Dr. Bruce M. Alberts  
President, National Academy of Sciences  
500 Fifth Street, NW  
Washington, DC  20001

Dear Dr. Alberts:

Perchlorate, a propellant critical to aerospace and defense operations since the 1950s has been identified at various levels in the environment near some past and current facilities. There are differing interpretations of the science associated with the impact on human health from low level exposure to perchlorate. The U. S. Environmental Protection Agency (EPA), in conjunction with the Department of Defense, the Department of Energy and the National Aeronautics and Space Administration, is requesting a review by the National Academy of Sciences (NAS) of the science about the health impacts of perchlorate. It is recognized that a review by the NAS of the available science, and the EPA's draft health risk assessment would be beneficial and informative as the Agency moves toward the finalization of the risk assessment.

It is most important to the sponsoring agencies that the correct expertise be engaged in this review. Specifically, the following expertise is considered essential:

Endocrinology (specifically clinical developmental endocrinologists)  
Neurotoxicology (anatomy and behavior with specialization in rat to human translation)  
Animal toxicology/thyroid physiology and carcinogenesis  
Developmental toxicology  
Physiologically-based pharmacokinetic (PBPK) modeling  
Veterinary pathology  
Thyroid endocrinology (research and clinical)  
Pediatrics or Neonatology  
Pediatric endocrinology  
Epidemiology  
Biostatistics (Bayesian, specifically)  
Risk Assessment

The sponsoring agencies are both willing and eager to meet with the review panel once it is established and to provide whatever information the review panel may need. Because of the priority that has been given to the perchlorate assessment and the crucial role of the NAS review, we would appreciate a timely, rigorous and thorough review. Appended please find our charge
questions. We look forward to receiving your proposal for addressing these needs and to assisting and facilitating your efforts in any appropriate way.

Sincerely yours,

[Signature]

Paul Gilman, Ph. D.
Science Advisor
to the Agency

Enclosure
Charge

Perchlorate has been the focus of several recent government analyses and other scientific studies, including a U.S. Environmental Protection Agency Draft Health Assessment. These studies have raised concerns among a number of federal agencies regarding how to best characterize the potential risk posed by chemicals that disrupt the function of the thyroid gland. There has been agreement among the Agencies that a set of scientific questions associated with our ability to understand the health implications of perchlorate exposure be forwarded to the National Academy of Sciences for immediate and accelerated review.

A cross-cutting issue is verification that the key studies underlying the Draft Health Assessment are of the quality, reliability and relevance that are required to draw conclusions about the health implications of exposure to low levels of perchlorate in drinking water among sensitive subpopulations.

For each of the questions posed below, a response may be best represented by either a point estimate or a range. Where specific numbers are lacking in the scientific literature, please use best scientific judgment to determine what range is scientifically defensible.

I. What is the current state-of-the-science or understanding regarding the potential adverse effects due to disruption of thyroid function in humans and other animals at various stages of life?

Multiple researchers have proposed a model that frames potential adverse neurodevelopmental and neoplastic effects of perchlorate to be a consequence of the perturbation of thyroid hormone regulation after disruption of iodide uptake by the gland. Does the state-of-the-science support this basic model?

What is your level of confidence in such a model?

Using best scientific judgment, at what level does the chronic inhibition of iodide uptake lead to adverse, not just adaptive, health effects in humans, especially sensitive subpopulations? Please indicate your level of confidence in each of these determinations.

Consider how the iodine-rich diet in the United States might influence the degree to which adverse effects might be expected in sensitive subpopulations.

II. Using best scientific judgment, what is the level where changes in thyroid hormones can lead to adverse, not just adaptive, health effects in humans, especially sensitive subpopulations? Please indicate your level of confidence in these determinations.
III. Evaluate the key animal studies available for understanding and assessing the implications of perchlorate ingestion. Endpoints of concern should include: brain morphometry, behavioral changes, thyroid hormone changes, and thyroid histopathology.

What is your level of confidence in extrapolating what the adverse changes documented in animals who have ingested perchlorate may mean for adverse effects in humans, especially sensitive subpopulations?

Specifically address the validity of models that extrapolate from studies of brain morphometry in rats to adverse effects in human populations, especially sensitive subpopulations.

IV. For estimating the safe lifetime exposure for humans, especially sensitive subpopulations, uncertainty factors are applied. This application of uncertainty factors involves a combination of scientific and policy judgments. With respect to the science, based on your evaluation of the available animal and human studies, provide insights that can inform the selection of uncertainty factors used in the approximation of a safe lifetime exposure for humans, especially sensitive subpopulations.

V. Would adverse effects other than those associated with iodide uptake inhibition be expected as a result of ingesting low levels of perchlorate on a daily basis?

VI. Based on the responses to the above questions:

Are the EPA foldings consistent with the panel's findings?

Did EPA properly evaluate and consistently critique all the relevant literature that supports, or fails to support, the conclusions in its risk assessment? Did EPA choose the best available scientific studies for use in supporting a health risk assessment?

If your review finds that any other key studies are appropriate but not properly considered by EPA, please provide advice regarding how EPA should use this information and modify their assessment.

What is the range of scientifically defensible values for the percent iodide uptake inhibition that would serve to protect individuals at various life stages and thyroid status? EPA used the lower limit on a 5% response for iodide uptake inhibition as a surrogate for a No-Observed-Adverse-Effect-Level (NOAEL) as a starting point to set a reference dose to be protective of various life stages and thyroid status.
VII. As you review and evaluate the available literature, please suggest specific research projects for reducing the uncertainty in our understanding of the human health effects of low-level perchlorate ingestion, particularly for clarifying safe levels of exposure for sensitive subpopulations. Please provide, for each suggestion, rough estimates for time needed for completion, cost, and the potential to reduce overall uncertainty.