UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

SEP 16 1992

THE ADMINISTRATOR

Dr. Raymond C. Loehr
Chair
Executive Committee
Science Advisory Board
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Dear Ray:

Thank you for your letter of May 12, 1992, in which you provided the Science Advisory Board's (SAB) response to the Office of Research and Development's (ORD) arsenic research recommendations. I appreciate the guidance that the SAB Drinking Water Committee (DWC) has provided to ORD over the past 18 months concerning research to improve the risk assessment for this important environmental contaminant. As you know, I have placed a high priority on making sure that decisions at the Environmental Protection Agency (EPA) are based on the best scientific knowledge. The work of the DWC on arsenic clearly supports this objective.

The Health Effects Research Laboratory (HERL) within ORD is conducting or planning research activities on arsenic that address many of the DWC's recommendations. This research is expected to produce some important results within a 3-5 year time frame, while other efforts are more long-term. Specific research on arsenic at HERL is discussed in the enclosure.

Thank you again for the SAB's commitment to improving the science at EPA. I look forward to your guidance on other scientific matters of concern to the Agency in the future.

Sincerely yours,

William K. Reilly

Enclosure

U.S. EPA RESEARCH ON ARSENIC

Laboratory and field research is being conducted or planned at HERL to improve our understanding of the toxicity of arsenic. This includes laboratory studies to evaluate the mechanism(s) by which arsenic causes toxicity, pharmacokinetic studies in animals to determine the relationship between metabolism and toxicity, and epidemiologic studies to evaluate metabolic parameters and dose-response relationships in humans. These research activities are part of an integrated research program that addresses many of the recommendations of the SAB. A brief description of these activities is provided below:

1. Mechanistic Studies

Research to address the DWC's Recommendation #1a includes studies to define the ability of arsenic and its metabolites to cause genetic damage (e.g., gene mutation, chromosomal breakage, endoreduplication). Preliminary experiments have been completed for sodium arsenate and sodium arsenite. Studies with two methylated derivatives will be initiated soon. These are short-term research activities that are expected to yield results over the course of the year.

A mechanistic study of the ability of arsenic and relevant derivatives to cause hypomethylation of DNA is being planned. This research will test the hypothesis that arsenic, which is known to be methylated by a methyl transferase, can deplete the pool of methyl groups needed for proper maintenance methylation of DNA. If arsenic can be shown to be a potent hypomethylator, it would imply that the "detoxification" of arsenic by methylation actually promotes a carcinogenic response.

2. Pharmacokinetic Studies

Studies have been initiated to investigate the relationship of the chemistry of inorganic arsenic to its uptake, metabolism, and disposition kinetics in biological systems. This research seeks to understand at the molecular level the factors that can control arsenic binding and complexation, the enzymology and chemical mechanisms underlying arsenic methylation, and the critical arsenic species and character of toxicologically relevant binding. A determination of the factors that control the delivery of the active form(s) of arsenic to critical target sites within the body will contribute to an understanding of the mechanism of arsenic-induced cancer (DWC Recommendation #1a).

These pharmacokinetic studies are relevant to the DWC recommendations for research in human populations (#1b-d). Such investigations are necessary for understanding the role of methylation in activation and/or deactivation (detoxification) of arsenic, and for assessing the variability of humans to methylate arsenic. This research is also a prerequisite to developing an animal model for arsenic toxicity (DWC Recommendation #2a).

3. Human Studies

Efforts are underway to identify arsenic-exposed populations in the U.S. and elsewhere that would be suitable for epidemiologic investigations. This approach will provide an opportunity to specifically address DWC Recommendations #1c and 1d, as well as to obtain dose-response data for quantitative risk assessment. Sites in California and Nevada are currently being considered as potential sites for human studies.