Gradient

November 15, 2010

Dr. Angela Nugent, Designated Federal Officer
US EPA Science Advisory Board (1400R)
1200 Pennsylvania Avenue, NW
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Dear Dr. Nugent:

I am writing to provide comment on the United States Environmental Protection Agency (US EPA) 2010 draft "Toxicological Review of Inorganic Arsenic" (2010 IRIS Draft) (US EPA, 2010a) and its review by the Science Advisory Board (SAB). The SAB meeting scheduled for November 22, 2010, is set to consider the report of the Arsenic Workgroup on its assessment of the sufficiency of US EPA's responses to the review of the 2005 draft "Toxicological Review of Inorganic Arsenic" (2005 IRIS Draft) (US EPA, 2005a) that was expressed in the SAB's 2007 review report (SAB, 2007).

The issue I wish to address in the present letter is an overarching one that applies not only to the current draft arsenic assessment, but also to other key carcinogenicity assessments for which the SAB is currently conducting peer review, in particular, to the draft assessment of dioxin (US EPA, 2010b). The issue is this: in both the dioxin and the arsenic draft assessment documents, the Agency suggests that, because the mode of action has not been fully defined, Agency Guidelines compel it to resort to a linear low-dose extrapolation. But an attentive reading of the Guidelines clearly shows that there is no such compulsion – indeed, the Guidelines *mandate* the Agency to *include nonlinear assessments* for agents having nonlinear modes of action as scientifically plausible (even if unproven) possibilities. Peer reviews of earlier versions of both the dioxin and arsenic documents by the SAB and NAS have called for addition of nonlinear analyses, and for dioxin, the discussion in a recent public SAB review meeting on that chemical seemed to indicate that the panel was intending to renew this recommendation to include nonlinear analyses. For both dioxin and arsenic carcinogenicity, there is strong and widely recognized scientific evidence that strongly supports at the biological plausibility of a nonlinear or threshold exposure-response relationship for carcinogenicity. For both dioxin and inorganic arsenic, the sole mode of action that would actively indicate low-dose linearity – a directly genotoxic action by reaction with DNA – has been ruled out, and the contending possibilities for mode of carcinogenic action are all nonlinear. Thus, the same considerations should apply to both.

Most importantly for the current deliberations, the SABs for arsenic and dioxin (SAB, 2007; US EPA, 2010b) and the recent National Research Council review of proposed US EPA carcinogenicity for dioxin (NRC, 2006) have specifically called attention to the substantial evidence for nonlinear exposure-response and have pointedly urged US EPA to revise its assessments to address the possibility in the form of fully developed and forthrightly presented nonlinear dose-response models. To quote the 2007 SAB review of US EPA's then current draft arsenic carcinogenicity assessment (SAB, 2007):

> *"At present the experimental evidence on MOA of inorganic arsenic supports a possible nonlinear dose-response at low exposure levels yet there is no clear indication of what shape a nonlinear dose-response would take for application to human cancer risks at low exposures (< 50 or < 100 ppb)…it is clear that effects are only seen at doses that induce cytotoxicity.* ***This implies a threshold.*** *" (p. 44)*

*"Studies of indirect genotoxicity strongly suggest the possibility of a threshold for arsenic carcinogenicity." (p. 6)*

*"Arsenic essentiality and the possibility of hormetic effects are in need of additional research to determine how they would influence the determination of a threshold for specific arsenic-associated health endpoints." (p. 6)*

*"[T]he Panel discusses studies of indirect genotoxic effects associated with iAs and/or its metabolites, as well as the notion that iAs might have some beneficial effects at very low doses. Taken together, these studies suggest the possibility of a threshold." (p. 27)*

It is notable that the SAB has taken this position even as it recognized that for neither chemical has the full basis for a nonlinear mode of action been completely or unassailably proven. The SAB reviews have noted that, in view of their substantial scientific support and plausibility, nonlinear assessments should be provided in addition to linear ones in order to provide a forthright and full characterization of the scientific understanding about the possibilities of low-exposure cancer risks.

*"The Panel recognizes the potential for a highly complex mode of action of iAs and its metabolites, and until more is learned about the complex PK and PD properties of iAs and its metabolites there is not a sufficient justification for the choice of a specific nonlinear form of the dose-response relationship." (p. 43)*

Unfortunately, it is also the case for both dioxin and arsenic that the current US EPA draft carcinogenicity assessments largely dismiss nonlinear approaches, addressing them only nominally (so as to comply with SAB review, if only in a technical sense). The US EPA documents' treatment of nonlinearity in these cases is largely focused on providing reasons to dismiss it as worthy of any real consideration.

It is critically important – not only for arsenic but also for the larger question of Agency risk assessment policy and the SAB's scientific advice on carcinogenicity assessments in general – to recognize that NCEA's reluctance to heed SAB's urging to forthrightly consider nonlinear models *is in violation of its own guidelines*. The 2005 US EPA Guidelines for Carcinogen Risk Assessment (US EPA, 2005b) state:

*"Where alternative approaches have significant biological support, and no scientific consensus favors a single approach, an assessment may present results using alternative approaches. A nonlinear approach can be used to develop a reference dose or a reference concentration." (Section 1.3.4, p. 1-15)*

*"A nonlinear approach should be selected when there are sufficient data to ascertain the mode of action and conclude that it is not linear at low doses and the agent does not demonstrate mutagenic or other activity consistent with linearity at low doses." (Section 3.3.1, p. 3-22)*

*"When risk assessments are performed using only one set of procedures, it may be difficult for risk managers to determine how much health protectiveness is built into a particular hazard determination or risk characterization. When there are alternative procedures having significant biological support, the Agency encourages assessments to be performed using these alternative procedures, if feasible, in order to shed light on the uncertainties in the assessment." (Section 1.3.1, p. 1-8)*

*"If critical analysis of agent-specific information is consistent with one or more biologically based models as well as with the default option, the alternative models and the default option are both carried through the assessment and characterized for the risk manager." (Section 1.3.1, p. 1-9)*

*"Extrapolation is based on extension of a biologically based model if supported by substantial data…Otherwise, default approaches can be applied that are consistent with current understanding of mode(s) of action of the agent, including approaches that assume linearity or nonlinearity of the dose-response relationship…." (Section 1.3.4, p. 1-14)*

*"Both linear and nonlinear approaches are available…when multiple estimates can be developed, the strengths and weaknesses of each are presented." (Section 3, p. 3-1)*

*"An assessment that omits or underestimates uncertainty can leave decision makers with a false sense of confidence in estimates of risk.… Model uncertainty is expressed through comparison of separate analyses from each model, coupled with a subjective probability statement, where feasible and appropriate, of the likelihood that each model might be correct…. Some aspects of model uncertainty that should be addressed in an assessment include…the use of effects observed at high doses as an indicator of the potential for effects at lower doses, [and] the effect of using linear or nonlinear extrapolation to estimate risks." (Section 3.6, p. 3-29)*

An argument against providing nonlinear alternative assessments is often made by claiming that, because the nonlinear mode of action cannot be fully described with confidence or modeled with precision, the guidelines compel choice of a linear extrapolation approach. The above quotations from the US EPA guidelines (US EPA, 2005b) make clear that this is not the case – on the contrary, the guidelines explicitly make a point of saying the opposite, noting:

*"A nonlinear extrapolation method can be used for cases with sufficient data to ascertain the mode of action and to conclude that it is not linear at low doses but with not enough data to support a toxicodynamic model." (Section 3.3.4, p. 3-23)*

*"Nonlinear extrapolation having a significant biological support may be presented in addition to a linear approach when the available data and a weight of evidence evaluation support a nonlinear approach, but the data are not strong enough to ascertain the mode of action applying the Agency's mode of action framework." (Section 3.3.4, p. 3-23)*

In its current deliberations, I urge the SAB not to abandon the sound advice that it gave the Agency in its 2007 review of the arsenic carcinogenicity assessment to give serious evaluation to nonlinear assessment approaches and to fully consider the scientific evidence (which has grown and strengthened since 2007) that suggests thresholds of arsenic exposure for affecting the carcinogenic process. The 2007 SAB review asked the Agency to take up the question of reconciling its low-dose extrapolation approaches with mechanistic understanding of arsenic carcinogenesis and with the lack of apparent dose-response effects in low-dose human studies conducted in the US. This was not only sound advice for the Agency, it is indeed the stance mandated by the Agency's own guidance.

I also urge the SAB to make sure that advice it now gives to US EPA is fully in accord with what the US EPA Guidelines for Carcinogen Risk Assessment and its Risk Characterization Handbook actually mandate, and not what they are sometimes presumed to say. Indeed, I would ask that the SAB bear in mind the larger risk assessment policy question about characterizing uncertainty and

scientifically supportable alternatives in low-dose extrapolation, including its bearing on assessments of other chemicals, as it considers its stance on the review of the current US EPA draft inorganic arsenic assessment. It is important that the SAB avoid focusing too narrowly on a restricted set of particular aspects of the arsenic assessment, thereby inadvertently making an implicit policy decision on the circumstances that, by precedent, might be taken to indicate, permit, or preclude consideration of nonlinear analyses, especially when the basis for the only substantial linear mechanism has been excluded. This larger issue of proper interpretation of existing Agency guidance will affect not only arsenic, but other chemicals as well.

The above comments are my own, prepared with the support of Luxembourg-Pamol, Inc.

Sincerely,

GRADIENT

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Principal

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