



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

October 29, 1984

OFFICE OF
THE ADMINISTRATOR

Honorable William D. Ruckelshaus
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Dear Mr. Ruckelshaus:

The Environmental Health Committee (EHC) of the Science Advisory Board (SAB) reviewed on July 25 an Agency analysis of a series of studies addressing the cancer risks associated with gasoline vapors. The EPA document was prepared by the staffs of the Office of Health and Environmental Assessment and the Office of Air Quality Planning and Standards, and was entitled, "Estimation of the Public Health Risk From Exposure to Gasoline Vapor Via the Gasoline Marketing Systems" (June 1984).

The Committee review encompassed a number of issues that bear directly on the assessment of the risk posed to public health from the complex mixture of pollutants contained in these emissions. In summary form, the major issues addressed by the Committee and its major conclusions include:

- o the scientific validity and quality of a chronic inhalation bioassay of wholly vaporized unleaded gasoline sponsored by the American Petroleum Institute. The Committee believes that the study was well designed and that the investigators utilized appropriate scientific protocols that support the reported results.

- o the conclusion reached by EPA staff that wholly vaporized unleaded gasoline vapors should be classified as probably carcinogenic to humans, according to the classification procedures developed by the International Agency for Research on Cancer. The Committee agrees with this conclusion.

- o EPA staff analysis of the degree of uncertainty associated with a qualitative and quantitative assessment of human health risk. The Environmental Health Committee believes that the analysis under represents the degree of uncertainty in assessing human health impacts from this complex mixture of pollutants. This is particularly true with respect to the need to more clearly demonstrate how the calculation of population exposures are utilized in the development of risk estimates.

Additional comments and recommendations are summarized in the enclosed report. The Science Advisory Board appreciates the opportunity to provide its review of this important public health issue. We would appreciate receiving a formal response from you on the scientific advice provided in this report. If you desire any further Committee review of this issue, we stand ready to provide the assistance that is requested.

Sincerely,


Herschel E. Griffin
Chairman
Environmental Health Committee


Norton Nelson
Chairman
Executive Committee

cc: Mr. Alvin L. Alm (A-101)
Mr. Joseph A. Cannon (ANR-443)
Dr. Bernard D. Goldstein (RD-672)
Dr. Terry F. Yosie (A-101)

Environmental Health Committee Key Findings and Conclusions
on the Draft Staff Paper, "Estimation of The Public Health
Risk From Exposure to Gasoline Vapor Via the Gasoline
Marketing System" (June 1984)

The Environmental Health Committee (EHC) reviewed only Chapters 5 and 6 of the Gasoline Vapor Staff Paper. The former chapter, entitled "Evaluation of The Carcinogenicity of Unleaded Gasoline" assesses the available scientific literature pertaining to these emissions whereas the latter chapter identifies issues to be addressed by the SAB. The remaining chapters in the document define the context for the Committee's review and present a discussion of the regulatory options identified by the Agency. The Agency did not request the Committee to review these latter chapters since they pertain largely to risk management, and the Committee concurred with this approach.

The Committee addressed three major issues during the course of its review. These include 1) the scientific validity and quality of a chronic inhalation bioassay of wholly vaporized unleaded gasoline sponsored by the American Petroleum Institute, plus other scientific studies bearing on unleaded gasoline vapors; 2) the EPA staff conclusion that, using the classification system developed by the International Agency for Research on Cancer (IARC), these vapors should be regarded as a probable human carcinogen; and 3) articulation of the degree of uncertainty associated with the assessment of human health risk.

Scientific Studies Bearing on Gasoline Vapors

1. The most critical piece of scientific evidence associated with the assessment stems from a chronic inhalation study of two rodent species exposed to unleaded gasoline in a wholly vaporized form sponsored by the

American Petroleum Institute and carried out by the International Research and Development Corporation. A final report of the study was submitted to EPA in March 1984 although previous drafts were also made available. The study reported increases in renal adenoma and carcinoma incidence in exposed male Fischer 344 rats and in hepatocellular adenoma and carcinoma incidence in exposed female B6C3F1 mice. The Environmental Health Committee finds that the study was well designed and that appropriate scientific protocols were observed to support the reported results. The Committee's major technical comments on the study are presented below.

o The issue of the representativeness of the inhaled vapors arose because the material inhaled by the animals is at variance with vapors that people inhale when they come in contact with these emissions. Specifically, the vapors subject to human inhalation contain more volatile and lower molecular weight materials than those administered to the test animals. In addition, there appears to a two to three year lag time before gasoline currently in use can be adequately evaluated for chronic effects. By the time such an analysis is completed, the composition of fuels in the marketplace may have changed. There is some question whether or not these changes would affect the bioassay results. In short, the Committee believes that the issue of the representativeness of the inhaled vapors, while certainly a complicating factor in the API bioassay, should not be regarded as a major flaw.

o The significance of the reported tumors is a factor of major importance in this study. Because the male Fischer rat is susceptible to high tumor incidence--sometimes these animals experience several tumors simultaneously in different organs--many scientists are skeptical of the significance of reported tumors in this species alone. However, this study reports tumors of the liver occurring in female mice, and this is relatively uncommon. From a toxicological perspective, the combined results should dispel concerns about the significance of these tumors.

o The Committee is not in a position to comment on whether the vapors inhaled by the test animals are mutagenic. ORD staff briefed the EHC on an in-house review of mutagenicity studies which led to their tentative conclusion of negative genotoxicity results. However, the Committee has not had the opportunity to review either the original studies or a formal EPA analysis of those studies.

2. Two synthetic fuels entitled RJ-5 and JP-10 were also analyzed. The results showed a pattern of renal carcinomas in Fischer 344 male rats but not females. This is a response similar to those found in the API study. In addition, The U.S. Air force is assessing JP-4 and JP-5 jet fuels. The Committee is informed that preliminary toxicity studies have been completed and show a response pattern of renal toxicity similar to the synthetic fuel studies. Longer term study results are not available. The Agency has appropriately surveyed these sets of studies, but at present, definitive conclusions cannot be drawn from them.

3. Several epidemiological studies were discussed including a number that were not included in the EPA staff document. The majority of these studies do not yield results that conclusively resolve the question of cancer incidence associated with gasoline vapors, although a summary of existing epidemiological information by Enterline provides some evidence of a small excess rate of kidney cancer in many older workers or workers exposed for long periods of time. In short, the EPA staff paper could, for the purpose of presenting a more thorough analysis, more completely reference the available epidemiological literature. The use of this data alone, however, is unlikely to conclusively resolve the issue of the relationship between unleaded gasoline exposure and cancer incidence.

Carcinogenicity and the IARC Criteria

On page 5-81 of the staff paper, EPA summarized its evaluation of the scientific data pertaining to the public health implications of unleaded gasoline vapors. The Agency concluded:

"The occurrence of a small but definite kidney tumor response in male rats and a significant hepatocellular response in female mice furnish sufficient evidence, using the criteria of the International Agency for Research on Cancer (IARC), for the carcinogenicity of unleaded gasoline

in animals. The similar pattern of response in rats to the synthetic fuels RJ-5 and JP-10, and the renal toxicity observed in chronic bioassays with JP-4 and JP-5, support the findings with unleaded gasoline, indicating that some agent or combination of agents common to these mixtures is responsible for the observed effects.

The scattered reports of kidney cancer in workers exposed to gasoline-related compounds hint that some effect may be occurring in humans, but the evidence is judged to be too poor to justify anything but a classification of inadequate under the IARC criteria for epidemiologic evidence. Therefore, unleaded gasoline should be placed in IARC category 2B, meaning that unleaded gasoline is a probable human carcinogen."

The Committee concurs with this statement, although it would more carefully caveat the degree of support the synthetic fuel studies provide to justify the carcinogenicity conclusion. At present, the EHC believes that these studies should not be as strongly weighted as the API chronic inhalation study.

Uncertainties in the Risk Assessment

A prominent feature of the staff paper is the calculation of cancer risk estimates using three mathematical models--multistage, probit and Weibull. Table 5-26 presents a series of estimates of lifetime risk at various dose levels using these extrapolation models. The table is particularly helpful in expressing the impact of the choice of model on the calculated risks.

The Committee has several major concerns with the quantitative risk assessment section of the staff paper. In general, it believes that the staff paper under represents the degree of uncertainty in assessing human health impacts. This Committee and other scientific panels assembled by the National Institute of Environmental Health Sciences and other scientific organizations have previously endorsed mathematical modeling as appropriate for the quantitative assessment of risk. The EHC still has some concern

as to how to identify the limits of such modeling and how to interpret the uncertainties associated with modeling. Specific examples of this concern are presented below.

o The issue of exposure has important implications for understanding human responses. It is difficult to develop precise estimates of human exposure because of uncertainties concerning the composition of what people inhale and the magnitude of exposures. It appears, from data supplied to the Committee, that people inhale the more volatile and lower molecular weight fractions of gasoline vapors whereas the test animals were administered both heavy and light fractions. The magnitude of human population exposures can be discussed qualitatively. It is reasonable to assume that general population exposures are considerably less than those confronting certain occupational groups such as truck drivers or gasoline vendors. The Committee believes that EPA should provide a more detailed analysis of how population exposures are calculated than is presented in this staff paper. Also, the Agency should articulate much more clearly how it plans to use exposure information in developing risk estimates. Absent this discussion, it is difficult to understand how the risk estimates generated from the use of mathematical models for the hazard assessment represent a meaningful set of numbers.

o Many examples of the complexities that should enter into the dose-response estimation process have been discussed within our Committee, both generically across chemicals and specifically for gasoline vapors. These issues include: 1) treatment of benign vs. malignant tumors. The rat kidney tumors observed in the API data were microscopic in size and apparently did not result in decreased life span of the animals. Do these tumors imply life-threatening tumors in man? 2) linearity through the origin versus nonlinearity or thresholds in the choice of dose-response model. Do the liver tumors in B6C3F1 mice and/or the kidney tumors in the Fisher 344 rats result from non-genotoxic cellular damage mechanisms implying that a linear nonthreshold model would be inappropriate for low dose extrapolation? and 3) is parts per million in air appropriate, or should mg/surface area, mg/kg of body weight, or some other method be used?

o An alternative to the preparation of the qualitative discussion alone is to supplement this discussion with sensitivity analysis cases showing that different assumptions can lead to risk estimates differing by many orders of magnitude, rather than the agreement within about a factor of two as shown in Table 1-3.

The EPA may not be able to resolve all of these issues based on the information available at this time. However, the Committee wishes to raise them for the purpose of comprehensiveness.