

**NCEA's Proposed Charge to External Reviewers for the
IRIS Toxicological Review of Inorganic Arsenic (cancer)
February, 2010**

Introduction

The current IRIS assessment for inorganic arsenic (iAs) was posted on the Integrated Risk Information System (IRIS) database in 1988. In 2003, the U.S. Environmental Protection Agency (EPA) decided to update the 1988 IRIS assessment to address recommendations made by a National Research Council (NRC 2001) panel which concluded that the cancer risk for iAs should be based on internal cancers (lung and bladder) instead of skin cancers. The EPA evaluated and implemented the NRC (2001) recommendations and in 2005 submitted a draft Toxicological Review of Inorganic Arsenic (or IRIS assessment) to the EPA's Science Advisory Board (SAB) for external peer review. The SAB review was completed and the final report was submitted to the EPA Administrator in June 2007 (see EPA-SAB-07-008 at www.epa.gov/sab). EPA now seeks to obtain a focused SAB review of the responses to several key SAB (2007) recommendations in the 2010 revised draft IRIS assessment. The assessment will appear on the Agency's online IRIS database when completed.

The 2010 draft IRIS assessment provides an overview of the sources of exposure to iAs, reviews the epidemiological and toxicological data for iAs and its metabolites, characterizes the hazard posed by iAs exposure for carcinogenic health effects based on the available scientific evidence, evaluates the utility of the available epidemiological studies for assessing cancer risk, includes the derivation of an oral slope factor for carcinogenic effects, and contains a series of sensitivity analyses of assumptions and alternatives in the risk assessment modeling. A summary of the SAB (2007) recommendations and EPA's response is provided in Appendix A of the 2010 draft IRIS assessment. This assessment does not derive noncancer human health toxicity values (e.g., chronic reference dose, RfD) for inorganic arsenic. The noncancer IRIS assessment is currently under development and has not yet been released for public comment or external peer review.

Charge Overview

The goal of this focused external peer review is to evaluate EPA's implementation of the key SAB (2007) external peer review recommendations. This focused review should concentrate on EPA's responses to the SAB comments in Appendix A and the corresponding revisions in the 2010 draft IRIS assessment. Please provide specific responses to the Charge below. If there are recommendations for further changes or additions to the assessment, please provide specific information on how those changes could be implemented with the currently available scientific information.

Please note, each of the following Charge questions is preceded by a brief overview of the recommendations and conclusions provided to the EPA by the SAB in their final report to the Administrator as well as an overview of EPA's response. This text is to provide context to the Charge that focuses on the key recommendations and conclusions made by the SAB. The complete SAB (2007) document is found at www.epa.gov/sab (EPA-SAB-07-008). Please refer to Appendix A of the 2010 draft IRIS assessment for EPA's response.

Charge to the SAB Arsenic Review Panel

Charge 1:

The SAB concluded that the Taiwanese dataset (Wu 1989; Chen et al., 1988, 1992) remains the most appropriate dataset to determine carcinogenic risk due to exposure to iAs. They recommended that EPA should evaluate other published epidemiology studies using a uniform set of criteria and document these findings in the assessment. They also stated that if one or more studies provide potential utility, comparisons should be provided in the assessment.

EPA agreed that the Taiwanese data were the best available for determining the carcinogenic risk due to exposure to iAs. In response to SAB's recommendation, an extensive review and evaluation of all available human studies for iAs using the criteria suggested by the SAB was performed and is summarized in Section 4.1 of the draft IRIS assessment and included in tabular format in Appendix B. EPA concluded in the 2010 draft IRIS assessment that there were no additional epidemiological studies that had comparable utility to the Taiwanese dataset (Wu 1989; Chen et al., 1988, 1992).

Please comment on EPA's response to the recommendations and the conclusions of the SAB (2007) Arsenic panel regarding the evaluation of the epidemiological literature.

Charge 2:

The SAB noted the possibility of a nonlinear dose-response at low exposures, but due to uncertainty in the mode of action (including pharmacokinetics and dynamics) the use of a linear low dose extrapolation approach to determine the cancer risk for iAs was recommended using cancer incidence from the Taiwanese dataset. In addition, the SAB stated that EPA should perform a sensitivity analysis for the variables in the cancer modeling with respect to the Taiwanese dataset (i.e., exposure metrics, subgroup of villages with more than one well measurement, and a multiplicative model that includes a quadratic term for dose). The SAB concluded that overall, EPA had implemented the recommended modeling by NRC (2001). Also, the SAB made recommendations to perform a sensitivity analysis regarding the robustness of the model and alternative formulations.

Consistent with the SAB recommendations, EPA used a linear low-dose extrapolation approach and conducted a sensitivity analysis of nonlinear forms of the dose-response in the 2010 draft IRIS assessment. EPA also explored nonlinear forms of the dose-response from the Taiwanese dataset (Wu 1989; Chen et al., 1988, 1992). Sensitivity analyses using alternative dose-response models produced potency estimates similar to the linear approach.

Please comment on EPA's response to the SAB's recommendations and conclusions regarding the approach to modeling inorganic arsenic cancer risks and the corresponding sensitivity analyses.

Charge 3:

The SAB did not recommend specific values for the exposure assumptions or parameters used in the cancer model. They did, however, recommend evaluating the impact on the cancer risk of using a range of values, assessing the variability, and conducting a sensitivity analysis for exposure parameters (e.g., water intake, background dietary exposure).

EPA evaluated the impact on the estimated cancer risk of using a range of exposure parameter values (e.g., water intake, background dietary exposure), assessed variability, and conducted a sensitivity analysis. After the completion of these analyses, values were chosen for exposure assumptions based upon the best available science taking into account the NRC (2001) recommendations.

Please comment on EPA's sensitivity analyses and choice of the exposure assumptions used in modeling cancer risk as recommended by the SAB (2007) Arsenic panel.