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Project Summary

Evaluation of the Carcinogenicity of Unleaded Gasoline

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In the final report, the likelihood that unleaded gasoline vapors are carcinogenic to humans is evaluated. From carcinogenicity data in animals, an estimate is made of the magnitude of cancer risk a person would experience, if exposed for a lifetime to 1 ppm in the ambient air, under the assumption that gasoline vapors are carcinogenic. All studies believed to be relevant to determining the potential carcinogenicity of unleaded gasoline vapors are reviewed including: (a) chronic and shorter-term animal studies of aerosolized whole gasoline, various gasoline fractions, and analogous hydrocarbon mixtures; and (b) epidemiologic studies of occupations involving exposure to gasoline vapors. Fifty-five epidemiologic studies involving gasoline exposure are reviewed. A quantitative analysis of cancer incidence in the two long-term animal gasoline inhalation studies is performed, an upper-bond cancer risk potency estimate is calculated, and the uncertainties in the estimate are discussed. The major conclusions are: (1) although employment in the petroleum refineries is possibly associated with cancers of the stomach, respiratory system, and lymphopoietic and hematopoietic tissues, exposure to gasoline cannot be implicated as a causative agent because of confounding exposure to other chemicals and inadequate information on gasoline exposure; (2) the occurrence of liver cancer in female mice and kidney cancer in male rats provides "sufficient" evidence in animals that inhalation of wholly aerosolized gasoline is carcinogenic; and (3) gasoline vapors from vehicle refueling might be less carcinogenic than indicated by animal experiments using wholly aerosolized gasoline, if the less volatile components, which are apparently responsible for acute kidney toxicity, also contribute to the observed carcinogenic response.

This Project Summary was developed by EPA's Office of Health and Environmental Assessment, Washington, DC, to announce key findings of the research project that is fully documented in a separate report of the same title (see Project Report ordering information at back).

Introduction

This document presents an evaluation of the likelihood that unleaded gasoline is a human carcinogen and provides a basis for estimating its possible public health impact, including a potency evaluation in relation to other carcinogens. The evaluation of carcinogenicity depends heavily on animal bioassays and epidemiologic evidence. However, other factors, including mutagenicity, metabolism (particularly in relation to interaction with DNA), and pharmacokinetic behavior have an important bearing on both the qualitative and quantitative assessment of carcinogenicity. This document presents an evaluation of the animal bioassays and relevant toxicity studies, the human epidemiologic evidence, the quantitative aspects of assessment, and finally, a summary and conclusions dealing with all of the relevant aspects of the carcinogenicity of unleaded gasoline.

Summary and Conclusions

Animal Studies

A lifetime inhalation bioassay of unleaded gasoline in rats and mice has induced a statistically significant in-

creased incidence (6/100) of renal carcinomas in the kidney cortex of male rats and a larger, also statistically significant, increase in the incidence (20/100) of hepatocellular carcinomas in female mice. Female rats and male mice had no significant treatment-related increase in tumors at any organ site. The increase of renal carcinomas in male rats was statistically significant at the highest dose tested (2,056 ppm) but not at the two lower doses (292 ppm and 67 ppm). However, the combined incidence of adenoma/carcinoma/sarcoma was also significantly increased at the intermediate dose. In mice, the incidence of liver carcinomas alone and adenoma and carcinoma combined was significantly increased in the highest but not the two lower dose groups. Moderate decrements in the body weight gain in the high-dose groups indicate that the maximum tolerated dose was reached. Glomerulonephrosis occurred in nearly all of the male rats, and mineralization of the pelvis was correlated with dose. However, there was no correlation between animals with tumors and those with mineralization.

The same pattern of glomerulonehpritis, as well as positive tumor responses, occured with chronic inhalation exposure to synthetic fuels (RJ-5 and JP-10). Chronic inhalation studies with jet fuels used by the Air Force and Navy (JP-4 and JP-5) have resulted in the same nephrotoxic lesions, but no information is available about the carcinogenic response.

In a series of exposures of male rats to a variety of distillate fractions and to individual components of gasoline, toxicity was correlated with the paraffin compounds present in the 145° to 280°F distillate fractions and not with aromatic compounds in the mixture. The most toxic compounds were branched-chain aliphatics, generally in the C6-C9 range, although some larger molecules such as 2,2,4,4-tetramethyl octane also showed a high level of activity. The acute and subchronic renal toxicity of decalin, a volatile hydrocarbon of the same general type as those found in gasoline, is confined to male rats and did not occur in female rats or in mice, dogs, or guinea pigs.

The renal toxicity pattern observed with exposure to hydrocarbon mixtures involving protein accumulation in renal tubules is clearly different than the kidney lesions occurring spontaneously in old rats, and occurs in males of both Fischer 344 and Sprague-Dawley strains, but not in females of these strains or in mice or monkeys. Mutagenesis tests of unleaded gasoline have been carried out in Salmonella, yeast, mouse lymphoma *in vivo* cytogenetics, in mouse dominant lethal systems, and in a rat kidney cell DNA repair model. Various gasoline feedstocks have been tested in mouse lymphoma and *in vivo* cytogenetics assays. The results of most of these assays have not met the criteria for positive responses.

Epidemiologic Studies

Fifty-five studies were reviewed to determine if there is any epidemiologic evidence for an association between gasoline exposure and cancer risk. Since unleaded gasoline was only introduced in the mid-1970's, even recent epidemiologic studies are not likely to show an unleaded gasoline effect because of the long latency period generally associated with cancer. Therefore, this review was not limited to unleaded gasoline exposure, but addressed any potential gasoline exposure.

None of the studies reviewed provided qualitative as well as quantitative estimates of gasoline exposure.

Seven studies were identified that evaluated the association between employment in the gasoline service industry and cancer risks; the industy here includes gasoline service station owners and attendants, garage workers, gasoline and fuel truck drivers, and those who reported working with gasoline. One study cited in the literature provided some evidence of an association between gasoline service station employment and risk of primary liver cancer. The remaining six studies were judged inadequate.

Twenty-five studies were reviewed that evaluated the association between employment in a petroleum refinery (a work environment with potential gasoline exposure) and cancer risk. Judged individually, these studies provided inadequate evidence of an association. However, judged collectively these studies provide suggestive evidence of an association between employment in a petroleum refinery and risk of stomach cancer, respiratory system cancer (i.e., lung, pleura, nasal cavity, and sinuses), and cancer of the lymphatic and hematopoietic tissues.

Nineteen case-control studies were reviewed which evaluated employment in the petroleum industry as a cancer risk factor. Another study cited in the literature provided limited evidence of an association between petroleum industry employment and risk of bladder cancer.

Also reviewed were four protocols of epidemiologic studies in progress. These studies may provide evidence of an association between gasoline exposure and cancer risk; however, these findings are 3 to 5 years in the future.

Quantitative — Data from the API study on kidney tumors in male rats and liver adenomas and carcinomas in female mice were used to derive an estimate of the incremental upper-limit unit risk due to continuous human exposure to 1 ppm of unleaded gasoline. Since the animals breathed an aerosol of whole gasoline under laboratory conditions, whereas humans are expected to breathe only the more volatile components of the mixture, the estimates are uncertain. If tumor induction is caused by the same, relatively nonvolatile C6-C9 branched hydrocarbons that are primarily responsible for the nephrotoxicity in male rats, then the quantitative estimates of the risk of breathing gasoline vapors may be overly conservative. The carcinogenic potency estimate for unleaded gasoline was derived from a continuous exposure study, whereas the actual human exposure is periodic in most cases. The available information is not adequate to determine if this will result in an overestimation or an underestimation of risk. The estimates from the mouse and rat data are similar: 2.1×10^{-3} $(ppm)^{-1}$ from mouse data and 3.5×10^{-3} $(ppm)^{-1}$ from rat data.

The presence of 2% benzene in the unleaded gasoline mixture could theoretically contribute to the response, although the mouse liver and rat kidney have not been the target organs in animal experiments with benzene. Based on those experiments, it is estimated that the contribution of benzene to the response observed in the API unleaded gasoline studies could be on the order of 20%. However, there is no qualitative evidence that benzene actually is contributing to the response.

Conclusions

On the basis of a small but definite kidney tumor response in male rats and a significant hepatocellular response in female mice, using EPA's Guidelines for Carcinogen Risk Assessment to classify the weight of evidence for carcinogenicity in experimental animals, there is sufficient evidence to conclude that gasoline vapors are carcinogenic 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 relevance of the rat kidney response to human carcinogenicity has been questioned on the basis of experiments showing that early-occurring kidney toxicity is apparently caused by the interaction of gasoline hydrocarbon components with a unique protein (alpha-2-microglobulin) produced in large quantities only by the male rat and not other species. If this toxicity were the cause of the kidney tumor response, the case for human carcinogenicity would be weakened. However, given the current evidence, the Carcinogen Assessment Group cannot disregard the rat kidney tumor response as an indication of potential human carcinogenicity for several reasons: (a) the link between hydrocarbon nephropathy and tumor induction is not proven; (b) with very few exceptions, chemicals causing cancer in humans also cause cancer in animals, indicating a similarity of response across the animal kingdom; and (c) the kidney of experimental animals is a demonstrated target organ for more than 100 carcinogenic chemicals.

The EPA Science Advisory Board and the Health Effects Institute have independently reviewed the earlier draft of this report. Both groups agreed that the evidence for carcinogenicity in animals meets the EPA Guidelines criteria for sufficient evidence in animals and inadequate evidence in humans. They both pointed out the uncertain relevance of rat kidney tumors as an indication of human response and the difficulty in making quantitative estimates of gasoline vapor potency from the animal study of whole gasoline when the identity of the carcinogenic component is unknown.

The epidemiologic studies collectively provide limited evidence that occupational exposure in the petroleum industry is associated with certain types of cancer. However, the evidence for evaluating gasoline as a potential carcinogen is considered inadequate under the EPA Guidelines criteria for epidemiologic evidence.

Based on sufficient evidence in animal studies and inadequate evidence in epidemiologic studies, the overall weight of evidence for unleaded gasoline is EPA category B2, meaning that unleaded gasoline is a probable human carcinogen.

The carcinogenic potency of unleaded gasoline, using data from the most sensitive species tested, is 3.5×10^{-3} per ppm. This is a plausible upper bound for the increased cancer risk from unleaded gasoline, meaning that the true risk is not likely to exceed this estimate and may be lower.

This Project Summary was prepared by staff of the Office of Health and Environmental Assessment, Washington, DC 20460.
***William E. Pepelko** is the EPA Project Officer (see below).*
The complete report, entitled "Evaluation of the Carcinogenicity of Unleaded Gasoline," (Order No. PB 87-186 151/AS; Cost: $36.95, subject to change) will be available only from:
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5285 Port Royal Road
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Telephone: 703-487-4650
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