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COMMENTS TO THE EPA SCIENCE ADVISORY BOARD ON EPA'S "NATIONAL PRIMARY DRINKING WATER REGULATIONS: PROPOSED LEAD AND COPPER RULE REVISIONS"

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As some of you know, I am Professor of environmental engineering with specialties in physical-chemical water treatment and reuse, and probabilistic risk assessment. As a member of the Board, I support the recommendations in the draft report, and would like to reinforce one point. That is, I support the recommendation of a 10 µg/L action level for lead. In fact, I would like to see 5 µg/L if not for limitations in chemical analysis and treatment capability, for the following reasons.

In environmental regulation of chemicals, we typically have information on health response (e.g., in animals) to doses that are orders of magnitude higher than the doses that might produce an acceptably-low population health response. Even using emerging "high throughput toxicokinetic" approaches, an understanding is needed of the relationship between biological perturbations to stress-response pathways such DNA-response, and the apical adverse outcomes of interest such as cancer, and truly predictive models bridging this gap are still a subject of active research. Hence, regulatory standard-setting has involved implicit low-dose extrapolation.

Our group has focused on this problem of low-dose extrapolation, and has derived the emergent first-order dose-response function from first principals, offering theoretical basis for low-dose extrapolation as a top-down approach. It should be noted that the linearized multistage model in general use is not biologically-based, but in fact assumes that "the time from cancer initiation in a single cell until an observable cancer develops in a tissue is … functionally independent of the dose rate"[(1)], and more generally that the numbers and severities of initiating events along a mode of action are independent (through its basis in the original multistage model). In contrast, the emergent first-order model recognizes the correlation among causes of illness, whether due to a higher-level common cause or to the propagation of severity through a cascading system, as well as the multiplicative or first-order relationship among causes along a pathway. This first-order model appears to fit all of the data we have analyzed more closely than competing models.[(2)]

While well-known as a neurotoxin, lead has been associated with many illnesses including cancer. With the approach just described, I analyzed the most informative dose-response dataset cited in the EPA IRIS entry for lead, described in IRIS as follows:

> "Azar et al. (1973)[3] administered 10, 50, 100, and 500 ppm lead as lead acetate in dietary concentrations to 50 rats/sex/group for 2 years. Control rats (100/sex) received the basal laboratory diet. In a second 2-year feeding study, 20 rats/group were given diets containing 0, 1000, and 2000 ppm lead as lead acetate. No renal tumors were reported in the control groups or in treated animals of either sex receiving 10 to100 ppm. Male rats fed 500, 1000, and 2000 ppm lead acetate had an increased renal tumor incidence of 5/50, 10/20, and 16/20, while 7/20 females in the 2000 ppm group developed renal tumors."

Data for males, which were more susceptible than females, were used. As can be seen, no tumors were detected in the first four dose groups including zero-dose, or in the control group.

The basic first-order dose-response function[1] is valid with or without the assumption of a threshold dose, generally assumed only for non-carcinogens, and can be implemented assuming that background stressors act by (a) the same pathogenic mode as the toxicant (lead), or (b) by a dissimilar mode.[2] Hence, it was first attempted to fit the common and dissimilar mode, non-threshold first-order models, and the multistage model, with and without background risk, to these cancer data, by maximizing the chi-squared *p*-value of the -2-log-likelihood ratio. However, none of the three 2-parameter models (no background risk) or three 3-parameter dose-response models (background risk) could be fitted adequately (no convergence following 5 million iterations). This result might be expected for a carcinogen, for which zero-level responses might not be likely if, say, one million mice were tested at those doses.

To address the issue that zero cancer responses are not likely across large populations, the plotting position of the zero-responses was adjusted to 0.025, noting that a response of zero in 100 mice tested (including females) indicates, on average, a response between zero and 0.5 mice in 100. The resulting data were successfully fitted to all three models, as shown in Figure 2. All three models suggest a significant population cancer risk, as zero dose is approached.

Currently the US cancer rate is almost three times the global average.[4] Recognizing that lead bio-accumulates in the body, that chemical analytical and water treatment capability limit the level at which an action level can be set, and that the simple analysis presented here cannot begin to address the uncertainties involved, my conclusion is that 10 μg/L is a practical, rather than conservative, value for the action level. I hope these comments are useful, and that the recommendations of the SAB are implemented.

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[1] $F(d) = \exp[-(d/\eta)^{-\eta}]$, in which d is dose, ξ is a scaling (units) parameter, and η indicates the span and internal autocorrelation of the toxicological pathway.

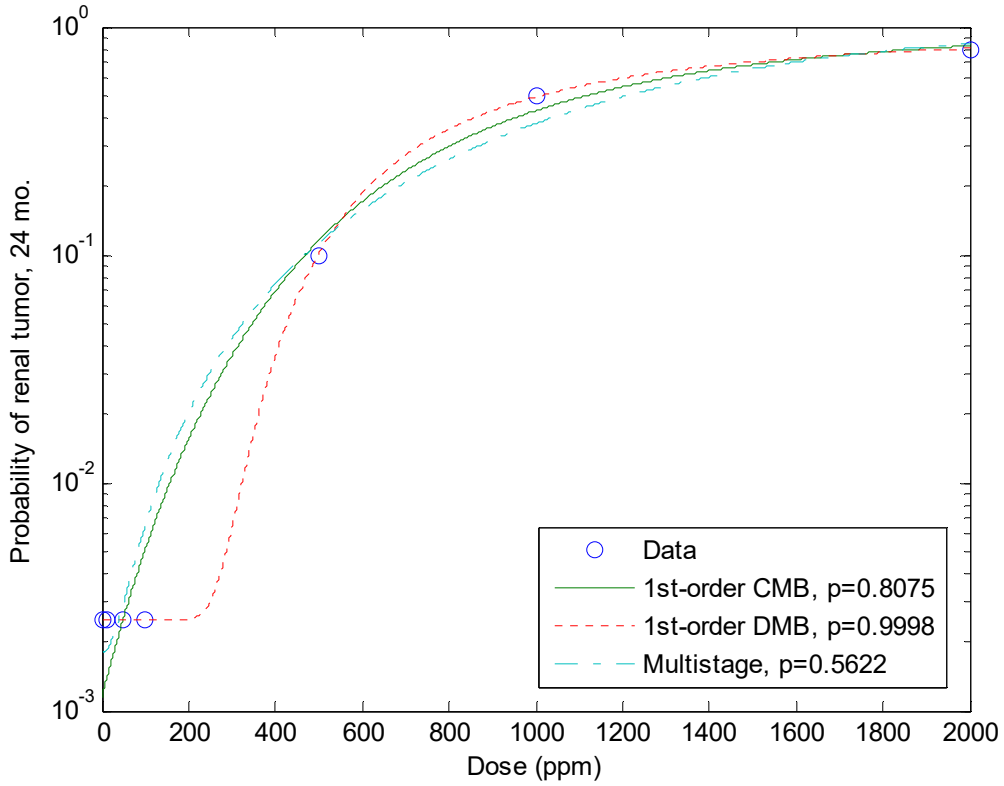

Figure 1. First-order non-threshold common-mode background (CMB), first-order non-threshold dissimilar-mode background (DMB), and multistage models, fitted to the data of Azar et al.[3] on 24-month lead acetate carcinogenicity in male rats.

References

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