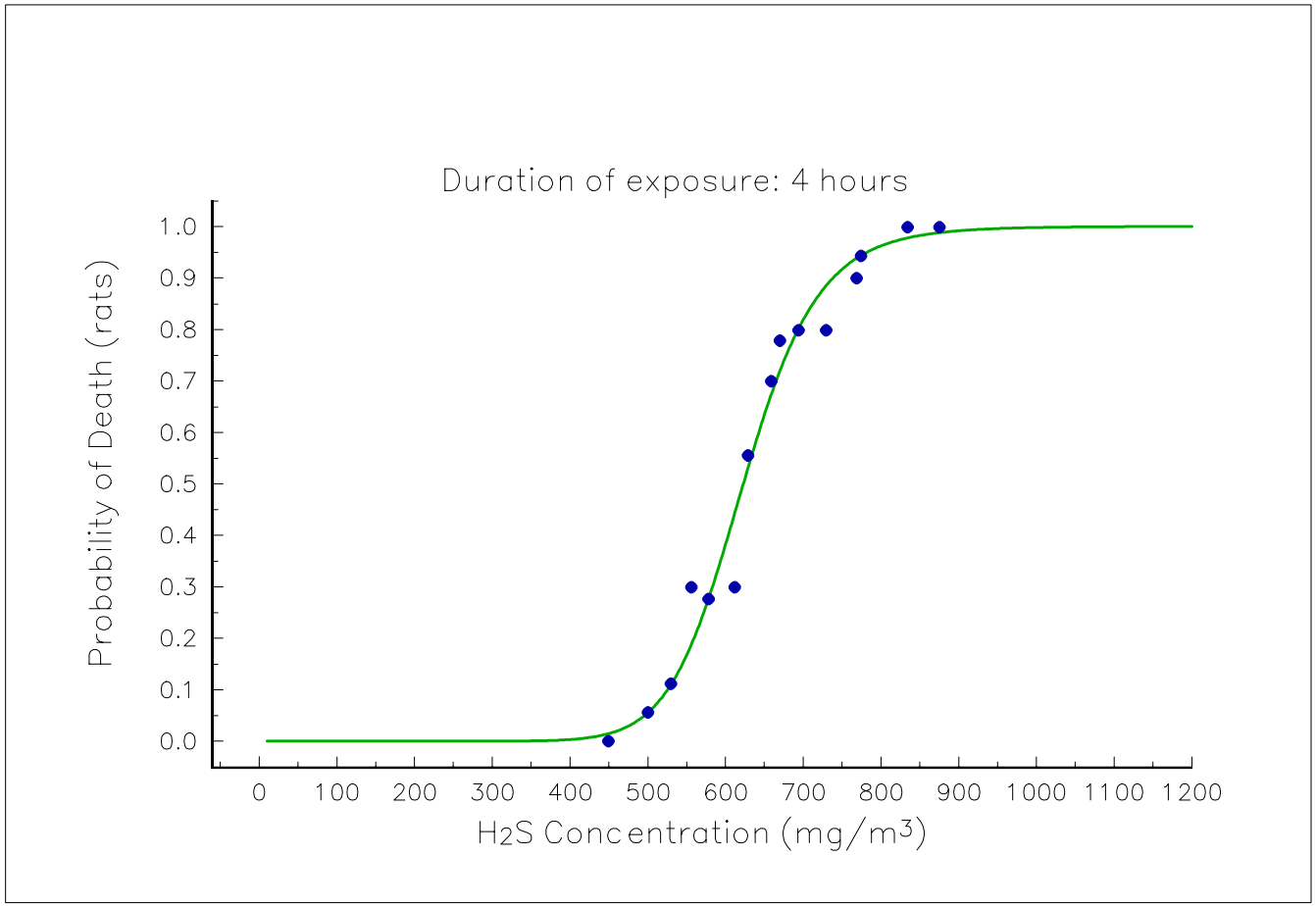


**Figure 2.** Example of dose-response (mortality of rats exposed to hydrogen sulfide fit with logistic regression to the log-transformed concentration).

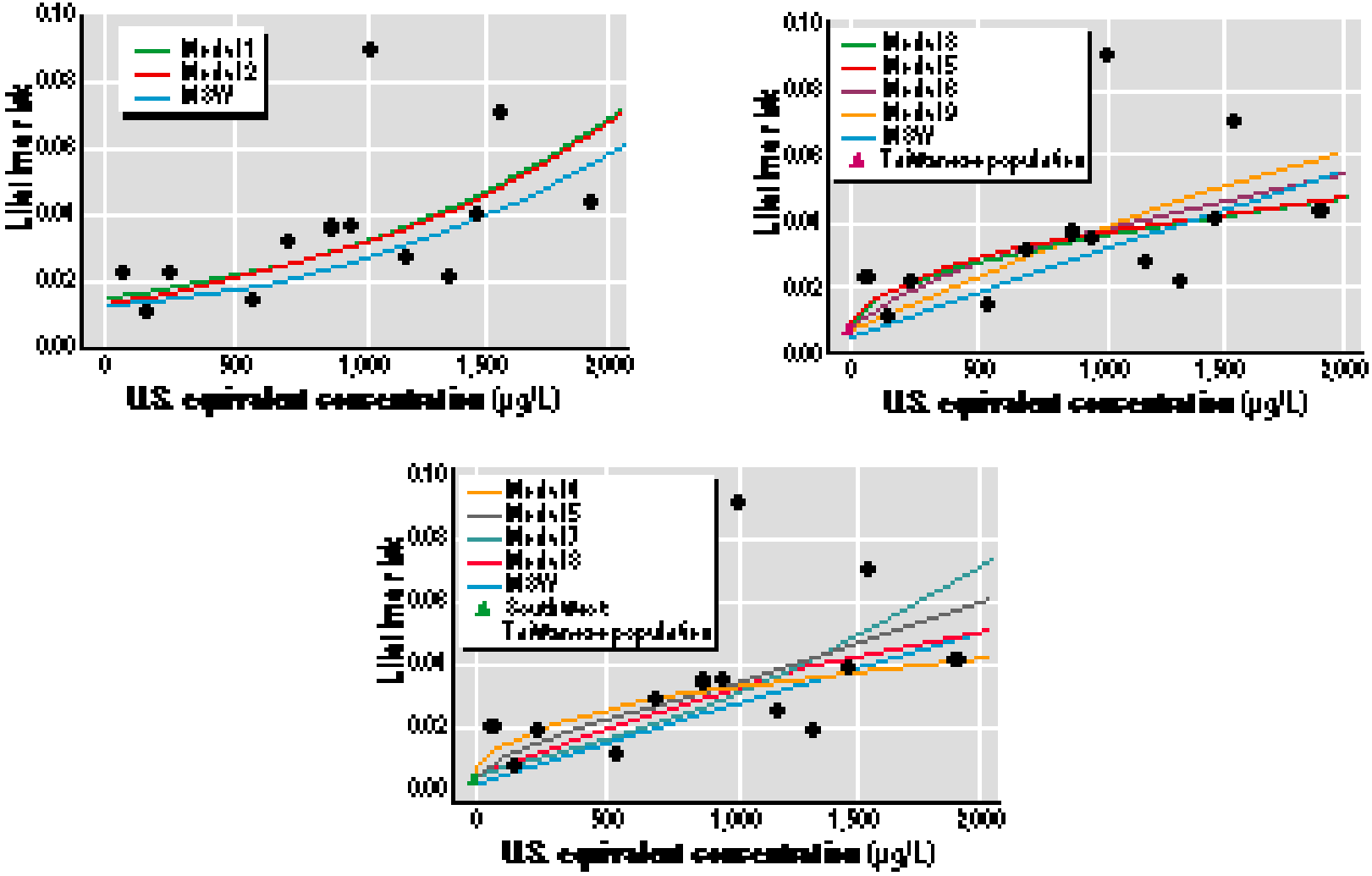


**Figure 3.** (clockwise from top left) Estimated lifetime death risk for male bladder cancer without comparison population, with Taiwanese-wide comparison population, with southwestern Taiwanese region comparison population. For a description of models, see Table 6 of Morales et al. (2000*)*. (Reprinted with permission of *Environmental Health Perspectives*)