

Free Executive Summary



Toxicologic Assessment of Jet-Propulsion Fuel 8

Subcommittee on Jet-Propulsion Fuel 8, Committee on Toxicology, National Research Council

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This book provides a critical review of toxicologic, epidemiologic, and other relevant data on jet-propulsion fuel 8, a type of fuel in wide use by the U.S. Department of Defense (DOD), and an evaluation of the scientific basis of DOD's interim permissible exposure level of 350 mg/m³.

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Summary

The U.S. Department of Defense (DOD) has, for many years, faced the logistical problem of using a variety of fuels for its aircraft, ground vehicles, and other equipment, such as cooking stoves and tent heaters. In the 1980s, DOD decided to initiate a 20-year (yr) fuel conversion process, in which most fuel-requiring equipment would be converted to exclusive use of jet propulsion fuel-8 (JP-8). With DOD and North Atlantic Treaty Organization (NATO) forces using an estimated 5 billion gallons of JP-8 each year, there is widespread exposure of DOD and NATO military personnel to JP-8.

In 1996, a previous subcommittee of the National Research Council's Committee on Toxicology (COT)¹ judged that the Navy's interim 8-hr time-weighted-average permissible exposure level (PEL) of 350 mg/m³ for JP-4, JP-5, and JP-8 was adequate to protect the health of Navy personnel occupationally exposed to vapors from those fuels, based on the data available at that time; however, it identified a number of data gaps and recommended that the PEL for the three jet-fuel vapors be considered interim until further research had been completed.

Since the release of the 1996 report, considerable data on JP-8 have been generated. Because JP-8 is now being used more widely by DOD, and be-

¹National Research Council. 1996. *Permissible Exposure Levels for Selected Military Fuel Vapors*. Washington, DC: National Academy Press.

cause occupational exposures to JP-8 vapors and aerosols are known to occur, the Air Force requested that the National Research Council (NRC) again review the available toxicologic, epidemiologic, exposure, and other relevant data on JP-8; independently reevaluate the scientific basis of the PEL of 350 mg/m³ for JP-8; identify data gaps; and make recommendations for future research relevant to deriving the PEL. The NRC assigned this project to the COT Subcommittee on Jet-Propulsion Fuel 8, which prepared this report.

THE SUBCOMMITTEE'S APPROACH TO ITS CHARGE

To address its charge, the subcommittee reviewed data on physical and chemical properties of JP-8, toxicokinetics of JP-8, epidemiologic and toxicologic evidence of adverse health effects of JP-8, and Air Force operational scenarios that might result in exposure to JP-8 vapors and aerosols. In addition to reviewing health-effects data on JP-8, the subcommittee reviewed toxicity data on kerosene and other kerosene-based fuels (such as JP-5) that are similar to JP-8. The subcommittee reviewed toxicity data on JP-8 vapors as well as JP-8 aerosols. The subcommittee used the available data to evaluate the scientific basis of the Air Force interim PEL of 350 mg/m³.

CONCLUSIONS

The health-effects data on JP-8 and related fuels were reviewed for the following end points: respiratory tract toxicity, neurotoxicity, immunotoxicity, liver toxicity, kidney toxicity, reproductive and developmental toxicity, cardiovascular toxicity, genotoxicity, and carcinogenicity. JP-8 was found to be potentially toxic to the immune system, respiratory tract, and nervous system at exposure concentrations near the interim PEL of 350 mg/m³. Those toxicities are summarized below.

Immune System

No immunotoxic effects were found in a study in which F344 rats and C57BL/6 mice were exposed to JP-8 *vapors* at concentrations up to 1,000 mg/m³ on a continuous basis for 90 days. However, in other studies, inhalation exposure of C57BL/6 mice to JP-8 *aerosols* at a concentration of 100 mg/m³ for 1 hr/day for 7 days led to decreased cellularity of the thymus;

exposure at 500 mg/m³ for 1 hr/day for 7 days led to decreased spleen weight and cellularity; and exposure at 1,000 mg/m³ for 1 hr/day for 7 days led to decreased ability of spleen cells to mediate several immune responses. The subcommittee reviewed the methods used to generate the exposure atmospheres in the studies using JP-8 aerosols and suspects that the total JP-8 concentrations in the atmosphere may have been underreported. However, even if the actual concentration was 10 times as high as the lowest concentration at which effects were observed (100 mg/m³) (that is, if exposure was at a concentration of 1,000 mg/m³), the observation of positive effects from a short exposure duration (1 hr/day for 7 days) at that concentration leads the subcommittee to conclude that the interim PEL of 350 mg/m³ might be too high to be protective of human health (assuming the application of commonly used uncertainty factors). Because the positive results from JP-8 exposure in immunotoxicity assays were reported from only one laboratory, the subcommittee strongly recommends further research be conducted to validate those findings (see section on research recommendations). Results from those studies would provide data for establishing the PEL for JP-8 with greater confidence.

Respiratory Tract

No respiratory tract effects were found in F344 rats and C57BL/6 mice exposed to JP-8 vapors at concentrations of 500 or 1,000 mg/m³ for 90 days. However, several animal studies conducted in F344 rats and C57BL/6 mice suggest that mixtures of JP-8 vapors and aerosols can result in pulmonary inflammation and alterations in pulmonary functions; such effects have been reported in C57BL/6 mice exposed at concentrations as low as 50 mg/m³ for 1 hr per day for 7 days. As in the immune-system studies described above, the subcommittee suspects that the JP-8 concentrations in these studies may have been underreported. However, even if the actual concentration was 20 times as high (that is, if exposure was at a concentration of 1,000 mg/m³), the observation of positive effects from a short exposure duration (1 hr/day for 7 days) at that concentration leads the subcommittee to conclude that the interim PEL of 350 mg/m³ might be too high to be protective of human health (assuming the application of commonly used uncertainty factors). Because the positive results from JP-8 exposure in respiratory toxicity assays were reported from only one laboratory, the subcommittee strongly recommends further research be conducted to validate those findings (see section on research recommendations). Results from those studies would provide data for establishing the PEL for JP-8 with greater confidence.

Nervous System

Animal studies have investigated the effects of several jet fuels on a number of neurobehavioral end points. Neurobehavioral effects were reported in Sprague-Dawley and F344 rats exposed to JP-8 or JP-5 vapors at concentrations of 1,000 mg/m³ for 6 hr/day, 5 days/wk for 6 wk or to JP-8 aerosols at concentrations of 1,059 mg/m³ for 1 hr/day, 5 days/wk for 4 wk. The relevance to humans of the toxicity end points evaluated in those studies is not known and no dose-response relationships were demonstrated in the studies. Furthermore, those positive findings need to be validated against other well-established neurotoxicity end points. However, the findings provide further indication that the interim PEL of 350 mg/m³ might be too high to be protective of human health.

Cancer

The carcinogenicity of JP-8 has not been investigated in epidemiologic studies or in chronic lifetime inhalation-exposure studies in experimental animals. Ninety-day continuous inhalation-exposure studies of JP-5 have been conducted in C57BL/6 mice exposed at a concentration of 750 mg/m³, and no increase in the incidence of tumors was observed. The carcinogenicity data available on mixtures similar to JP-8 (such as other jet fuels and middle distillates) indicate that most of these materials induce skin tumors in mice when topically applied in excessive amounts and under conditions of excessive skin irritation.

The subcommittee is aware of a suspected cluster of acute lymphocytic leukemias (ALL) in Fallon, Nevada, and that exposure to JP-8, originating from a naval base located in that town, is under investigation as a possible cause of the ALL cluster (exposures to other chemicals are being investigated as well). However, no scientific studies were found in the published literature that examined a potential relationship between ALL and JP-8 exposure; therefore, the subcommittee could not reach any conclusion concerning exposure to JP-8 and this suspected cancer cluster.

Other Toxicity End Points

The subcommittee also reviewed toxicologic and epidemiologic data on other end points: hepatotoxicity, renal toxicity, reproductive and developmental toxicity, cardiovascular toxicity, and genotoxicity of JP-8. No relevant adverse effects were observed for hepatotoxicity, renal toxicity, and cardiovas-

cular toxicity, although the exposure concentration did not exceed 1,000 mg/m³. Adequate studies have not been conducted to assess the toxicity potential of inhaled JP-8 for reproductive toxicity, developmental toxicity, and genotoxicity.

Subcommittee's Evaluation of the Interim PEL of 350 mg/m³ for JP-8

On the basis of the available toxicologic data, the subcommittee concludes that the interim PEL of 350 mg/m³ for JP-8 proposed by the Air Force might be too high to be protective of human health. It is beyond the charge to the subcommittee to propose a specific PEL for JP-8; such decisions necessarily involve more than scientific considerations. In addition, further studies on JP-8 are necessary to provide the requisite data to establish a PEL with greater confidence. Because JP-8 vapors and aerosols have different toxic potencies, the Air Force should consider developing separate PELs for vapors and aerosols.

The subcommittee further concludes that in addition to inhalation exposures, the potential exists for a substantial contribution to the overall JP-8 exposure by the dermal route, including mucous membranes and the eyes, either by contact with vapors and aerosols or by direct skin contact with JP-8. It should be noted that earlier this year, the American Conference of Governmental Industrial Hygienists proposed a Threshold Limit Value for kerosene and jet fuels, as a total hydrocarbon vapor, of 200 mg/m³.² Also, ExxonMobil Biomedical Sciences, Inc., has set an occupational exposure level of 5 mg/m³ for kerosene and middle distillate fuel aerosols.³

RESEARCH RECOMMENDATIONS

Because findings from several studies indicate the potential for adverse health effects from exposure to JP-8 aerosols at concentrations below the interim PEL of 350 mg/m³ and because the JP-8 vapor concentrations tested were approximately 1,000 mg/m³ (that is, less than three times the interim PEL), the subcommittee strongly recommends that a battery of inhalation-toxicity tests in experimental animals be conducted with JP-8 vapors and mixtures of vapors and aerosols. The animal studies should include evalua-

²ACGIH (American Conference of Governmental Industrial Hygienists). 2002. Threshold Limit Values and Biological Exposure Indices. Cincinnati, Ohio.

³ExxonMobil Biomedical Sciences, Inc. 2001. ExxonMobil Occupational Exposure Limits for Chemical Contaminants. Annandale, New Jersey.

tions of immune, nervous system, respiratory, hepatic, renal, cardiovascular, reproductive, developmental, and in vivo genetic toxicity end points, including basic evaluations of clinical effects and histopathology.

Because the composition of JP-8 varies from batch to batch, scientists with expertise in petroleum toxicology should be consulted to design the best approach for testing the toxicity of JP-8 in animal studies (for example, testing JP-8 samples at the extremes of their composition ranges or testing JP-8 samples so that the concentrations of component classes can be correlated with toxic end points).

Animal studies involving exposures to aerosols should be designed in collaboration with scientists knowledgeable in aerosol generation, aerosol physics, and atmospheric quantification of vapors and aerosols to ensure accurate characterization of exposure atmospheres. The exposure conditions in the animal studies should mimic exposures encountered in the workplace (such as proper ratios of vapors to aerosols).

Because inhalation exposures greater than approximately 1,000 mg/m³ for pure JP-8 vapors are difficult to achieve, the Air Force should consider conducting studies using saturated vapor atmospheres on larger numbers of animals or employ longer exposure durations (that is, longer than 90 days) to increase the power of the studies for observing adverse effects in various organ systems.

The lifetime carcinogenicity of JP-8 has not been studied; therefore, the subcommittee recommends that 2-yr inhalation carcinogenicity bioassays be conducted in two experimental animal species.

The subcommittee recommends that human blood samples from JP-8-exposed persons be assayed for indicators of immunotoxicity to determine whether effects observed in experimental animals are also observed in humans.

Preliminary positive findings were reported in two neurologic tests (eyeblink and postural-sway tests) conducted as part of a recent Air Force human study. The subcommittee recommends that results from those two tests be validated with standard neurologic tests.

The subcommittee also recommends that toxicokinetic studies be conducted so that existing human studies on JP-8 and related fuels can be better interpreted. Those studies should provide quantitative information on the relationship of blood and tissue concentrations of JP-8 components after vapor and aerosol exposures to JP-8. Traditional compartmental and physiologically-based toxicokinetic models that take into account absorption, distribution, metabolism, and elimination should include studies on JP-8 and on longer-chain *n*-alkanes, naphthalene, benzene, and other components of JP-8. With improved dosimetry, available human data from a recently com-

pleted Air Force human study should be reevaluated on the basis of body burden of JP-8.

The Air Force should conduct studies to estimate exposures of its personnel to JP-8 vapors or mixtures of vapors and aerosols. Health-effect assessments and blood analysis for JP-8 components should be conducted in conjunction with exposure assessments so that correlations between actual exposures and adverse effects can be made. Those data are likely to be useful for validating any toxicokinetic modeling based on rodent toxicity studies.

The subcommittee recommends that dermal exposures to Air Force personnel in some occupational settings (such as maintenance of aircraft fuel tanks) be minimized by the use of appropriate protective clothing or other measures. It also recommends that DOD evaluate the effectiveness of various protective clothing for personnel who are likely to come into contact with JP-8 and that it use the most effective protective clothing. Furthermore, the subcommittee recommends that other industrial hygiene practices be instituted to reduce or prevent exposures to JP-8 vapors or aerosols.

Toxicologic Assessment of Jet-Propulsion Fuel 8

Subcommittee on Jet-Propulsion Fuel 8

Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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Preface

In the 1980s, the U.S. Department of Defense (DOD) selected jet-propulsion fuel 8 (JP-8) as its primary fuel. JP-8 is widely used by the military not only for aircraft, but also for ground vehicles and other equipment, such as generators, cooking stoves, and tent heaters. Military personnel can be exposed to JP-8 vapors and aerosols during a number of operational scenarios, including aircraft refueling and maintenance. To protect the health of its personnel, DOD recommended an interim permissible exposure level (PEL) of 350 mg/m³.

The Air Force requested that the National Research Council (NRC) review the available toxicologic, epidemiologic, and other relevant data on JP-8 and evaluate independently the scientific basis of the DOD's interim PEL of 350 mg/m³ for JP-8. The NRC assigned this project to the Committee on Toxicology (COT), which assembled the Subcommittee on Jet-Propulsion Fuel 8 to prepare this report.

We thank the following Air Force personnel for providing valuable background information to the subcommittee: Brian Blazicko, Roger Gibson, John Hinz, David Mattie, James McDougal, and Richard Stotts. We also wish to express our gratitude to Geraldine Grant (George Mason University, Fairfax, Virginia), David Harris (University of Arizona, Tucson, Arizona), Glenn Ritchie (Geo-Centers, Inc., Wright-Patterson Air Force Base, Ohio), Mark Smulson (Georgetown University, Washington, D.C.), Steve Ullrich (M.D. Anderson Cancer Center, Houston, Texas), Russell White (Chevron Research

and Technology Company, Richmond, California), and Mark Witten (University of Arizona, Tucson, Arizona) for providing background information to the subcommittee. We also thank Stephen Channel (U.S. Air Force), Thomas Neal (U.S. Air Force), and Kenneth Still (U.S. Navy) for their support of this project.

This report has been reviewed in draft form by persons chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid, critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following for their review of this report: Edward Bishop, Parsons Engineering Sciences, Inc., Fairfax, Virginia; Judith Graham, American Chemistry Council, Arlington, Virginia; Karl Kelsey, Harvard School of Public Health, Boston, Massachusetts; Carole Kimmel, U.S. Environmental Protection Agency, Washington, D.C.; Kannan Krishnan, University of Montreal, Quebec, Canada; David Lawrence, New York State Department of Health, Albany, New York; Judith MacGregor, Toxicology Consulting Services, Arnold, Maryland; Ceinwen Schreiner, C & C Consulting in Toxicology, Meadowbrook, Pennsylvania; and Bailus Walker, Jr., Howard University Medical Center, Washington, D.C.

Although the reviewers provided many constructive comments and suggestions, they were not asked to endorse the report's conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by Dean Carter, University of Arizona, Tucson, who was appointed by the NRC to ensure that an independent examination of this report was conducted in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of the report rests entirely with the subcommittee and the institution.

We are also grateful for the assistance of members of the NRC staff in the preparation of this report. The subcommittee acknowledges Abigail Mitchell, project director, and Kulbir Bakshi, program director of the Committee on Toxicology. Other staff members contributing to this report were James Reisa, director of the Board on Environmental Studies and Toxicology; Jessica Brock, senior project assistant; Norman Grossblatt, editor; and Kelly Clark, assistant editor.

Finally, we thank all members of the subcommittee for their expertise and dedicated effort throughout the study.

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Abbreviations

| | |
|-------|---|
| ACGIH | American Conference of Governmental Industrial Hygienists |
| ATSDR | Agency for Toxic Substances and Disease Registry |
| COT | Committee on Toxicology |
| CNS | central nervous system |
| DFM | diesel fuel marine |
| DNA | deoxyribonucleic acid |
| DOD | U.S. Department of Defense |
| FOB | functional observation battery |
| HDS | hydrodesulfurized |
| IARC | International Agency for Research on Cancer |
| JP-8 | jet-propulsion fuel 8 |
| LDH | lactate dehydrogenase |
| MDF | middle distillate fraction |
| MMAD | mass mean aerodynamic diameter |
| MN | micronucleus |
| NATO | North Atlantic Treaty Organization |
| NIOSH | National Institute for Occupational Safety and Health |
| NOAEL | no-observed-adverse-effect level |
| NRC | National Research Council |
| NTP | National Toxicology Program |

xx *Abbreviations*

| | |
|------------------|---|
| OR | odds ratio |
| PEL | permissible exposure level |
| PB-PK model | physiologically based pharmacokinetic model |
| RD ₅₀ | respiratory depression in 50% of the animals tested |
| REL | recommended exposure limit |
| SCE | sister chromatid exchange |
| TOMM | test of memory and motivation |
| TWA | time-weighted average |
| UDS | unscheduled DNA synthesis |
| USAF | U.S. Air Force |

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