THE SECRETARY OF VETERANS AFFAIRS
WASHINGTON

September 15, 2023

The Honorable Jon Tester
Chairman
Committee on Veterans' Affairs
United States Senate
Washington, DC 20510

Dear Mr. Chairman:

In accordance with the requirements of section 510 of the Honoring our PACT Act of 2022, enclosed is the Department of Veterans Affairs (VA) report on the health effects of jet fuels used by the Armed Forces. VA remains committed to honoring our Nation's Veterans by ensuring a safe environment to deliver exceptional health care.

In addition, as required by 38 U.S.C. § 116, a statement of cost for preparing the report is included. This report has been sent to the leaders of the House and Senate Committees on Veterans' Affairs.

Sincerely,

Denis McDonough

Enclosures

DEPARTMENT OF VETERANS AFFAIRS

Congressionally Mandated Report:
Health Effects of Jet Fuels Used by Armed Forces

September 2023

TABLE OF CONTENTS

Executive Summary

Section 510 of the Sergeant First Class Heath Robinson Honoring Our Promise to Address Comprehensive Toxins Act of 2022 (the PACT Act, Public Law 117-168) requires the Secretary of Veterans Affairs (VA) submit to the House and Senate Veterans' Affairs Committees a report on the health effects of jet fuels used by the Armed Forces. The report must include (1) a discussion of the effect of various different types of jet fuels used by the Armed Forces on the health of individuals by length of exposure; (2) an identification of the immediate symptoms of jet fuel exposure that may indicate future health risks; (3) a chronology of health safeguards implemented by the Armed Forces intended to reduce the exposure of members of the Armed Forces to jet fuel; and (4) an identification of any areas relating to jet fuel exposure about which new research needs to be conducted.

To fulfill the requirements of this law, VA collaborated with the Department of Defense (DoD) to access data and information from DoD and each branch of the Armed Forces on relevant safeguard policies or guidance and studies/assessments on jet fuels that had been conducted by DoD investigators. In addition, DoD is participating in ongoing and future VA research efforts and has provided data to VA investigators to define jet fuel exposure, including occupational information and exposure monitoring data.

To respond to the call for a chronology of health safeguards (subsection (b)(3)), VA obtained 53 documents from DoD and the Services that describe the historic and current policies in place to safeguard Service members against potential adverse effects of jet fuels (see Part 1 and Appendix A). Most of the military health safeguards obtained from DoD and reviewed for this report were established or updated in the last 20 years, with only five publications preceding the year 2000 and nearly half being as recent as the last 5 years. Of the 53 documents, 14 provided policies and guidance specific to reducing jet fuel exposure. Policy and guidance documents primarily described administrative controls (i.e., training on safety procedures and proper use of personal protective equipment (PPE), programs for monitoring exposure and defining exposure limits) and PPE (i.e., wearing protective clothing and footwear, gloves, face shield and hearing protection).

To discuss the health effects of types of fuels on health by length of exposure and identify immediate symptoms that may indicate future health risks (subsection (b)(1) and (b)(2)), VA's Health Outcomes Military Exposures (HOME) commissioned a review of the available evidence and 28 unique primary epidemiological studies, 19 reviews and 14 case reports or case series were identified that specifically investigated or described adverse health effects associated with jet fuel exposure among military or civilian occupational populations. The review found slight evidence of associations between jet fuel exposure and certain organ system-level health outcomes, including the nervous system (e.g., decreased performance on memory tests, hearing impairment and

increased ocular conditions), mental health (e.g., decrements in attention, cognitive function, social-emotional behavior and regulation, visual-spatial performance and depression), the respiratory system (e.g., decreased lung function, increased obstructive disease and increased respiratory symptoms, such as labored breathing or dyspnea, cough with phlegm and stuffy and runny nose) and cancers (e.g., kidney and bladder cancer) (Table 1 below). There is indeterminate evidence for all other health outcome categories represented in the published literature. See Box 1 to the right for strength-of-evidence judgment definitions. Further, no primary epidemiological studies in occupational cohorts reported metabolic, developmental, endocrine or musculoskeletal and connective tissue effects.

BOX 1. Strength-of-Evidence Judgement Definitions
Slight strength-of-evidence judgement indicates one or more studies reporting an association between exposure and the health outcome, but considerable uncertainty exists and supporting coherent evidence is sparse. In general, the evidence is limited to a set of consistent low confidence studies, or higher confidence studies with significant unexplained heterogeneity or other serious residual uncertainties.
Indeterminant strength-of-evidence judgement indicates there were no studies in humans or situations when the evidence is highly inconsistent and primarily of low confidence.
See Appendix B for additional information.

Table 1. Health Outcomes Associated With Jet Fuels Exposure for Which the Weight of Evidence is Slight.

Health Outcomes	Number of Studies	Major Gaps/Sources of Uncertainty
Nervous System		
Hearing Impairment	4	○ Three of four studies present high risk of bias[a] due to uncertainty around participant selection, jet fuel exposure, potential confounding effects and study sensitivity. ○ Only two studies examine acute health outcomes, limiting analytical power by type of outcome.
Memory Impairment	4	○ Three of four studies present high risk of bias due to uncertainty around participant selection, jet fuel exposure, health outcome ascertainment, potential confounding effects and study sensitivity.
Ocular Conditions	5	○ All studies (five of five) present high risk of bias due to uncertainty around participant selection, jet fuel exposure, health outcome ascertainment, potential confounding effects and study sensitivity. ○ Only two studies examine long-term health outcomes, limiting analytical power by type of outcome. ○ Inconsistent measure of effects limits analysis across studies.

Health Outcomes	Number of Studies	Major Gaps/Sources of Uncertainty
		Mental Health
Attention	4	○ Three of four studies present high risk of bias due to uncertainty around participant selection, jet fuel exposure, potential confounding effects and study sensitivity. ○ Self-reported health outcome assessment creates uncertainty around outcomes across reported cases.
Cognitive Function	3	○ All studies (three of three) present high risk of bias due to uncertainty around participant selection, jet fuel exposure, potential confounding effects and study sensitivity. ○ Self-reported health outcome assessment and imprecise health outcome definitions create uncertainty around outcomes across reported cases.
Visual-spatial Performance	3	○ Two of three studies present high risk of bias due to uncertainty around participant selection, jet fuel exposure, potential confounding effects and study sensitivity. ○ Self-reported health outcome assessment creates uncertainty around outcomes across reported cases.
Social-Emotional Behavior and Regulation	1	○ Only one study examines this health outcome, and it presents high risk of bias due to uncertainty around participant selection, jet fuel exposure and potential confounding effects. ○ Self-reported health outcome assessment creates uncertainty around outcomes across reported cases.
Depression	2	○ Only two studies examine this health outcome and both studies (two of two) present high risk of bias due to uncertainty around participant selection, jet fuel exposure, potential confounding effects and study sensitivity. ○ Self-reported health outcome assessment creates uncertainty around outcomes across reported cases.
		Respiratory
Decreased Lung Function	2	○ Only two studies examine this health outcome, and one of two studies present high risk of bias due to uncertainty around participant selection, jet fuel exposure and potential confounding effects.

Health Outcomes	Number of Studies	Major Gaps/Sources of Uncertainty
Respiratory Symptoms	5	○ All studies (five of five) present high risk of bias due to uncertainty around participant selection, jet fuel exposure, health outcome ascertainment, potential confounding effects and study sensitivity. ○ Only one study examines long-term health outcomes, limiting analytical power by type of outcome.
Obstructive Disease (Long-term)	2	○ Only two studies examine this health outcome and both studies (two of two) present high risk of bias due to uncertainty around jet fuel exposure and potential confounding effects.
Cancer		
Kidney Cancer	3	○ Two of three studies present high risk of bias due to uncertainty around jet fuel exposure and potential confounding effects.
Bladder Cancer	3	○ All (three of three) studies present high risk of bias due to uncertainty around jet fuel exposure, potential confounding effects and study sensitivity.

[a]High risk of bias refers to studies that were evaluated as low confidence or uninformative; see Appendix B for additional information.

Few studies included adequate follow-up to observe long-term health outcomes many months or years after exposure began, or to evaluate whether any acute outcome resolved after exposure has ceased; most studies assessed health outcomes among current workers who were actively working and exposed to jet fuels, rather than in Veterans who have not been exposed to jet fuels for a long time. Therefore, the persistence of these health outcomes after exposure and the development of long-term effects is not well understood.

The ability to draw conclusions about associations between jet fuel exposure and health outcomes is limited by the availability and quality of epidemiological data. As this review focused on evidence among military and civilian occupational populations only, other streams of evidence, including other kinds of human exposure (such as environmental exposure to jet fuels), toxicological data from animal studies and mechanistic data, could be useful to fill some of the gaps in the epidemiological data. These additional evidence streams may provide support for evidence seen in the military and occupational populations, enhance the understanding of the relationship between jet fuel exposure and health outcomes (i.e., provide coherence) and potentially show a biological gradient (i.e., dose response).

There are no studies that examined health effects by length of exposure. Although studies reported contextual information, such as average duration of employment, statistical analyses or qualitative comparisons to distinguish between shorter and longer durations were not reported. Furthermore, health effects related to specific types of jet fuel could not be determined.

None of the primary studies provided direct evidence regarding whether immediate symptoms or acute effects resulting from jet fuel exposure developed into more severe and/or chronic health risks. Early signs and symptoms indicative of future health risks (i.e., long-term health outcomes) could be identified from the broader knowledge of specific health conditions. However, there was not enough evidence of adequate quality with sufficient follow-up to reach reliable conclusions about whether jet fuel exposure was associated with risks of future long-term health outcomes. In the absence of an understanding about long-term health outcomes that would persist or develop after the exposure has ended, it is not possible to determine early symptoms or signs that would predict future health risks.

There are several gaps and limitations in the current evidence that would benefit from additional research (as called for by subsection (b)(4)), including expanded literature review and additional epidemiologic studies. To gain a better understanding of what is known about the relationship between jet fuel exposure and health effects, additional literature reviews and synthesis of the following types of information should be conducted (if available):

- Expand the scope of the evidence review to include non-occupationally exposed populations, if available, such as those unintentionally exposed through environmental releases or spills.
- Review the toxicological literature, including animal studies and mechanistic data, to provide supporting evidence and further develop an understanding of potential health outcomes in humans.

VA will extend the review of the literature to include these additional types of information and will include the findings of that review with a synthesis of all available information in the follow-up report due in 5 years.

Several research gaps were identified in the literature review that must be addressed to better understand the long-term impact of jet fuel exposure in the military. Specifically, the following types of research should be pursued:

- Well-designed studies of neurological, mental health, respiratory and cancer outcomes, for which there is currently slight evidence of an association with jet fuel exposure, to confirm associations with specific outcomes in these categories. These studies should also consider co-morbidities and potential impact of co-exposures which might act as effect modifiers. The observed associations will be strengthened by establishing certain characteristics, such as consistency, specificity, temporality, biological gradient, plausibility and coherence of the associations.
- Studies that explore associations between jet fuel exposure and health outcomes that are not well studied.

- Studies that make statistical comparisons based on duration of exposure to jet fuel.
- Studies with adequate and long-term follow-up after the onset of exposure to observe long-term health outcomes.
- Studies that follow participants over time to observe the natural history of jet fuel-related health effects and the resolution, persistence or progression of immediate symptoms.
- Studies in populations from underrepresented groups, such as women and racial/ethnic minorities.
- Studies that integrate epidemiological methods with biological endpoints to elucidate mechanisms of toxicity in jet fuel-exposed Service members and Veterans.

To address these research gaps, VA's HOME, in collaboration with the U.S. Air Force School of Aerospace Medicine and the Defense Centers for Public Health–Aberdeen and Portsmouth–is conducting a larger, retrospective study using administrative data collected by DoD and VA databases, exposure monitoring data, health care data, disability compensation claims data and mortality data obtained from VA and DoD databases to investigate the long-term health effects of occupational jet fuel exposure. Study subjects served between 1995 and 2020, allowing for the ability to observe some long-term effects in Veterans in occupations likely exposed to jet fuel compared to those who were likely unexposed. Exposure monitoring data obtained from the Defense Occupational and Environmental Health Readiness System–Industrial Hygiene database will be used to characterize relevant levels of exposure and duration of exposure will be incorporated into analyses. Results of the initial analyses are expected in early 2024. In collaboration with the Naval Health Research Center, a study is planned to use serum samples of Millennium Cohort Study participants held at the DoD Serum Repository to validate exposure to jet fuels and establish early biomarkers of effect.

These studies will aid in the understanding of the long-term impact of exposure to jet fuels during military service. Although this research will rely on occupation as a proxy for jet fuel exposure and time spent under a fuel-exposed job code as a proxy for exposure duration, it will also incorporate monitoring data to characterize exposure intensity. Furthermore, it will contribute the largest cohort studied for adverse effects of jet fuel exposure during service in the U.S. military, with sufficient follow-up to account for latencies of certain health outcomes and adequate statistical power to evaluate conditions in all body systems, including rare conditions. Findings from these studies will be discussed among the totality of evidence in the follow-up report to Congress due in 5 years.

In conclusion, the available evidence establishing relationships between occupational jet fuel exposure and long-term health outcomes is sparse and very few studies of adequate quality have been published. The available evidence suggests that associations may exist with certain outcomes and cancers; however, more studies are needed to confirm links to specific diagnoses in these categories, as well as other categories for which there is little or no evidence. Additional studies and literature review are needed to better understand the impact of length of exposure on long-term health outcomes and whether immediate symptoms are indicative of long-term outcomes. VA will continue to pursue these efforts to improve our ability to care for Veterans that may have been impacted by jet fuel exposure during their military service.

Acronyms

The following table describes the significance of various abbreviations and acronyms used throughout the report and appendices.

Abbreviation	Meaning
1-NAP	1-naphthol
2-NAP	2-naphthol
8-h TWA	8-hour Time-Weighted Average
ABR	Auditory Brainstem Response
ACGIH	American Conference of Governmental Industrial Hygienists
ADHD	Attention-Deficit/Hyperactivity Disorder
AEGL	Acute Exposure Guideline
AFI	Air Force Instruction
AFIOH	Air Force Institute for Operational Health
AFPD	Air Force Policy Directive
AFRL	Air Force Research Lab
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANAM4	Automated Neuropsychological Assessment Metrics 4
ANG	Air National Guard
AR	Army Regulation
AST	Aspartate Aminotransferase
ATF	Aviation Turbine Fuel
ATP	Army Techniques Publication
ATSDR	Agency for Toxic Substances and Disease Registry
AVGAS	Aviation Gasolines
BHT	Butylhydroxytoluene
BMI	Body Mass Index
BTEX	Benzene, Toluene, Ethylbenzene and m,p,o-xylenes
BUN	Blood Urea Nitrogen
CI	Confidence Interval
Cm	Centimeters
COPD	Chronic Obstructive Pulmonary Disease
CPT	Continuous Performance Test
CR	Conditioned Responses
CS	Conditioned Stimulus
DA	Department of the Army
DA PAM	Department of the Army Pamphlet
DAF	Department of the Air Force
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
DoD HAZCOM	Department of Defense Hazard Communication
DoD IHWG	Department of Defense
DoD OMWG	DoD Occupational Medicine Working Group
DoD SOH	Department of Defense Safety and Occupational Health
DoDI	Department of Defense Instruction

Abbreviation	Meaning
DON	Department of the Navy
DPOAE	Distortion Product Otoacoustic Emissions
DTIC	Defense Technical Information Center
DSRS	Deseal/Reseal
E13G	Estrone 3-Glucuronide
EASA	European Aviation Safety Agency
EBCC	Eyeblink Classical Conditioning
EC	Eyes Closed
eGFR	Estimated Glomerular Filtration Rate
ENG	Electronystagmography
EO	Eyes Open
EPA	Environmental Protection Agency
ESRD	End Stage Renal Disease
F-24	Grade F-24 Jet Fuel
F, EC	Eyes Closed, on Foam Support
F, EO	Eye Open, on Foam Support
FEV1	Forced Expiratory Volume in the First/One Second
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GFR	Glomerular Filtration Rate
GGT	Gamma-Glutamyl Transferase
GM	Geometric Mean
GST	Glutathione S-transferase
GSTM1	Glutathione-S-transferase M 1
GSTT1	Glutathione-S-transferase Theta 1
GTA	Graphic Training Aid
HDL	High-Density Lipoprotein
HEMMT	Heavy Expanded Mobility Tactical Truck
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
HOME	Health Outcomes Military Exposures
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-6	Interleukin 6
iPTH	Intact Parathyroid Hormone
IRIS	Integrated Risk Information System
IU/L	Interna Tonal Units per Liters
JEM	Job Exposure Matrix
JP	Jet Propellent
kHz	kilohertz
LDL	Low-Density Lipoprotein
LH	Luteinizing Hormone
LOD	Limit of Detection
mAIAD	modified Amsterdam Inventory for Auditory Disability
MCAS	Marine Corps Air Station

Abbreviation	Meaning
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MCWP	Marine Corps Warfighting Publication
MEG	Military Exposure Guideline
Mg/dL	Milligram per Deciliter
Mg/m^3	Milligram per Cubic Meter
Mg/mL	Milligram per Milliliter
MIL-HDBK	Military Handbook
MIL-STD	Military Standard
mL/min	Milliliter per Minute
mL/min/1.73m^2	Milliliter/Minute/1.73 Meter Squared
mmHg	Millimeters of Mercury
mmol/L	Millimole per Liter
MPV	Mean Path Velocity
MSDSs	Material Safety Data Sheets
NAP	Naphthalene
NAS	National Academy of Sciences
NATOPS	Naval Air Training and Operating Procedures Standardization
NAVAIR	Naval Air Systems Command
NAVMC DIR	Navy and Marine Corps Directive
NAVSUP	Naval Supply Systems
Ng/ml	Nanograms per Milliliters
NIOSH	National Institute for Occupational Safety and Health
NQO1	NAD(P)H Quinone Oxidoreductase
NRC	National Research Council
NSSC	Naval Supply Systems Command
NWP	Naval Warfare Publication
OEH	Occupational and Environmental Health
OSHA	Occupational Safety and Health Administration
OPNAVINST	Operational Naval Instruction
OR	Odds Ratio
PBPK	Physiologically based Pharmacokinetic
PCOS	Polycystic Ovary Syndrome
PD3G	Pregnanediol 3-glucuronide
PECO Statement	Population, Exposure, Comparator and Outcome Statement
PEF	Peak Expiratory Flow
PEL	Permissible Exposure Limit
PK	Pharmacokinetic
PPE	Personal Protective Equipment
ppm	Parts per Million
PTSD	Posttraumatic Stress Disorder
PTSS	Posttraumatic Stress Syndrome
QA/QC	Quality Assurance/Quality Control

Abbreviation	Meaning
RAAF	Royal Australian Air Force
REL	Recommended Exposure Limit
SA	Sway Area
SD	Standard Deviation
SE	Standard Error
SIN	Speech Intelligibility in Noise
SIQ	Speech Intelligibility in Quiet
SL	Sway Length
STD	Sexually Transmitted Disease
STP	Soldier Training Program
T3	Triiodothyronine
T4	Thyroxine
TAA	Total Angular Area
TBI	Traumatic Brain Injury
TC	Training Circular
THC	Total Hydrocarbon
TM	Technical Manual
TSH	Thyroid Stimulating Hormone
TWA	Time Weighted Average
U.S.	United States
UFC	Unified Facilities Criteria
UFGS	Unified Facilities Guide Specifications
US	Unconditioned Stimulus
USAF	United States Air Force
USAPHC	United States Army Public Health Command
USD (AT&L)	Under Secretaries of Defense, Acquisition, Technology, & Logistics
USMC	United States Marine Corps
VA	Veterans Affairs
VHA	Veterans Health Administration
WAIS-III Digit Span Test	Wechsler Adult Intelligence Scale III (WAIS-III) Digit Span Test
WBC	White Blood Cells
WHO	World Health Organization

Introduction to Honoring our PACT Act of 2022

This report is submitted pursuant to section 510 of the Sergeant First Class Heath Robinson Honoring Our Promise to Address Comprehensive Toxins Act of 2022 (Honoring our PACT Act of 2022).

On August 10, 2022, President Biden signed the Honoring our PACT Act of 2022 (the PACT Act) into law, expanding eligibility for VA health care and benefits for Veterans exposed to burn pits and other toxic substances; this includes Veterans of the Vietnam, Gulf War and post-9/11 eras.

This law significantly expands Veterans' benefits, health care and research, empowering VA to help millions of people by providing generations of Veterans—and their survivors—the care and benefits they have earned and deserve.

Section 510 (Box 2 below) requires VA to provide a report on the health effects of jet fuels used by the Armed Forces. This report discusses the effects of various different types of jet fuels used by the Armed Forces on the health of individuals by length of exposure; an identification of the immediate symptoms of jet fuel exposure that may indicate future health risks; a chronology of health safeguards implemented by the Armed Forces intended to reduce the exposure of members of the Armed Forces to jet fuel; and an identification of any areas relating to jet fuel exposure about which new research needs to be conducted. To fulfill the requirements of section 510, VA collaborated with the Department of Defense (DoD) to access data and information from DoD and each of the Services on relevant safeguard policies or guidance and studies/assessments on jet fuels that had been conducted by DoD investigators. In addition, DoD is participating in ongoing and future VA research efforts and has provided data to VA investigators to define jet fuel exposure, including occupational information and exposure monitoring data. The following report responds to this mandate.

Box 2. Excerpt from Section 510 of PACT Act.

(a) INITIAL REPORT.—Not later than one year after the date of the enactment of this Act, the Secretary of Veterans Affairs shall submit to the Committee on Veterans' Affairs of the Senate and the Committee on Veterans' Affairs of the House of Representatives, and make publicly available, a report on health effects of jet fuels used by the Armed Forces.

(b) CONTENTS.—The report submitted under subsection (a) shall include the following:

1) A discussion of the effect of various different types of jet fuels used by the Armed Forces on the health of individuals by length of exposure.
2) An identification of the immediate symptoms of jet fuel exposure that may indicate future health risks.
3) A chronology of health safeguards implemented by the Armed Forces intended to reduce the exposure of members of the Armed Forces to jet fuel.
4) An identification of any areas relating to jet fuel exposure about which new research needs to be conducted.

Background

Jet fuel, or aviation turbine fuel, is a common chemical exposure among military personnel. Jet fuels are heterogeneous mixtures that consist of aromatic and aliphatic hydrocarbons and non-hydrocarbon performance additives, with kerosene being the primary component (>98%). Toxic hydrocarbons, such as benzene, toluene and naphthalene, are minor constituents of bulk fuel, but their volatility presents a high potential for inhalation among military personnel working with fuels. Exposure to jet fuels in occupational settings can occur via dermal absorption, inhalation and accidental ingestion. Technical assessments, such as the Toxicological Profile for JP-5, JP-8 and Jet A Fuels (ATSDR, 2017), have reported acute health outcomes associated with exposure to the constituents of jet fuels, including hematological and neurological effects; less is known about long-term, chronic outcomes. This report summarizes the state of the science regarding the major jet fuels used by the U.S. military: JP-4, JP-5, JP-8 and Jet A.

Types of Jet Fuels

JP-4, JP-5, JP-8 and Jet A are kerosene-based, colorless, flammable liquids. These fuels are a mixture of many hydrocarbons, which are found naturally as crude oil. Additives are included in jet fuels based on the requirements for performance (e.g., icing inhibition or corrosion resistance).

JP-4 (jet propellant-4), first introduced in 1951, was the first fuel produced from a broad distillation temperature range and contains a wide array of carbon chain lengths, from 4 to 16 carbons long. It was initially developed to be broadly available for military use in times of need. The composition of JP-4 is approximately 13% aromatic hydrocarbons, 1.0% olefin hydrocarbons and 86% saturated hydrocarbons (ATSDR, 1995). It has a distillation temperature range of 60°C to 270°C (ATSDR, 1995).

JP-5 (jet propellant-5) was introduced in 1952 and JP-8 (jet propellant-8) was introduced in 1978. The primary difference between these two military fuels is the flash point temperature, which is higher for JP-5 (60°C) compared to JP-8 (38°C). The higher flash point for JP-5 is more suitable for safe handling and fueling aboard aircraft carriers and this is the primary fuel used by the U.S. Navy (ATSDR, 2017). JP-8 was specifically developed as a less flammable and safer alternative to JP-4. Bases worldwide began converting to JP-8 in the late 1970s and the conversion was completed in the 1990s (2012). Typical additives to JP-5 and JP-8 include antioxidants, static inhibitors, corrosion inhibitors, fuel system icing inhibitors, lubrication improvers, biocides and thermal stability improvers.

Jet A, also introduced in the 1950s, is used predominantly in the United States and Canada in commercial aircraft and is the base fuel used to produce JP-8 (NRC, 2003). It has a carbon number distribution between approximately 8 and 16 carbon atoms per molecule. A variation of Jet A, Jet A-1, is the standard specification fuel used in the rest of the world, except for the former Soviet states, where TS-1 is the most commonly used fuel. Jet A and Jet A-1 have flash points higher than 38°C (100°F), with autoignition temperatures of 210°C (410°F). The primary difference between the two is the lower freezing point of A-1; Jet A freezes at −40°C (−40°F), whereas Jet A-1 freezes at −47°C (−53°F) (DAF, n.d.-a).

The only other jet fuel commonly used in commercial turbine-engine-powered aviation is Jet B, which is used for its enhanced cold-weather performance; however, Jet B's lighter composition makes it more dangerous to handle. For this reason, it is rarely used except in very cold climates, such as in Northern Canada, Alaska and Russia. A blend of approximately 30% kerosene and 70% gasoline, it is known as a “wide-cut” fuel. It has a very low freezing point of −60°C (−76 °F) and a low flash point, as well. Other jet fuels that have been used by the U.S. military include JP-1, JP-2, JP-3, JP-6, JP-7, JP-9, JP-10 and TS-1; however, this report does not focus on these, as they have not been widely used or studied (2014).

Kerosene and diesel are petroleum fuels derived from crude oil; however, they each vary significantly from jet fuels in composition and use. Although jet fuels are kerosene-based, they are refined under more stringent conditions than kerosene and contain various additives not found in kerosene. Kerosene has fewer hydrocarbons (12-15 carbons long) and a lower boiling point (under 572 °F) than diesel and has various domestic uses, such as heating and cooking. Diesel, which is reddish in color, is at least 16 carbons long, has a maximum boiling point of 662 °F and is generally used to power automobile engines (Kelechava, 2022; Madisha, 2018; 2021). This report does not explore the U.S. military’s use of kerosene and diesel, as they are not aviation fuels.

Components of Jet Fuels

Many of the components in the complex mixtures that make up jet fuels have been studied at length. In addition to kerosene, gasoline and variations of hydrocarbon mixtures that include alkanes, cycloalkanes, alkylbenzenes, indanes/tetralins and polycyclic aromatic hydrocarbons (PAHs) such as naphthalenes, jet fuels can also be composed of many other well-known chemicals. These include toluene, which causes central nervous system dysfunction; benzene, which is a known carcinogen and hexane, which is a neurotoxin (NTP, 2021; EPA, 2000; EPA, 2012a; EPA, 2012b). Some additives include surfactants, metal deactivators, antioxidants, antistatic agents, corrosion inhibitors and icing inhibitors.

Although there is extensive information in the published literature, and from authoritative bodies (e.g., IARC, EPA, NIH) about the health effects of some of the constituents of jet fuels (such as benzene), the effects of these components as a mixture and whether they elicit greater or different effects, are not well understood. Further, the effects of individual components may be modified by other chemical exposures and stressors. Therefore, this report will focus on exposure to jet fuels as a mixture in occupational settings, rather than exposure to individual component chemicals.

Exposed Military Populations

Existing literature has identified a variety of occupational settings and tasks that put workers or military personnel at risk for jet fuel exposure (D'Mello & Yamane, 2007; NRC, 2003; Rhodes, 2001; Smith et al., 2010). Such tasks include performing aircraft fuel-cell maintenance; working in fuels-specialty and fuels-transportation shops; operating, fueling and defueling aircrafts; fuel tank entry, cleaning and performance testing; maintenance of military aircrafts, vehicles and other machinery; transporting jet fuel; and maintenance of jet fuel storage tanks (ATSDR, 2017; NRC, 2003; Pleil et al., 2000; Rhodes, 2001). Other military-related uses of jet fuels include fueling generators, tent heaters and stoves; using fuel as an aircraft sink heat; using fuel as a cleaning or degreasing substance; and tending burn pits (NRC, 2003). Exposure to jet fuel is a potential risk for military personnel performing these types of jobs; however, duties may vary from day to day and from shop to shop.

Report Organization

To respond directly to Congress's request, this report is organized in parts that address the requirements outlined in section 510 of the PACT Act, as follows:

Part 1, Health Safeguards (subsection (b)(3)), organizes policies and guidelines issued by DoD, as well as by each of the Services over time. In a review of more than 50 policies, this section will outline the history of previous and existing guidance for reducing the exposure of military personnel to jet fuel and for governing its use.

Part 2, Health Effects (subsection (b)(1) and (b)(2)), includes a fit-for-purpose, systematic review of human health effects, including acute and long-term health outcomes, with information on duration of exposure (where available), as well as a summary of the quality and quantity of available research.

Finally, Part 3, Gaps and Next Steps (subsection (b)(4)), outlines the gaps in research and examines proposed areas for further study. This section also includes a description of the current collaboration between VA's Health Outcomes Military Exposures (HOME) and DoD on an investigation of the long-term outcomes in Veterans who had occupational exposure to jet fuels and discusses how this study may address research needs and support decision-making.

As required by the PACT Act, a follow-up report on the health effects related to jet fuel exposure in the military will be due to Congress in 5 years. That report will include an expanded review of the medical and scientific literature and integration of findings from VA's jet fuel study.

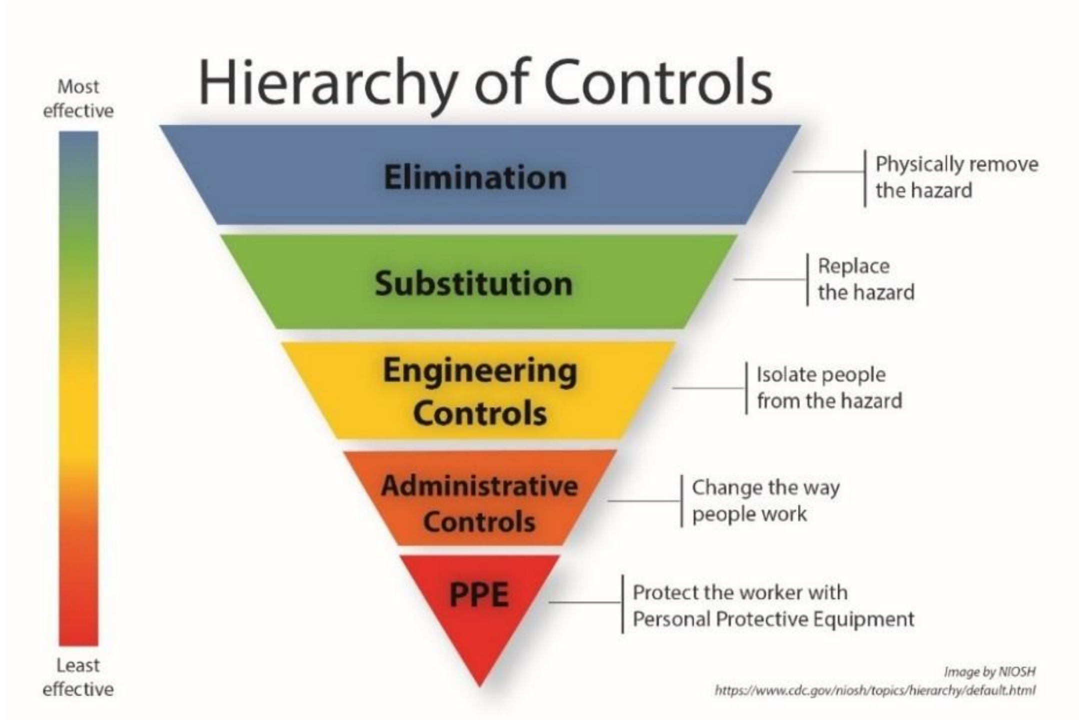
Part 1: Health Safeguards

1.1. Objective

This section summarizes DoD's health safeguards against exposure to jet fuel. DoD has established and updated several policy and guidance documents over time to ensure the safe use and management of jet fuels and other chemical substances. DoD's ongoing, protective measures to safeguard health are described chronologically to provide context. For this review, "health safeguards" is interpreted broadly as any guidance that ensures combat readiness, including broad health and safety programs, risk management and safety criteria that apply to jet fuel. However, to address concerns related to the health effects of exposure to jet fuel specifically, industrial hygiene controls intended to reduce exposure to jet fuels are highlighted. Controls meant to prevent accidental combustion and fires, such as use of static-dissipating fabrics, or response to jet fuel fires, such as controls for firefighters or emergency response plans, are not included in the scope of this review.

The following review of DoD policies is informed by journal articles, research articles, military handbook resources, technical manuals, fact sheets and training presentations including those regarding general airfield operations, petroleum operations, public health and emergency management provided by DoD and the Services. Additional information was gathered from internet searches, including the Defense Technical Information Center (https://discover.dtic.mil/) and the Defense Centers for Public Health (https://phc.amedd.army.mil/Pages/default.aspx). This review aims to provide descriptive information about policies and guidance; however, the review neither analyzes nor critiques the policies and guidance, nor does it comment on the extent to which the exposure controls were implemented or followed. While the review aims to be comprehensive, it is limited to the documents made available by DoD in response to VA's request for this information. In all, 53 documents were reviewed—as listed in Appendix A—and inform the summary of policies and guidance below.

1.2. Exposure Control Strategies



Source: NIOSH, 2023

Figure 1-1. NIOSH Hierarchy of Controls.

DoD's safeguards align with the National Institute for Occupational Safety and Health (NIOSH) Hierarchy of Controls, a framework of five levels of actions to reduce or eliminate hazards (Figure 1-1 above) (DoD, 2018). These controls include elimination or reduction of the hazard; substitution of a less toxic or hazardous chemical; engineering controls, such as installation of ventilation; administrative controls, such as training; and use of personal protective equipment (PPE). Within the hierarchy of controls, removing or reducing hazardous exposures by other approaches is preferred over the use of PPE, as its effectiveness depends on consistent and correct usage (NIOSH, 2023). DoD policies reviewed in this section were considered in the context of the NIOSH Hierarchy of Controls and focused on personal protection from aviation fuel inhalation and dermal exposure, rather than control of fire and static electricity hazards within petroleum aviation fuel product operations. DoD-recommended exposure controls included elimination (e.g., use of safer alternate fuels such as renewable or bioenergy); substitution (e.g., the phasing out of JP-4 in favor of the less flammable, less hazardous JP-8); engineering controls (e.g., installation of ventilation within aircraft maintenance areas); administrative controls (training on equipment safety inspection and appropriate use of PPE, formal medical surveillance programs); and PPE (e.g., protective clothing, which may include static dissipative fuel resistance protection, hearing and eye protection, which may include field wear, splash and spray resistant eye protection, hearing protection, fuel-resistant gloves, as well as NIOSH approved air-purifying respirators or positive pressure, air-supplied respirators) (DA, 2022). Controls to eliminate jet fuels were not proposed. Individual Service policies and guidance focused on administrative controls and PPE are described below.

1.3. Occupational Exposure Standards and Guidelines

Several Federal agencies and national organizations set or recommend occupational exposure limits or guidelines, including the Occupational Safety and Health Administration (OSHA), the National Research Council (NRC) and the American Conference of Governmental Industrial Hygienists (ACGIH), in addition to NIOSH. OSHA sets permissible exposure limits (PEL) to protect workers, which are legally enforceable. However, OSHA recognizes that many of its permissible exposure limits (PELs) are outdated and inadequate for ensuring protection of worker health. Other agencies and organizations set limits that serve as guidance, such as NIOSH's recommended exposure limits (REL), which are often used for risk assessment.

Although OSHA and other Federal agencies have limited authority and jurisdiction over the U.S. military, the U.S. military relies on them in their policies and guidance for all nonmilitary-unique DoD operations and workplaces. The DoD Safety and Occupational Health (SOH) Program adopts applicable OSHA laws and regulations, including emergency temporary standards that are OSHA-issued under the provision of the Occupational Safety and Health Act and national consensus standards by reference (DoD, 2021a). In addition, the Services cite OSHA and other national standards. The Army relies on OSHA standards stating:

> Army occupational safety and health criteria are derived from the provisions of the Occupational Safety and Health Act; the regulations, standards and criteria promulgated by the Occupational Safety and Health Administration (OSHA) and consensus standards. The Army must comply with OSHA standards for all nonmilitary-unique operations and must apply, in whole or in part, as practicable, OSHA standards to uniquely military equipment, systems, operations, or workplaces" (DA, 2020).

Furthermore, the Defense Centers for Public Health—Aberdeen (formerly the Army Public Health Center) reports Military Exposure Guidelines (MEG) for use in risk assessment and decision-making to manage occupational and environmental risks to deployed military personnel that rely on existing exposure standards and guidelines (including those from OSHA, NIOSH, EPA and NRC detailed below) for jet fuels and a wide range of potential exposures (USAPHC, 2013).

To date, OSHA, NIOSH and ACGIH exposure limits are not specific to jet fuels, but instead they are based on broader exposure to petroleum products or kerosene during the average workday (see Table 1.1 on page 19), or specific chemicals that are constituents of jet fuels, such as benzene. OSHA's exposure limits (29 CFR 1910.1000) regulate levels of air contaminants from petroleum distillates with a PEL of 2,000 mg/m^3 for an 8-hour workday over a 40-hour workweek (Table 1-1 below). OSHA does not provide a PEL for kerosene. NIOSH set an 8-hour REL time-weighted average (TWA) of 350 mg/m^3 for petroleum distillates and a REL of 100 mg/m^3 for kerosene in air averaged over a 10-hour workday. ACGIH has set an 8-hour TWA of 200 mg/m^3 for kerosene and jet fuels. Military guidance also points to OSHA and NIOSH national standards for benzene as part of the controls for jet fuel exposure (DA, 2020; DA, 2021; Hinz et al., 2011; Rolls, 2016a).

Table 1-1. U.S. Jet Fuel Exposure Limits and Guidelines, as Kerosene and Petroleum Products.

Agency or Organization	Kerosene, Kerosene Jet Fuels	Petroleum Distillates	Benzene
OSHA PELs	none	2,000 mg/m^3 (8-hour TWA)	3.19 mg/m^3 (8-hour TWA) 31.95 mg/m^3 (8-hour TWA)[a]
NIOSH RELs	100 mg/m^3 (10-hour TWA)	350 mg/m^3 (8-hour TWA)	0.32 mg/m^3 (10-hour TWA)
ACGIH Threshold Limit Values	200 mg/m^3 (8-hour TWA)	none	1.6 mg/m^3 (8-hour TWA)

OSHA = Occupational Safety and Health Administration; NIOSH = National Institute for Occupational Safety and Health; ACGIH = American Conference of Governmental Industrial Hygienists; ppm = parts per million; TWA = time weighted average. Sources: (OSHA, 2021; OSHA, 2021a; OSHA, 2021b)
[a]This permissible exposure limit is applicable to industry segments exempt from the benzene standard at 29 CFR 1910.1028.

Risk-based exposure limits specific to jet fuel exposure are available. At the request of DoD and the U.S. Environmental Protection Agency (EPA), the NRC evaluated the Acute Exposure Guidelines (AEGL) published in 2011 for jet fuel vapor in the environment, specifically JP-5 and JP-8 (NRC, 2011). AEGLs represent varying degrees of adverse health effects that might be expected in the general population following acute exposure to the level reported for durations from 10 minutes to 8 hours and are meant to inform emergency response (EPA, 2022a). For JP-5 and JP-8, AEGLs are as follows:

- AEGL-1 is the airborne concentration of a substance above which it is predicted that the general population could experience notable discomfort, irritation or asymptomatic, non-sensory effects, which are transient and reversible upon cessation of exposure. The 8-hour AEGL-1 for JP-5 and JP-8 is 290 mg/m3.
- AEGL-2 is the airborne concentration of a substance above which it is predicted that the general population could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape. The 8-hour AEGL-2 for JP-5 and JP-8 is 1,100 mg/m^3.

- AEGL-3 is the airborne concentration of a substance above that it is predicted that the general population could experience life-threatening health effects or death. An 8-hour AEGL-3 for JP-5 and JP-8 has not been established due to insufficient data.

1.4. DoD Safeguards and Jet Fuel Exposure Controls

Across the policies and guidance documents reviewed, relatively few were specific to jet fuels. Most documents provided technical guidance, provided for safety management and training programs or focused on emergency response to incidents related to the combustion of jet fuels. The following section provides an illustrative summary of the kinds of guidance available and their evolution over time. More information limited to specific jet fuel exposure controls by service follows. Documents are listed in Appendix A by service.

The earliest reviewed policy—originally published as "Identification Methods for Bulk Petroleum Products Systems Including Hydrocarbon Missile," Military Standard (MIL-STD) 161-F and G on January 6, 1972, two decades after the introduction of jet fuels—promotes greater safety to personnel by providing uniformity in the identification of products and product groups. Policies, such as the Army's Operator's Manual for the Heavy Expanded Mobility Tactical Truck (HEMMT) Tanker Aviation Refueling System (NSN 4930-01-269-2273) Model Number 50-0051, (DA, 1989), included detailed instructions describing procedures for the performance of aviation refueling from a fuel tanker, in addition to general safety precautions to protect personnel from fuel and fire hazards.

Policies and guidance introduced before the 1990s have been superseded by new or revised guidance, as in the case of DoD's updated MIL-STD (DoD, 2005), DA's Petroleum Supply Operations (DA, 2022) and Naval Air Systems Command (NAVAIR) Aircraft Refueling Naval Air Training and Operating Procedures Standardization (NATOPS) Manual (NAVAIR, 2022). These more recent changes illustrate the 50-year evolution of health safeguards instructing personnel how to navigate petroleum products in various environments (e.g., in bulk supply, water logistics and specifically during refueling activities for aircraft) and operate fuel systems.

Although the original Aircraft Refueling Handbooks for Navy/Marine Corps Aircraft via Military Handbook (MIL-HDBK)-844A (AS), DoD Handbook was released in 1992 (DoD, 2003), it has been revised six times, superseded by a 2019 version and ultimately reframed as a supplement to the Aircraft Refueling NATOPS Manual, NAVAIR 00-80T-109 (updated in 2022) (NAVAIR, 2022). This handbook provided background information and guidance on requirements and procedures, now contained in the most recent NATOPS manual, distinguishing between two different types of aircraft fuels in use at Navy and Marine Corps air activities: turbine engine fuels and aviation gasolines (AVGAS). Many of the early publications that provided guidance for jet fuel operations, maintenance and refueling, were replaced with revised versions, or iterative changes, such as DoD's Unified Facilities Criteria (UFC) Policies (DoD, 2022). For example, UFC 3-460-03 was originally published in 2003, updated as Petroleum Fuel Systems Maintenance in 2017 and later superseded in 2021 by other military publications that incorporate several industry standards, recommended practices and codes (DoD, 2021b). Updates were intended to harmonize requirements and guidance documents from the Army, Navy, U.S. Marine Corps and Air Force, as well as industry guidelines and to unify definitions and requirements for military contractors and government personnel in maintaining petroleum fuel facilities. Similarly, UFC 460-01 Design: Petroleum Fuel Facilities was originally released in 2019 and was revised in 2020 and 2022 (DoD, 2022). The latest update incorporated changes to the design requirements for fuel facilities based on lessons learned from the previous guidelines, new technologies, updated requirements by the Services for fuel handling and quality, new regulations, coordination with unified facilities guide specifications (UFGS) and other reference documents. UFC-460-01 also references Service-specific documents (DoD, 2022). These documents are not overseen by the tri-Service fuel community, as each service has its own requirements for fuel quality and operations.

1.4.1. DoD-wide Policies and Guidance Regarding Jet Fuel Safeguards

Most of the reviewed DoD-wide documents primarily focus on general safety; training and emergency standards; and management programs and comprehensive guidance for managing and maintaining jet fuels and petroleum. However, there were a few documents also describing exposure limits, sampling analysis and response. Jet fuel use is not unique to the military, as it also has public and private sector uses (e.g., in commercial and private aircraft).

The extent of available DoD exposure guidance is reflected by DoD's Hazard Communication (HAZCOM) Program, which focuses on logistics, communications policies and standards (DoD, 2019), as well as by the Occupational and Environmental Health (OEH) policy (DoD, 2018). DoD's OEH policy expanded risk management procedures to anticipate, recognize, evaluate and control health hazards associated with occupational and environmental exposures to chemical, physical and biological hazards in DoD workplaces, including military operations and deployments; established industrial hygiene and occupational medical surveillance performance metrics and established the DoD Industrial Hygiene Working Group (IHWG) and the DoD Occupational Medicine Working Group (OMWG). The aims of these efforts include an annual goal to reduce all mishaps, injuries and illnesses; compliance with DoD safety and health standards and policies and an ultimate goal of zero incidents (DoD, 2018).

Of the nine documents available describing DoD-wide policies and guidance to safeguard Service members, two provided information regarding engineering controls around fueling areas and for fuel laboratory personnel (DoD, 2021b; DoD, 2022), two provided information on administrative controls specific to reducing exposure to jet fuels (DoD, 2021b; DoD, 2022) and one provided information regarding PPE use for petroleum fuel facilities (DoD, 2021b).

Engineering controls:

- UFC 3-460-03 (2021), includes safety guidance regarding installation of emergency safety showers and eyewash fountains around fueling areas and pumphouses as well as the installation of appropriate ventilation hoods within fuel laboratories (DoD, 2021b).

- UFC 3-460-01 (2022) describes safety requirements including those for the installation of eyewash and shower facilities in workshops, safety relief valves, facility respirator air systems and overall considerations for health and safety in the design of fuel facilities (DoD, 2022).

Administrative controls:

- UFC 3-460-03 (2021) includes safety guidance such as training in the proper selection, use, care and maintenance of PPE, as well as implementation of petroleum fuel facility industrial hygiene surveys, programs for confined space entry in accordance with applicable military service requirements, OSHA requirements and ACGIH guidelines (DoD, 2021b).

PPE:

- UFC 3-460-03 (2021) includes safety guidance on conventional PPE polyester and cotton-blend coveralls for routine maintenance of fuel facilities in areas that do not pose a fire hazard as well as guidance on PPE for tasks where petroleum fuel is present in fuel facilities, such as tank cleaning, including the use of disposable protective coveralls and respiratory protection (DoD, 2021b).

1.4.2. Air Force Policies and Guidance Regarding Jet Fuel Safeguards

Air Force policies and guidance emphasize the need for overall standards and management programs that address safety, training and emergency prevention. These safeguards appeared across Air Force Policy Directives (DAF, 2017, 2019), as well as in Air Force Instruction and Manuals (DAF, 2021, 2022a). In addition, the 711th Human Performance Wing/U.S. Air Force School of Aerospace Medicine provided jet fuel fact sheets specified by type, in-depth guidance and directives to support measuring exposures, responding effectively and potentially assessing health risks (DAF, 2022a; 2022b, n.d.-b, n.d.-a; NAVAIR, 2022; Rolls, 2016a, 2016b). It also detailed the Jet Fuel Health Hazard Training, a comprehensive briefing packet for Air Force Base-level bioenvironmental engineers to use when training personnel on potential health hazards from exposure to jet fuel.

Of the 11 documents available describing Air Force-wide policies and guidance to safeguard Servicemembers, one provided information regarding engineering controls for fuels personnel (DAF, 2021), six provided information on administrative controls specific to reducing exposure to jet fuels (Brown, 2016; DAF, 2021; n.d.-a; Hinz et al., 2011; Rolls, 2016a, 2016b) and seven provided information on PPE (DAF, 2021; 2022a, n.d.-b, n.d.-a; Hinz et al., 2011; Rolls, 2016a, 2016b):

Engineering controls:

- Air Force Instruction (AFI) 23-201 (2021) lists the availability (installation) of emergency showers and eye wash stations for fuels personnel (DAF, 2021).

Administrative controls:

- AFRL-SA-WP-SR-2012-0002 (2011) provides guidance for exposure sampling programs of JP-8 jet fuel vapor using NIOSH Method 1550, "Naphthas." Medical surveillance program recommendations, including physical exam and health history, apply to workers exposed above the action level for JP-8 or who have significant dermal exposure to jet fuel including tasks in which workers come into prolonged contact with jet fuel on a routine basis (Hinz et al., 2011).

- 711th Human Performance Wing/U.S. Air Force School of Aerospace Medicine, Fact Sheet Jet A and Jet A-1 Fuel (2016) includes guidance for medical monitoring programs and states that occupational medical exams for Jet A and Jet A-1 exposures should be the same as for JP-8 exposure and refers to DoD 6055.05-M, Occupational Medical Examination and Surveillance Manual (Rolls, 2016a).

- 711th Human Performance Wing/U.S. Air Force School of Aerospace Medicine, Fact Sheet Jet Fuel Vapor Sampling and Information (2016) described the exposure sampling program methods for JP-8 jet fuel is NIOSH 1550 for “naphthas” with further specification of the preferred collection materials. Medical surveillance program guidance specifies initial and annual medical surveillance including a health history and physical examination (Rolls, 2016b).

- Air Force Research Lab (AFRL)-SA-WP-SR-2016-0023 (2021) provides guidance on jet fuel sampling and analysis programs and cites NIOSH 1550 for “naphthas” as the preferred method for analysis of hydrocarbon mixtures for environmental sampling (Brown, 2016).

- Air Force Instruction (AFI) 23-201 (2021) specifies training on risk management techniques per AFI 90-802, requiring proper certification per AFI 36-2670 and CFETP 2F0X1 requirements. Training on emergency response showers/eyewash and spill clean-up are required as detailed in T.O. 00-25-172 and T.0. 42B-1-1 (DAF, 2021).

- 711th Human Performance Wing/U.S. Air Force School of Aerospace Medicine, Jet Fuel Health Hazard Training, (n.d.) provides general guidance on jet fuel health hazard training (DAF, n.d.-b).

PPE:

- AFRL-SA-WP-SR-2012-0002 (2011) states that respiratory protection shall be worn in accordance with Air Force Occupational Safety and Health Standard 48-137 and describes appropriate PPE, including butyl and nitrile rubber gloves, neoprene rubber headwear/footwear, coveralls for those who may come into contact with JP-8, as well as tri-layer coveralls with booties for fuel cell workers (Hinz et al., 2011).

- 711th Human Performance Wing/U.S. Air Force School of Aerospace Medicine, Fact Sheet Jet A and Jet A-1 Fuel (2016) describes PPE requirements to prevent contact with Jet A and Jet A-1. Nitrile/butyl gloves, neoprene headwear/footwear, coveralls and/or face shield/eye protection are noted as appropriate PPE for all personnel who may come in contact with JP-8. Personnel who may have prolonged, direct contact with JP-8, such as fuel cell workers, must wear tri-layer coveralls with booties. Cites Technical Order 1-1-3 that Bioenvironmental Engineering will determine respiratory protection requirements (Rolls, 2016a).
- 711th Human Performance Wing/U.S. Air Force School of Aerospace Medicine, Fact Sheet Jet Fuel Vapor Sampling and Information (2016) provides a description of PPE for personnel who may come in contact with JP-8 including nitrile gloves, neoprene headwear/footwear and coveralls. For prolonged jet fuel contact, a tri-layer anti-static laminate consisting of a nylon filament face, a Teflon® or Gor-Tex® membrane and nylon knit with anti-static filaments incorporated into the fabric structure are recommended (Rolls, 2016b).
- AFI 48-145, (2018) mentions use of PPE; however, the types of PPE are not further specified (DAF, 2022a).
- Air Force Instruction (AFI) 23-201 (2021) notes PPE requirements per Air Force Manual (AFMAN) 91-203 and T.O. 00-25-172; however, the type of PPE is not further specified(DAF, 2021).
- 711th Human Performance Wing/U.S. Air Force School of Aerospace Medicine, Health Risk Assessment Information for Alternative to F-24/JP-8 Jet Fuels, (n.d.) notes PPE shall be worn to prevent contact with JP-8 and alternatives. Nitrile-/butyl gloves, neoprene headwear/footwear, coveralls and/or face shield eye protection. Technical Order 1-1-3 states that Bioenvironmental Engineering will determine respiratory protection requirements (DAF, n.d.-a).
- 711th Human Performance Wing/U.S. Air Force School of Aerospace Medicine, Jet Fuel Health Hazard Training, (n.d.) specifies that Bioenvironmental Engineering will determine respiratory protection requirements and lists general PPE requirements (DAF, n.d.-b).

1.4.3. Army Policies and Guidance Regarding Jet Fuel Safeguards

The Army provided a comprehensive set of safeguards. The Army has specific, targeted policies and guidance across a wide variety of training materials, Technical/Technical Manuals (TM), Training Circular (TC), Graphic Training Aid (GTA), Soldier Training Publication (STP), Army Techniques Publications (ATP), Army Regulations (AR) and Department of the Army (DA) Pamphlets (PAM).

Of the 23 documents available describing Army-wide policies and guidance to safeguard Service members, two provided information regarding engineering controls for chemical agent operations and fuel site operations (DA, 2018b; DA, 2022); and four provided information on PPE that were specific to reducing jet fuel exposure (DA, 1992; DA, 2010; DA, 2018a; DA, 2022):

Engineering:

- Department of the Army Pamphlet DA PAM 385-61(2018) provides guidance requiring installation of emergency shower facilities for all personnel involved in chemical agent operations (DA, 2018b).
- ATP 4-43 (2022) requires establishment of eyewash facilities at refueling sites and well-ventilated areas for handling and transfer of fuels (DA, 2022).

PPE:

- TM 1-1500-204-23-3 (1992) provides guidance for aircraft maintenance personnel. General recommendations include using gloves and other protective clothing to protect skin from contact with fuels. The manual also recommends PPE for various specific situations (e.g., use of an apron, respirator, face shield and rubber gloves when working with fuel cells) (DA, 1992).
- STP 10-92F15-SM-TG (2010) provides guidance for petroleum supply specialists. While PPE guidelines are largely focused on firefighting situations, the report also includes a general recommendation for the use of gloves, goggles and hearing protection during fueling operations (DA, 2010).
- ATP 3-04.17 (2018) recommends the use of PPE such as gloves, eyewear and hearing protection when handling aircraft fuel and performing aircraft refueling operations (DA, 2018a).
- ATP 4-43 (2022) provides guidance on petroleum supply operations and includes recommendations for PPE for fuel handlers, including use of protective eyewear, gloves and protective outer garments (DA, 2022).

1.4.4. Navy and Marine Corps Policies and Guidance Regarding Jet Fuel Safeguards

The Navy and Marine Corps' exposure guidance, updated as recently as, addressed needs for analysis of exposures and appropriate responses to manage potential health effects (NAVAIR, 2022). However, policies within the category of Comprehensive Fuel and Petroleum Guidance offered specific and iterative policies to support Service members' operational, maintenance and refueling knowledge. Some of those policies, such as Gasoline and JP-5 Fuel Systems (2010) and Petroleum and Water Logistics Operations (2010) were updated in the early 2000s. Most recently, the Navy issued updated Safety Training and Emergency Standards and Management Programs, specifically Operational Naval Instruction (OPNAVINST) for Navy Safety and Occupational Health Program Manual for Forces Afloat (Office of the Chief of Naval Operations, 2019) and Navy Safety and Occupational Health Program (Office of the Chief of Naval Operations, 2020). Broad guidance on occupational health and safety includes engineering controls beyond PPE and administrative controls. For example, the Marine Corps Occupational Safety and Health (OSH) Program Manual (USMC, 2006) discusses engineering controls as the preferred method to mitigate exposure to hazards, including installation of emergency eye wash stations and on the installation of exhaust or ventilation systems (e.g., general ventilation or local exhaust ventilation) and use of local exhaust ventilation over general ventilation. However, none of these engineering controls are framed as specific to jet fuel exposure.

Of the nine available documents describing Navy and Marine Corps policies and guidance to safeguard Service Members, four provided jet fuel specific controls: two provided information on administrative controls (NSSC, 1994; USMC, 2006) and four provided information on PPE (2010; NAVAIR, 2022; NSSC, 1994; Rolls, 2016a).

Administrative controls:

- The Naval Supply Systems (NAVSUP) Command's guidance for Fuel Systems Ashore (NSSC, 1994), originally issued in 1987 and updated in 1994, provides technical details on how to operate and maintain petroleum facilities, including receipt, storage, issue and maintenance. It calls for administrative controls including training and certification, medical surveillance programs, recordkeeping, training on fuel tank confined space entry IH assessment, use of emergency eye wash and shower training and vapor and sludge monitoring requirements.
- The Marine Corps Occupational Safety and Health (OSH) Program Manual (USMC, 2006) outlines requirements for health and safety training for personnel, which includes training on ventilation, appropriate PPE use and entry in fuel cells. The manual also describes operational and infrastructure safety inspections to detect hazards, identify safeguards and inspect infrastructure such as ventilation. Administrative controls discuss general occupational health and safety and are not specific to jet fuel exposure.

PPE:

- The NAVSUP guidance for Fuel Systems Ashore (NSSC, 1994) called for the use of respirators for work in confined spaces, eye, ear and nose protection and coveralls/aprons to protect from jet fuel exposure in addition to PPE related to physical hazards and fire.
- The Marine Corps Occupational Safety and Health (OSH) Program Manual (USMC, 2006) provides guidance on the use of respirators when personnel are exposed to gases, fumes and vapors. The manual specifies that NIOSH-approved PPE use should be implemented when engineering and administrative controls are not available or effective. Information on appropriate PPE to protect hearing function from noise hazards, including jet aircraft noise, is also included.
- Chapter 542 of the Naval Ships' Technical Manual (DON, 2010) on Gasoline and JP-5 Fuel Systems outlines precautions to avoid various exposure to JP-5, including the use of goggles, face shield, apron and foot covers to avoid dermal exposure and eye washing if JP-5 enters the eyes.

- NATOPS General Flight and Operating Instructions Manual (NAVAIR, 2022) details PPE for aircrew, such as helmets, gloves and fireproof boots, but none of these controls are specific to jet fuel-related exposures.

1.5. Chronological Trends of Policies and Guidance Regarding Jet Fuel Safeguards Obtained from DoD

Although JP-4, JP-5 and Jet A fuels entered the U.S. market in the early 1950s, regulations of these chemical substances (and others) in workplace settings were not established until much later. Most of the military health safeguards obtained from DoD and reviewed for this report were established or updated in the last 20 years, with only 5 publications preceding the year 2000 and nearly half being as recent as the last 5 years. Figure 1-2 below depicts the issue dates of the general health safeguard policies and guidance compared to those that describe the jet fuel-specific controls included in this review. For reference, milestones regarding the understanding of health effects related to jet fuel exposure include the publication of ATSDR's Toxicological Profiles for JP-4 and JP-7 in 1995; for JP-5, JP-8 and Jet-A in 2017 and NRC's AEGLs for JP-5 and JP-8 in 2011 (ATSDR, 1995; ATSDR, 2017; NRC, 2011).

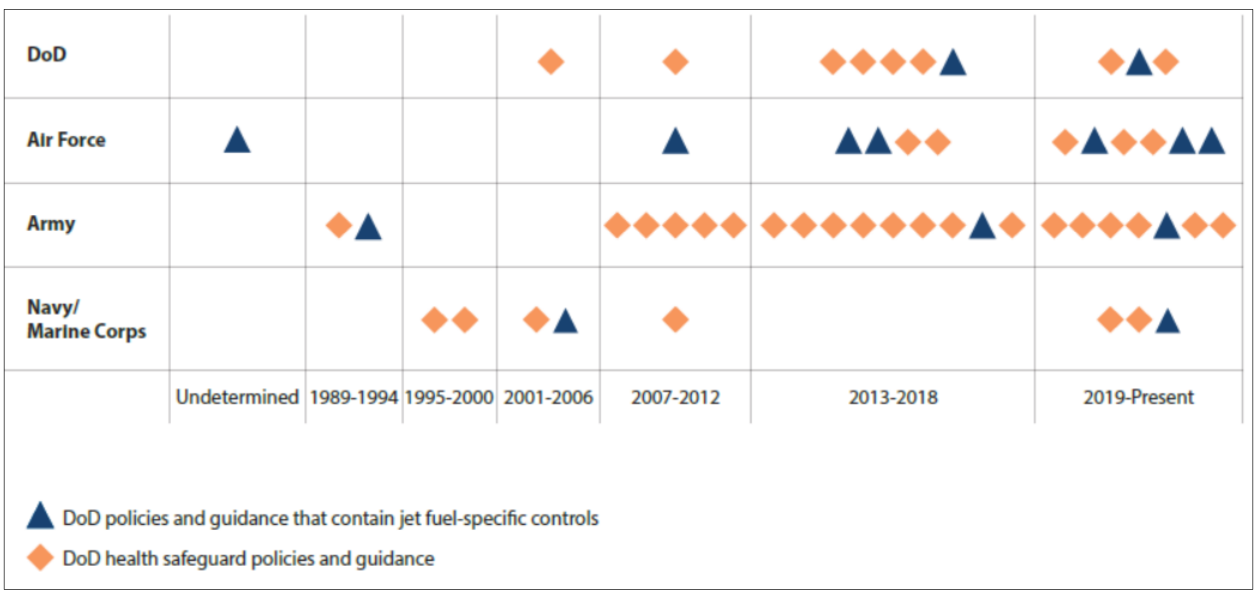


Figure 1-2. Chronology of Policy and Guidance Documents.

Part 2: Health Effects Systematic Literature Review

2.1. Objective

To discuss the health effects of types of fuels on health by length of exposure and identify immediate symptoms that may indicate future health risks (subsection (b)(1) and (b)(2)), the following fit-for-purpose systematic literature review was designed to inform a discussion of the health effects associated with exposure to jet fuels among members of the Armed Forces. Several thorough systematic reviews have been conducted by authoritative bodies (ATSDR, 1995; ATSDR, 2017; IOM, 2003; NRC, 2003) to understand the health effects of jet fuels and reported symptoms including changes in neurological function, such as increased reaction time; however, information about long-term health effects is lacking. This review paid special attention to the impact of length of exposure on the effects and to the relationship between immediate (acute) effects and long-term effects when available.

2.1.1. Approach

VA approached this review with explicit attention to the requirements in section 510 and the specific context and needs of Service members and Veterans to define the scope and the use of an appropriate methodology for assessing scientific evidence.

The PACT Act requires a discussion of the "effect of various different types of jet fuels" on health by "length of exposure"; it also requires an identification of the "immediate symptoms" of jet fuel exposure that may indicate "future health risks." For the purposes of this review, we refer to "effects" as "health outcomes," and those terms are interpreted and discussed as follows:

Effects: Specifically, health outcomes are conditions, physiologic signs or symptoms reported in the literature as potentially related to jet fuel exposure. This review organizes health outcomes into categories according to organ system, such as respiratory health outcomes, then into subsections for specific health outcomes, such as chronic bronchiolitis.

Immediate symptoms: Referred to as acute health outcomes, these are conditions, physiologic signs or symptoms that manifest concurrent with or shortly after jet fuel exposure. This review discusses effects that occur within about 6 months of exposure as acute health outcomes. In some cases, acute health outcomes resolve, whereas others continue over a long period of time or evolve to become long-term health outcomes.

Future health risks: Described in this review as long-term health outcomes, such health outcomes are conditions, physiologic signs or symptoms that continue for a long period of time or manifest long after exposure. This review discusses effects that persist or occur more than 6 months after exposure to jet fuels as long-term health outcomes.

Length of exposure: Health outcomes associated with jet fuel exposure are described by duration of exposure when information is available about how much time during a single event or over the length of a career Service members or workers spent working with jet fuel or in occupations where jet fuel exposure is common.

2.1.2. Scope

The scope of this review is limited by population and exposure to ensure that conclusions are specific to Veterans who have had jet fuel exposure. VHA's goal is to support the health and well-being of Veterans who were exposed to jet fuels as part of their military duties. Therefore, the systematic literature review focused on effects in exposed military populations. Occupational exposures, such as workers at commercial airports, were also included to ensure a robust evidence base that is specific to working adults. Studies of the general population exposed through other means were not included because such studies include heterogenous populations (such as children, the elderly or susceptible populations) and exposures (such as contaminated ground water or residential use of kerosene) with unknown relevance to Veterans.

The health impacts of jet fuels can be informed by the broader evidence base regarding jet fuel components such as kerosene, individual chemical constituents (such as particulate matter, naphthalene or benzene) or jet fuel additives (chemicals added to enhance performance and impart anti corrosive or anti-icing properties). However, understanding how the effects of those individual components combine to cause health outcomes is an area of ongoing research. To account for the effects of all components of jet fuels as a mixture and reflect the real-world context of Veteran exposures, this review concentrated on exposure to jet fuels only. In addition, this review included instances in which epidemiological studies measured components or constituents as a surrogate for jet fuel exposure.

Because of the specificity of the scope, this review took a broad view of the types of evidence to consider. Case reports or case series (documentation of effects in one or a few people with no comparison to unexposed people) are included in the discussion as supporting information. Other reviews are also included in this review (referred to as secondary reviews), including those that do not use systematic methodology. Although case reports, case series and reviews provide less reliable evidence to support conclusions, they are included as part of the synthesis of the evidence (as supporting information, as well as context for gaps in the existing body of evidence).

2.2. Summary of Assessment Methods

2.2.1. Introduction to the Systematic Review Assessment Methods

The methods used to conduct the literature review for jet fuels drew from those used by the EPA to develop Integrated Risk Information System (IRIS) assessments (Thayer et al., 2022; EPA, 2022b) (hereafter referred to as the IRIS Handbook). The mission of the IRIS program is to identify and characterize the health hazards of chemicals found in the environment. EPA's IRIS Handbook has incorporated feedback from the National Academy of Sciences (NAS) at workshops held in 2018 and 2019 and was well regarded by the NAS review panel for reflecting "significant improvements made by EPA to the IRIS assessment process, including systematic review methods for identifying chemical hazards" (NAS, 2022). Furthermore, EPA's IRIS program has used the IRIS Handbook to develop toxicological reviews for numerous chemicals.

For this literature review, systematic review methods used were comparable with those in the IRIS Handbook for the steps of literature search, screening, study evaluation, data extraction and the display of study quality evaluation results for all health outcomes (EPA, 2022b). VHA then synthesized the data on health outcomes. Deviating from the EPA IRIS approach, this protocol is focused on the impact of length of exposure (duration) on health outcomes and the relationship between immediate (acute) health outcomes and long-term health outcomes, as required by section 510 of the PACT Act. While the methods of this review draw from the systematic review methods described in the IRIS Handbook, VHA tailored this approach to suit the priorities of the PACT Act. The review protocol, provided in Appendix B, provides a detailed description of the methods that were used. The following summary of methods provides important context for interpreting the results of the review. Where evidence was lacking, for example health outcome categories for which there were no epidemiologic studies of sufficient quality, gaps in the evidence base were identified.

2.2.2. Literature Screening

This section summarizes the literature screening methods used to identify which references are potentially relevant for further assessment. Briefly, the Population, Exposure, Comparator and Outcome (PECO) statement established the criteria used to screen all the references identified in the search. The comprehensive PECO criteria used for screening the literature are provided in the Appendix (see Appendix B).

In some instances, multiple references reported on the same epidemiologic study. In such cases, the process for designating the "parent" references included several considerations: the peer-reviewed reference, or the reference with the largest number of participants, the most accurate outcome measures, or the most comprehensive reporting was given preference and was assigned as the "parent" reference while the others were assigned as "child" references for a given study. The parent reference underwent study evaluation and data extraction and is represented in tables. However, parent and child references are cited together in the discussion and documented as unique references reporting overlapping data from the same study. This approach avoids misinterpretation about the quantity of evidence available for a given health outcome.

2.2.3. Study Evaluation

All relevant primary studies identified in the literature search underwent study evaluation by a primary reviewer and a secondary reviewer. First, the primary reviewer assessed the quality of the study according to seven rating domains (see Appendix B for further details). For each domain, the primary reviewer recorded strengths, weaknesses and possible sources of bias before assigning a domain rating to indicate study data quality (see Figure 2-1 on page 30). Studies were evaluated on an outcome-specific basis. Differences in how outcomes were analyzed may result in mixed confidence ratings.

Good	Intended to represent a judgment that there was appropriate study conduct relating to the domain (as defined by consideration of the criteria listed below) and any minor deficiencies that were noted would not be expected to influence interpretation of the study findings.
Adequate	Indicates a judgment that there were study design limitations relating to the domain (as defined by consideration of the criteria listed below), but that those limitations are not likely to be severe and are expected to have minimal impact on interpretation of the study findings.
Deficient	Denotes identified biases or limitations that are interpreted as likely to have had a substantial impact on the results or that prevent reliable interpretation of the study findings. **Note: Not reported** indicates that the information necessary to evaluate the domain was not available in the study. Generally, this term carries the same functional interpretation as **Deficient** for the purposes of the study confidence classification.
Critically Deficient	Reflects a judgment that the study design limitations relating to the domain introduced a flaw so serious that the study should not be used without exceptional justification (e.g., it is the only study of its kind and may highlight possible research gaps). This judgment should only be used if there is an interpretation that the limitation(s) would be the primary driver of any observed effect(s), or if it makes the study findings uninterpretable.

Figure 2-1. Possible Domain Ratings for Study Evaluation.

After all domains had been individually evaluated and rated, the primary reviewer recorded a high-level summary of the study's primary strengths and weaknesses before assigning one of the following ratings for overall study confidence (see Figure 2-2 below).

High Confidence	No notable concerns identified (e.g., most or all domains rated **Good**).
Medium Confidence	Some concerns identified but expected to have minimal impact on the interpretation of the results (e.g., most domains rated **Adequate** or **Good**; may include studies with **Deficient** ratings if concerns are not expected to strongly impact the magnitude or direction of the results). Any important concerns should be carried forward to evidence synthesis.
Low Confidence	Identified concerns expected to significantly impact the study results or their interpretation (e.g., generally, **Deficient** ratings for one or more domains). The concerns leading to this confidence judgment must be carried forward to evidence synthesis.
Uninformative	Serious flaw(s) make the study results unusable for informing hazard identification (e.g., generally, **Critically Deficient** rating in any domain; many **Deficient** ratings).

Figure 2-2. Overall Study Confidence Classifications.

After completion of the primary review, a secondary reviewer conducted an evaluation following the same criteria as the primary reviewer and revised the evaluation as warranted. Case reports, case studies, case series, secondary reviews and overlapping 'child' references did not undergo study evaluation.

2.2.4. Evidence Synthesis

The evidence synthesis provides a summary of the causal interpretations between jet fuels exposure and health outcomes based on results of the available studies. Considerations when evaluating the available studies included risk of bias, sensitivity, consistency, strength (effect magnitude) and precision. The ability to reach conclusions about health outcomes or health outcome categories was determined by the availability of epidemiologic evidence (i.e., quantity of studies) and certainty in the results (based on the parameters listed above), also known as a weight-of-the-evidence assessment. Where evidence was lacking, for example health outcome categories for which there were no epidemiologic studies of sufficient quality, gaps in the evidence base were identified. Strength-of-evidence judgments were made for each health outcome using standard terminology (i.e., robust, moderate, slight, indeterminate) and definitions according to the framework described in the IRIS Handbook and described in the Appendix (see Appendix B) and summarized as follows in Box 2-1.

Box 2-1. Summary of Interpretations for Strength-of-Evidence Judgments.

- *Robust*: *High* or *medium* confidence studies that report an association between exposure and health outcomes with reasonable confidence that alternative explanations can be ruled out across studies.
- *Moderate*: Evidence that does not meet requirement for 'robust' but does include at least one *high* or *medium* confidence study that reports an association and additional evidence that increases certainty in the evidence.
- *Slight*: One or more studies reporting an association between exposure and the health outcome, but considerable uncertainty exists and supporting coherent evidence is sparse. In general, the evidence is limited to a set of consistent *low* confidence studies, or higher confidence studies with significant unexplained heterogeneity or other serious residual uncertainties.
- *Indeterminate*: No available evidence in humans or situations where the evidence in inconsistent and of *low* confidence.
- *Compelling evidence of no effect*: A set of *high* confidence studies examining a reasonable spectrum of health outcomes showing null results, ruling out alternative explanations with reasonable confidence.

2.3. Results of the Systematic Review

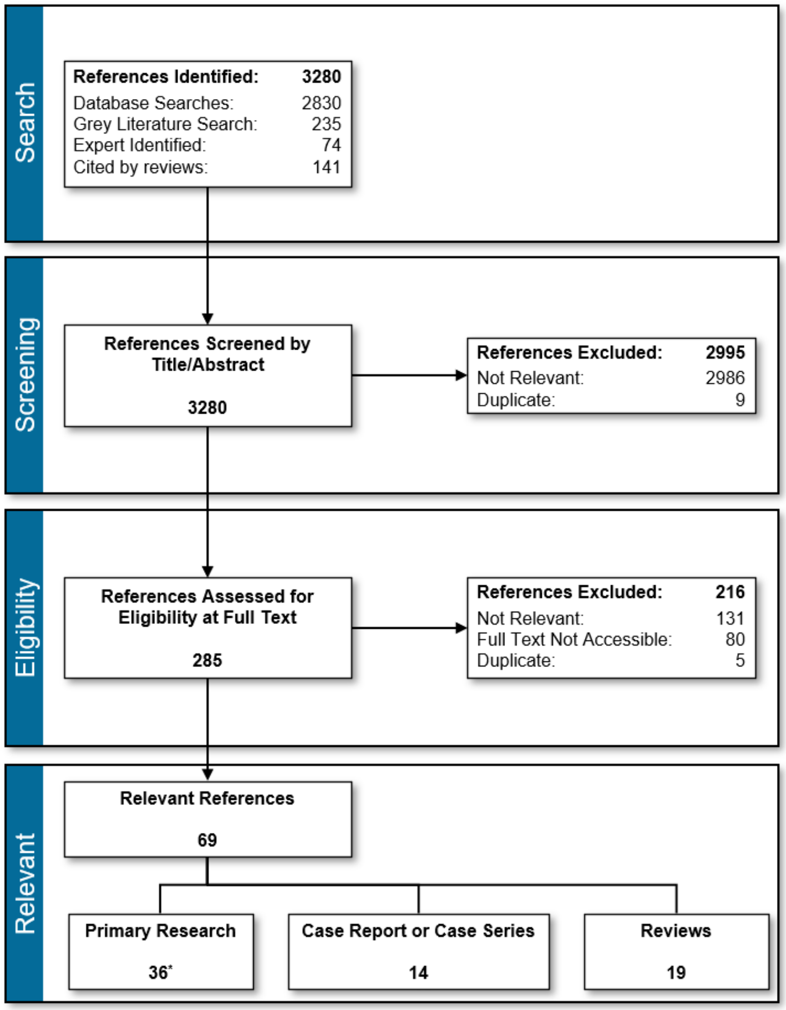
2.3.1. Literature Search and Screening Results

The literature search was conducted on January 10, 2023 with no date limit on the search. Removing duplicates resulted in a total of 3,280 unique references. These

3,280 references were moved to title and abstract screening using Litstream®[1]. Of the 3,280 unique references, 285 were potentially relevant and 2,995 were excluded during title and abstract screening. Of the 285 potentially relevant references, PDFs of 80 references were inaccessible due to the age of the reference (e.g., references published before 1985 were mostly not available online) or were hosted by an international publisher that did not accept American currency. Full text for the remaining references were retrieved and screened at the full-text level; 69 references met eligibility criteria for inclusion in this review (see Appendix B).

The 69 references reviewed included 36 reports of epidemiological (human) studies that reported original data (referred to as primary studies throughout this review), 19 studies that were literature reviews (referred to as secondary reviews) and 14 case reports or case series. Eight references reported on the same epidemiological studies and results as other references, resulting in 28 unique epidemiology studies represented for review. These overlapping studies were cited within the appropriate health outcome sections below but were not reported in tables to prevent misinterpretation of the amount of data available. Details of the literature search and screening process are shown in Figure 2-3 on page 34.

[1]Tool that allows researchers to collaborate on literature screening and data extraction through an efficient platform that tracks the literature process meticulously and across multiple team members working simultaneously. Managers can design fit-for-purpose review steps, make assignments and monitor progress at a granular level. Litstream® helps ensure transparent documentation of the review process while prioritizing the most relevant literature.



*Eight references reported on the same epidemiologic study as other references, thus counting the same epidemiologic study multiple times. After accounting for multiple references, there are 28 unique epidemiologic studies included in this body of literature.

Figure 2-3. Summary of Literature Search and Screening Process for Jet Fuels.

Among the 28 primary epidemiological studies reviewed in the following sections, a variety of fuel types, populations and geographic locations are represented. The studies reported on a range of health outcomes across 14 organ systems. In addition, they used a variety of study designs and methods to collect and analyze data that affected their quality and the confidence in the validity and reliability of the results. These qualities are briefly summarized below (Table 2-1 on page 35).

Table 2-1. Summary of Characteristics of Unique Primary Studies of Jet Fuels Exposure by Population.

Study Characteristic	Population		
	Military (n = 18)	Non-Military Occupational (n = 10)	Total (n = 28)
Jet Fuel Type[a]			
JP-4	7	2	9
JP-5	2	0	2
JP-8	11	0	11
Jet A	0	0	0
Other	1	1	2
Not Specified	2	7	9
Country			
Australia	2	0	2
Canada	0	2	2
Denmark	1	0	1
India	1	0	1
Sweden	0	2	2
Taiwan	0	1	1
United Kingdom	0	2	2
United States	14	2	16
Not Reported	0	1	1
Study Design			
Case-control	1	2	3
Cohort	4	5	9
Controlled Trial	1	0	1
Cross-sectional	12	3	15
Overall Study Quality[a]			
High confidence	0	0	0
Medium confidence	7	1	8
Low confidence	10	7	17
Uninformative	2	4	6
Health Outcomes[a]			
Cardiovascular	0	1	1
Dermal	2	0	2
Developmental	0	0	0
Digestive	1	3	4
Endocrine	0	0	0

Study Characteristic	Population		
	Military (n = 18)	Non-Military Occupational (n = 10)	Total (n = 28)
Hematologic	1	0	1
Hepatic	2	0	2
Immune	2	1	3
Mental Health	3	2	5
Metabolic	0	0	0
Musculoskeletal	0	0	0
Nervous	8	5	13
Renal	2	0	2
Reproductive, Female	2	0	2
Reproductive, Male	1	0	1
Respiratory	3	4	7
Other	1	0	1
Cancers	3	5	8

[a]One study may have multiple ratings in this category; as such, the total for the category may be greater than the total number of studies.

Population. The populations represented in the 28 primary studies fell into two categories: military (n = 18) and non-military occupational (n = 10).

Jet fuel type. The most commonly studied jet fuel was JP-8, with 11 out of 28 primary studies reporting on effects related to this exposure. JP-4 was assessed in nine studies. JP-5 was assessed in two studies and three other jet fuels were discussed across two studies: aviation turbine fuel was discussed in one study (Radhakrishnan et al., 2017) and MC 75 and MC 77 were discussed in another (Knave et al., 1976). No relevant primary studies on Jet A exposure were identified; however, nine studies reported outcomes for unspecified jet fuels. It is important to note that some studies reported on multiple types of jet fuels, for example JP-4 and JP-8, so the counts presented are not mutually exclusive.

Country. The 28 primary studies reported data originating in eight different countries. The United States was the most common country (n = 16), with all other countries being reported in 1-2 studies: Australia (n = 2), Canada (n = 2), Sweden (n = 2), the United Kingdom (n = 2), Denmark (n = 1), India (n = 1) and Taiwan (n = 1). One study did not report the country (Knave et al., 1978).

Study design. Of the 28 epidemiological studies that met the inclusion criteria, 15 had a cross-sectional design, nine had a cohort study design, three had a case-control design and one had a controlled trial design.

Overall study quality. Of the 28 studies that met the inclusion criteria, eight were rated as medium confidence for at least one health outcome, 17 were rated as low confidence and six were considered uninformative. Three studies received mixed confidence ratings across health outcomes, with each receiving ratings of low confidence for some outcomes and uninformative for others (Knave et al., 1978; Olsen et al., 1998; Tunnicliffe et al., 1999). None were considered high confidence.

Health outcomes. Studies were categorized into 18 health outcome categories (Table 2-2 on page 38). Most studies reported on nervous system outcomes (n = 13), cancers (n = 8) or respiratory system outcomes (n = 7). No relevant primary studies were identified for several categories of outcomes, including developmental, endocrine, metabolic and musculoskeletal outcomes.

Health outcomes related to the nervous system received the most medium confidence ratings (four studies), with cancers and outcomes related to the immune system, mental health, the female reproductive system and the respiratory system each receiving one medium confidence rating. Most confidence ratings fell into the low confidence category; among low confidence studies, there were seven studies each on cancers and nervous system outcomes, three studies on respiratory system and mental health outcomes and two studies on renal system and hepatic system health outcomes. One low confidence study each was identified for several other organ systems, including digestive, hematological, immune, female reproductive, male reproductive and other outcomes (i.e., all-cause mortality and health care encounters). Digestive system health outcomes, nervous system health outcomes and respiratory health outcomes were each reported in three uninformative studies and dermal system health outcomes were reported in two uninformative studies. Outcomes in other health systems, including cardiovascular, immune and mental health, were reported in one uninformative study each.

The following sections describe the results of the review for each organ system. All non-cancerous outcomes are presented first and ordered by weight of the evidence, followed by cancers.

Table 2-2. Summary of Unique Primary Studies of Jet Fuels Exposure by Health System and Overall Study Quality.

Health System	Overall Study Quality				Total
	High	Medium	Low	Uninformative	
Nervous	0	4	7	3	13[a]
Mental Health	0	1	3	1	5
Respiratory	0	1	3	3	7
Metabolic	0	0	0	0	0
Immune	0	1	1	1	3
Reproductive, Female	0	1	1	0	2
Reproductive, Male	0	0	1	0	1
Renal	0	0	2	0	2
Cardiovascular	0	0	0	1	1
Digestive	0	0	1	3	4
Hepatic	0	0	2	0	2
Hematological	0	0	1	0	1
Dermal	0	0	0	2	2
Developmental	0	0	0	0	0
Endocrine	0	0	0	0	0
Musculoskeletal/Connective Tissue	0	0	0	0	0
Other	0	0	1	0	1
Cancers	0	1	7	0	8

[a] Studies occasionally describe outcomes within a health system at different overall study quality levels. The total reports the overall number of studies that were represented in each health system.

2.4. Nervous System Health Outcomes

2.4.1. Summary of Nervous System Health Outcomes

Jet fuel exposure may impact nervous system health as a result of dermal, inhalation or oral exposures. Nervous system health may be assessed by measuring peripheral nervous system function, vestibular system function, deficits in motor function, hearing impairment, ocular conditions, memory impairment, symptoms of neurological pain or discomfort or other neurological symptoms. Peripheral nervous system function, vestibular function and motor function are the most informative indicators of central and peripheral nervous system function, while neurological pain or discomfort and other neurological symptoms have low specificity or sensitivity. Hearing impairment and ocular conditions are the most informative indicators for neurosensory function and memory impairment is the most informative indicator of short- and long-term memory function.

In this review, neurological outcomes are frequently characterized as long-term health outcomes due to the plasticity of the brain and continued development over the course of an individual's lifespan. While neurological "development" or "neurodevelopment" is frequently attributed to time periods in early life (e.g., in utero, infancy or early childhood), changes in the brain structure, function and organization continue to develop throughout adulthood. In evaluating the relationship between jet fuel exposure and neurological outcomes, the nature and timing of the exposure also plays a critical role. In occupational settings, employees may come into contact with jet fuel through accidental exposures via releases or spills. These types of exposures are typically of short duration and high intensity, which may result in acute nervous system symptoms (i.e., changes in neurological function due to intoxication). More commonly, however, employees observed in occupational studies are exposed to lower levels of jet fuel over longer periods of time. Persistent low-level exposure would result in smaller changes in nervous system outcomes over time.

Of the 13 studies with primary data examining the association between jet fuel exposure and nervous system health outcomes, four were considered medium confidence (Bell et al., 2005; Heaton et al., 2017; Kaufman et al., 2005; Maule et al., 2013), six were considered low confidence (Dreisbach et al., 2022; Fuente et al., 2019; Olsen et al., 1998; Smith et al., 1997; Tunnicliffe et al., 1999; Yang et al., 2003), one was of mixed (low and uninformative) confidence (Knave et al., 1978) and two were considered uninformative (Knave et al., 1976; Odkvist et al., 1987) (Figure 2-4 on page 40). Conclusions from reviews with results that overlap with the primary studies are summarized in Table D-1 in Appendix D on page 302.

Among the studies rated as low confidence and uninformative, sources of potential bias included lack of recruitment detail and potential for selection bias (Dreisbach et al., 2022; Fuente et al., 2019; Knave et al., 1978; Knave et al., 1976; Olsen et al., 1998; Smith et al., 1997; Tunnicliffe et al., 1999), exposure measurement methods (Dreisbach et al., 2022; Fuente et al., 2019; Knave et al., 1978; Knave et al., 1976; Olsen et al., 1998; Smith et al., 1997; Tunnicliffe et al., 1999; Yang et al., 2003), use of self-reported symptoms for health outcome measures (Knave et al., 1978; Olsen et al., 1998; Tunnicliffe et al., 1999; Yang et al., 2003), potential for residual confounding (Fuente et al., 2019; Knave et al., 1978; Knave et al., 1976; Odkvist et al., 1987; Olsen et al., 1998; Tunnicliffe et al., 1999), presentation of results as significant or non-significant only (Knave et al., 1978; Knave et al., 1976) and decreased study sensitivity (Dreisbach et al., 2022; Fuente et al., 2019; Knave et al., 1976; Odkvist et al., 1987; Olsen et al., 1998; Smith et al., 1997; Yang et al., 2003).

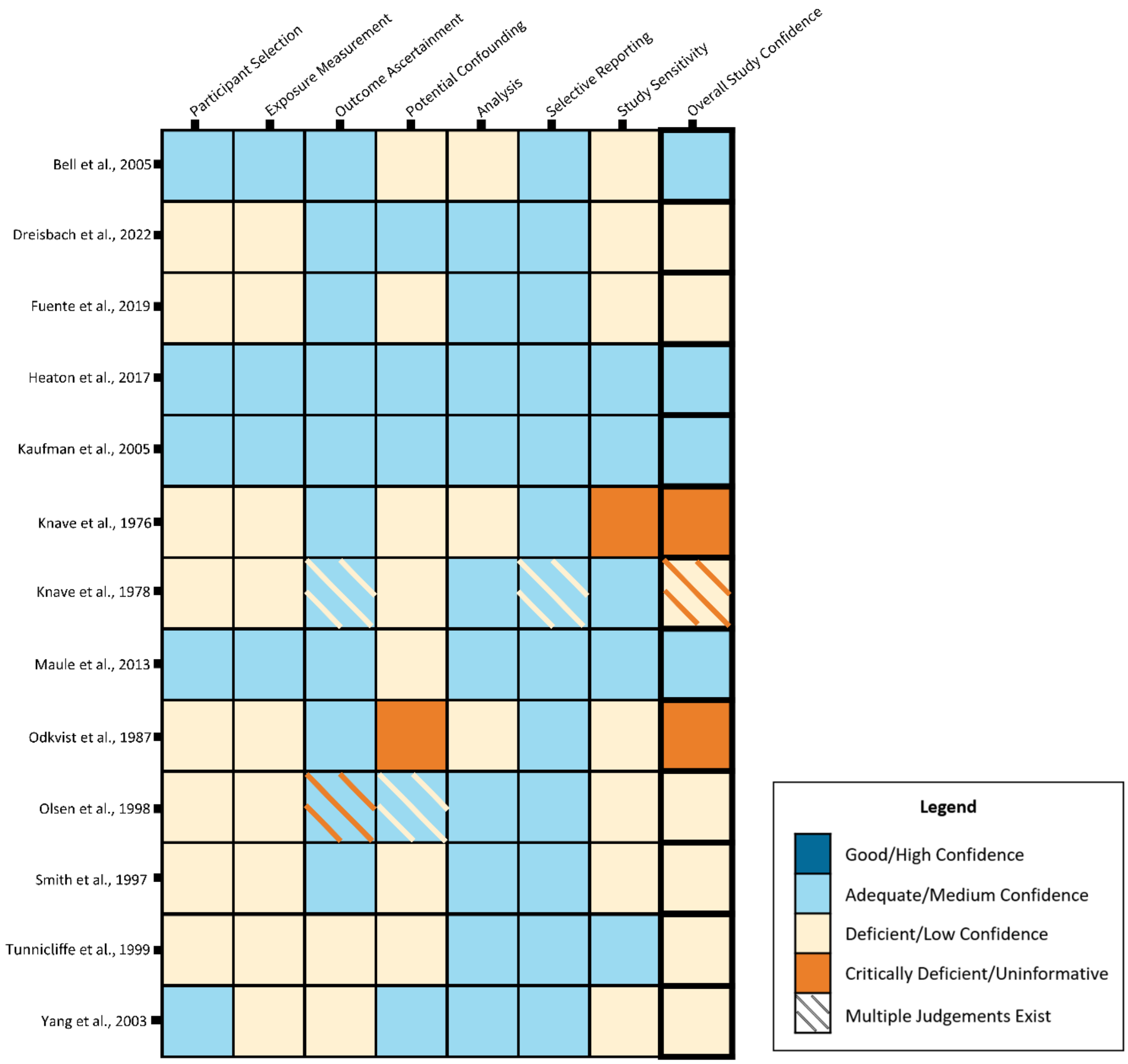


Figure 2-1. Study Quality Evaluations for Epidemiology Studies of Jet Fuel Exposure and Nervous System Health Outcomes.

Table 2-3 on page 42 summarizes the number of studies with acute (e.g., measurements taken within 6 months of jet fuel exposure) and long-term (e.g., measurement taken at least 6 months after jet fuel exposure) nervous system health outcomes.

Four studies examined hearing impairments, such as pure tone thresholds, audiometric hearing threshold, speech intelligibility in noise (SIN), auditory brainstem responses (ABR), central auditory function, otoacoustic emissions, hearing loss, cortical response, interrupted speech discrimination, speech discrimination, speech reception threshold and modified Amsterdam Inventory for Auditory Disability (mAIAD), with two studies examining short- and long-term hearing impairment (Dreisbach et al., 2022; Kaufman et al., 2005) and two studies examining long-term hearing impairment only (Fuente et al., 2019; Odkvist et al., 1987).

Four studies examined long-term memory impairments, such as auditory consonant trigrams, retention scores, memory recognition and memory reproduction (Heaton et al., 2017; Knave et al., 1978; Knave et al., 1976; Olsen et al., 1998).

Three studies examined long-term motor deficits, such as finger tapping tests, grooved pegboard tests, simple reaction time, manual dexterity, coordination and Romberg’s test (Heaton et al., 2017; Knave et al., 1978; Odkvist et al., 1987).

Five studies examined ocular conditions, such as eye irritation, broad-frequency rotatory test, broad-frequency smooth pursuit test, electronystagmography and Saccade tests, with three studies examining short-term ocular conditions (Knave et al., 1978; Olsen et al., 1998; Yang et al., 2003) and two studies examining long-term ocular conditions (Odkvist et al., 1987; Tunnicliffe et al., 1999).

Four studies examined neurological pain or discomfort, such as headaches, with two studies examining only short-term neurological pain or discomfort (Olsen et al., 1998; Yang et al., 2003) and two studies examining short- and long-term neurological pain and discomfort (Knave et al., 1978; Knave et al., 1976).

Three studies examined neurological symptoms, such as central reaction time, peripheral reaction time, fatigue, sleep disturbances, dizziness and sweating, with one study examining short-term neurological symptoms only (Bell et al., 2005) and two studies examining long-term neurological symptoms only (Knave et al., 1978; Olsen et al., 1998).

Three studies examined long-term peripheral nervous system outcomes, such as nociception, tremors, numbness of extremities, neurasthenia, polyneuropathy, nerve conduction velocity and vibration sensation thresholds (Knave et al., 1978; Knave et al., 1976; Olsen et al., 1998).

Two studies examined long-term vestibular function outcomes, such as postural sway (Maule et al., 2013; Smith et al., 1997).

Table 2-3. Number of Studies Reporting on the Acute and Long-term Nervous System Health Outcomes Following Jet Fuel Exposures.

Health Outcomes	Acute[a]	Long-term[b]	Total Unique Studies
Hearing impairment[c]	2	4	4
Memory impairment[d]	0	4	4
Motor deficits[e]	0	3	3
Neurological pain or discomfort[f]	4	2	4
Neurological symptoms[g]	1	2	3
Ocular conditions[h]	3	2	5
Peripheral nervous system[i]	0	3	3
Vestibular function[j]	0	2	2

[a]Acute health outcomes are considered those that were measured within 6 months of exposure.
[b]Long-term health outcomes are considered those that were measured at least 6 months after exposure.
[c]Hearing impairment includes pure tone thresholds, audiometric hearing threshold, speech intelligibility in noise (SIN), auditory brainstem response (ABR), central auditory function, otoacoustic emissions, hearing loss, cortical response, interrupted speech discrimination, speech discrimination, speech reception threshold and modified Amsterdam Inventory for Auditory Disability (mAIAD).
[d] Memory impairment includes auditory consonant trigrams, Hopkins Verbal Learning Test, memory impairment, memory recognition, memory reproduction and memory.
[e]Motor deficits include finger tapping tests, grooved pegboard tests, simple reaction time, manual dexterity, co-ordination and Romberg's test.
[f]Neurological pain or discomfort includes headaches.
[g]Neurological symptoms include central reaction time, peripheral reaction time, fatigue, dizziness, sleep disturbances and sweating.
[h]Ocular conditions include eye irritation, broad-frequency rotatory test, broad-frequency smooth pursuit test, electronystagmography and Saccade tests.
[i]Peripheral nervous system health outcomes include nociception, tremors, numbness of extremities, neurasthenia, polyneuropathy, nerve conduction velocity and vibration sensation thresholds.
Vestibular function includes postural sway.

2.4.2. Acute Nervous System Health Outcomes

2.4.2.1. Hearing Impairment

One medium confidence study (Kaufman et al., 2005) and one low confidence study (Dreisbach et al., 2022) examined short-term health outcomes on hearing impairment and observed mixed results.

Hearing loss was evaluated in a cross-sectional study of workers at a United States Air Force (USAF) installation by performing otoscopy and audiometry tests (Kaufman et al., 2005). JP-4 exposure was determined using a job exposure matrix, which collected information on noise dosimetry and solvent air sampling, including collection time, results and task descriptions. The mean exposure duration in exposed workers was 10.6 years, while unexposed workers were selected with no known workplace exposure to JP-4. Jet fuel exposure status or duration were not associated with hearing loss (see Table C-1 in Appendix C on page 223).

A cross-sectional study in military personnel at Marine Corps Air Station Miramar evaluated hearing thresholds in a group exposed to jet fuel and noise and a group exposed to noise only (Dreisbach et al., 2022). No significant differences for pure tone thresholds were observed between the two groups.

A case report described a male aircraft mechanic presenting to a clinic with left-sided hearing loss one day following accidental exposure to JP-8 (Shah & Wise, 2015). Hearing loss was determined with audiometric testing during the initial visit. At the 2-week follow-up, the mechanic had normal hearing results.

2.4.2.2. Memory Impairment

Two secondary references reported short-term memory impairment associated with jet fuel exposures. Memory impairment was evaluated in the Air Force Institute for Operational Health's (AFIOH) final risk assessment of acute exposure to JP-8 (Kendall et al., 2001). Air Force personnel were categorized as high, medium or low exposure based on job duties and asked to complete questionnaires on self-reported symptoms. Odds of self-reported forgetfulness were significantly elevated in high and medium exposure groups compared to the low exposure group and the association remained significant for the medium exposure group after accounting for multiple testing (see Table C-1 on page 221). Personnel were only asked whether they had experienced the symptom at least once during the past 6 months, therefore it is unclear whether these are long- or short-term health outcomes.

One review article described memory impairment in an early case report of a USAF pilot exposed to JP-4 (NRC, 1996). The pilot indicated feeling "abnormal" for approximately 36 hours post-exposure. Memory impairment as an acute symptom was also reported in Material Safety Data Sheets (MSDS) for JP-8 fuel (Ritchie et al., 2001).

2.4.2.3. Motor Deficits

Two review articles described a staggering walk in a case report of a USAF pilot exposed to JP-4 (NRC, 1996; Ritchie, et al. 2001). The pilot indicated they felt "abnormal" for approximately 36 hours post-exposure.

2.4.2.4. Neurological Pain or Discomfort

Three low confidence studies (Knave et al., 1978; Olsen et al., 1998; Yang et al., 2003) and one uninformative study (Knave et al., 1976) observed no increases in acute headaches in workers exposed to jet fuels. The cross-sectional study among Swedish aircraft mechanics (Knave et al., 1978) reported 7 out of 30 exposed subjects experiencing acute headaches, but no comparisons were made with the control group.

A cohort study of active-duty and civilian personnel at Hill Air Force Base evaluated neurological symptoms over 18 months; first, while JP-4 was used and then at 6 and 18 months after conversion to JP-8 (Olsen et al., 1998). Personnel were categorized as exposed or unexposed based on job titles. At each timepoint, personnel were administered a questionnaire and reported the frequency of neurological symptoms in the preceding month. The mean frequency of each symptom was assessed on a scale from zero to five ranging from "never happens" to "every day." There was no difference in mean frequency of headache symptoms between exposed and unexposed groups at any timepoints.

A cross-sectional study of male workers at Kaohsiung International Airport observed no differences in self-reported headache symptoms comparing exposed and unexposed workers (Yang et al., 2003). The study determined exposure status to jet fuel exhaust by job title.

One uninformative cohort study in Swedish aircraft fuel system mechanics examined headaches (Knave et al., 1976). Two groups of workers exposed to an unspecified jet fuel were assigned as “heavily exposed” or “less heavily exposed.” There were fewer acute headache symptoms in the heavily exposed (n = 3/13) than the less heavily exposed (n = 5/16) group, but no statistical comparison between the groups was conducted.

One case series (Lombardi & Lurie, 1957) and one case study (Porter, 1990) reported on acute neurological pain or discomfort after exposure to jet fuel. Lombardi and Lurie (1957) reported on physical examinations of 12 airmen who carried out fuel cell repair at Smoky Hill (or Schilling) Air Force Base, Kansas. One man reported headache symptoms and study authors noted the man did not wear a mask while working. The case study of the accidental exposure of two Navy Aviators (Porter, 1990) reported that one of the aviators experienced acute headache following the exposure, which resolved after an unreported length of time.

2.4.2.5. Neurological Symptoms

One medium confidence controlled-exposure study examined symptoms of fatigue among Gulf War and Gulf War-era Veterans (Bell et al., 2005). Veterans were exposed to either very low levels (0.00057 parts per million [ppm]) of JP-8 jet fuel fumes or clean air in a randomized design and asked to complete a computer-administered visual vigilance task. Participants were asked to visually track a moving stimulus while responding to stimuli appearing in the center or periphery of their vision. Poorer performance was reported to correspond to symptoms of fatigue or cognitive difficulties. No differences were observed for central reaction time, but JP-8-exposed Veterans exhibited faster peripheral reaction times (see Table C-1 on page 221).

A case report described neurological symptoms following exposure to JP-5 in two military aviators (Porter, 1990). After landing, the aviators reported feelings of intoxication and fatigue while they had difficulty removing flight gear and filling out typical post-flight forms. The pilots recovered 1 and 4 days after exposure. One review article noted slurred speech as another symptom of both aviators (NRC, 1996).

Secondary references included one risk assessment (Kendall et al., 2001), two review articles (Houtzager, 2017; Ritchie et al., 2003) and one medical textbook (Wang, 2004). Self-reported excess sweating and dizziness were evaluated in the AFIOH final risk assessment of acute exposure to JP-8 (Kendall et al., 2001). Elevated odds of self-reported excess sweating and dizziness were significant in the medium exposure group when compared to the low exposure group and odds of dizziness were significantly elevated for high exposure participants compared to low exposure participants (see

Table C-1 on page 221). Multiple cases of neurological symptoms, such as fatigue, exhaustion, lethargy and dizziness, were reported in a review of several civilians, mostly flight crews, exposure incidents (Houtzager, 2017). One medical textbook noted neurological symptoms, such as dizziness, as a result of short-term exposure to an unspecified jet fuel (Wang, 2004).

2.4.2.6. Ocular Conditions

Three low confidence studies (Knave et al., 1978; Olsen et al., 1998; Yang et al., 2003) examined acute ocular disorders among workers exposed to jet fuel and observed mixed results.

A cross-sectional study in Swedish aircraft mechanics observed a significant positive increase in eye irritation symptoms in 9 of 30 jet fuel-exposed participants compared to 1 out of 30 controls (Knave et al., 1978).

A cohort study of active-duty and civilian personnel at Hill Air Force Base evaluated ocular conditions over a period of 18 months (Olsen et al., 1998). There was an increase in eye irritation symptoms in the exposed group at baseline and at 18 months after the JP-4 to JP-8 transition compared to the unexposed. There was decreased eye irritation 6 months after JP-8 transition in exposed compared to unexposed; however, statistical comparisons were not performed.

A cross-sectional study compared male workers at Kaohsiung International Airport in Taiwan (Yang et al., 2003) and observed no differences in eye irritation symptoms measured using a health questionnaire comparing exposed and unexposed workers. There were significant differences in age and duration of employment between the groups, with 50.9% of exposed workers 40 years of age or older compared to 14.8% in the unexposed group and 68.9% of exposed workers employed for at least 10 years compared to 6.6% in the unexposed.

Acute ocular conditions after exposure to jet fuel are also discussed in a risk assessment (Kendall et al., 2001), one review article (Karanikas et al., 2021), one case study (Porter, 1990) and one case series (Lombardi & Lurie, 1957).

The JP-8 final risk assessment of acute exposure to jet fuel conducted by AFIOH (Kendall et al., 2001) reported an analysis of eyeblink classical conditioning (EBCC) following JP-8 exposure. The EBCC test evaluates the ability of the reflexive eyeblink response to be paired with a conditioned stimulus ([CS]; e.g., a tone) after training with an unconditioned stimulus ([US]; e.g., a puff of air to the eye). Significant findings were reported in the morning session among those in the high exposure group, with fewer conditioned responses (CR) and shorter latencies for CR peak and CR onset. Fewer CRs suggest the need for more trials for personnel to pair the CS with the CR (i.e., eyeblink) and shorter latencies for the CR suggest the timing of the CR was less well-trained.

Several case reports also describe eye irritation. A review article (Karanikas et al., 2021) cited mild-to-moderate eye irritation following exposure to JP-8 fuel from a collection of case reports. A case series of 12 men employed as fuel cell repair technicians at Smoky Hill Air Force Base, Kansas, evaluated non-specific symptoms reported among those who did not wear masks while performing their duties; one of the 12 individuals with 400 hours of exposure to jet fuels experienced blurry vision (Lombardi & Lurie, 1957). A case report of two Navy Aviators exposed via inhalation to JP-5 fuel vapors during a training flight reported a burning sensation in their eyes immediately following the exposure. One of the aviator's symptoms resolved by the following day and the other continued to complain of watery and itchy eyes over the next 4 days (Porter, 1990).

2.4.2.7. Peripheral Nervous System

One review (Ritchie et al., 2001) and one risk assessment (Kendall et al., 2001) provided information on short-term peripheral nervous system health outcomes after exposure to jet fuel. Ritchie et al. (2001) described a case report of a pilot who had feelings of reduced nociception (i.e., noxious stimulation) after exposure to an estimated 3,000 to 7,000 ppm JP-4 vapor during a case of jet fuel leakage into a cockpit while in flight.

The AFIOH final risk assessment of acute exposure to JP-8 reported a significant elevated rate of tremors and numbness in the high exposure group compared to low exposure personnel; however, the association was not significant after correction for multiple comparisons (Kendall et al., 2001).

2.4.2.8. Vestibular Function

No primary studies reported on short-term vestibular function. One case report described short-term vestibular function health outcomes after accidental exposure to JP-5 jet fuel (Long & Charles, 2018). A military aviation technician reported accidentally splashing JP-5 fuel on his face after removing his headgear to complete a task in a compact space. Immediately following exposure, the technician flushed his eyes and mouth, but he did not flush his ears. The next day, the worker reported feelings such as "drifting to one side of the hallway while walking, then overcorrecting and stumbling," which was determined to be a case of vertigo. One review article described increased postural body sway in a case report of a USAF pilot exposed to JP-4 (Ritchie et al., 2001). The pilot indicated they felt "abnormal" for approximately 36 hours post-exposure.

2.4.3. Long-term Nervous System Health Outcomes

2.4.3.1. Hearing Impairment

One medium confidence study (Kaufman et al., 2005), two low confidence studies (Dreisbach et al., 2022; Fuente et al., 2019) and one uninformative study (Odkvist et al., 1987) examined long-term hearing impairments following exposure to jet fuel and observed significant increases in hearing deficits.

A cross-sectional study of workers at a USAF installation (Kaufman et al., 2005) reported a significant positive association between duration of jet fuel exposure and persistent hearing loss (see Table C-1 on page 221).

A cross-sectional study in military personnel at Marine Corps Air Station Miramar reported no significant differences in hearing difficulties (measured using the mAIAD questionnaire) between workers exposed to JP-5 (13.6 months on average) and noise compared to workers with noise exposure but no exposure to jet fuel (Dreisbach et al., 2022). While no significant differences were observed, workers exposed to jet fuel and noise generally reported lower scores (i.e., more difficulties) compared to workers only exposed to noise, but the study authors note a high degree of variability in responses from both groups.

A cross-sectional study evaluated hearing outcomes among personnel in the Royal Australian Air Force (RAAF) (Fuente et al., 2019). Personnel were categorized into low, medium and high JP-8 jet fuel exposure groups based on previous and current task groups, self-reported exposure levels for each task group, findings of previous exposure assessment evaluations by independent contractors and expert evaluation by an RAAF occupational hygienist. Personnel were also exposed to noise, categorized as low, medium and high by a comparison of historic records of noise measurements and exposure questions in the study questionnaire. The study assessed pure-tone air and bone-conduction thresholds for frequencies between 0.5 and 12 kilohertz (kHz), distortion product otoacoustic emissions (DPOAE) between 1 and 8 kHz, ABR for absolute latencies and inter-peak latencies and central auditory function. Significant hearing impairment among exposed compared to unexposed personnel was observed based on some measures (see Table C-1 on page 221). There were associations between jet fuel exposure and auditory tests of temporal resolution, dichotic digits and duration pattern sequence (see Table C-1 on page 221).

A cohort study in three groups of Swedish industrial workers (Odkvist et al., 1987) observed abnormalities in cortical frequency glides in four of the eight participants and in interrupted speech discrimination in three of the eight participants in the jet fuel exposed group but no statistical comparisons were performed. The study notes that cortical responses to frequency glides are sensitive to cerebellopontine angle tumors and lesions, which can affect hearing and speech discrimination. No abnormalities were observed in this group in speech reception threshold, speech discrimination, interrupted speech discrimination and ABR.

2.4.3.2. Memory Impairment

One medium confidence study (Heaton et al., 2017), two low confidence studies (Knave et al., 1978; Olsen et al., 1998) and one uninformative study (Knave et al., 1976) analyzed long-term memory impairments among workers exposed to jet fuel and observed decreased performance on memory tests in one medium confidence and one low confidence study.

In a population of active-duty USAF personnel, Heaton et al. (2017) examined memory tests, including auditory consonant trigrams and the retention scores across a work week. Personnel were categorized as high or low exposure based on job titles. A significant decrease in performance on the retention score was observed in high-exposure compared to low-exposure personnel; no other differences were observed between groups for memory tests, or in models using average daily naphthalene concentrations, average daily total hydrocarbon (THC) and years of active-duty service (see Table C-1 on page 221). No association was observed for the recognition discrimination index and performance on auditory consonant trigrams.

In the cross-sectional study of Swedish aircraft mechanics, Knave et al. (1978) observed no differences in performance on a verbal recall task. However, memory impairment was reported in standardized interviews by exposed subjects (n = 5/30) and not observed (0/30) in the unexposed group.

The study in civilian personnel at the Hill Air Force Base examined various memory symptoms at 6 and 18 months after transition from JP-4 to JP-8 fuel at baseline (Olsen et al., 1998). There were no differences in performance on the memory index in the unexposed group compared to the exposed group at baseline and at 6 and 18 months (see Table C-1 on page 221). There was no difference between effects of JP-4 and JP-8 fuels considering the consistency of the result across timepoints. There was also significant improvement across trials for each test, regardless of exposure group, suggesting practice effects from repeated testing.

The cohort study in Swedish aircraft fuel system mechanics observed physician-reported memory impairment in heavily exposed (2 of 13) and less heavily exposed (2 of 16) groups, but statistical comparisons were not performed (Knave et al., 1976).

2.4.3.3. Motor Deficits

One medium confidence study (Heaton et al., 2017), one low confidence study (Knave et al., 1978) and one uninformative study (Odkvist et al., 1987) examined long-term motor deficits following jet fuel exposure in occupational populations and observed improved motor test performance, but this may be partially explained by practice effects from repeated testing and elevated fitness levels of young military personnel.

A cross-sectional study examined motor tests in active-duty Air Force personnel from different USAF bases with an average active-duty service length of 5.8 years (Heaton et al., 2017). A significantly faster time to complete the grooved pegboard test using the non-dominant hand was observed for models using average daily naphthalene and average daily THC (see Table C-1 on page 221). Similarly, a significantly increased number of finger taps was observed on the finger tapping test (dominant hand) with average daily THC, but there was no significant association for average daily naphthalene. There were no associations between average daily naphthalene and average daily THC exposure concentrations and simple reaction time and finger tapping. There was no association between years of active duty in the Air Force and motor tests results. The mean time in current occupation was similar for high-exposure and low-exposure personnel (58.4 and 55.4 months, respectively). The 8-hour time-weighted average (8-h TWA) across the study period for the high-exposure group (mean = 7.62 mg/m^3; range: 0.3-33.7 mg/m^3) was considerably lower than the Air Force guideline (200 mg/m^3).

The cross-sectional study of Swedish aircraft mechanics exposed to a non-specified type of jet fuel compared to a randomly selected unexposed group observed no differences in manual dexterity (Knave et al., 1978). Details on each group of participants were minimal, although authors suggest the two groups were similar except for increased alcohol consumption among the control group.

A cohort study on three groups of Swedish industrial workers observed no abnormal coordination in the jet-fuel exposed group (Odkvist et al., 1987).

Secondary references include one case series (Lombardi & Lurie, 1957), one review of a case report (Houtzager, 2017) and one risk assessment (Kendall et al., 2001), which reported on long-term motor function after exposure to jet fuel. Lombardi and Lurie (1957) performed physical examinations on 12 airmen who carried out fuel cell repair. Several men complained of ataxia or an occasional wobbly sensation, but study authors noted those men did not wear masks or other forms of personal protective equipment (PPE). In addition, EASA (2017) described a case of fine motor impairment among crew members exposed to jet oil emissions on a Bae 146 aircraft and a case of incoordination in a military C-130A aircraft pilot.

Motor function was evaluated in the AFIOH final risk assessment of acute exposure to JP-8 (Kendall et al., 2001). Air Force personnel completed the Behavioral Assessment and Research System hand tapping test and a questionnaire for self-reported symptoms. Performance on hand tapping trials using the preferred hand was significantly lower in the high exposure group compared to the low exposure group. High and moderate exposure personnel reported greater frequency of trouble gripping things, but the association was not significantly different.

2.4.3.4. Neurological Pain or Discomfort

One low confidence study (Knave et al., 1978) and one uninformative study (Knave et al., 1976) examined long-term neurological pain or discomfort in Swedish jet motor factory workers and aircraft fuel system mechanics and observed a non-significant increase in chronic headache symptoms.

The cross-sectional study of Swedish jet motor factory workers (Knave et al., 1978) observed a slight increase in the incidence of chronic headache in the exposed group (5 of 30) in comparison to the control group (1 of 30).

The study of Swedish aircraft fuel system mechanics exposed to jet fuels (Knave et al., 1976) observed chronic headache symptoms in the heavily exposed (4 of 13) and less heavily exposed (5 of 16) groups with no statistical comparison between the groups.

One secondary source, a risk assessment (Kendall et al., 2001) reported on long-term neurological pain or discomfort after exposure to jet fuel. The JP-8 final risk assessment of acute exposure to jet fuel conducted by AFIOH (Kendall et al., 2001) reported no differences in the percentage of workers with self-reported chronic pain symptoms at least once in the last 6 months when comparing three levels of eight fuel exposure in 328 Air Force workers with and without JP-8 exposures (Kendall et al., 2001).

2.4.3.5. Neurological Symptoms

Two low confidence studies (Knave et al., 1978; Olsen et al., 1998) examined long-term neurological symptoms following exposure to jet fuel in occupationally exposed subjects and observed higher frequency of neurological symptoms in one low confidence study, but statistical comparisons were not made.

The study in Swedish aircraft mechanics observed higher frequency of fatigue, dizziness and sleep disturbances in the exposed compared to the unexposed group (Knave et al., 1978).

The study in civilian personnel at the Hill Air Force Base, Utah, observed no differences in frequency of dizziness or fatigue between exposed and unexposed personnel at baseline, 6 and 18 months after beginning work with JP-8 jet fuel (Olsen et al., 1998).

Two reviews (ATSDR, 2017; Karanikas et al., 2021) provided information on long-term neurological symptoms following jet fuel exposure. Karanikas et al. (2021) cited the central nervous system symptoms such as dizziness reported in the three cases in Fife et al. (2018). ATSDR (2017) cited changes to neurological function as a potential health outcome of jet fuel exposure, duration was not discussed.

2.4.3.6. Ocular Conditions

One low confidence (Tunnicliffe et al., 1999) and one uninformative study (Odkvist et al., 1987) examined long-term ocular conditions in workers exposed to unspecified jet fuel and observed no differences in ocular conditions by exposure status.

In a cross-sectional study of current workers at the Birmingham International Airport in the United Kingdom, Tunnicliffe et al. (1999) observed no differences in symptoms of watery eyes when comparing the high to the medium exposure group. Medium exposure workers were employed for 8.1 years on average and high exposure workers were employed for 8.4 years on average.

The cohort study in three groups of Swedish industrial workers reported on a group of jet fuel-exposed workers with a mean exposure duration of 25 years (Odkvist et al., 1987). There were incidences of abnormal ocular conditions in the jet fuel-exposed group in electronystagmography (n = 1 of 8), saccade testing (n = 1 of 8), broad-frequency visual suppression testing (n = 4 of 8) and broad-frequency smooth pursuit (n = 4 of 8) (Odkvist et al., 1987). However, no statistical comparisons were conducted. Each of these tests utilize eye-tracking to assess sensory function of the central nervous system.

2.4.3.7. Peripheral Nervous System

Two low confidence studies (Knave et al., 1978; Olsen et al., 1998) and one uninformative study (Knave et al., 1976) examined long-term peripheral nervous system health outcomes after jet fuel exposure in occupational settings and observed greater frequency of self-reported symptoms of polyneuropathy in one low confidence study and one uninformative study.

There were no significant differences in frequency of hand numbness or tingling at baseline, 6 months or 18 months between the jet fuel-exposed workers (e.g., F-16 grounds crews, fuel distribution personnel and F-16 fuel system mechanics) and the selected controls in civilian personnel at Hill Air Force Base (Olsen et al., 1998).

The cross-sectional study of Swedish aircraft mechanics exposed to a non-specified type of jet fuel compared to a randomly selected unexposed group showed higher incidence of self-reported symptoms of polyneuropathy (i.e., the dysfunction of multiple peripheral nerves) in exposed workers (n = 12) compared to unexposed (n = 5) (Knave et al., 1978). However, when physical examinations for early signs of polyneuropathy were conducted, the difference between exposed (n = 18) and unexposed (n = 15) workers exhibiting signs was reduced.

The cohort study on Swedish aircraft fuel system mechanics reported on the differences in peripheral nervous system function between heavily exposed subjects (n = 13) and less heavily exposed subjects (n = 16) (Knave et al., 1976). Peripheral nervous system function was assessed through self-reported symptoms and physical examination for signs of polyneuropathy, self-reported symptoms of neurasthenia (i.e., a historically ill-defined condition sometimes characterized as general weakness), nerve conduction velocity testing (sensory nerve conduction velocity, nerve action potentials and maximal conduction velocity of motor nerves) and vibration sensation threshold testing. Although no statistical comparisons were made, self-reported symptoms of polyneuropathy were greater in the heavily exposed group (n = 11) compared to the less heavily exposed group (n = 6), as were symptoms of neurasthenia (n = 12 and 9, respectively) and signs of polyneuropathy reported from a physician's examination (n = 11 and 8, respectively). There were no differences in nerve conduction velocities and vibration sensation thresholds between the heavily exposed and less heavily exposed groups after adjusting for age. Compared to a previously studied population of subjects working with industrial solvents, less heavily jet fuel-exposed workers had significantly higher vibration sensation thresholds on the hand suggesting that the less heavily exposed group was less sensitive to vibration stimuli. Exposed workers also reported apparent muscle atrophies and paresis of the hands and fingers, suggesting peripheral nerve damage.

One secondary reference, a medical textbook, noted peripheral sensory neuropathy as a result of long-term exposure to jet fuel (Wang, 2004).

2.4.3.8. Vestibular Function

One medium confidence study (Maule et al., 2013) and one low confidence study (Smith et al., 1997) examined long-term health outcomes on vestibular function following exposure to jet fuel in occupational populations and observed significantly reduced vestibular function in one low confidence study.

Balance disturbances were evaluated in a cross-sectional study (Maule et al., 2013) of active-duty USAF base personnel by examining their total angular area (TAA) and mean path velocity (MPV) during a postural sway test. There were no differences between the high and low exposure group in either measure. Personal air monitors were used to capture average daily exposure levels to JP-8, as measured by THC and naphthalene breathing zone concentrations, in high (THC geometric mean [GM] = 4.4 mg/m^3; naphthalene GM = 4.8 μg/m^3) and low exposure groups (THC GM = 0.9 mg/m^3; naphthalene GM = 0.7 μg/m^3). Exposure to JP-8, measured by 8-h TWA THC personal breathing zone air samples, was not associated with increased sway velocity MPV or

TAA (see Table C-1 on page 221). Similarly, pre- and post-shift creatinine-adjusted levels of 1- and 2-naphthol were not associated with changes in performance on postural sway tests; however, study authors noted that active-duty personnel consistently outperformed (i.e., exhibited less postural sway) the reference values provided for the postural sway tests, sometimes performing significantly better.

A cross-sectional study of USAF employees working in JP-8-exposed work areas at two Air Force bases evaluated postural sway by examining sway length (SL) and sway area (SA) (Smith et al., 1997). Vestibular function test performance by JP-8-exposed personnel was compared to unexposed volunteers from the military and other sources, which were not well described. Personal breathing zone samples were taken at two timepoints to assess JP-8 exposure by measuring concentrations of benzene, toluene, total naphthas and m-, o- and p-xylene. Cumulative exposure values for JP-8 and all jet fuels (JP-4, JP-5 and JP-8) were then calculated from personal monitoring results and work history questionnaires. JP-8-exposed personnel performed worse compared to an unexposed group on SL (mean = 68.90 and 29.72 centimeters [cm], respectively) and SA (mean = 4.85 and 1.62 cm2, respectively). Greater SL and SA indicate worse performance. Cumulative exposure to JP-8 assessed by breathing zone benzene concentrations was significantly associated with increased SL. In the cumulative JP-8 benzene model, SA was significantly increased for the foam board, eyes closed condition only (see Table C-1 on page 221). Associations between SL and SA performance and other cumulative indicators of exposure to JP-8 and all jet fuels (i.e., toluene and m-, o- and p-xylene) were mixed and total naphthas were not associated with postural sway performance.

Both studies (Maule et al., 2013; Smith et al., 1997) examined differences in postural sway between a high exposure group and a reference group, however, only one study (Smith et al., 1997) observed a significant difference. The mean ages of the exposed and unexposed groups in (Smith et al., 1997) (average age = 37.5 and 34.0 years, respectively) were higher than in the high and low exposure groups evaluated in (Maule et al., 2013) (average age = 26.4 and 24.4 years, respectively). Similarly, the average service time for high exposed workers in (Smith et al., 1997) was greater than participants in (Maule et al., 2013) (average = 12.0 and 6.5 years, respectively). Both studies noted that postural sway typically increases with age, which may alter the ability to detect an effect of chemical exposure on vestibular function and exposure concentrations reported in (Maule et al., 2013) were below the Air Force limits for jet fuel exposure (200 mg/m^3).

Secondary references include a JP-8 risk assessment (Kendall et al., 2001) and a review (Fife et al., 2018). Vestibular function was evaluated in the AFIOH final risk assessment of acute exposure to JP-8 (Kendall et al., 2001). Air Force personnel completed a postural sway test with varying conditions (i.e., eyes open or eyes closed, standing on foam). Study authors noted that significant associations between exposure concentrations and post-shift postural SL on two conditions were no longer significant after adjusting for pre-shift postural sway performance. However, decreased performance was observed in a combined JP-8 exposed group of high and medium exposure personnel compared to an older, unexposed group. Details on the additional control groups were not provided.

Fife et al. (2018) reported on 1 military aircraft refueler and 2 non-military warehouse workers with workstations located only 75 feet from a common jet flight path. The military aircraft refueler reported several years of progressing feelings of imbalance or loss of equilibrium. The refueler had worked as a mechanic and refueler for approximately 4 years and was exposed to JP-4 and JP-8 during that time. Biomonitoring results demonstrated high concentrations of 3-methylpentane (27 nanograms/milliliter, ng/mL) and n-hexane (15.7 ng/mL) in the blood. Similarly, the two warehouse workers reported several years of progressing symptoms, including feelings of imbalance or loss of equilibrium. The warehouse was separated from the flight path by a metal-coated chain-link fence. The air conditioning vents in the warehouse "were found to be malfunctioning such that air was able to enter the building but unable to escape." An independent analysis observed detectable concentrations of numerous JP-8 constituents (i.e., undecane, dodecane, tridecane, tetradecane and toluene) in the warehouse carpet, which authors suggest reflected the warehouse's poor indoor air quality.

2.4.4. Summary of Nervous System Health Outcomes by Duration of Exposure

Six studies presented results by duration of exposure (Heaton et al., 2017; Kaufman et al., 2005; Olsen et al., 1998) or included discussions of exposure duration (Knave et al., 1978; Knave et al., 1976; Maule et al., 2013).

Duration of jet fuel exposure was evaluated in analyses of persistent hearing loss in groups exposed to jet fuel and noise (Kaufman et al., 2005). When jet fuel and noise exposure increased equally, the effect of jet fuel duration remained significant, and the magnitude of association increased from "70% at 3 years exposure to 140% at 12 years (OR = 2.41)." Additionally, a large increase in risk of persistent hearing loss (OR = 8.25, 95% CI: 1.67, 55.6) was observed at 12 years of jet fuel exposure when holding duration of noise exposure to three years (i.e., the minimum in this population), suggesting duration of jet fuel exposure is an important factor in persistent hearing loss with concurrent exposure to noise.

The relationship between pre-shift concentrations of 1- and 2-naphthol in urine and repeated test performance was examined in a study evaluating performance on motor and memory tests over the course of a work week (Heaton et al., 2017). No associations were observed between repeated urinary naphthol measurements and neurocognitive performance. Years of Air Force service was not a significant predictor of any test. Study day (i.e., Day 2, Day 4 or Day 6) was a significant predictor for multiple test health outcomes, which suggests a practice effect from repeated testing.

Maule et al. (2013) evaluated the relationship between exposure to JP-8 fuel and pre- and post-shift performance on a postural sway test (MPV and TAA). Results for 8-hr TWA for THC and naphthalene were mixed. Creatinine-adjusted levels of 1- and 2-naphthol in urine were not associated with performance on postural balance tests but results for most test conditions suggested an inverse association, indicating better performance. Pre-shift performance was significantly associated with post-shift performance. The study authors note that pre-shift performance and demographic variables “accounted for 45.2% to 65.9% of the variance in post-shift MPV and 39.3% to 62.2% of variance in post-shift TAA suggesting that JP-8 fuel is not the main driver of pre- and post-shift performance changes.

In the examination of health outcomes following Hill Air Force Base’s transition from JP-4 to JP-8 jet fuel, Olsen et al. (1998) reported no differences in frequency of neurological symptoms, such as numbness, tingling of the hands, dizziness or fatigue across the three timepoints. Frequency of eye irritation symptoms was elevated among exposed subjects, but there was little change across months in the exposed personnel. For tests of memory, there was a significant increase in scores between baseline and 18 months in the exposed and unexposed groups, but these increases were similar between groups and attributed to a practice effect from repeated testing.

Two other studies (Knave et al., 1978; Knave et al., 1976) discussed duration of exposure but did not present neurological health outcomes by varying duration or discuss how duration may have affected each health outcome. Knave et al. (1976) used employment duration to determine categories of exposure: “heavily exposed” and “less heavily exposed.” Comparisons were made between the groups, but employment duration and other measures of exposure gradient between “heavily exposed” and “less heavily exposed” subjects were not discussed. Knave et al. (1978) also discussed employment duration among exposed subjects, noting the range was between 2 and 32 years (mean = 17.1 years).

2.4.5. Conclusion

There is slight evidence that jet fuel exposure negatively impacts neurological health, leading to adverse neurological health outcomes including hearing impairment, memory impairment and ocular conditions (see Table 2-4 on page 56). Results for other health outcomes such as peripheral nervous system health outcomes, neuropsychological pain and discomfort and other neurological symptoms were consistent among low confidence and uninformative studies, indicating greater frequency of symptoms; however, the types of health outcomes assessed were heterogeneous and were not always compared statistically. No studies provided information indicating that immediate neurological health outcomes were associated with an increased risk of subsequent neurological health outcomes. In addition, data were insufficient to assess the risks of adverse neurological health outcomes by duration of exposure. While some studies provided information on duration of employment or exposure, duration was not always directly considered in risk estimates.

Some studies observed jet fuel-related hearing impairment and one low confidence study noted effects on vestibular function. Hearing and vestibular function rely on structures within the ear and its related sensory neurons which suggests a coherent effect. Studies of civilian subjects provided evidence of increased neurological symptoms, such as self-reported symptoms of polyneuropathy and memory impairment, but these studies were frequently limited by ill-defined health outcome assessment. Studies of military personnel frequently utilized standardized test instruments which improved the quality of health outcome assessment by limiting subjective interpretations. Information from case reports supported observations of increased frequency of neurological symptoms following acute exposures to jet fuel exhaust. Medium confidence studies also suggested apparent improvements among jet fuel-exposed workers for vestibular function and motor function; however, study authors noted these findings may have been influenced by practice effects from repeated testing and/or exceptional performance of fit, young military personnel. Practice effects and exceptional performance may make it more difficult to observe differences as a result of jet fuel exposure in these populations. Exposure levels from the medium confidence studies reporting positive results were also notably well below the Air Force guideline for jet fuel exposure (measured by THC).

Overall, there is slight evidence for an association between jet fuel exposure and detrimental neurological health in humans, with many low-quality studies and inconsistent directions of effect between types of neurological health outcome.

Further, there is insufficient evidence to determine the length of exposure required to experience long-term neurological outcomes or what immediate symptoms are indicative of long-term neurological outcomes.

Table 2-4. Summary of Nervous System Health Outcomes Associated With Jet Fuel Exposure.

Studies and Interpretation	Summary and Key Findings[a]	Factors That Increase Certainty	Factors That Decrease Certainty	Summary Judgment
Acute Health Outcomes[b]				⊕⊙⊙ Slight Two medium confidence studies and one low confidence study reported detrimental long-term neurological health outcomes with jet fuel exposure; and one low confidence study reported detrimental short-term neurological health outcomes with jet fuel exposure. Directions of effect were consistent within several types of health outcomes (e.g., memory impairment and hearing impairment), but there were some inconsistencies within (i.e., vestibular function) and across different health outcomes (i.e., a detrimental effect was observed for memory impairment, but a positive effect was observed for motor function). Detrimental effects were observed in studies on sensory functions dependent on proper otologic function (i.e.,
Hearing Impairment 1 Medium confidence study 1 Low confidence study	One medium confidence study observed a non-significant increase in the odds of hearing loss among exposed participants compared to an unexposed group.	• Medium confidence study	• Limited number of studies examining health outcome	

Studies and Interpretation	Summary and Key Findings[a]	Factors That Increase Certainty	Factors That Decrease Certainty	Summary Judgment
				hearing impairment and vestibular function), suggesting a coherent effect. Study authors noted practice effects or exceptional performance in military populations on some tests (e.g., motor and vestibular function) which may cause deficits as a result of jet fuel exposure more difficult to detect. Uncertainty remains due to the limited number of quality studies examining neurological health outcomes.
Neurological Pain or Discomfort 3 Low confidence studies 1 Uninformative study	Greater frequency of headache symptoms was reported in three low confidence studies. Results were either non-significant or not compared statistically.		• Low confidence and uninformative studies	
Ocular Conditions	One low confidence study reported a significant		• Low confidence studies	

Studies and Interpretation	Summary and Key Findings[a]	Factors That Increase Certainty	Factors That Decrease Certainty	Summary Judgment
3 Low confidence studies	increased frequency of eye irritation among exposed participants compared to unexposed controls (1/3). Greater frequency of eye irritation symptoms was reported in two studies. Results were either non-significant or not compared statistically.	• No factors noted	• Inconsistent measure of effects	
Neurological Symptoms 1 Medium confidence study	One randomized controlled exposure study to very low levels of JP-8 fuel fumes observed significantly increased peripheral reaction time, a measure of vigilance, among Gulf War Veterans compared to Veterans receiving clean air (1/1).	• Medium confidence study	• Limited number of studies examining health outcome	
Long-term Health Outcomes[c]				
Hearing Impairment 1 Medium confidence study 2 Low confidence studies	One medium confidence study reported significant increased odds of persistent hearing loss among exposed subjects compared to an unexposed control group (1/4). One low confidence study reported increased audiometric hearing thresholds with increasing jet	• Medium confidence study	• Low confidence and uninformative studies	

Studies and Interpretation	Summary and Key Findings[a]	Factors That Increase Certainty	Factors That Decrease Certainty	Summary Judgment
1 Uninformative study	fuel exposure at most frequencies evaluated, with some being significantly elevated (1/4). Similarly, mean auditory brainstem response latency was increased for most wavelengths, indicating poorer hearing.			
Memory Impairment 1 Medium confidence study 2 Low confidence studies 1 Uninformative study	High-exposure participants performed significantly worse on one subtest of the Hopkins Verbal Learning Test—Revised compared to low exposure participants in a medium confidence study. Non-significant decreases observed using personal monitoring (THC and naphthalene) and years of service as exposure terms. Significantly decreased performance on memory tasks in one low confidence study (1/2) and one low confidence study reporting higher frequency of self-reported memory impairment among exposed subjects.	• Medium confidence study	• Low confidence and uninformative studies	

Studies and Interpretation	Summary and Key Findings[a]	Factors That Increase Certainty	Factors That Decrease Certainty	Summary Judgment
Motor Deficits 1 Medium confidence study 1 Low confidence study 1 Uninformative study	Naphthalene and THC concentrations were positively associated (1/3) with better performance on motor function tests such as simple reaction time, finger tapping using the non-dominant hand and grooved pegboard in a medium confidence study in a young military population. No significant associations were observed with years of active-duty service.	• Medium confidence study • Coherence across motor function tests	• Low confidence and uninformative studies	
Peripheral Nervous System 2 Low confidence studies 1 Uninformative study	One (1/2) low confidence study observed a non-significant increased frequency of polyneuropathy symptoms compared to an unexposed group. No differences in nerve conduction velocity between a “heavily exposed” group and a “less heavily exposed” group in an uninformative study.	• No factors noted	• Low confidence and uninformative studies	
Vestibular Function	A low confidence study observed greater postural sway (1/2) among exposed subjects compared to	• Medium confidence study	• Limited number of studies examining outcome	

Studies and Interpretation	Summary and Key Findings[a]	Factors That Increase Certainty	Factors That Decrease Certainty	Summary Judgment
1 Medium confidence study 1 Low confidence study	unexposed subjects. Cumulative exposure to JP-8, assessed by personal monitoring of benzene concentrations, was significantly associated with greater sway length. Results for other exposures (quantified by other JP-8 components such as toluene and xylene) were mixed and inconsistent.		• Inconsistency across exposures and outcome measures	
Neurological Symptoms 2 Low confidence studies	One low confidence study (1/2) reported greater frequency of neurological symptoms such as fatigue, dizziness, sleep disturbances and excess sweating among exposed participants compared to an unexposed group; however, statistical comparisons were not made.	• No factors noted	• Limited number of studies examining outcome • Low confidence studies	
Ocular Conditions 1 Low confidence study	One low confidence study reported a non-significant negative association between symptoms of watery eyes and jet fuel exposure in a "high" exposure group compared to a "medium	• No factors noted	• Limited number of studies examining outcome • Low confidence and uninformative studies	

Studies and Interpretation	Summary and Key Findings[a]	Factors That Increase Certainty	Factors That Decrease Certainty	Summary Judgment
1 Uninformative study	exposure group." One uninformative study reported abnormalities in a jet fuel exposed group in electronystagmography, saccade testing, broad-frequency visual suppression testing and broad-frequency smooth pursuit testing.			
Neurological Pain or Discomfort 1 Uninformative study	An uninformative study reported chronic headache in a "heavily exposed" group and a "less heavily exposed" group with no statistical comparison between groups.	• No factors noted	• Limited number of studies examining outcome • Uninformative study	

[a]Health outcomes are summarized in this column by a ratio of (number of studies that found a significant association for that health outcome/the number of studies reporting on that health outcome).
[b]Acute health outcomes are considered those that were measured within 6 months of exposure.
[c]Long-term health outcomes are considered those that were measured at least 6 months after exposure.

2.5. Mental Health Outcomes

2.5.1. Summary of Mental Health Outcomes

Jet fuel exposure may impact mental health, including cognitive and behavioral health outcomes, as a result of dermal, inhalation and oral exposures. Mental health may be assessed by measuring attention (e.g., reaction time testing), social-emotional behavior and regulation (e.g., physician assessment), cognitive function (e.g., calculation and reasoning testing), executive function (e.g., working and recall memory testing, sustained attention testing), depression (e.g., physician assessment) or visuospatial performance (e.g., visual organization testing). Mental health outcomes are frequently characterized as long-term health outcomes in this document due to the plasticity of the brain and continued development over the course of an individual's lifespan, including throughout adulthood. In evaluating the relationship between jet fuel exposure and mental health outcomes, the nature of the exposure also plays a critical role. In occupational settings, employees may come into contact with jet fuel through accidental exposures via releases or spills. These types of exposures are typically acute and concentrated, which may result in acute mental health outcomes (i.e., changes in cognitive function due to intoxication). More commonly, however, employees in occupational studies are exposed to lower levels of jet fuel over longer periods of time. Consistent, low-level exposure would result in smaller changes in mental health outcomes over time; thus, those health outcomes are described as long-term health parameters below.

Of the five studies examining the association between jet fuel exposure and mental health outcomes, one was considered medium confidence (Heaton et al., 2017), three were considered low confidence (Knave et al., 1978; Olsen et al., 1998; Tu et al., 2004) and one was considered uninformative (Knave et al., 1976) (see Figure 2-2 on p. 63).

The medium confidence study (Heaton et al., 2017) employed adequate exposure assessment methodology and analytical methods and appropriately accounted for important confounders. While the lack of reporting on whether the examiner was blinded to participant exposure categorization during health outcome assessment raised concerns, the potential impact on the study's overall conclusions was deemed minimal.

Among studies rated as low confidence and uninformative, sources of potential bias included participant selection approach (Knave et al., 1978; Knave et al., 1976; Olsen et al., 1998; Tu et al., 2004), exposure measurement methods (Knave et al., 1978; Knave et al., 1976; Olsen et al., 1998), use of self-reported health outcome measures (Knave et al., 1976), potential for residual confounding (Knave et al., 1978; Knave et al., 1976; Olsen et al., 1998; Tu et al., 2004) and limited sample size (Knave et al., 1976; Olsen et al., 1998). Conclusions from reviews with results that overlap with the primary studies are summarized in Table D-2 in Appendix D on page 305.

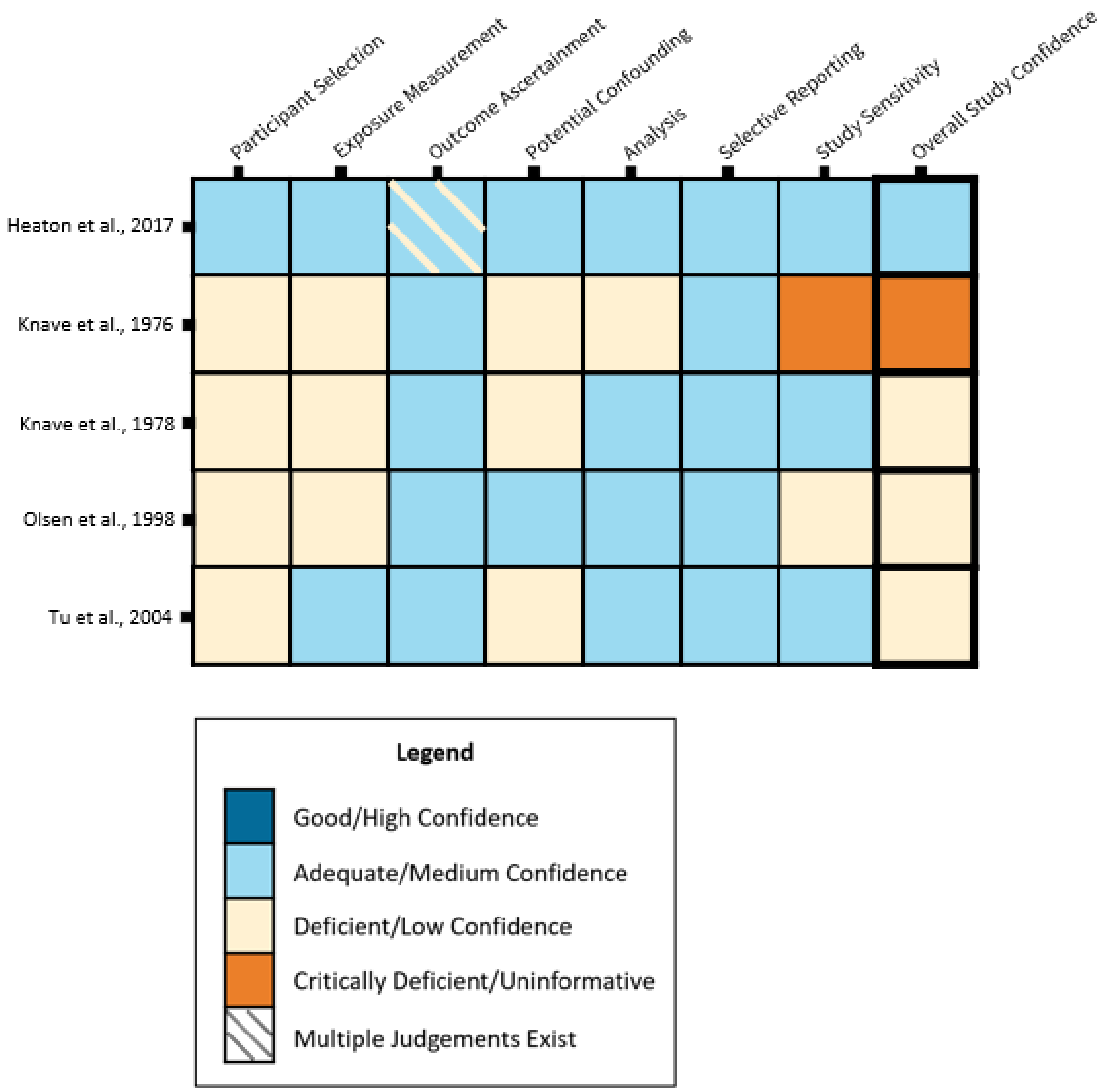


Figure 2-2. Study Quality Evaluations for Epidemiology Studies of Jet Fuel Exposure and Mental Health Outcomes.

Table 2- on page 65 summarizes the number of studies with acute (e.g., measurement taken within 6 months of jet fuel exposure) and long-term (e.g., measurement taken at least 6 months after jet fuel exposure or occurring over multiple months) mental health outcomes. None of the primary studies examined acute mental health outcomes.

- Four studies examined long-term attention outcomes (Heaton et al., 2017; Knave et al., 1978; Olsen et al., 1998; Tu et al., 2004).
- Four studies examined long-term executive function outcomes (Heaton et al., 2017; Knave et al., 1978; Olsen et al., 1998; Tu et al., 2004).

- Three studies measured long-term cognitive function outcomes (Knave et al., 1978; Olsen et al., 1998; Tu et al., 2004).
- Three studies assessed visuospatial performance outcomes (Heaton et al., 2017; Olsen et al., 1998; Tu et al., 2004).
- One study examined long-term social-emotional behavior and regulation outcomes (Knave et al., 1978).
- Two studies assessed long-term depression (Knave et al., 1978; Knave et al., 1976).

A case report (Porter, 1990), a case series (Lombardi & Lurie, 1957) and seven secondary data sources (ATSDR, 2017; B'Hymer, 2015; EASA, 2017; Karanikas et al., 2021; Kendall et al., 2001; NRC, 2003; Ritchie et al., 2001) also provided information on the association between jet fuel exposure and mental health outcomes.

Table 2-5. Number of Studies Reporting on the Acute and Long-Term Mental Health Outcomes Following Jet Fuel Exposures.

Health Outcomes	Acute[a]	Long-term[b]	Total Unique Studies
Attention[c]	0	4	4
Cognitive Function[d]	0	3	3
Depression[e]	0	2	2
Executive Function[f]	0	4	4
Social-Emotional Behavior and Regulation[g]	0	1	1
Visuospatial Performance[h]	0	3	3

[a]Acute health outcomes are considered those that were measured within 6 months of exposure.
[b]Long-term health outcomes are considered those that were measured at least 6 months after exposure.
[c]Attention measurements include CogScreen divided attention test, CogScreen shifting attention test, trouble/difficulty concentrating, reaction time, continuous performance tests (CPTs), reaction time addition-speed and regularity, simple reaction time, simple reaction time-regularity and speed.
[d]Cognitive function measures include CogScreen math test, CogScreen sequence comparison test, CogScreen auditory sequence comparison test, CogScreen pathfinder test, CogScreen symbol-digit coding test, CogScreen dual tasking test, disorientation, neurocognitive dysfunction, mental symptoms, general cognitive function and proficiency, reasoning and confusion.
[e]Depression measures include a medical history of or information gained from an interview about depression and/or anxiety, mental depression, depressed mood, lack of initiative and neurasthenia.
[f]Executive function measures include CogScreen digit span test, CogScreen matching-to-sample test, CogScreen visual sequence comparison test, information processing speed, WAIS-III DigitSspan backward and forward, perceptual speed (Bourdon-Wiersma) and information processing accuracy.
Social-emotional behavior and regulation measures include anxiety, euphoria and laughing, behavior disturbance, irritability, repetition of thought, acute and chronic neurobehavioral symptoms, neuropsychiatric symptoms and neuropsychiatric disorders.
[h]Visuospatial performance measures include CogScreen manikin test, Hooper Visual Organization test, match to sample, throughput and spatial processing.

2.5.2. Acute Mental Health Outcomes

2.5.2.1. Social Emotional

A case report, which is considered supplemental information for this review, reported short-term effects, specifically euphoria and laughter, in two Navy Aviators after accidental exposure via inhalation to JP-5 fuel vapors during a training flight (Porter, 1990).

2.5.3. Long-term Mental Health Outcomes

2.5.3.1. Attention

One medium confidence study (Heaton et al., 2017) and three low confidence studies (Knave et al., 1978; Olsen et al., 1998; Tu et al., 2004) examined long-term attention health outcomes following exposure to jet fuel, with attention measures significantly decreased in all but one low confidence study.

In a cross-sectional study, Heaton et al. (2017) conducted neuropsychological tests in a population of active-duty USAF personnel from three different bases. Participants were assigned to high or low exposure groups based on primary job activities. Exposures were quantified for each group using personal breathing zone monitoring and urinalysis of naphthalene and THC exposure concentrations. On the first day of testing, high exposure participants exhibited significantly diminished attention compared to low exposure participants. No differences were observed in reaction time in models evaluating post-shift or pre-shift urinary markers of exposure and years of Air Force service.

A cohort study of active-duty and civilian personnel at Hill Air Force Base evaluated self-reported difficulty concentrating and used neurocognitive functioning tests of attention/mental control and reaction time (Olsen et al., 1998). Health outcomes were measured at baseline while JP-4 fuel was in use and at 6 and 18 months after transition to JP-8 jet fuel. No differences were observed in any outcome at baseline or at 18 months. At the 6-month time point, a significantly slower Reaction Time Index was observed in the exposed group compared to the unexposed group, indicating poorer performance in those exposed to JP-8 (see Table C-2 in Appendix C on page 249). Study authors noted that performance was significantly better on all tests when comparing 18-month scores to baseline, regardless of exposure group, indicating a practice effect.

A cross-sectional study of 63 workers at the Warfield Air National Guard Base in Essex, Maryland, evaluated reaction time and inhibitory control (Tu et al., 2004). Pre- and post-shift levels of hydrocarbons in exhaled breath were used to evaluate JP-8 exposure levels by job title. The exposed Warfield group was compared to an age- and education-matched unexposed control group with no exposure to JP-8. The exposed workers exhibited significantly faster reaction times on a divided attention task than the unexposed group. However, this effect was also accompanied by a significantly greater number of errors or premature responses, suggesting faster reaction times but greater impulsivity in JP-8 exposed personnel. Respirators and gloves were provided for the fuel cell workers (at risk for inhalation exposure) and fuel specialists (at risk for dermal exposure), respectively. Still, it was noted that fuel cell workers commonly switched tasks during the day, which involved removing the respirator and the clothing of fuel specialists was commonly soaked with fuel, suggesting potential for exposure despite implementing PPE measures in both cases.

In a cross-sectional study in Swedish jet engine factory workers, Knave et al. (1978) observed no significant differences in attention (measured using reaction time) between the group of workers exposed to an unspecified type of jet fuel compared to the unexposed age-matched group. The workers had an average duration of employment of 17 years (range: 2–32 years).

Three secondary data sources reported on the relationship between occupational jet fuel exposure and attention deficits, including impaired reaction time (ATSDR, 2017; EASA, 2017; Kendall et al., 2001). A review on the toxicity of aviation turbine engine oils after pyrolysis conducted by the European Aviation Safety Agency (EASA) (EASA, 2017) reported significant impairment of reaction time in a group of eight female commercial aircrew members following exposure to jet fuel oil emissions during flights over the course of 2 to 12 years. An ATSDR review of JP-5, JP-8 and Jet A fuels cited changes in reaction time and impaired performance on other non-specified neurological function tests in military personnel but did not include details about duration of exposure (ATSDR, 2017).

A JP-8 Final Risk Assessment (Kendall et al., 2001) reported on the prevalence of experiencing self-reported trouble concentrating and forgetfulness over the preceding 6 months in 328 healthy, active-duty Air Force personnel, excluding individuals with autoimmune disease, cancer or diabetes and those using immune system-altering drugs. Air Force personnel were categorized as having had high, medium or low JP-8 exposure based on job duties. Compared to unexposed workers, highly exposed and moderately exposed workers were 2.5 and 3.39 times more likely to have trouble concentrating, respectively and were 2.7 and 4.35 times more likely to report forgetfulness, respectively (see Table C-2 on page 249).

2.5.3.2. Cognitive Function

Three low confidence studies (Knave et al., 1978; Olsen et al., 1998; Tu et al., 2004) assessed long-term cognitive function following jet fuel exposures and observed slower response times in one study, as well as greater psychiatric symptoms in another study, although the psychiatric symptoms were not well-defined.

The cohort study in personnel at the Hill Air Force Base, Utah, (Olsen et al., 1998) evaluated cognition using neurocognitive functioning tests related to reasoning and calculation and general cognitive functioning and proficiency. There were no differences in all health outcomes in the JP-4-exposed group compared to the unexposed group at any timepoint following the start of working with JP-8 fuel and the transition away from JP-4 jet fuel, although there was some suggestion of impaired cognitive functioning at baseline (see Table C-2 on page 249). Performance was significantly better on all tests comparing 18-month scores to baseline, regardless of exposure group, indicating a practice effect.

The cross-sectional study of 63 JP-8-exposed workers at the Warfield Air National Guard Base in Essex, Maryland, observed that response times on numerous cognitive tests were significantly slower in JP-8-exposed personnel compared to the unexposed group (Tu et al., 2004). Accuracy on the same set of tests was significantly reduced for only the math test. Mechanics had the slowest response times on two tests, but trends in response accuracy were not observed in comparisons of job titles. A dual task test assessed multiple aspects of cognitive function simultaneously and a significantly greater response time was observed in JP-8-exposed personnel on one test condition, while accuracy was significantly decreased on two test conditions, suggesting slower cognitive function.

In a cross-sectional study in Swedish jet-engine factory workers (Knave et al., 1978), the exposed group had more psychiatric symptoms compared to the unexposed group (see Table C-2 on page 249). However, there was little information about the items that constituted the psychiatric interview, making the results difficult to interpret.

2.5.3.3. Executive Function

One medium confidence (Heaton et al., 2017) and three low confidence studies (Knave et al., 1978; Olsen et al., 1998; Tu et al., 2004) assessed long-term executive function health outcomes following exposure to jet fuel and observed mixed results, with decreased executive function in two low confidence studies and no associations observed in other studies.

A cross-sectional study in a population of active-duty USAF personnel from three bases (Heaton et al., 2017) observed no difference in executive function in the high exposure personnel compared to low exposure personnel (see Table C-2 on page 249). Performance improved between test days, suggesting a practice effect.

The cross-sectional study of 63 JP-8 exposed workers at the Warfield Air National Guard Base in Essex, Maryland, evaluated executive function using various tests (Tu et al., 2004). JP-8-exposed personnel performed significantly worse than the unexposed group based on time to complete and accuracy for certain tasks, indicating diminished executive function.

The cross-sectional study in Swedish jet engine factory workers exposed to an unspecified jet fuel (Knave et al., 1978) observed a significant increase for perceptual speed in the exposed group compared to unexposed controls (see Table C-2 on page 249), indicating impaired executive functioning in the exposed workers.

The cohort study in personnel at the Hill Air Force Base, Utah, (Olsen et al., 1998) observed no differences in information processing speed and accuracy at any time point following the start of working with JP-8 jet fuel and the transition away from JP-4 jet fuel (see Table C-2 on page 249).

The review conducted by the EASA (EASA,2017) reported significant impairment of information processing speed in a group of eight female commercial aircrew members following exposure to jet fuel oil emissions during flights over the course of 2 to 12 years.

2.5.3.4. Visuospatial Performance

One medium confidence study (Heaton et al., 2017) and two low confidence studies (Olsen et al., 1998; Tu et al., 2004) assessed visuospatial performance health outcomes following jet fuel exposure and decreased visuospatial function was observed in the medium confidence study.

In the population of active-duty USAF personnel from three Air Force bases, Heaton et al. (2017) measured visuospatial performance across a work week. No differences were observed between the high and low exposure groups on the first day of testing. Across the work week, visual organization was significantly decreased in the high exposure group compared to low exposure group, but no differences were observed in models evaluating average daily naphthalene or THC exposure concentrations (see Table C-2 on page 249).

Other studies evaluating visuospatial performance (spatial processing; (Olsen et al., 1998)) or function (speed or accuracy; (Tu et al., 2004)) observed no differences in workers exposed to jet fuels compared to unexposed workers.

2.5.3.5. Social-Emotional Behavior and Regulation

One low confidence cross-sectional study (Knave et al., 1978) evaluated long-term social-emotional behavior and regulation health outcomes in Swedish jet engine factory workers following exposure to an unspecified jet fuel. Incidence of irritability was determined from medical histories and standardized interviews and no differences were observed between the exposed and unexposed groups (see Table C-2 on page 249).

One case series reported repetition of thoughts, including “echoing” and “racing” thoughts, in 12 airmen who rarely wore masks at work following long-term occupational exposure to jet fuels at Smoky Hill Air Force Base, Kansas (Lombardi & Lurie, 1957).

The JP-8 Final Risk Assessment report (Kendall et al., 2001; NRC, 2003) described an analysis of data from electronic medical records comparing ambulatory care visits over the previous year in Air Force workers with and without JP-8 exposures (5,706 personnel per group). Only the first visit for each health issue was counted. Rates of mental illness were similar across exposure groups for men and women.

2.5.3.6. Depression

One low confidence study (Knave et al., 1978) and one uninformative study (Knave et al., 1976) assessed long-term depression health outcomes following jet fuel exposure and observed increased neurasthenia, anxiety and/or depression symptoms.

In the cross-sectional study of Swedish jet engine factory workers, Knave et al. (1978) observed that a significantly higher number of subjects in the exposed compared to unexposed group experienced “neurasthenia, anxiety and/or mental depression” symptoms and had been diagnosed and treated by a physician, based on medical histories and standardized interviews (see Table C-2 on page 249). There is no discussion on a clear distinction between neurasthenia (also known as depressed mood) and mental depression classifications.

In a cohort study, Knave et al. (1976) evaluated two groups of Swedish aircraft jet engine factory workers for self-reported long-term symptoms of depression and anxiety. Both groups were exposed to an unspecified type of jet fuel with one group identified as "heavily exposed," and the other identified as "less heavily exposed" based on job titles. Chronic depression and anxiety symptoms were observed in the heavily exposed and less heavily exposed groups, but no formal statistical comparison was conducted (see Table C-2 on page 249).

2.5.4. Summary of Mental Health Outcomes by Duration of Exposure

Five studies discussed duration of jet fuel exposure in relation to mental health outcomes. Only one of these studies (Heaton et al., 2017) directly assessed associations between duration of exposure and mental health outcomes, while the other four studies did not present mental health outcomes by varying exposure durations but discussed and/or considered it in the design of the study (Knave et al., 1978; Knave et al., 1976; Olsen et al., 1998; Tu et al., 2004).

A cross-sectional study of Air Force personnel who had served 5 years on average observed no associations between mental health outcomes and years of Air Force service (Heaton et al., 2017).

A cohort study looked at mental health outcomes in 29 workers with at least 5 years of occupational exposure to an unspecified jet fuel at an aircraft fuel systems installation factory in Sweden (Knave et al., 1976). The study compared mental health outcomes between exposed and unexposed individuals, as well as between "heavily" and "less heavily" exposed individuals within the exposed group. The classifications for heavily/less heavily exposed considered duration and intensity of exposure. Heavily exposed workers had continuous exposure for several hours daily to high concentrations of jet fuel or intermittent exposure to high concentrations for at least 20–30 minutes each time with an average frequency of at least every second or third week; the less heavily exposed workers had less frequent intermittent exposure than the heavily exposed. Comparisons were made between the groups, but employment duration and other measures of exposure gradient between "heavily exposed," and "less heavily exposed" subjects were not discussed. The study observed chronic anxiety and depression symptoms in 8 of 13 heavily exposed subjects and 4 of 16 less heavily exposed subjects.

A cross-sectional study of Swedish aircraft mechanics also considered length of employment when categorizing subjects' exposure status (Knave et al., 1978). Mean length of employment was 17.7 years in the exposed compared to 19.8 years in the unexposed group. The study observed a significantly higher incidence of "neurasthenia, anxiety and/or mental depression" in exposed compared to unexposed workers.

A cohort study in exposed and unexposed personnel at the Hill Air Force Base, Utah, (Olsen et al., 1998) compared mental health outcomes at baseline, 6 and 18 months following the transition from JP-4 to JP-8. Subjects in the exposed group had been exposed to JP-4 for at least 6 months at baseline. At 6 months, researchers observed significantly faster reaction time in unexposed subjects compared to exposed subjects and no differences in information processing speed or general cognitive function between the two groups.

The cross-sectional study of workers exposed to JP-8 for at least 1 year at the Warfield Air National Guard Base in Essex, Maryland, evaluated several aspects of mental health (Tu et al., 2004). Personnel were categorized by job title, but not duration of exposure, although mean duration of employment for each job title group was given. Pre- and post-shift exhaled breath analysis demonstrated differences in daily exposure between the job title groups. The study observed faster reaction times in JP-8 exposed compared to unexposed personnel, but this increased speed was accompanied by a greater number of errors. Performance on other tests of cognitive and executive function was mostly slower, with decreased accuracy on some tests.

2.5.5. Conclusion

There is slight evidence that jet fuel exposure negatively impacts mental health, leading to certain adverse health outcomes, such as decrements in attention, cognitive function, visual-spatial performance, social-emotional behavior and regulation and depression (see Table 2- on page 73). All studies reporting primary data evaluated long-term mental health outcomes; however, determining acute changes in mental health responses is challenging given the eligibility criteria for occupational studies frequently required more than 6 months of employment. No studies provided information indicating immediate mental health outcomes were associated with an increased risk of subsequent neurological health outcomes. In addition, data were insufficient to assess the risks of adverse mental health outcomes by duration of exposure. Some studies provided information on duration of employment or exposure, but duration was not always directly considered in risk estimates. Results were largely consistent across different aspects of mental health, demonstrating negative impacts of jet fuel exposure. Standardized mental health outcome assessment instruments were used in two studies, but health outcomes from other studies were less well-defined, resulting in some uncertainty. Evidence from a medium confidence study suggested apparent improvement in executive function; however, study authors noted these findings may have been influenced by practice effects from repeated testing. Information from case reports and reviews supported observations of detrimental effects of jet fuel exposure to attention, cognitive function, executive function and social-emotional behavior and regulation.

Overall, there is slight evidence for an association between jet fuel exposure and adverse mental health, with many low-quality studies and uncertainty in health outcome assessments. Further, there is insufficient data to determine the length of exposure at which long-term mental health outcomes would be expected or if there are immediate symptoms that indicate long-term outcomes. Additional studies are needed to better understand specific mental health outcomes that are related to jet fuel exposure and how risk changes with duration of exposure.

Table 2-6. Summary of Mental Health Outcomes Associated With Jet Fuel Exposure.

Studies and Interpretation	Summary and Key Findings[a]	Factors That Increase Certainty	Factors That Decrease Certainty	Summary Judgment
		Long-term Health Outcomes[b]		
Attention 1 Medium confidence study 3 Low confidence studies	One medium confidence study observed significantly more false positive errors on a continuous performance test among high exposure workers compared to low exposure workers and one low confidence study observed more errors in an attention task comparing JP-8 exposed to unexposed subjects (2/4). Comparisons by exposure concentrations from personal monitoring and biomonitoring were not significant. One low confidence study observed non-significant decreases in attention indices among exposed workers compared to unexposed workers.	• Medium confidence study	• Self-reported health outcome assessment	(⊕⊙⊙) Slight One medium confidence study and three low confidence studies reported detrimental long-term mental health outcomes with jet fuel exposure. No studies with primary data evaluated short-term health outcomes with jet fuel exposure. Significant differences were observed comparing exposed groups to unexposed groups, but analyses utilizing personal breathing zone monitoring or biomonitoring were non-significant. Direction of effect across different aspects of mental health (e.g., Attention, Cognitive Function, Visuospatial Performance, Social-Emotional Behavior and Regulation and Depression) were generally consistent, but positive results were also observed (i.e., Executive Function). Study authors noted practice effects for some tests which
Executive Function	One medium confidence study observed a non-	• No factors noted	• Low confidence studies	

Studies and Interpretation	Summary and Key Findings[a]	Factors That Increase Certainty	Factors That Decrease Certainty	Summary Judgment
1 Medium confidence study 3 Low confidence studies	significant positive association between exposure levels from personal monitoring and performance in executive function tests such as WAIS-III Digit Spans. One low confidence study observed significantly decreased speed and accuracy on executive function tests in JP-8 exposed compared to unexposed subjects. One low confidence study observed non-significant decreases comparing exposed subjects to unexposed subjects on executive function tests such as information processing speed and accuracy.		• Self-reported health outcome assessment	may cause deficits as a result of jet fuel exposure more difficult to detect. Health outcomes from low confidence studies were not well-defined, increasing uncertainty regarding results from these studies. Uncertainty remains due to the limited number of quality studies examining mental health outcomes.
Visuospatial Performance 1 Medium confidence study	One medium confidence study observed non-significant reductions in visuospatial performance with increasing exposure, measured by personal breathing zone samples.	• No factors noted	• Low confidence study • Self-reported health outcome assessment	

Studies and Interpretation	Summary and Key Findings[a]	Factors That Increase Certainty	Factors That Decrease Certainty	Summary Judgment
2 Low confidence study	Results from one low confidence study were non-significant and varied by timepoint and results from the other low confidence study were non-significant.			
Cognitive Function 3 Low confidence studies	One low confidence study observed significant decreases in the General Cognitive Index were observed among exposed participants in one study at baseline (1/2); results at other timepoints were consistent but non-significant. One low confidence study reported significantly slower response times on numerous cognitive function tests and decreased accuracy on one test in JP-8 exposed compared to unexposed subjects. One low confidence study observed significantly greater psychiatric symptoms in exposed	No factors noted	• Low confidence studies • Self-reported health outcome assessment • Imprecise health outcome definition	

Studies and Interpretation	Summary and Key Findings[a]	Factors That Increase Certainty	Factors That Decrease Certainty	Summary Judgment
	subjects compared to controls (1/2), but the health outcome was not well-defined.			
Depression 1 Low confidence study 1 Uninformative study	One low confidence study observed significantly increased frequency of having experienced anxiety and/or depression or had been diagnosed and treated by a physician for exposed subjects compared to unexposed controls (1/2).	• No factors noted	• Low confidence and uninformative studies • Limited number of studies examining health outcome • Self-reported health outcome assessment	
Social-Emotional Behavior and Regulation 1 Low confidence study	One low confidence study observed a non-significant increase in irritability among exposed subjects compared to an unexposed control group.	• No factors noted	• Low confidence study • Limited number of studies examining health outcome • Self-reported health outcome assessment	

[a] Health outcomes are summarized in this column by a ratio of (number of studies that found a significant association for that health outcome/the number of studies reporting on that health outcome).
[b]Long-term health outcomes are considered those that were measured at least 6 months after exposure.

2.6. Respiratory Health Outcomes

2.6.1. Summary of Respiratory Health Outcomes

Jet fuel exposure may impact respiratory health due to the potential for inhalational exposure. Respiratory health may be assessed by measuring lung function, pulmonary structure, respiratory symptoms, history of respiratory illnesses or respiratory mortality.

Of the seven studies examining the association between jet fuel exposure and respiratory health outcomes, one was considered medium confidence (Andersen et al., 2021), three were considered low confidence (Radican et al., 2008; Tunnicliffe et al., 1999; Yang et al., 2003) and three were considered uninformative (Knave et al., 1978; Knave et al., 1976; Olsen et al., 1998) (see Figure on p. 76).

The medium confidence study (Andersen et al., 2021) employed adequate outcome ascertainment and analytical methods and appropriately accounted for important confounders, such as smoking. While low participation rates raised concerns of selection bias, the potential impact on the study's overall conclusions was deemed minimal.

Among studies rated as low confidence and uninformative, sources of potential bias included exposure measurement methods (Knave et al., 1978; Knave et al., 1976; Olsen et al., 1998; Radican et al., 2008; Tunnicliffe et al., 1999; Yang et al., 2003), potential for residual confounding (Knave et al., 1978; Knave et al., 1976; Olsen et al., 1998; Radican et al., 2008; Tunnicliffe et al., 1999), use of self-reported health outcome (Knave et al., 1978; Knave et al., 1976; Olsen et al., 1998; Tunnicliffe et al., 1999), participant selection approach (Knave et al., 1978; Knave et al., 1976; Olsen et al., 1998; Tunnicliffe et al., 1999) and limited sample size (Olsen et al., 1998). Conclusions from reviews with results that overlap with the primary studies are summarized in Table D-3 in Appendix D on page 307.

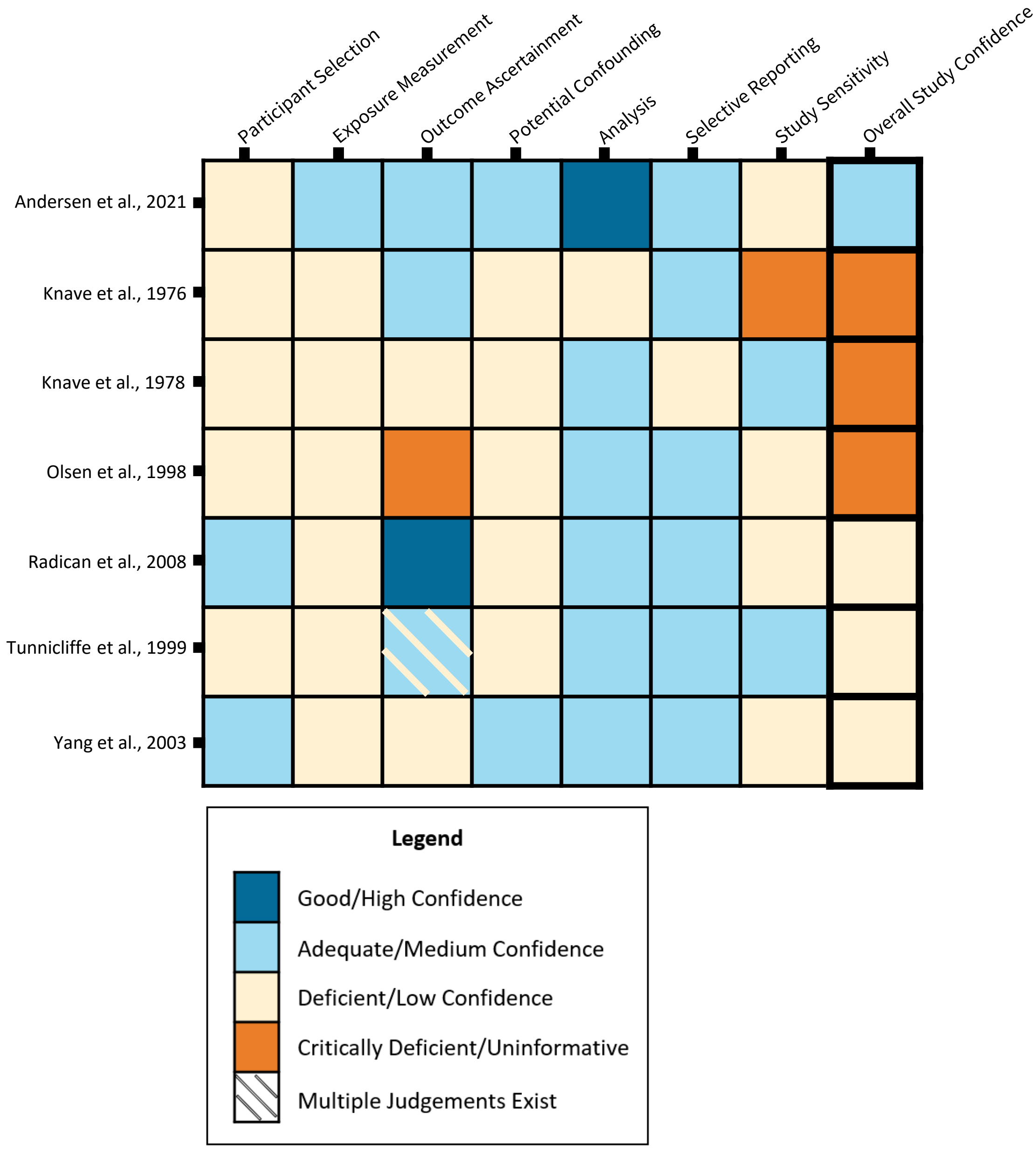


Figure 2-3. Study Quality Evaluations for Epidemiology Studies of Jet Fuel Exposure and Respiratory Health Outcomes.

Table 2- on page 78 summarizes the numbers of studies with acute (e.g., measurement taken within 6 months of jet fuel exposure) and long-term (e.g., measurement taken after at least 6 months of jet fuel exposure or occurring over multiple months) respiratory health outcomes. One medium confidence study (Andersen et al., 2021) and one low confidence study (Tunnicliffe et al., 1999) examined acute lung function. Two low confidence studies (Radican et al., 2008; Yang et al., 2003) measured long-term obstructive disease health outcomes, including non-malignant respiratory disease

mortality, emphysema mortality and chronic bronchitis. One low confidence study (Tunnicliffe et al., 1999) assessed acute respiratory hypersensitivity, such as wheeze and asthma. Two low confidence studies (Tunnicliffe et al., 1999; Yang et al., 2003) and three uninformative studies examined respiratory symptoms (e.g., nose irritation, throat irritation, runny nose, cough, dyspnea) (Knave et al., 1978; Knave et al., 1976; Olsen et al., 1998). Of those studies, all five studies measured acute symptoms (Knave et al., 1978; Knave et al., 1976; Olsen et al., 1998; Tunnicliffe et al., 1999; Yang et al., 2003), but only one study measured long-term symptoms (Yang et al., 2003).

Two secondary data sources provided information on pneumonitis. No studies with primary data assessed this health outcome. Additional secondary data sources, including case reports and review papers, are summarized for applicable health outcome categories below.

Table 2-7. Number of Studies Reporting on the Acute and Long-term Respiratory Health Outcomes Following Jet Fuel Exposures.

Health Outcomes	Acute[a]	Long-term[b]	Total Unique Studies
Lung function measures[c]	2	0	2
Obstructive disease[d]	0	2	2
Respiratory hypersensitivity[e]	1	0	1
Respiratory symptoms[f]	5	1	5

[a]Acute health outcomes are considered those that were measured within 6 months of exposure.
[b]Long-term health outcomes are considered those that were measured at least 6 months after exposure.
[c]Lung function measures include forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), FEV1/FVC and peak expiratory flow (PEF).
[d]Obstructive disease include nonmalignant respiratory disease mortality, emphysema mortality and chronic bronchitis.
[e]Respiratory hypersensitivity includes wheezing and asthma.
[f]Respiratory symptoms include nose irritation, throat irritation, cough, shortness of breath, respiratory tract symptoms, dyspnea, cough with phlegm, stuffy nose and runny nose.

2.6.2. Acute Respiratory Health Outcomes

2.6.2.1. Lung Function

One medium confidence study (Andersen et al., 2021) and one low confidence study (Tunnicliffe et al., 1999) examined acute lung function measures following jet fuel exposures and observed no associations.

In a cross-sectional study among Danish Air Force ground crew personnel exposed to JP-8, Andersen et al. (2021) observed no differences in lung function measures in the exposed compared to the unexposed groups (see Table C-3 in the Appendix on page 265). Personnel were assigned to exposed and unexposed groups based on job title and category.

In a cross-sectional study of current workers at the Birmingham International Airport in the United Kingdom, Tunnicliffe et al. (1999) observed no differences in lung function across groups of low, medium and high exposure to aircraft fuel or jet stream exhaust. The high exposure group consisted of baggage handlers, airport hands, marshallers, operational engineers, fitters and engineering technicians. The medium exposure group consisted of security staff, fire fighters and airfield operations managers who would expect to spend some of their working time on the airport apron, some in reasonable proximity to aircraft and some within the terminal buildings. The low exposure group consisted of terminal and office workers (see Table C-3 on page 265).

2.6.2.2. Pneumonitis

No studies with primary data examined the association between jet fuel exposure and acute pneumonitis. Two secondary data sources discussed pneumonitis following jet fuel exposure (Aboudara & Yun, 2006; Wang, 2004). In a case report, Aboudara and Yun (2006) reported on a military corporal who developed pneumonitis following accidental aspiration of JP-8. The authors noted that the long-term implications of acute pneumonitis are uncertain. The occurrence of pneumonitis following jet fuel aspiration via accidental ingestion is also mentioned in a medical toxicology textbook (Wang, 2004). The author also notes the potential for pulmonary edema following acute exposures to jet fuels.

2.6.2.3. Respiratory Hypersensitivity

The cross-sectional study of workers at Birmingham International Airport (Tunnicliffe et al., 1999). Observed no differences in self-reported wheeze or whistling in the chest in the past 12 months in men in the high exposure group when compared with men in the medium exposure group (see Table C-3 on page 265). Analyses were restricted to male participants; thus, data on wheeze among female workers were not available.

A case report on an aircraft engineer mechanic describes wheezing symptoms after starting to work with aircraft and being exposed to aviation fuel (Makker & Ayres, 1999). The mechanic’s symptoms worsened over the course of 4 years, leading to a diagnosis of asthma. Authors report that asthma control was improved after the subject limited exposure to jet fuels while at work.

2.6.2.4. Respiratory Symptoms

Two low confidence studies (Tunnicliffe et al., 1999; Yang et al., 2003) and three uninformative studies (Knave et al., 1978; Knave et al., 1976; Olsen et al., 1998) reported increases in respiratory symptoms (e.g., nose irritation, throat irritation, stuffy and runny nose, cough, phlegm, shortness of breath, dyspnea and general respiratory tract symptoms) with increasing jet fuel exposure.

In a cross-sectional study of male workers at the Kaohsiung International Airport in Taiwan, Yang et al. (2003) observed significantly increased self-reported dyspnea in workers exposed to unspecified jet fuel compared to unexposed workers. There were no differences in nose and throat irritation between exposed and unexposed workers (see Table C-3 on page 265).

In the cross-sectional study of workers at Birmingham International Airport, Tunnicliffe et al. (1999) examined acute respiratory symptoms (e.g., cough with and without phlegm, shortness of breath, stuffy nose, runny nose) and observed significantly increased cough with phlegm and runny nose in men in the high exposure group compared to men in the medium exposure group (see Table C-3 on page 265); however, no differences in cough, stuffy nose and shortness of breath were observed between the groups. Respiratory symptoms in female workers were not assessed (see Table C-3 on page 265). The study observed no association between improved symptoms and time away from work, although the authors noted that limited sample sizes may have hampered statistical power.

Results from Yang et al. (2003) and Tunnicliffe et al. (1999) are supported by results from Knave et al. (1976), Knave et al. (1978) and Olsen et al. (1998), though these three studies were rated uninformative and the results should be interpreted with caution. In a cohort study of aircraft factory workers, Knave et al. (1976) reported higher numbers of self-reported acute respiratory tract symptoms (e.g., “pain upon inhalation,” “feelings of suffocation,” “slight cough”) among those highly exposed to an unspecified jet fuel compared to those with low exposure, but statistical tests were not conducted (Knave et al., 1976) (see Table C-3 on page 265). Six subjects from the highly exposed group also reported feelings of suffocation, which Knave et al. (1976) considered chronic respiratory tract symptoms.

In a cross-sectional study of workers at a jet motor factory in Sweden, Knave et al. (1978) observed no difference in the number of workers reporting acute respiratory tract symptoms (“pain upon inhalation,” “feelings of suffocation,” “slight cough”) between workers exposed to an unspecified jet fuel and unexposed workers (Knave et al., 1978) (see Table C-3 on page 265). Workers reported that respiratory symptoms were recurrent with exposure.

Among personnel from the Hill Air Force Base, Utah, Olsen et al. (1998) observed increased frequency of nose and throat irritation, cough and shortness of breath in those exposed to JP-4 and JP-8 compared to those who were not exposed; however, statistical comparisons were not conducted (Olsen et al., 1998).

Eight secondary sources (EASA, 2017; Kendall et al., 2001; Merzenich et al., 2021; NRC, 1996; NRC, 2003; Ritchie et al., 2003; Touri et al., 2013; Wang, 2004) discussed acute respiratory symptoms (including cough, dyspnea, tachypnea, difficulty breathing and chest tightness) that may develop following jet fuel exposure. The USAF’s JP-8 risk assessment (Kendall et al., 2001) and a review (Ritchie et al., 2003) summarized self-reported health outcomes in military personnel following jet fuel exposures, including blocked nasal passages, respiratory distress and irritation of respiratory mucous membranes. The Toxicologic Assessment of Jet-Propulsion Fuel 8 (NRC, 2003) also included results from a report that observed no significant differences in the number of medical visits for respiratory symptoms between exposed and unexposed Air Force personnel. Wang (2004) briefly noted that respiratory symptoms (i.e., cough, dyspnea, tachypnea) improved after jet fuel exposure ceases. The other reviews restated results found in the primary epidemiological studies described above (see Table D-3 in Appendix D on page 308).

One case report discussed acute respiratory symptoms following exposure to jet fuel(Makker & Ayres, 1999). A 42-year-old aircraft engineer mechanic describes coughing and shortness of breath after starting to work with aircraft and being exposed to aviation fuel.

2.6.3. Long-term Respiratory Health Outcomes

2.6.3.1. Obstructive Disease

Two low confidence studies examined long-term obstructive disease in jet fuel exposed occupational populations (Radican et al., 2008; Yang et al., 2003) with mixed results.

In a cohort study of former civilian workers at the Hill Air Force Base, Utah, Radican et al. (2008) observed significantly increased non-malignant respiratory disease mortality in male workers exposed to JP-4 jet fuel compared to unexposed male workers (see Table C-3 on page 265). Among female civilian workers, there were no differences in non-malignant respiratory disease mortality and in emphysema mortality comparing exposed and unexposed female workers (see Table C-3 on page 265).

In the cross-sectional study of male workers at the Kaohsiung International Airport in in Taiwan, Yang et al. (2003) observed no differences in chronic bronchitis among those exposed to unspecified jet fuels compared to unexposed workers (see Table C-3 on page 265). Bronchitis was characterized as “a cough and/or phlegm on most days for 3 months or more in a year” (Yang et al., 2003). Authors refer to this as a chronic health outcome; thus, it is considered a long-term obstructive disease, although it should be noted that given the cross-sectional study design, exposure was concurrent with health outcome assessment.

The association between jet fuel exposure and obstructive pulmonary disease was also discussed in one review and one case report. A review article on occupational aviation fuel exposure and subsequent health outcomes (Karanikas et al., 2021) cites the case report of a Veteran who presents with recurrent spontaneous pneumothorax after long-term JP-8 exposure (Poon et al., 2019).

2.6.3.2. Respiratory Symptoms

One low confidence study examined long-term respiratory symptoms following jet fuel exposure and observed positive associations (Yang et al., 2003).

In the cross-sectional study of male workers at the Kaohsiung International Airport in Taiwan, Yang et al. (2003) observed significantly increased chronic cough in workers exposed to unspecified jet fuels compared to unexposed workers (see Table C-3 on page 265). The study reported no differences in phlegm production in exposed workers compared to unexposed workers (see Table C-3 on page 265). Chronic cough and phlegm production were defined as those experienced for a partial or full day for at least 3 months within a year; thus, these health outcomes were considered long-term despite the cross-sectional study design and concurrent nature of exposure and health outcome assessment.

2.6.4. Summary of Respiratory Health Outcomes by Duration of Exposure

Four studies presented results by duration of exposure (Olsen et al., 1998) or included discussions of duration of exposure (Andersen et al., 2021; Knave et al., 1978; Knave et al., 1976).

In the examination of health outcomes following Hill Air Force Base's transition from JP-4 to JP-8 jet fuel, Olsen et al. (1998) presented mean frequency of respiratory symptoms among exposed and unexposed active-duty and civilian workers at baseline (i.e., transition from JP-4 to JP-8) and after 6 and 18 months of JP-8 use (Olsen et al., 1998). However, no statistical comparisons were provided that would allow conclusions to be drawn about JP-8 exposure duration and its association with subsequent health outcomes.

Two other studies discussed duration of exposure but did not present respiratory health outcome results by duration or discuss how duration may be associated with respiratory health outcomes (Knave et al., 1978; Knave et al., 1976). Knave et al. (1976) considered duration of exposure when assigning aircraft factory workers to high and low exposure groups and included only subjects with 5 or more years of employment; however, duration of exposure is not discussed further in the study. Knave et al. (1978) assessed the mean exposure duration (mean = 17 years) among the occupationally exposed and interpreted the non-significant increase in self-reported respiratory symptoms as a reflection of long-term exposure to jet fuel. The most highly exposed subjects were selected for this group after consideration of intensity and duration of exposure.

No other studies examined or discussed duration of exposure and its potential impacts on respiratory health outcomes.

2.6.5. Conclusion

There is slight evidence that jet fuel exposure negatively impacts respiratory health, leading to some adverse respiratory health outcomes, including acute decreased lung function, long-term obstructive diseases and acute and long-term respiratory symptoms (see Table 2- on page 84). Results from the limited number of studies were largely consistent; however, with the exception of one medium confidence study, most studies were of low and uninformative confidence. In addition, most studies examined respiratory health outcomes following civilian occupational exposure to jet fuels, limiting the ability to draw conclusions about health outcomes in military populations.

No studies provided information indicating immediate respiratory health outcomes were associated with increased risk of subsequent respiratory health outcomes, although a case report suggested that chronic wheezing led to an asthma diagnosis. Data were insufficient to assess the risks of adverse respiratory health outcomes by duration of exposure. While some studies provided information on duration of employment or exposure, duration was not always directly considered in risk estimates.

Overall, there is slight evidence for an association between jet fuel exposure and adverse respiratory health outcomes, although the number of studies examining this association is limited and of low quality. Further, there is insufficient data to determine the length of exposure at which long-term adverse respiratory outcomes would be expected or if there are immediate symptoms that indicate long-term outcomes. Additional studies are needed to better understand specific respiratory health outcomes that are related to jet fuel exposure and how risk changes with duration of exposure.

Table 2-8. Summary of Respiratory Health Outcomes Associated With Jet Fuel Exposure.

Studies and Interpretation	Summary and Key Findings[a]	Factors That Increase Certainty	Factors That Decrease Certainty	Summary Judgment
Acute Health Outcomes[b]				⊕⊙⊙ *Slight* One *medium* confidence and three *low* confidence studies reported detrimental acute and long-term respiratory health outcomes with jet fuel exposure. While directions of effect were largely consistent across studies and observed health outcomes were biologically coherent, uncertainty remains due to the limited number of quality studies examining respiratory health outcomes.
Lung function 1 Medium confidence study 1 Low confidence study	One medium confidence study in Danish Air Force base personnel observed non-significant decreases in FEV_1, FVC and PEF. One study in airport workers observed no changes in FEV_1, FVC and FEV_1/FVC, with jet fuel exposure.	• Medium confidence study • Coherence of findings	• Limited number of studies examining health outcome	
Respiratory symptoms 2 Low confidence studies 3 Uninformative studies	A low confidence study in an occupational population observed significantly increased odds of dyspnea (1/5), cough with phlegm (1/5) and runny nose (1/5). Non-significant increases were also observed for nose and throat irritation, cough, stuffy nose and other respiratory tract symptoms in low confidence and uninformative studies.	• Large magnitude of effects • Coherence of findings • Consistent direction of effect in occupational populations •	• Low confidence and uninformative studies	
Respiratory hypersensitivity 1 Low confidence study	One study in airport workers observed non-significant decreased odds of wheezing or whistling in chest in men with jet fuel exposure.	• No factors noted.	• Limited number of studies examining health outcome	

Studies and Interpretation	Summary and Key Findings[a]	Factors That Increase Certainty	Factors That Decrease Certainty	Summary Judgment
			• Low confidence study	
Long-term Health Outcomes[c]				
Obstructive disease 2 Low confidence studies	One study observed significantly increased non-malignant respiratory disease mortality in former male civilian workers at Hill Air Force Base (1/2). In male airport workers, one study observed non-significantly increased odds of chronic bronchitis.	• Coherence of findings • Consistent direction of effect in male populations	• Limited number of studies examining health outcome • Low confidence studies	
Respiratory symptoms 1 Low confidence study	One study of male airport workers observed significant increased odds of chronic cough (1/1) and non-significant increased odds of phlegm production.	• No factors noted.	• Limited number of studies examining health outcome • Low confidence study	

[a]Health outcomes are summarized in this column by a ratio of (number of studies that found a significant association for that health outcome/the number of studies reporting on that outcome).
[b]Acute health outcomes are considered those that were measured within 6 months of exposure.
[c]Long-term health outcomes are considered those that were measured at least 6 months after exposure.

2.7. Metabolic Health Outcomes

2.7.1. Summary of Metabolic Health Outcomes

Metabolic health pertains to the chemical reactions that occur in cells to break down energy and maintain bodily functions. Commonly researched metabolic health outcomes include resting metabolic rate (i.e., the amount of energy used by the body over a specified time period), anthropometric measures (e.g., adiposity, waist circumference, body mass index, body weight changes), diabetes (including gestational diabetes), insulin measurements (e.g., insulin resistance, serum insulin), glucose measurements (e.g., serum glucose, glucose intolerance), hormones involved in metabolic processes (e.g., adiponectin, leptin) and metabolic syndrome (the co-occurrence of multiple metabolic conditions).

The review identified no studies with primary data that assessed jet fuel exposures and metabolic health outcomes.

2.7.2. Conclusion

Data are not available to assess possible immediate metabolic health outcomes associated with an increased risk of subsequent endocrine health outcomes or to assess the risks of adverse metabolic health outcomes by duration of exposure. Due to the lack of primary and secondary data, the available epidemiological evidence examining jet fuel exposure and metabolic health is considered indeterminate. Studies are needed to better understand how jet fuel exposure may impact metabolic health.

2.8. Immune Health Outcomes

2.8.1. Summary of Immune Health Outcomes

Jet fuel exposure may impact immune health due to the potential for inhalational or dermal exposure. Immune health may be assessed by measuring immune system function through cell counts (e.g., white blood cells, neutrophils, lymphocytes, monocytes, eosinophils, basophils, T-cells, T-helper cells, T-suppressor cells, natural killer cells or B-cells) or by history of infection. Immune health may also be assessed by measuring immune hypersensitivity, such as positive responses to allergens. Immune system cell counts below normal clinical ranges may indicate immune system impairment, while cell counts above normal clinical ranges may result from immune system dysregulation or as a response to pathogens.

Of the three studies with primary data examining the association between jet fuel exposure and immune health outcomes, one was considered medium confidence (Rhodes et al., 2003), one was considered low confidence (Olsen et al., 1998) and one was considered uninformative (Tunnicliffe et al., 1999).

The medium confidence study (Rhodes, 2001) had adequate participant selection and health outcome assessment methods and it appropriately adjusted for important confounders, such as smoking. The exposure assessment was based on job title with limited information on PPE, likely limiting the sensitivity of the study. Results were presented only as r-squared estimates and p-values; however, the potential impact of these factors on the study's overall conclusion was deemed minimal.

The low confidence study (Olsen et al., 1998) used adequate outcome ascertainment and analysis methods. However, this study was considered low confidence due to a small sample size, a lack of quantitative exposure assessment in statistical analyses and the potential for selection bias and residual confounding due to a lack of consideration of socioeconomic status.

The uninformative study (Tunnicliffe et al., 1999) did not adjust for any potential confounders in the analysis of immune health outcomes. Additional concerns included potential for selection bias due to a lack of information on the recruitment and sampling process and possible exposure misclassification since no direct measurements of jet fuel concentrations were used.

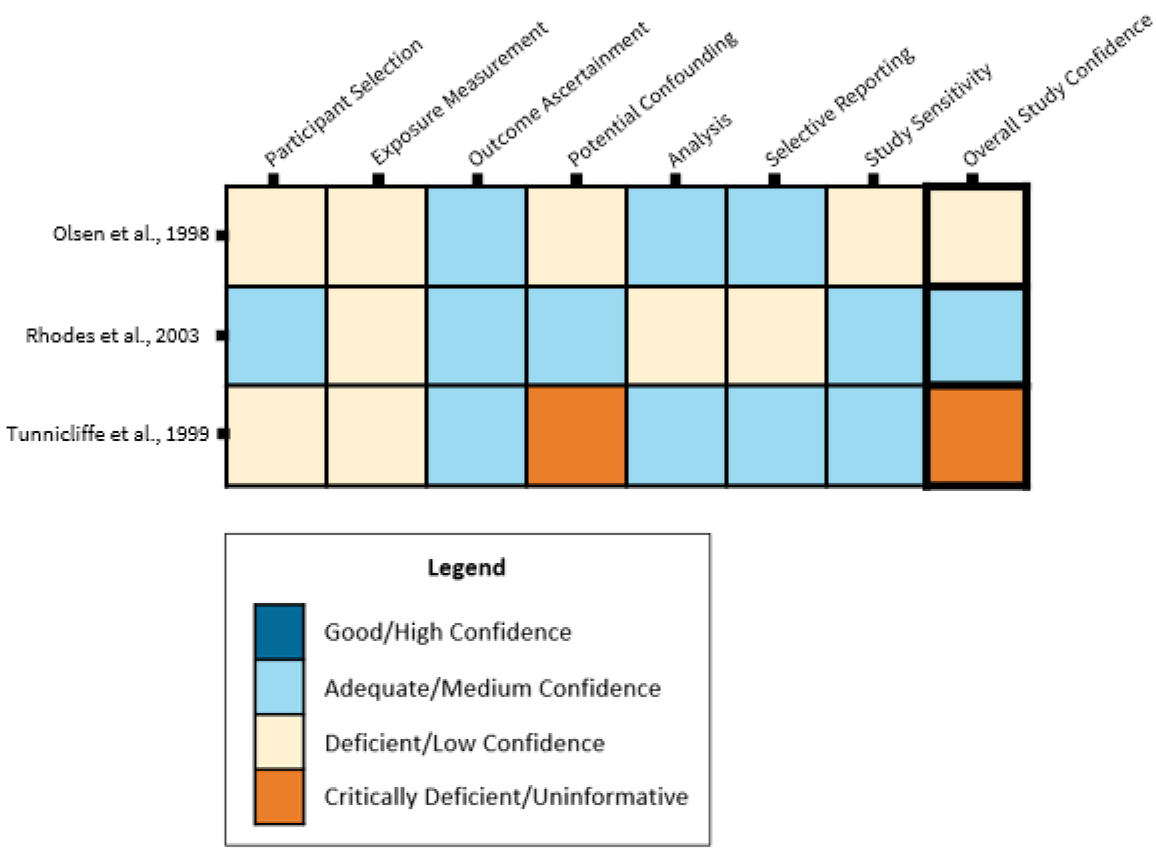


Figure 2-4. Study Quality Evaluations for Epidemiology Studies of Jet Fuel Exposure and Immune Health Outcomes.

Table 2-9 on page 88 summarizes the number of studies with acute (e.g., measurement taken within 6 months of jet fuel exposure) immune health outcomes. The review identified no studies with primary data on the association between jet fuel exposure and long-term immune health outcomes (e.g., measurements taken after at least 6 months of jet fuel exposure or occurring over multiple months). One medium confidence study

(Rhodes et al., 2003) and one low confidence study (Olsen et al., 1998) examined immune system function outcomes, such as immune cell counts and infection history. One uninformative study (Tunnicliffe et al., 1999) examined immune hypersensitivity outcomes such as dermal atopy.

Three secondary reports, including a risk assessment (Kendall et al., 2001) and two reviews (NRC, 2003; Ritchie et al., 2003), provided information on immune system function. One literature review provided information on immune hypersensitivity (Touri et al., 2013). Conclusions from reviews with results that overlap with the primary studies are summarized in Table D-4 in Appendix D on page 309.

Table 2-9. Number of Studies Reporting on the Acute and Long-term Immune Health Outcomes Following Jet Fuel Exposures.

Health Outcomes	Acute[a]	Long-term[b]	Total Unique Studies
Immune system function[c]	2	0	2
Immune hypersensitivity[d]	1	0	1

[a]Acute health outcomes are considered those that were measured within 6 months of exposure.
[b]Long-term health outcomes are considered those that were measured at least 6 months after exposure.
[c]Immune system function includes immune system cell counts (white blood cells, neutrophils, basophils, eosinophils, lymphocytes, monocytes T-cells, T-suppressor cells, T-helper cells, Natural killer cells and B-cells) and infection history.
[d]Immune hypersensitivity includes dermal atopy.

2.8.2. Acute Immune Health Outcomes

2.8.2.1. Immune System Function

In one medium confidence cross-sectional study of 123 Air Force personnel at three bases across the Southeastern United States, personnel were assigned to exposure levels by job title, with fuel system maintenance workers categorized as high exposure and personnel in jobs unrelated to jet fuels categorized as low or no exposure (Rhodes et al., 2003). The study observed significant increases in total white blood cell, neutrophil and monocyte counts in the high exposure to JP-8 group compared to a group with low or no exposure (see Table C-4 in Appendix C on page 273). However, all counts of immune system cells were within normal clinical ranges and there were no differences between the groups for other types of immune system cells, including lymphocyte, eosinophil, basophil, T-cell, T-helper cell, T-suppressor cell, natural killer cell, or B-cell counts. Air sampling measures of naphthalene, a major component of JP-8, were collected for all workers with sampling monitors worn outside of any PPE. Breath sample analyses for naphthalene 30 minutes before and after work assignments were also conducted. Personnel in the high exposure group had significantly higher levels of exposure to naphthalene compared to the low or no exposure group in personal air sampling and post-breath analysis. Workers wore PPE. Thus, the higher levels of naphthalene in the high exposure group workers suggest evidence of either dermal exposure and/or poor respiratory protection. However, these measured concentrations were not used in statistical analyses of immune health outcomes. The authors noted that a possible explanation for the significantly elevated levels of certain immune system cells may be microbial colonization due to jet fuel exposure.

One low confidence study examined complete blood count parameters in a cohort of active duty and civilian personnel at Hill Air Force Base, Utah (Olsen et al., 1998). Personnel were assigned to exposed and unexposed groups based on job duties. The study evaluated immune system function through immune system cell counts 4 times over a period of 18 months; first, at the transition from JP-4 to JP-8 and then at 3, 6 and 18 months after conversion to JP-8. The study measured counts of white blood cells, neutrophils, lymphocytes, monocytes, eosinophils and basophils and qualitatively reported no changes in any immune system function parameters between JP-4 and JP-8 use. In addition, no differences were observed between exposed and unexposed groups. The study conducted air sampling to assess exposure to exact vapor, aerosol and particulate components of JP-8, although this was not used in statistical analysis of immune health outcomes. The study reported that exposure to vapors of JP-8 were extremely low and there was no detectable benzene exposure.

The JP-8 final risk assessment of acute exposure to jet fuel conducted by the AFIOH summarized studies that reviewed medical record information to determine if differences existed in health care encounter rates when JP-8 exposed workers were compared to those who did not routinely encounter jet fuel in the performance of their duties. An analysis of 265 active-duty personnel from the JP-8 final risk assessment reported no differences in visits related to infectious or parasitic illnesses related to jet fuel exposure (Kendall et al., 2001).

2.8.2.2. Immune Hypersensitivity

In a cross-sectional study among 432 airport workers at the Birmingham International Airport in the United Kingdom, Tunnicliffe et al. (1999) observed no differences in the incidence of allergic reactions across groups of low, medium and high exposure aircraft fuel or jet stream exhaust (see Table C-4 on page 273). Exposure groups were determined based on official job titles, with employees classified as high exposure if they were determined to spend a considerable portion of their working day close to service aircraft (e.g., baggage handlers, airport hands, marshallers, operational engineers, fitters and engineering technicians), medium exposure if they were expected to spend “some” of their working time near service aircraft and low exposure if they were terminal or office workers. The study measured allergic reactions as dermal atopy, defined as at least one positive skin test to an allergen. The authors observed a dose-dependent relationship with dermal atopy, as the condition occurred in 48%, 52% and 56% of the participants in the low, medium and high exposure groups, respectively. The cross-sectional design of this study precludes establishing temporality between exposure to jet fuels and health outcome measurement.

2.8.3. Summary of Immune Health Outcomes by Duration of Exposure

There was limited discussion of duration of exposure in the reviewed literature. Fuel system maintenance personnel in Rhodes et al. (2003) were required to have one or more hours of tank entry twice a week for at least 9 months. Personnel in the high exposure group had a mean 47 months of employment compared to 50 months in the low exposure group. However, the results were not presented by exposure or employment duration and there was no discussion of how duration may have influenced immune health outcomes. Olsen et al. (1998) measured immune health outcomes in workers at Hill Air Force Base at the transition from JP-4 to JP-8 and at 3, 6 and 18 months after a conversion to JP-8. Mean values of immune system cell counts were presented by time of sampling and no changes were observed across time points. Tunnicliffe et al. (1999) reported that the duration of employment was similar across low, medium and high exposure groups with a mean value of 7.6 years of employment in all groups combined. The results were not presented by exposure duration and the health outcome was measured concurrently with exposure.

2.8.4. Conclusion

The evidence evaluating an association between jet fuel exposure and immune toxicity in humans is considered indeterminate based on the limited number of studies and inconsistent and non-significant findings. No health outcome was evaluated in more than one study, making consistency hard to establish. One medium confidence study and one uninformative study assessed immune health outcomes. In Air Force personnel, there was evidence of a positive association between jet fuel exposure and immune system function as measured by total white blood cells, neutrophils and monocytes. These increased levels were within normal clinical ranges, making it unlikely that observed changes were clinically adverse. There was no evidence of an association between jet fuel exposure and allergic reaction in airport employees.

No studies provided information indicating that immediate immune health outcomes were associated with an increased risk of subsequent, long-term immune health outcomes. In addition, data were insufficient to assess the risks of adverse immune health outcomes by duration of exposure. While some studies provided information on duration of employment or exposure, duration was not always directly considered in risk estimates. Additional studies are needed to better understand specific immune health outcomes that are related to jet fuel exposure and how risk changes with duration of exposure.

Table 2-10. Summary of Immune Health Outcomes Associated With Jet Fuel Exposure.

Studies and Interpretation	Summary and Key Findings	Factors That Increase Certainty	Factors That Decrease Certainty	Summary Judgment
Acute Health Outcomes[a]				⊙⊙⊙ Indeterminate Overall, findings were limited due to the review only containing one medium confidence study, one low confidence study and one uninformative study.
Immune system function 1 Medium confidence study 1 Low confidence study	The medium confidence study of Air Force personnel observed significantly increased counts of total white blood cells, neutrophils and monocytes, although these were all within normal clinical ranges. No associations were observed for lymphocyte, eosinophil, basophil, T-cell, T-helper cell, T-suppressor cell, natural killer cell or B-cell counts. The low confidence study of active-duty and civilian personnel at Air Force Base observed no significant differences in counts of white blood cells, neutrophils, monocytes, lymphocytes, eosinophils and basophils	• No factors noted	• Limited number of studies examining health outcome	
Immune hypersensitivity 1 Uninformative study	A study of airport personnel observed no difference in allergic reaction results across high, medium and low exposure groups.	• No factors noted	• Uninformative study • Limited number of studies examining health outcome	

[a]Acute health outcomes are considered those that were measured within 6 months of exposure.

2.9. Female Reproductive Health Outcomes

2.9.1. Summary of Female Reproductive Health Outcomes

Jet fuel exposure may impact female reproductive health following inhalational or dermal exposure. Female reproductive health may be assessed by measuring female reproductive hormones, menstrual cycle characteristics or decreases in fertility.

Of the two studies with primary data examining the association between jet fuel exposure and female reproductive health outcomes, one was considered medium confidence (Reutman et al., 2002) and one was considered low confidence (Gordley et al., 2000) (see Figure 2-5 below). Both studies examined female reproductive health outcomes in the same population of female civilian and military personnel from 10 USAF bases. The medium confidence study (Reutman et al., 2002) employed adequate exposure methods and outcome ascertainment and appropriately accounted for potential confounders, such as use of alcohol and race. There was some concern for selection bias due to the low participation rate and lack of information on excluded subjects; however, the potential impact on the study's overall conclusions was deemed minimal. Sources of potential bias in the low confidence study (Gordley et al., 2000) included exposure measurement methods, since self-reported job category was used to assign exposure and outcome ascertainment, since subject perception and self-report were used to define the health outcomes.

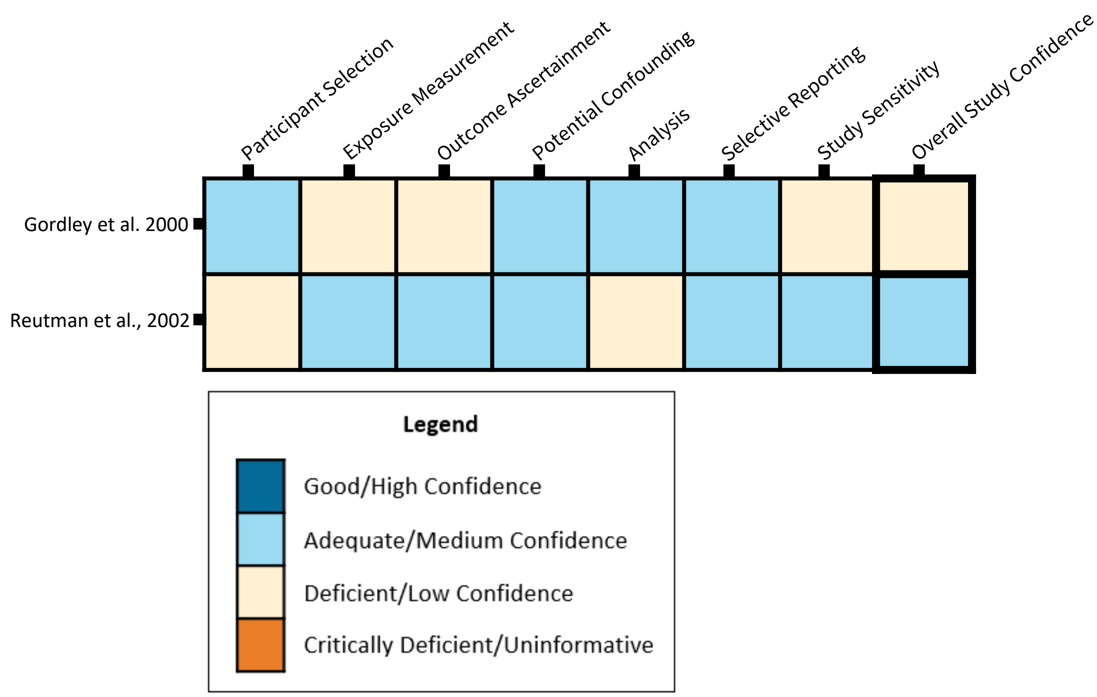


Figure 2-5. Study Quality Evaluations for Epidemiology Studies of Jet Fuel Exposure and Female Reproductive Health Outcomes.

Table 2- below summarizes numbers of studies with acute (e.g., measurement taken within 6 months of jet fuel exposure) reproductive health outcomes. One medium confidence study (Reutman et al., 2002) examined acute changes in reproductive hormones and one low confidence study (Gordley et al., 2000) assessed acute changes in menstrual cycle characteristics, such as dysmenorrhea and abnormal cycle length. The review identified no primary studies that assessed long-term (e.g., measurement taken at least 6 months after jet fuel exposure or occurring over multiple months) reproductive health outcomes.

Two secondary reviews provided additional information on reproductive hormones and menstrual cycle characteristics (ATSDR, 1995; Van Dyke, 2010).

Table 2-11. Number of Studies Reporting on the Acute and Long-term Female Reproductive Health Outcomes Following Jet Fuel Exposures.

Health Outcomes	Acute[a]	Long-term[b]	Total Unique Studies
Female reproductive hormones[c]	1	0	1
Menstrual cycle characteristics[d]	1	0	1

[a]Acute health outcomes are considered those that were measured within 6 months of exposure.
[b]Long-term health outcomes are considered those that were measured at least 6 months after exposure.
[c]Female reproductive hormones include follicular pregnanediol 3-glucuronide, luteal pregnanediol 3-glucuronide, midluteal estrone 3-glucuronide and preovulatory luteinizing hormone (LH).
[d]Menstrual cycle characteristics include dysmenorrhea, hypermenorrhea, abnormal cycle length and menstrual disorders.

2.9.2. Acute Female Reproductive Health Outcomes

2.9.2.1. Female Reproductive Hormones

One medium confidence cross-sectional study examined reproductive hormone levels in urine following jet fuel exposures in 100 female civilian and active military personnel at 10 USAF bases (Reutman et al., 2002). The hormones were selected because they were predictive of conceptive menstrual cycles as subclinical markers of female reproductive dysfunction. Some JP-8 constituents (i.e., aliphatic hydrocarbons, benzene, toluene, ethylbenzene and m,p,o-xylenes) were assessed in exhaled breath samples to characterize jet fuel exposure. Personnel were assigned to high and low exposure groups based on median levels of JP-8 constituents. Personnel in the high exposure group for aliphatic hydrocarbons had significantly lower preovulatory LH levels compared to those in the lower exposure group. There were no differences in the levels of midluteal estrone 3-glucuronide or midluteal pregnanediol 3-glucuronide (PD3G) levels in correlation with the JP-8 constituent levels when comparing the exposure groups (Reutman et al., 2002). Additional information about this study is provided in Table C-5 in Appendix C on page 276.

2.9.2.2. Menstrual Cycle Characteristics

One low confidence study assessed the association between JP-8 exposure and menstrual cycle characteristics in a cross-sectional study of 170 female USAF personnel (Gordley et al., 2000). Fuel exposure was ascertained by asking the women to self-report whether they had a job handling fuel. Women were asked about their menstrual patterns over the previous 3 months. There was a slight increase in odds of dysmenorrhea (i.e., lower abdominal discomfort or pain during menstruation) and a slight decrease in odds of abnormal cycle length when comparing fuel-handling with non-fuel-handling personnel (Table C-5 on page 276). The authors observed a difference between military and civilian personnel in risk of hypermenorrhea (i.e., heavy or prolonged menstrual flow); however, it did not reach statistical significance.

2.9.3. Summary of Female Reproductive Health Outcomes by Duration of Exposure

Female civilian and active military personnel at 10 USAF bases that participated in the described studies were assessed cross-sectionally and information on duration of employment or exposure was not discussed.

2.9.4. Conclusion

The evidence examining jet fuel exposure and reproductive health outcomes in females is considered indeterminate due to the limited number of studies examining this association and the inconsistent and non-significant findings (see Table 2-1 on page 95). One study reported a significant decrease in a single reproductive hormone in civilian and military personnel exposed to JP-8, but no differences were observed for other hormones and changes were not correlated with all JP-8 constituents. While lower levels of certain hormones have been linked to infertile cycles, it is unknown whether the decrements observed in this study are of sufficient magnitude to reduce fertility. In the same population, there were slight increases in dysmenorrhea and slight decreases in abnormal cycle lengths between fuel handling and non-fuel-handling personnel; however, there were no differences in risk of hypermenorrhea or in overall menstrual disorders. No studies reported on long-term female reproductive health outcomes and no studies provided information indicating that immediate female reproductive health outcomes were associated with an increased risk of subsequent female reproductive health outcomes. In addition, data were not available to assess risks of adverse female reproductive health outcomes by duration of exposure. Additional studies are needed to better understand specific reproductive health outcomes that are related to jet fuel exposure and how risk changes with duration of exposure.

Table 2-12. Summary of Female Reproductive Health Outcomes Associated With Jet Fuel Exposure.

Studies and Interpretation	Summary and Key Findings	Factors That Increase Certainty	Factors That Decrease Certainty	Summary Judgment
Acute Health Outcomes[a]				⊙⊙⊙ Indeterminate One medium confidence study reported adverse acute female reproductive health outcomes with jet fuel exposure. Uncertainty remains due to the limited number of studies examining female reproductive health outcomes.
Female reproductive hormones 1 Medium confidence study	One medium confidence study of female USAF personnel observed significant decreases in preovulatory LH levels and no differences with other hormone levels	• Medium Confidence Study	• Limited number of studies examining health outcome	
Menstrual cycle characteristics 1 *Low* confidence study	One *low* confidence study of female USAF personnel observed no differences in the odds of menstrual cycle disorders.	• No factors noted.	• *Limited number* of studies examining health outcome • *Low* confidence study	

USAF = United States Air Force; LH = luteinizing hormone.
[a]Acute health outcomes are considered those that were measured within 6 months of exposure.

2.10. Male Reproductive Health Outcomes

2.10.1. Summary of Male Reproductive Health Outcomes

Jet fuel exposure may impact male reproductive health following inhalational and dermal exposure. Reproductive health may be assessed by measuring reproductive function through reproductive hormones (e.g., follicular stimulating hormone, LH, prolactin and testosterone) or semen parameters (e.g., sperm motility, sperm concentration and sperm size). Semen parameters below normal clinical ranges may indicate reproductive system impairment or infertility.

One low confidence study examined the association between jet fuel exposure and male reproductive health outcomes (Lemasters et al., 1999). Sources of potential bias in the study included concerns about selective reporting and sensitivity due to a small sample size (see Figure 2-6 below).

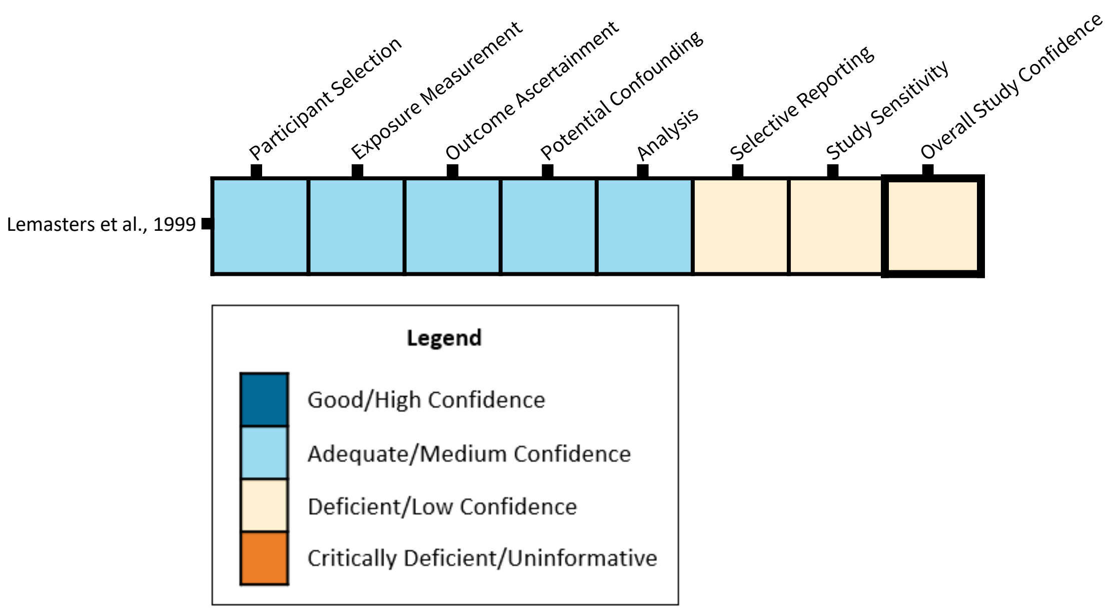


Figure 2-6. Study Quality Evaluations for Epidemiology Studies of Jet Fuel Exposure and Male Reproductive Health Outcomes.

Table 2- on page 97 summarizes the single study with acute (e.g., measurement taken within 6 months of jet fuel exposure) and long-term (e.g., measurement taken after at least 6 months of jet fuel exposure or occurring over multiple months) male reproductive health outcomes. The one study identified (Lemasters et al., 1999) examined acute and long-term semen parameters including sperm concentration, length, width/length, motility, velocity and linearity, which were measured after 15 and 30 weeks of employment.

In addition, two secondary reviews provided information on male reproductive health parameters, such as sperm concentration and male reproductive hormones. One secondary data source provided information on male reproductive hormones. No primary epidemiological studies assessed endpoints related to male reproductive hormones. Conclusions from reviews with results that overlap with Lemasters et al. (1999) are summarized in Table D-6 in Appendix D on page 310.

Table 2-13. Number of Studies Reporting on the Acute and Long-term Male Reproductive Health Outcomes Following Jet Fuel Exposures.

Health Outcomes	Acute[a]	Long-term[b]	Total Unique Studies
Semen parameters [c]	1	1	1

[a]Acute health outcomes are considered those that were measured within 6 months of exposure.
[b]Long-term health outcomes are considered those that were measured at least 6 months after exposure.
[c]Semen parameters include sperm length, sperm width/length, percent motile sperm, straight line velocity and linearity.

2.10.2. Acute Male Reproductive Health Outcomes

2.10.2.1. Semen Parameters

In a cohort study of male aircraft maintenance workers at an Air Force installation in the United States, job categories were used as a proxy for exposure to JP-4 (Lemasters et al., 1999). Exposed flight line workers had significantly increased sperm concentrations at 15 weeks of employment compared to baseline (see Table C-6 in Appendix C on page 278). No differences were observed in the exposed and unexposed groups for other acute sperm parameters, including sperm length, sperm width/length, percent motile sperm, straight line velocity and linearity, at 15 weeks of employment compared to baseline.

2.10.2.2. Reproductive Hormones

The review identified no studies with primary data examining the association between jet fuel exposure and male reproductive hormones. The USAF JP-8 final risk assessment of acute exposure to jet fuel (Kendall et al., 2001) summarized a study that observed increased serum levels of follicle stimulating hormone (FSH) in exposed workers compared to unexposed workers. Exposed workers were male tank-entry personnel with at least 9 months of persistent exposure to jet fuel (i.e., 1-hour entry, twice a week, validated against shop records). There was no evidence of an association between jet fuel exposure and serum levels of testosterone, estradiol, LH and prolactin.

2.10.3. Long-term Male Reproductive Health Outcomes

2.10.3.1. Semen Parameters

In the same cohort study of male aircraft maintenance workers at an Air Force installation, Lemasters et al. (1999) assessed semen parameters at 30 weeks of employment. The study found significantly increased sperm concentrations compared to baseline in-flight line workers and significantly decreased sperm linearity compared to baseline in jet fuel workers (see Table C-6 on page 278). No differences were observed for either group for other sperm parameters, including sperm length, sperm width/length, percent motile sperm and straight-line velocity, at 30 weeks of employment compared to baseline.

2.10.4. Summary of Male Reproductive Health Outcomes by Duration of Exposure

Lemasters et al. (1999) presented results by duration of employment, a proxy for duration of exposure. Male reproductive health outcomes were assessed at baseline, or before subjects initiated a job with jet fuel exposure, after 15 weeks of employment and after 30 weeks of employment. In the flight line crew exposure group, sperm concentrations significantly increased over the 30 weeks.

The USAF JP-8 final risk assessment (Kendall et al., 2001) summarized a study of participants that were persistently exposed to jet fuel for at least 9 months. However, there was no further discussion of exposure duration as the risk assessment was focused on acute exposures.

2.10.5. Conclusion

The evidence examining the association between jet fuel exposure and reproductive health outcomes in males is considered indeterminate due to the limited number of quality studies examining this association (see Table 2- on page 99). Lemasters et al. (1999) observed increases in sperm concentrations in-flight line workers with increasing jet fuel exposure when comparing outcomes at baseline and after 15 and 30 weeks of employment. There was decreased sperm linearity in jet fuel workers at 30 weeks compared to baseline, but no other differences were observed (Lemasters et al., 1999). In a separate study, serum FSH levels were elevated in exposed workers compared to unexposed JP-8 USAF workers (Kendall et al., 2001), but no differences were found for other male reproductive health outcomes. While lower levels of sperm concentration and FSH have been linked to infertility, it is unknown whether the decrements observed in this review are of sufficient magnitude to reduce male fertility.

No studies provided information indicating immediate male reproductive health outcomes were associated with an increased risk of subsequent male reproductive health outcomes. In addition, data were insufficient to assess the risks of adverse male reproductive health outcomes by duration of exposure. While some studies provided information on duration of employment or exposure, duration was not always directly considered in risk estimates. Additional studies are needed to better understand male reproductive health outcomes that are related to jet fuel exposure and how risk changes with duration of exposure.

Table 2-14 Summary of Male Reproductive Health Outcomes Associated With Jet Fuel Exposure.

Studies and Interpretation	Summary and Key Findings	Factors That Increase Certainty	Factors That Decrease Certainty	Summary Judgment
Acute Health Outcomes[a]				⊙⊙⊙ Indeterminate One low confidence study reported changes in male reproductive health outcomes with jet fuel exposure. Directions of effect were inconsistent between acute and long-term health outcomes. Uncertainty remains due to the limited number of quality studies examining male reproductive health outcomes.
Semen parameters 1 Low confidence study	One low confidence study in male USAF employees observed significantly increased sperm concentrations in-flight line workers at 15 weeks of employment compared to baseline.	• No factors noted	• Limited number of studies examining health outcome • Low confidence study	
Long-term Health Outcomes[b]				
Semen parameters 1 Low confidence study	One low confidence study in male U.S. Airforce employees observed significantly increased sperm concentration in-flight line workers at 30 weeks of employment and significantly decreased linearity in jet fuel workers at 30 weeks of employment.	• No factors noted	• Limited number of studies examining health outcome • Low confidence study	

USAF = United States Air Force.

[a]Acute health outcomes are considered those that were measured within 6 months of exposure.

[b]Long-term health outcomes are considered those that were measured at least 6 months after exposure.

2.11. Renal Health Outcomes

2.11.1. Summary of Renal Health Outcomes

Jet fuel exposure may impact renal health due to the potential for dermal and inhalational exposure. Renal health may be assessed by measuring serum or urinary biomarkers (e.g., creatinine, blood urea nitrogen (BUN), albumin, total urinary proteins or proteinuria) as indicators of the kidney's ability to filter out substances from blood. Glomerular filtration rate is a measure of the speed at which the kidneys filter out substances from blood and acute renal failure indicates that the kidneys are unable to filter out waste products from blood. Urinary alpha- or pi-glutathione s-transferase (GST) are used as indicators of early damage to the proximal and distal tubules in the kidney, respectively.

Two low confidence studies that examined the associations between jet fuel exposure and renal health outcomes were identified (Olsen et al., 1998; Tu et al., 2004). Both studies used adequate outcome ascertainment and analysis methods. Sources of potential bias included a lack of quantitative exposure measurement methods (Olsen et al., 1998), potential for selection bias (Olsen et al., 1998; Tu et al., 2004), residual confounding due to lack of consideration of key confounders, such as socioeconomic status (Olsen et al., 1998; Tu et al., 2004) or smoking and alcohol use (Tu et al., 2004) and low sensitivity due to small sample size (Olsen et al., 1998) (see Figure 2-7 below). Three secondary data sources and two case reports were identified that reported on renal health outcomes and acute or long-term jet fuel exposure.

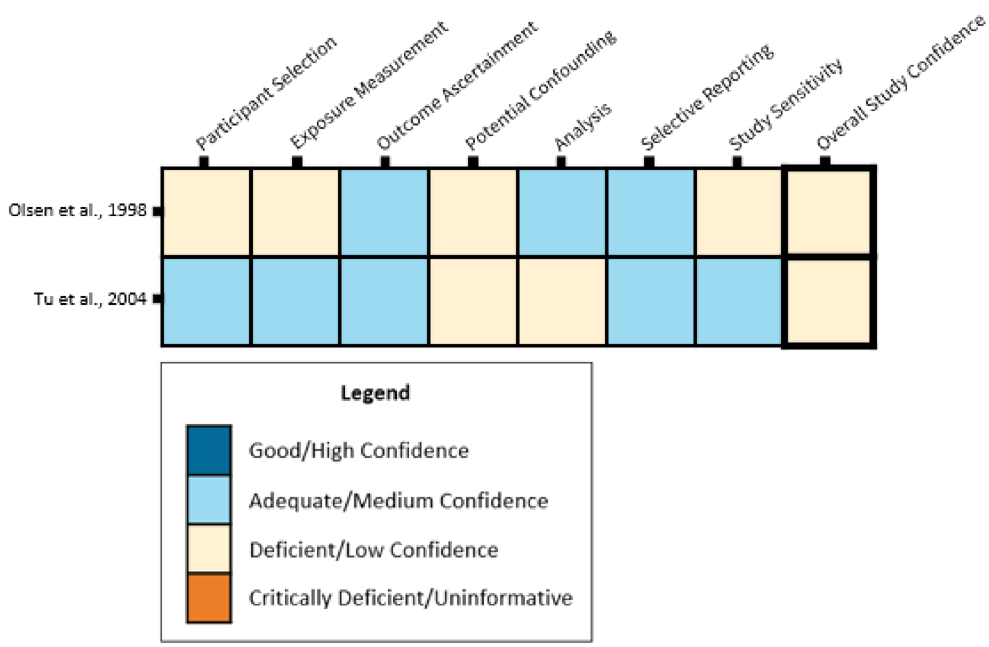


Figure 2-7. Study Quality Evaluations for Epidemiology Studies of Jet Fuel Exposure and Renal Health Outcomes.

Table 2- below summarizes the number of studies with acute (e.g., measurement taken within 6 months of jet fuel exposure) and long-term (e.g., measurement taken after at least 6 months of jet fuel exposure) renal health outcomes. Two low confidence studies (Olsen et al., 1998; Tu et al., 2004) assessed acute kidney function as measured by serum or urinary biomarkers. No studies assessed long-term renal health outcomes.

Table 2-15. Number of Studies Reporting on the Acute and Long-term Renal Health Outcomes Following Jet Fuel Exposures.

Health Outcomes	Acute[a]	Long-term[b]	Total Unique Studies
Kidney function, measured by serum or urinary biomarkers [c]	2	0	2

[a]Acute health outcomes are considered those that were measured within 6 months of exposure.
[b]Long-term health outcomes are considered those that were measured at least 6 months after exposure.
[c]Kidney function measures include blood urea nitrogen (BUN), creatinine, color, appearance, pH, ketone bodies, bilirubin, glucose and hemoglobin.

2.11.2. Acute Renal Health Outcomes

2.11.2.1. Kidney Function, Measured by Serum or Urinary Biomarkers

A low confidence study examined complete blood count parameters in a cohort of active-duty and civilian personnel at Hill Air Force Base, Utah (Olsen et al., 1998). Personnel were assigned to exposed and unexposed groups based on job duties. The study evaluated kidney function 4 times over a period of 18 months starting at the transition from JP-4 to JP-8 (baseline) and at 3, 6 and 18 months after conversion to JP-8. BUN and creatinine levels were not different in the exposed compared to the unexposed group at any time point (see Table C-7 in Appendix C on page 281). The study conducted air sampling to assess exposure to exact vapor, aerosol and particulate components of JP-8, although these data were not used in the statistical analyses of renal health outcomes. The study reported that exposure to vapors of JP-8 were extremely low and there was no detectable benzene exposure.

A low confidence study examined urinary biomarkers of kidney function in 63 volunteers at the Warfield Air National Guard Base in Essex, Maryland (Tu et al., 2004). Participants were grouped by their potential exposure to JP-8, with one group of participants who had direct contact with jet fuel (fuel cell workers, fuel specialists, mechanics and crew chiefs) and another group of incidental workers who were not expected to be in contact with jet fuel (supply workers, environmental officers and engineers working with non-fuel aspects of aircraft maintenance). There were no observed differences in urinalysis results that were related to JP-8 exposure. The use of PPE for two job titles with the highest exposure levels, fuel cell workers (i.e., inhalation exposure) and fuel specialists (i.e., dermal exposure), was discussed. Respirators and gloves were provided for the fuel cell workers and fuel specialists, respectively; however, it was noted that fuel cell workers commonly switched tasks during the day, which involved removing the respirator and the clothing of fuel specialists that was commonly soaked with fuel, suggesting potential for exposure despite implementing PPE measures in both cases.

Two risk assessments (Kendall et al., 2001; NRC, 2003) and two case reports examined kidney function as measured by urinary biomarkers. The JP-8 final risk assessment of acute exposure to jet fuel conducted by the AFIOH summarized several studies on tank-entry personnel with at least 9 months of persistent exposure to JP-8 (Kendall et al., 2001).The risk assessment reported an analysis of 107 healthy active-duty employees with 3 levels of JP-8 exposure: highly exposed fuel system repair workers with at least 9 months of persistent exposure (routinely enter fuel tank for at least an hour twice a week); moderately exposed workers with regular physical contact through activities, such as fuel handling, distribution, recovery and testing and unexposed workers whose job did not involve routine contact with fuels (Kendall et al., 2001). Work shifts were a minimum of 4 hours and exposure was confirmed using breathing zone measures of benzene and naphthalene. The analysis observed similar pre- vs. post-shift levels of urinary alpha- or pi-GST, which were in the normal range. Highly exposed individuals had significantly higher levels of urinary creatinine in their post-shift samples compared to unexposed individuals, although the mean values of creatinine still fell within the normal range of 0.25-4.0 milligram/milliliter (mg/mL) (Kendall et al., 2001). In a sample of 316 healthy active-duty personnel from the AFIOH, no differences were observed in urinary alpha- or pi-GST levels in participants with different genetic variants in three toxicant metabolizing enzymes. These three genetic variants were evaluated as risk factors for developing acute toxicity from jet fuel exposure.

Two case reports examined patients self-reporting inhalation and dermal exposure to jet fuels. One reported on a man who self-reported exposure to jet fuels in the aviation industry as an aircraft refueler; serum chemistry analysis showed elevated levels of BUN and creatinine that were approximately 20 times over the normal limits and indicative of kidney failure (Salam et al., 2020). A second case report presented a man with self-reported occupational exposure to jet fuel, although the exact industry and job function were not specified. The man had elevated serum creatinine levels, a slowed clearance of creatinine and a high degree of proteinuria, all of which are indicators of impaired kidney function (Alsuwaida, 2010).

2.11.2.2. Kidney Function, Measured by Glomerular Filtration Rate

The review identified no studies with primary data that examined the association between jet fuel exposure and decreased kidney function as measured by decreased glomerular filtration rate. The two case reports described above reported decreased glomerular filtration rates among an aircraft refueller (Salam et al., 2020) and a man self-reporting occupational exposure to jet fuels (Alsuwaida, 2010).

2.11.2.3. Acute Renal Failure

The review identified no studies with primary data that examined the association between jet fuel exposure and acute renal failure.

The JP-8 final risk assessment of acute exposure to jet fuel conducted by the AFIOH summarized studies that reviewed medical record information to determine if differences exist in health care encounter rates when JP-8-exposed workers were compared to those who do not routinely encounter jet fuel in the performance of their duties. An analysis of 265 active-duty personnel from the JP-8 final risk assessment reported no significant differences in urogenital complaints (as measured by medical record review) across the three levels of jet fuel exposure, as described above (Kendall et al., 2001).

Also reported in the JP-8 final risk assessment was a larger analysis of 5,706 randomly sampled active-duty personnel whose duties involved working with jet fuel compared to 5,706 active-duty personnel whose duties involved minimal or no exposure to jet fuel and used data from the Air Force Personnel Center's electronic medical records system. Five exposure groups were considered: 0 (personnel/administration workers), 1 (services and supply workers), 2 (civil engineers), 3 (re-fuelers; fuel vehicle maintenance workers and those who work with petroleum, oil and lubricants) and 4 (fuel cell workers). No significant differences were observed in genitourinary-related illnesses across the five exposure groups for males or females.

A report by the NRC Subcommittee on Permissible Exposure Levels for Military summarized a case study of a 44-year-old worker with kidney failure after "acute exposure" to an unspecified jet fuel mixture (NRC, 1996).

The two case reports described above reported physician-diagnosed acute renal failure in two men with self-reported inhalation and dermal exposure to jet fuels (Alsuwaida, 2010; Salam et al., 2020).

2.11.3. Summary of Renal Health Outcomes by Duration of Exposure

There was limited discussion of duration of exposure in the reviewed literature. Olsen et al. (1998) measured biomarkers of kidney function in active-duty and civilian workers at Hill Air Force Base at transition from JP-4 to JP-8 (baseline) and at 3, 6 and 18 months after a conversion to JP-8. There was no significant difference in mean BUN and creatinine across time points. Tu et al. (2004) also measured biomarkers of kidney function in members of the Air National Guard who were reported to have long-term exposure to JP-8; however, all renal outcomes were measured concurrently with exposure. The JP-8 final risk assessment of acute exposure to jet fuel conducted by the AFIOH summarized the findings of a study that included exposed participants with at least 9 months of persistent exposure to jet fuels. However, the evaluated health outcomes were measures of acute renal toxicity only, results were not presented by exposure duration and there was no discussion of how duration may influence renal health outcomes (Kendall et al., 2001). The 2003 NRC toxicologic assessment (NRC, 2003) also did not mention exposure duration in detail. None of the risk assessments identified evidence of renal toxicity.

2.11.4. Conclusion

Two low confidence studies examined acute renal health outcomes associated with jet fuel exposure (Olsen et al., 1998; Tu et al., 2004) and no studies examined long-term renal health outcomes (see Table 2-2 on page 105). Overall, the evidence examining the association between jet fuel exposure and renal outcomes is considered indeterminate, due to the very limited number of studies examining this health outcome category. Both primary studies were of low confidence and observed no significant differences in serum or urinary biomarkers of kidney function in those exposed compared to those unexposed.

No studies provided information indicating that immediate renal symptoms were associated with an increased risk of subsequent renal health outcomes. In addition, data were insufficient to assess the risks of adverse renal health outcomes by duration of exposure. While some studies provided information on duration of exposure, duration was not always directly considered in risk estimates. Additional studies are needed to better understand specific renal health outcomes that are related to jet fuel exposure and how risk changes with duration of exposure.

Table 2-26 Summary of Renal Health Outcomes Associated With Jet Fuel Exposure.

Studies and Interpretation	Summary and Key Findings	Factors That Increase Certainty	Factors That Decrease Certainty	Summary Judgment
Acute Health Outcomes[a]				⊙⊙⊙ Indeterminate Evidence was limited to two low confidence studies reporting kidney function parameters between exposed and unexposed groups.
Kidney function 2 Low confidence studies	One low confidence study of active-duty and civilian Air Force personnel found no differences in serum or urinary biomarkers of kidney function between workers exposed versus unexposed to JP-4 and JP-8. One low confidence study of Air National Guard members found no association between JP-8 exposure and kidney function.	• No factors noted	• Limited number of studies examining this health outcome • Low confidence studies	

[a]Acute health outcomes are considered those that were measured within 6 months of exposure.

2.12. Cardiovascular Health Outcomes

2.12.1. Summary of Cardiovascular Health Outcomes

Jet fuel exposure may affect cardiovascular health due to inhalation exposure. Cardiovascular health can be evaluated using events (such as myocardial infarction and heart failure), subclinical measures (such as blood pressure, arrhythmias, atherosclerosis or arterial stiffness) and vascular function and biomarkers (such as lipoproteins, lipids, inflammatory markers and troponins).

This review identified one primary study, rated as uninformative, that examined jet fuel exposure and a cardiovascular health outcome (Knave et al., 1978) (see Figure 2-8 **below**). Limitations of this study included potential for selection bias due to selection of exposed participants by a “committee,” potential for exposure misclassification due to lack of quantitative measurements, self-reported health outcomes, non-specificity of the health outcomes (self-reported palpitations may be related to stress, anxiety or other concerns, as well as cardiac issues) and potential for residual confounding due to the lack of consideration of important covariates, such as alcohol use.

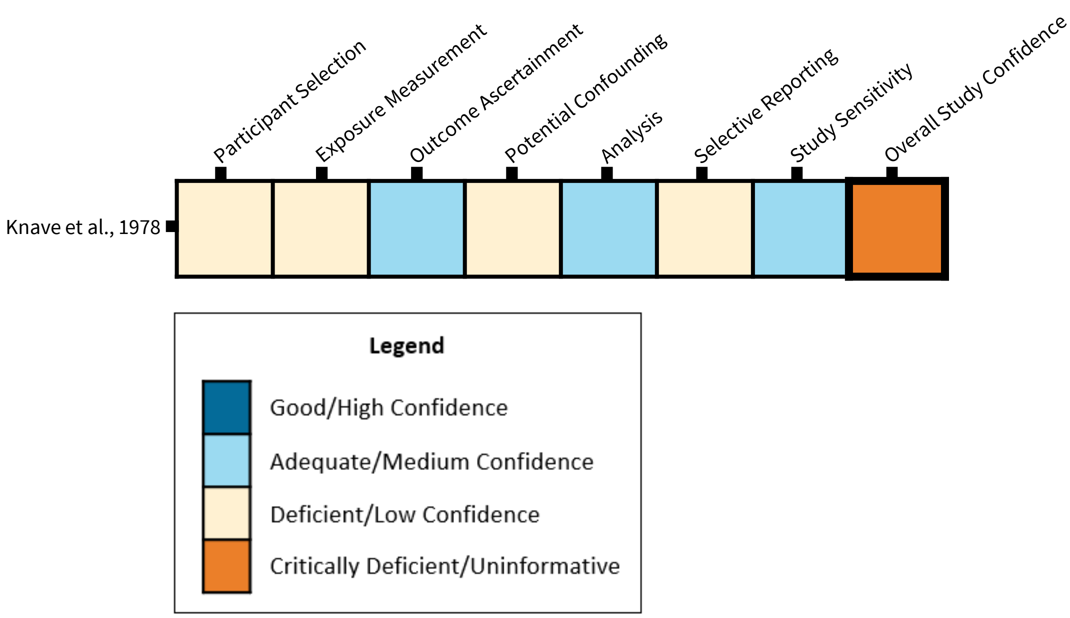


Figure 2-8. Study Quality Evaluations for Epidemiology Studies of Jet Fuel Exposure and Cardiovascular Health Outcomes.

Table 2- on page 107 summarizes the single study with acute (e.g., measurement taken within 6 months of jet fuel exposure) cardiovascular health outcomes. One study assessed acute palpitations, which include perceived fast, hard or irregular heartbeats. No studies were identified with primary data on the association between jet fuel

exposure and long-term cardiovascular health outcomes (e.g., measurements taken after at least 6 months of jet fuel exposure or occurring over multiple months).

Three secondary reports, including a risk assessment (Kendall et al., 2001) and two reviews (NRC, 2003; Ritchie et al., 2003), summarized additional evidence on the association between exposure to jet fuel and cardiovascular health. Two case reports also described transient elevations in blood pressure in individuals following acute jet fuel exposures (Alsuwaida, 2010; Porter, 1990).

Table 2-17. Number of Studies Reporting on the Acute and Long-term Cardiovascular Health Outcomes Following Jet Fuel Exposures.

Health Outcomes	Acute [a]	Long-term [b]	Total Unique Studies
Palpitations [c]	1	0	1

[a]Acute health outcomes are considered those that were measured within 6 months of exposure.
[b]Long-term health outcomes are considered those that were measured at least 6 months after exposure.
[c]Palpitations include perceived fast, hard or irregular heartbeats.

2.12.2. Acute Cardiovascular Health Outcomes

2.12.2.1. Cardiovascular Symptoms

A cross-sectional study of 60 workers at a Swedish jet motor factory compared workers exposed to unspecified jet fuels to unexposed controls (Knave et al., 1978). Exposed workers self-reported experiencing significantly more palpitations or a feeling of "thoracic oppression" than unexposed workers (see Table C-8 in Appendix C on page 283). Health outcomes were reported as acute symptoms upon exposure. Exposed workers had an exposure duration ranging between 2 and 32 years and had been employed an average of 17.7 years compared to 19.8 years for the unexposed group. The frequency, number and duration of palpitation episodes was not described, nor was the timing of episodes in relation to exposure patterns. Diagnostic follow-up to evaluate self-reported palpitations (e.g., electrocardiograms) was not discussed.

Two secondary sources reported cardiovascular symptoms associated with jet fuel exposure. A JP-8 Final Risk Assessment (Kendall et al., 2001) reported on the prevalence of self-reported heart palpitations and chest tightness over the preceding 6 months among 328 healthy, active-duty Air Force personnel. Exposure to JP-8 was classified based on job function. The study excluded individuals with autoimmune disease, cancer or diabetes and those using immune system-altering drugs. Three occupational jet fuel exposure groups were compared: (i) highly exposed fuel tank workers with at least 9 months of persistent exposure to JP-8; (ii) moderately exposed workers engaged in activities, such as fuel handling, distribution, recovery and testing; and (iii) unexposed workers whose jobs did not involve routine contact with fuels (e.g., administrative staff). Fuel tank worker exposure involved at least 1-hour tank entry at least twice a week. The prevalence of self-reported symptoms in the high, moderate and unexposed exposure groups was 39.7%, 52.3% and 17.2%, respectively, for chest tightness and 19.7%, 32.6% and 6.4%, respectively, for heart palpitations. Those in the moderately exposed group tended to report significantly more symptoms than those in the high and low exposure groups. Compared to unexposed workers, highly exposed and moderately exposed workers were 3.6 and 7 times more likely to have reported heart palpitations, respectively. Compared to unexposed workers, highly exposed and moderately exposed workers were 3.16 and 5.26 times more likely to report chest tightness, respectively (see Table C-8 on page 283).

A key issue is that perceived health risks related to jet fuel exposure could influence the occurrence and self-reporting of symptoms. In this assessment, workers exposed to JP-8 routinely or occasionally were more likely to believe past and current work was impacting their health (58.1%, 54.8% and 13.2%, respectively, for the high, moderate and unexposed exposure groups).

The JP-8 Final Risk Assessment report (Kendall et al., 2001; NRC, 2003) also described an analysis of data from electronic medical records comparing ambulatory care visits over the previous year in Air Force workers with and without JP-8 exposures (5,706 personnel per group). Only the first visit for each health issue was counted. Rates of circulatory system visits were similar across exposure groups, even when assessing males and females separately.

When health encounters were abstracted from the medical records review in a subset of 265 personnel, the mean number of visits for cardiovascular conditions in the males were similar in the high, medium and low exposure groups and there were no cardiovascular-related visits for the females. There was no information on specific conditions included in the circulatory and cardiovascular conditions.

2.12.2.2. Blood Pressure

A case report described mildly elevated blood pressure in one Navy aviator who had been intoxicated by JP-5 fuel vapors during a training flight. The aviator recovered completely over the next 4 days (Porter, 1990). A second case report presented a man with self-reported occupational exposure to unspecified type of jet fuel by inhalation and direct skin contact for 1 week prior to his illness (Alsuwaida, 2010). The exact industry and job function were not specified. The patient was given antihypertensive medication, which was stopped after 1 week. Neither report discussed longer-term follow-up.

2.12.3. Summary of Cardiovascular Health Outcomes by Duration of Exposure

There was limited discussion of duration of exposure in the reviewed literature. In Knave et al. (1978), exposed jet motor factory workers had been employed for a mean of 17.7 years, but there was no discussion of symptom patterns associated with longer employment. The JP-8 final risk assessment of acute exposure to jet fuel conducted by the AFIOH did not describe whether the frequency of medical visits or self-reported symptoms varied by exposure or employment duration in highly compared to less-exposed job functions (Kendall et al., 2001).

2.12.4. Conclusion

There is very limited evidence available on jet fuel exposure and cardiovascular health. This review identified only one primary study, considered uninformative (Knave et al., 1978) reporting elevated frequencies of heart palpitations or thoracic pressure in jet motor factory workers compared to unexposed workers (see Table 2- on page 110). Self-reported palpitations and chest tightness were associated with unspecified types of jet fuel exposure. In Air Force personnel, there was evidence of increased self-reported palpitations and chest tightness during the past 6 months in those highly and moderately exposed to JP-8 compared to those unexposed (Kendall et al., 2001). However, these associations may reflect the perception that jet fuel exposure affects cardiovascular health rather than a causal relationship. Palpitations and chest tightness, in the absence of diagnostic confirmation and further detail, are not uniquely specific to cardiovascular health. An analysis of medical records in Air Force personnel was inconsistent with the self-reported data, since these medical record records did not indicate any association between health care visits for circulatory and cardiovascular complaints and occupational jet fuel exposure (Kendall et al., 2001).

Two case reports observed mild, transient elevations in blood pressure following acute exposures via inhalation to JP-5 in a Navy pilot (Porter, 1990) and via inhalation and dermal to unspecified jet fuel in an unspecified occupational setting (Alsuwaida, 2010). Both patients recovered completely in a short amount of time, and there was no indication that these short-term symptoms had long-term consequences. A review by Ritchie et al. (2003) discussed the lack of literature on components of jet fuels and cardiovascular health in humans. The review noted that "[l]iterally all personnel working at military bases with aircraft, on military aircraft carriers or at commercial airports experience jet fuel exhaust on a daily basis." (Ritchie et al., 2003). Ubiquitous exposure and background risks pose serious challenges to evaluating health outcomes of fuel combustion exhaust (which are not unique to jet fuels) in populations occupationally exposed to jet fuels.

The evidence examining the association between jet fuel exposure and cardiovascular health is considered indeterminate, due to the limited data. No studies provided information indicating immediate cardiovascular health outcomes were associated with an increased risk of subsequent cardiovascular health outcomes. In addition, data were insufficient to assess the risks of adverse cardiovascular health outcomes by duration of exposure. While some studies provided information on duration of employment, duration was not always directly considered in risk estimates. Additional studies are needed to better understand cardiovascular disease risk that might be related to jet fuel exposure and how risk changes with duration of exposure.

Table 2-18. Summary of Cardiovascular Health Outcomes Associated With Jet Fuel Exposure.

Studies and Interpretation	Summary and Key Findings	Factors That Increase Certainty	Factors That Decrease Certainty	Summary Judgment
Acute Health Outcomes[a]				
Cardiovascular symptoms 1 Uninformative study	One uninformative study of Swedish jet motor factory workers observed significantly more frequent self-reported heart palpitations or thoracic pressure in exposed compared to unexposed workers.	• No factors noted	• Limited number of studies examining this health outcome • Uninformative study	⊙⊙⊙ Indeterminate Evidence was limited to one uninformative study reporting the frequency of non-specific self-reported symptoms of heart palpitations.

[a]Acute health outcomes are considered those that were measured within 6 months of exposure.

2.13. Digestive Health Outcomes

2.13.1. Summary of Digestive Health Outcomes

Jet fuel exposure may impact digestive health due to the potential for oral exposures, such as accidental ingestion. Assessment measures for digestive health include self-reported symptoms and history, as well as physical examination. Digestive health outcomes include nausea, gastritis, diarrhea and vomiting.

Of the four studies examining the association between jet fuel exposure and digestive health outcomes, one was considered low confidence (Yang et al., 2003) and three were considered uninformative (Knave et al., 1978; Knave et al., 1976; Olsen et al., 1998) (see Figure 2-9 on page 110).

The low confidence study used adequate participant selection and analysis strategies and adjusted for important confounding variables, such as smoking and previous occupational dust or fume exposure (Yang et al., 2003). However, sources of potential bias in this study included the lack of a quantitative exposure measure and the use of self-reported health outcome measures. In addition, as this study did not include a quantitative exposure measure, it is not possible to determine whether there was sufficient contrast in exposure levels between the exposed and unexposed groups (i.e., adequate study sensitivity).

Among the three studies considered uninformative, sources of potential bias included the participant selection approach (Knave et al., 1978; Knave et al., 1976; Olsen et al., 1998), exposure measurement methods (Knave et al., 1978; Knave et al., 1976; Olsen et al., 1998), outcome ascertainment methods (Knave et al., 1978; Olsen et al., 1998), potential for residual confounding (Knave et al., 1978; Knave et al., 1976; Olsen et al., 1998), analysis strategy (Knave et al., 1976); selective reporting (Knave et al., 1978) and low sensitivity due to small sample size (Knave et al., 1976; Olsen et al., 1998).

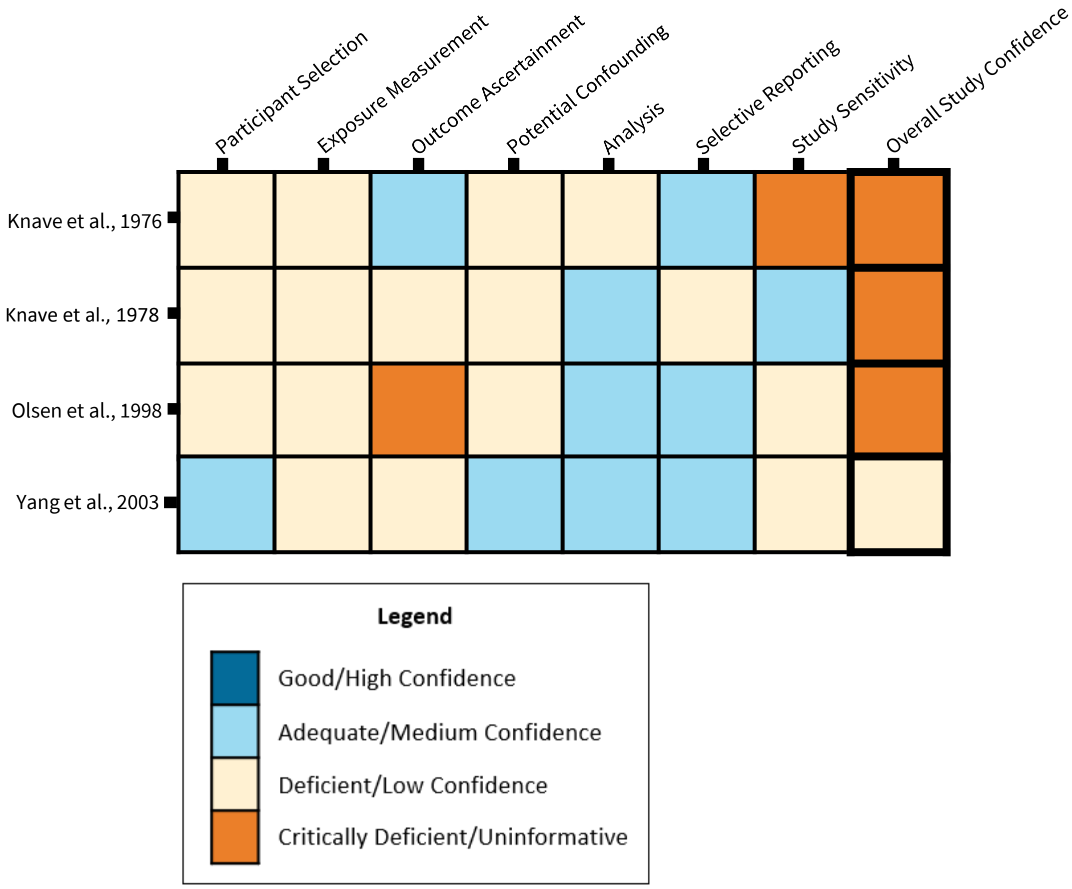


Figure 2-9. Study Quality Evaluations for Epidemiology Studies of Jet Fuel Exposure and Digestive Health Outcomes.

Table 2- on page 113 summarizes the number of studies with acute (e.g., measurement taken within 6 months of jet fuel exposure) and long-term (e.g., measurement taken after at least 6 months of jet fuel exposure) digestive health outcomes.

Three studies (Knave et al., 1978; Knave et al., 1976; Yang et al., 2003) examined acute nausea and gastrointestinal symptoms, including gastritis. One study examined acute diarrhea and vomiting (Olsen et al., 1998). No studies examined long-term digestive health outcomes.

Several secondary reports and case studies provided information on acute nausea and gastrointestinal symptoms following jet fuel exposure (EASA, 2017; Karanikas et al., 2021; Lombardi & Lurie, 1957; NRC, 1996; Porter, 1990; Ritchie et al., 2003; Salam et al., 2020; Wang, 2004), as well as on acute diarrhea and vomiting (EASA, 2017; Wang, 2004). Conclusions from reviews with results that overlap with the primary studies are summarized in Table D-7.

Table 2-19. Number of Studies Reporting on the Acute and Long-term Digestive Health Outcomes Following Jet Fuel Exposures.

Health Outcomes	Acute[a]	Long-term[b]	Total Unique Studies
Nausea and gastrointestinal symptoms [c]	3	0	3
Diarrhea and vomiting	1	0	1

[a]Acute health outcomes are considered those that were measured within 6 months of exposure.
[b]Long-term health outcomes are considered those that were measured at least 6 months after exposure.
[c]Nausea and gastrointestinal symptoms include nausea and gastritis.

2.13.2. Acute Digestive Health Outcomes

2.13.2.1. Nausea and Gastrointestinal Symptoms

One low confidence study (Yang et al., 2003) found no evidence of an association between jet fuel exposure and acute nausea and gastrointestinal symptoms and two uninformative studies (Knave et al., 1978; Knave et al., 1976) found mixed evidence of an association. The results of all three studies should be interpreted with caution due to their confidence ratings. Specific results are detailed below.

In a cross-sectional study of male workers at Kaohsiung International Airport in Taiwan, Yang et al. (2003) observed lower odds of self-reported nausea among exposed workers compared to unexposed workers, but differences were not statistically significant (see Table C-9 in Appendix C on page 284). In this study, workers were classified as either exposed or unexposed to unspecified jet fuel based on airport job types.

In a cohort study of Swedish aircraft fuel system mechanics, Knave et al. (1976) reported a higher proportion of workers with self-reported nausea among those highly exposed to jet fuel (4/13) than those less exposed to jet fuel (2/16). While these results appear to contrast those reported by Yang et al. (2003), they are difficult to compare due to the lack of statistical testing of differences between groups in the Knave et al. (1976) study.

In a cross-sectional study of Swedish male workers at a jet motor factory, out of 30 workers exposed to unspecified jet fuels, 4 self-reported symptoms of acute nausea (Knave et al., 1978) upon exposure. When analyzing the exposed workers by job-type, 1/15 of those in jobs with greater assumed exposure to jet fuels (fuel system testers) reported nausea, compared to 3/15 of those in jobs with lesser assumed exposure (engine testers and mechanics). The frequency of self-reported acute nausea among the 30 unexposed workers was not reported and no statistical tests were conducted.

Knave et al. (1978) also assessed the association between unspecified jet fuel exposure and self-reported gastritis. Among 30 workers exposed to jet fuel, 15/30 self-reported gastritis and 22/30 had a record of gastritis in plant physician journals. The proportion of workers with gastritis was lower among a control group of 30 unexposed workers (10/30 self-reported, 15/30 recorded in plant physician journals). There was no statistical evaluation of the differences in the number of symptoms between these groups.

Several secondary sources provided information on acute nausea following exposure to unspecified jet fuels (EASA, 2017; Karanikas et al., 2021; NRC, 1996; Wang, 2004). In a systematic review of the health outcomes of aviation turbine engine oil, EASA (2017) summarized prior studies that reported nausea or gastrointestinal symptoms among flight crew, pilots and passengers on commercial and military aircraft exposed to fumes, contaminated air and aerosolized or vaporized engine oil. In a medical toxicology textbook, Wang (2004) summarized reports of nausea following acute exposure to jet fuels.

Case studies also documented acute digestive symptoms following exposure. Porter (1990) presented a case study of two aviators who experienced nausea and anorexia following acute inhalation of JP-5 exhaust. Lombardi and Lurie (1957) described a case series of 12 workers performing fuel cell maintenance at Smoky Hill Air Force Base, Kansas, one of whom reported symptoms of dyspepsia and indigestion. Salam et al. (2020) described a male aircraft refueler who presented to the emergency department with epigastric pain, nausea and vomiting. The refueler reported wearing a respiratory mask approximately 60% of the time during refueling and further reported skin contact with jet fuels on the arms despite wearing gloves, suggesting jet fuel exposure via inhalation or dermal routes.

2.13.2.2. Diarrhea and Vomiting

One uninformative study (Olsen et al., 1998) examined self-reported nausea and vomiting in a cohort of 36 active-duty and civilian personnel at Hill Air Force Base who were classified as exposed or unexposed to jet fuel based on job duties. Unexposed personnel were matched to exposed personnel on age and sex. Self-reported health outcomes were assessed on a scale from 0 (never happens) to 5 (every day) at the transition from JP-4 to JP-8 (baseline), as well as 6 and 18 months after conversion to JP-8 fuel. There was no evaluation of differences between groups at specific time points; however, the study reported that there were no significant trends across time points.

Some secondary sources provided information on acute vomiting following exposure to unspecified jet fuels (EASA, 2017; Wang, 2004). A systematic review of the health outcomes of aviation turbine engine oil (EASA, 2017) summarized a prior study of a pilot flying a military aircraft who experienced acute vomiting after exposure to aerosolized or vaporized engine oil. In a medical toxicology textbook, Wang (2004) reported that acute exposure to jet fuels causes vomiting.

2.13.3. Long-term Digestive Health Outcomes

The review identified no studies assessing the association between jet fuel exposure and long-term digestive health outcomes.

2.13.4. Summary of Digestive Health Outcomes by Duration of Exposure

There was limited discussion of duration of exposure in the reviewed literature. Olsen et al. (1998) assessed self-reported nausea and vomiting in active-duty and civilian workers at Hill Air Force Base at the transition from JP-4 to JP-8 and at 6 and 18 months after a conversion to JP-8 fuel. While means of symptom frequency, as measured by a self-reported scale, among exposed and unexposed participants were reported at each time point, no statistical comparisons were provided that would allow conclusions to be drawn about JP-4 or JP-8 exposure duration and its influence on subsequent digestive health outcomes.

Two uninformative studies (Knave et al., 1978; Knave et al., 1976) included discussion of duration of employment or exposure but did not present results by varying duration or discuss how duration may influence digestive health. Among participants in the Knave et al. (1976) study, all 29 exposed workers had at least 5 years of exposure during employment, but duration of exposure was not discussed further in the study. Knave et al. (1978) reported that the exposure duration among exposed workers ranged from 2 to 32 years (mean: 17.1 years, median: 18.5 years). The most highly exposed subjects were selected for the exposed group after consideration of intensity and duration of exposure.

2.13.5. Conclusion

Of the four studies that examined digestive health outcomes, two uninformative studies provided limited evidence of an association between unspecified jet fuel exposure and acute nausea (Knave et al., 1976) and gastritis (Knave et al., 1978) (see Table 2- on page 116). The results of these studies should be interpreted with caution due to their uninformative confidence ratings. Knave et al. (1978) also reported the frequency of self-reported nausea among exposed workers but did not provide a comparison to an unexposed group. Two other studies (Olsen et al., 1998; Yang et al., 2003) found no evidence of an association with digestive health outcomes. No studies provided information indicating that immediate digestive health outcomes were associated with an increased risk of subsequent digestive health outcomes. In addition, data were insufficient to assess the risks of adverse digestive health outcomes by duration of exposure. While some studies provided information on duration of employment or exposure, duration was not always directly considered in risk estimates.

In summary, the evidence for an association between digestive health outcomes and jet fuel exposure is considered indeterminate, due to the low quality and limited number of studies examining this health outcome category. Additional studies are needed to better understand specific digestive health outcomes that are related to jet fuel exposure and how risk changes with duration of exposure.

Table 2-20 Summary of Digestive Health Outcomes Associated With Jet Fuel Exposure.

Studies and Interpretation	Summary and Key Findings[a]	Factors That Increase Certainty	Factors That Decrease Certainty	Summary Judgment
Acute Health Outcomes[b]				⨀⨀⨀ Indeterminate Evidence was limited to one low confidence and three uninformative studies which reported workers exposed to jet fuels with acute and long-term digestive health outcomes.
Nausea and gastrointestinal symptoms 1 Low confidence study 2 Uninformative studies	One low confidence study of airport workers observed non-significant lower odds of self-reported nausea among exposed workers compared to unexposed workers and one uninformative study of aircraft factory workers observed a higher proportion of workers with nausea in the highly exposed category with no significance testing provided (0/3). One uninformative study of jet motor factory workers observed higher proportions of workers with self-reported and physician-diagnosed gastritis among exposed workers with no significance testing provided (0/3).	• No factors noted	• Lack of statistical comparisons • Low confidence and uninformative studies	
Diarrhea and vomiting 1 Uninformative study	One uninformative study of active-duty and civilian Air Force personnel observed similar rates of self-reported nausea and vomiting among workers exposed and	• No factors noted	• Limited number of studies examining this health outcome • Uninformative study	

Studies and Interpretation	Summary and Key Findings[a]	Factors That Increase Certainty	Factors That Decrease Certainty	Summary Judgment
	unexposed to JP-4 and JP-8 (0/1).			

[a]Health outcomes are summarized in this column by a ratio of (number of studies that found a significant association for that health outcome/the number of studies reporting on that health outcome).
[b]Acute health outcomes are considered those that were measured within 6 months of exposure.

2.14. Hepatic Health Outcomes

2.14.1. Summary of Hepatic Health Outcomes

Jet fuel exposure may impact hepatic health due to inhalation and dermal exposure. Hepatic health can be assessed using liver enzymes, imaging, or biopsy, if warranted. Common measures of liver dysfunction are aspartate aminotransferase (AST) and alanine aminotransferase (ALT), which are indicators of hepatocellular damage and alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT), which are indicators of cholestasis (i.e., partial obstruction impairing bile acid elimination).

Two low confidence studies with primary data on the association between jet fuel exposure and hepatic health (liver enzyme) outcomes were identified (Olsen et al., 1998; Tu et al., 2004) (see Figure 2-10 below). Two secondary reports (Kendall et al., 2001; NRC, 2003) also examined liver enzymes as indicators of liver function.

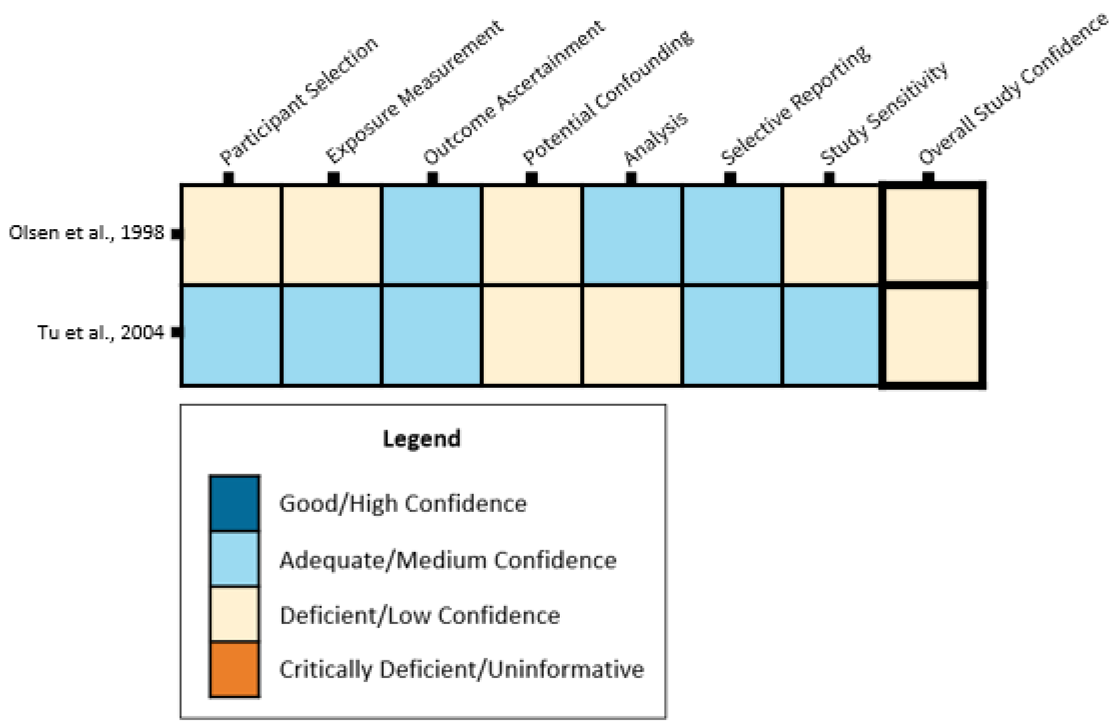


Figure 2-10. Study Quality Evaluations for Epidemiology Studies of Jet Fuel Exposure and Hepatic Health Outcomes.

Table 2- on page 119 summarizes the two studies with acute (e.g., measurement taken within 6 months of jet fuel exposure) and long-term (e.g., measurement taken at least 6 months after jet fuel exposure) hepatic health outcomes. Two studies (Olsen et al., 1998; Tu et al., 2004) examined liver enzyme changes following acute exposure. No studies examined long-term hepatic health outcomes. Several secondary reports provided information on symptoms related to liver function following jet fuel exposure (Kendall et al., 2001; NRC, 2003; Wang, 2004).

Table 2-21. Number of Studies Reporting on the Acute and Long-term Hepatic Health Outcomes Following Jet Fuel Exposures.

Health Outcomes	Acute[a]	Long-term[b]	Total Unique Studies
Liver enzymes[c]	2	0	2

[a]Acute health outcomes are considered those that were measured within 6 months of exposure.
[b]Long-term health outcomes are considered those that were measured at least 6 months after exposure.
[c]Liver enzymes include aspartate transferase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP).

2.14.2. Acute Hepatic Health Outcomes

2.14.2.1. Liver Enzymes

The review identified two studies (Olsen et al., 1998; Tu et al., 2004) with primary data that examined the association between jet fuel exposure and acute health outcomes on liver function, as measured by serum biomarkers. Two risk assessments (Kendall et al., 2001; NRC, 2003) also examined liver function, as measured by serum biomarkers.

One low confidence study measured AST, ALT and ALP in a cohort of personnel from Hill Air Force Base (Olsen et al., 1998). Exposure was assigned based on job duties and unexposed were persons defined as not exposed to jet fuel or other hydrocarbons other than gasoline. The study recruited 17 jet fuel-exposed and 18 unexposed subjects matched on gender and age within 3 years (mean age 32.3–32.8, n = 5 women, 94% Caucasian). Participants had worked on their current assignments for at least 6 months. Liver enzymes were measured up to four times: at baseline when transitioning from JP-4 to JP-8 and at 3, 6 and 18 months after JP-8 use was initiated. Mean levels of all enzymes were similar over time and when comparing exposed and unexposed groups (see Table C-10 in Appendix C on page 288). The authors stated that no significant differences in mean concentrations for any enzyme were found between exposed and unexposed groups at any time point when accounting for multiple comparisons.

A low confidence study measured concentrations of ALT, AST and GGT in blood samples from 63 volunteers at the Warfield Air National Guard Base in Essex, Maryland (Tu et al., 2004). Pre- and post-work exhaled breath samples were analyzed for concentrations of JP-8-related constituents to quantify overall exposure, with separate measures of volatile and non-volatile species as indicators of inhalation and dermal exposure, respectively. Exposure levels and patterns reflected job duties and smoking habits, as well as background exposures at Warfield Air National Guard. For example, fuel cell workers had the highest levels of JP-8 constituents and fuel specialists had the highest levels of JP-8 non-volatile during the workdays. There was some variability in the results of liver function tests, but these were not statistically related to JP-8 exposures (no data were presented). Respirators and gloves were provided for the fuel cell workers (at risk for inhalation exposure) and fuel specialists (at risk for dermal exposure), respectively; however, it was noted that fuel cell workers commonly switched tasks during the day, which involved removing the respirator and the clothing of fuel specialists was commonly soaked with fuel, suggesting potential for exposure despite implementing PPE measures in both cases.

The JP-8 risk assessment of acute exposure to jet fuel conducted by the AFIOH summarized results from a study of active-duty fuel tank-entry personnel with at least 9 months of persistent exposure to JP-8 (defined as at least 1-hour entry, twice a week) (Kendall et al., 2001). The risk assessment reported an analysis of 107 healthy active-duty employees with three levels of JP-8 exposure: highly exposed fuel system repair workers with at least 9 months of persistent exposure (routinely enter fuel tank for at least an hour twice a week); moderately exposed workers with regular physical contact through activities, such as fuel handling, distribution, recovery and testing; and unexposed workers whose job did not involve routine contact with fuels (Kendall et al., 2001). Shifts were a minimum of 4 hours and exposure was confirmed using breathing zone measures of benzene and naphthalene. The AFIOH report described similar pre- and post-shift levels of serum alpha-GST levels, which were in the normal range. There were no differences across groups after classifying personnel based on genetic variants in three toxicant metabolizing enzymes (Kendall et al., 2001; NRC, 2003). Variants of these genes could influence susceptibility to health outcomes on the liver from jet fuel exposure.

2.14.3. Long-term Hepatic Health Outcomes

2.14.3.1. Liver Enzymes

The 2003 NRC toxicologic assessment of jet fuels summarized the findings of a study in a non-military setting that evaluated liver function in 91 JP-4-exposed fuel-filling attendants who had been employed for a mean of 6.4 years compared to 47 unexposed office workers. There were no differences in AST or ALP levels within or between groups. Notably, the clearance of an anti-inflammatory drug was enhanced during JP-4 exposure compared to an exposure-free period in exposed workers, suggesting that jet fuel exposure might be an inducer of hepatic drug metabolism in humans (NRC, 2003).

A chapter on hydrocarbons in a medical toxicology book also asserts that liver function tests are usually normal following exposure to jet fuels, although exposure duration is not discussed (Wang, 2004).

2.14.4. Summary of Hepatic Health Outcomes by Duration of Exposure

There was limited discussion of duration of exposure in the reviewed literature. Repeated measures of three liver enzymes collected by Olsen et al. (1998) at baseline (JP-4) and at 3, 6 and 18 months after conversion to JP-8 did not suggest meaningful changes in liver function (Table C-10 on page 288). Similarly, Tu et al. (2004) did not discuss duration of exposure or employment. Liver enzymes were measured in a single blood sample concurrently with active JP-8 exposures.

The JP-8 final risk assessment of acute exposure to jet fuel conducted by the AFIOH summarized the findings of a study that included exposed participants with at least 9 months of persistent exposure to jet fuels; however, the evaluated health outcomes were measures of acute hepatic toxicity. Levels of serum alpha-GST were similar before and after work shifts and there were no differences compared to less exposed and unexposed personnel from the same bases. This JP-8 final risk assessment did not evaluate whether longer exposure duration affects levels of liver enzymes or other hepatic health outcomes (Kendall et al., 2001). The 2003 NRC toxicologic assessment found no differences in AST or ALT levels when comparing fuel-filling attendants employed for a mean of 6.4 years to unexposed workers (NRC, 2003). No report identified evidence of hepatic toxicity associated with longer duration of occupational exposure to jet fuels.

2.14.5. Conclusion

The limited evidence available (Kendall et al., 2001; NRC, 2003; Olsen et al., 1998; Tu et al., 2004) does not indicate adverse health outcomes of non-accidental exposure to jet fuels on liver function (see Table 2- on page 122). No studies examined whether liver health may be affected by longer durations of persistent jet fuel exposure and of studies examining health outcome measures reflecting long-term outcomes in the liver (e.g., steatosis, cirrhosis, fibrosis). The current literature evaluated only healthy individuals with ongoing exposure and these studies did not include previously exposed workers who may have changed job tasks due to sensitivity and/or symptoms or retired/separated from service.

No studies provided information indicating immediate hepatic health outcomes were associated with an increased risk of subsequent hepatic health outcomes. In addition, data were insufficient to assess the risks of adverse hepatic health outcomes by duration of exposure. Additional studies are needed to better understand specific hepatic health outcomes that are related to jet fuel exposure and how risk changes with duration and level of exposure.

Due to the limited amount of primary data, the evidence for an association between hepatic health outcomes and jet fuel exposure is considered indeterminate.

Table 2-22. Summary of Hepatic Health Outcomes Associated With Jet Fuel Exposure.

Studies and Interpretation	Summary and Key Findings	Factors That Increase Certainty	Factors That Decrease Certainty	Summary Judgment
Acute Health Outcomesa				⊙⊙⊙ Indeterminate
Liver enzymes 2 Low confidence studies	One low confidence study of active duty and civilian Air Force personnel found no differences in mean ALT, AST and ALP[b] among workers exposed versus unexposed to JP-4 and JP-8. One low confidence study of Air National Guard members found no association between JP-8 exposure and AST, ALT and GGTb.	• No factors noted	• Limited number of studies examining this health outcome • Low confidence studies	Evidence was limited to two low confidence studies reporting no differences in liver enzymes between exposed and unexposed groups.

[a]Acute outcomes are considered those that were measured within 6 months of exposure.
[b]Alanine transaminase (ALT), aspartate transferase (AST), alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT).

2.15. Hematologic Health Outcomes

2.15.1. Summary of Hematologic Health Outcomes

Jet fuel exposure may impact hematologic health due to the potential for dermal and inhalational exposure. Hematologic health may be assessed by hematology tests (for levels of calcium, erythrocytes, ferritin, fibrinogen, hematocrit, hemoglobin, iron), blood coagulation tests, Vitamin D levels, deficiency and anemia.

The review identified one low confidence study (Olsen et al., 1998) that examined the association between jet fuel exposure and acute hematologic health outcomes. The study used adequate outcome ascertainment and analysis methods. Sources of potential bias included a lack of quantitative exposure measurement methods, potential for selection bias and residual confounding due to lack of consideration of education and low sensitivity due to the small sample size (see Figure 2-11 below).

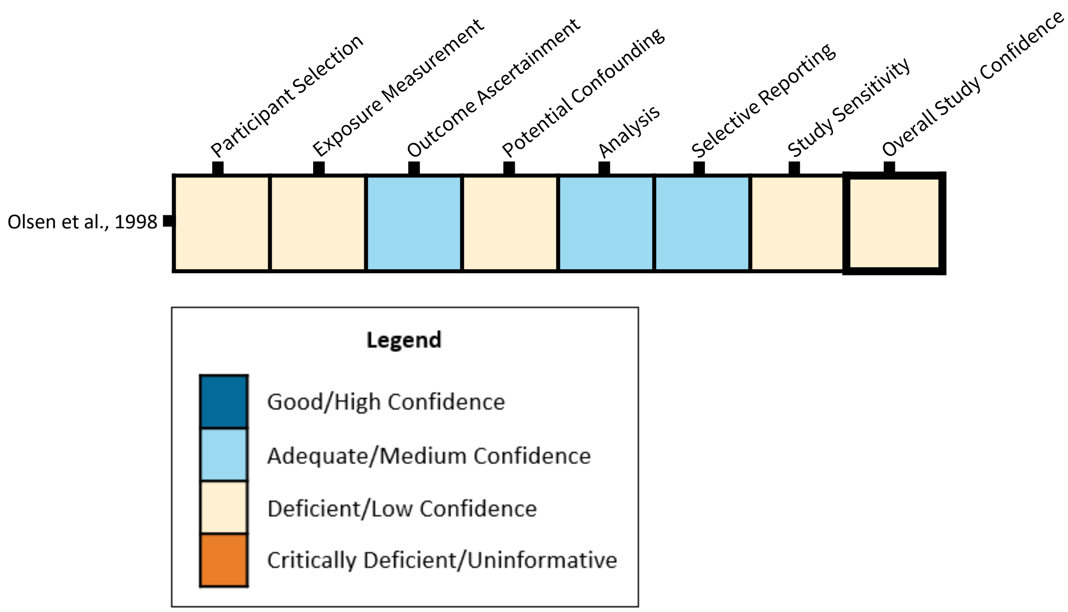


Figure 2-11. Study Quality Evaluations for Epidemiology Studies of Jet Fuel Exposure and Hematologic Health Outcomes.

Table 2- on page 124 summarizes the single study with acute (e.g., measurement taken within 6 months of jet fuel exposure) and long-term (e.g., measurement taken at least 6 months after of jet fuel exposure) hematologic health outcomes. One low confidence study assessed acute measures of anemia and whole blood hemoglobin. No studies assessed long-term hematologic health outcomes.

One case study provided information on acute blood chemistry. No studies with primary data assessed this health outcome.

Table 2-23. Number of Studies Reporting on the Acute and Long-term Hematologic Health Outcomes Following Jet Fuel Exposures.

Health Outcomes	Acute[a]	Long-term[b]	Total Unique Studies
Anemia and whole blood hemoglobin[c]	1	0	1

[a]Acute health outcomes are considered those that were measured within 6 months of exposure.
[b]Long-term health outcomes are considered those that were measured at least 6 months after exposure.
[c]Anemia and whole blood hemoglobin measures include mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), hemoglobin, red blood cells, hematocrit and platelet counts.

2.15.2. Acute Hematologic Health Outcomes

2.15.2.1. Anemia and Whole Blood Hemoglobin

One low confidence study examined complete blood count parameters in a cohort of active-duty and civilian personnel at Hill Air Force Base (Olsen et al., 1998). Personnel were assigned to exposed and unexposed groups based on job duties. The study evaluated hematologic function four times over a period of 18 months; first, at transition from JP-4 to JP-8 (baseline) and then at 3, 6 and 18 months after conversion to JP-8. Significant differences were observed for mean corpuscular volume (MCV) defined as volume of packed red cells divided by red cell count, mean corpuscular hemoglobin (MCH) defined as hemoglobin divided by red cell count and mean corpuscular hemoglobin concentration (MCHC) defined as hemoglobin divided by volume of packed red cells (see Table C-11 in Appendix C on page 291). Specifically, MCV and MCH levels were significantly lower in the exposed group than in the unexposed group at all time points. The authors hypothesized that this suggests an effect of jet fuel exposure generally rather than of JP-4 or JP-8 specifically. In contrast, MCHC values were significantly higher in the exposed group at all time points except baseline. The direction of change in these parameters across the four time points was similar in the exposed and unexposed groups, suggesting the influence of factors other than jet fuel exposure. For example, MCH and MCHC were lower at the 18-month time point than at baseline in exposed and unexposed groups. In contrast, MCV levels were higher at 6 months than at baseline in exposed and unexposed groups. The study authors suggested that factors influencing both groups may be responsible for these changes over time, such as seasonal variation, weather or pollution. Decreased in MCV and MCH and elevated MCHC may indicate low iron levels or anemia. No differences were observed between exposed and unexposed groups at any time point for hemoglobin, red blood cells, hematocrit, or platelet counts.

2.15.2.2. Blood Chemistry

The review identified no studies with primary data on the association between jet fuel exposure and blood chemistry measures.

A case study of an aircraft refueler who self-reported exposure to jet fuels documented normal serum potassium, magnesium and calcium levels, as well as slight hyponatremia (or low serum sodium) and modest hyperphosphatemia (or high serum phosphate). The refueler reported wearing a respirator approximately 60% of the time during refueling, suggesting exposure via inhalation may have taken place. The refueler also reported dermal contact with jet fuels (Salam et al., 2020).

2.15.3. Long-term Hematologic Health Outcomes

The review identified no studies assessing the association between jet fuel exposure and long-term hematologic health outcomes.

2.15.4. Summary of Hematologic Health Outcomes by Duration of Exposure

There was limited discussion of duration of exposure in the reviewed literature. Olsen et al. (1998) measured hematologic health outcomes in active-duty and civilian workers at Hill Air Force Base at transition from JP-4 to JP-8 and at 3, 6 and 18 months after a conversion to JP-8. The study observed changes in some hematologic health outcomes over time, as jet fuel exposure was ongoing in the exposed group. However, these changes occurred in exposed and unexposed study participants. The authors hypothesize that these changes were due to factors other than jet fuel exposure.

2.15.5. Conclusion

One low confidence study examined the association between jet fuel exposure and acute hematologic health outcomes (Olsen et al., 1998) and no studies examined long-term hematologic health outcomes (see Table 2- on page 126). MCV and MCH levels were lower in the exposed compared to the unexposed group at all study time points, while the average values of MCHC were higher among exposed participants at all time points except the baseline assessment. However, these findings should be interpreted with caution due to the small sample size and the potential for bias. No studies provided information indicating immediate hematologic health outcomes were associated with an increased risk of subsequent long-term hematologic health outcomes. In addition, data were insufficient to assess the risks of adverse hematologic health outcomes by duration of exposure.

Overall, the evidence for an association between adverse hematologic health outcomes and jet fuel exposure is indeterminate, due to the very limited number of studies examining this health outcome category. Additional studies are needed to better understand specific hematologic health outcomes that are related to jet fuel exposure and how risk changes with duration of exposure.

Table 2-24 Summary of Hematologic Health Outcomes Associated With Jet Fuel Exposure.

Studies and Interpretation	Summary and Key Findings	Factors that Increase Certainty	Factors that Decrease Certainty	Summary Judgment
Acute Health Outcomes[a]				⨀⨀⨀ Indeterminate Evidence was limited to one *low* confidence study reporting differences in complete blood count parameters between exposed and unexposed groups.
Anemia and whole blood hemoglobin 1 Low confidence study	One low confidence study of active-duty and civilian Air Force personnel found differences in MCV[b], MCH[b] and MCHC[b] among workers exposed versus unexposed to JP-4 and JP-8.	• No factors noted	• Limited number of studies examining this health outcome • Low confidence study	

[a]Acute health outcomes are considered those that were measured within 6 months of exposure.
[b]Mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC).

2.16. Dermal Health Outcomes

2.16.1. Summary of Dermal Health Outcomes

Jet fuel exposure may impact health due to potential for inhalation and dermal exposure. Direct dermal exposure can occur through spills on skin, clothing or gloves, or contact between fuel vapors or aerosolized fuel and skin. Dermal health outcomes include dry skin, itching, redness, rashes, scaling, cracking and blisters.

The review identified two primary epidemiological studies examining the association between jet fuel exposure and dermal health outcomes and both were considered uninformative (Olsen et al., 1998; Radhakrishnan et al., 2017). The studies were limited by multiple sources of potential bias. Olsen et al. (1998) conducted a pilot study that lacked a description of how participants were recruited. Other concerns included lack of quantitative exposure assessment among workers assumed to be unexposed, use of self-reported symptoms, potential for residual confounding by socioeconomic status, educational status, length of service or rank and low sensitivity due to the small sample size. Radhakrishnan et al. (2017) conducted a cross-sectional study of Indian Air Force ground crew limited by a potential for exposure misclassification based on occupation without confirmation by direct measurement of exposure to jet fuels. Other concerns included potential for residual confounding related to socioeconomic status, smoking or recreational exposure to skin irritants and limited statistical analyses.

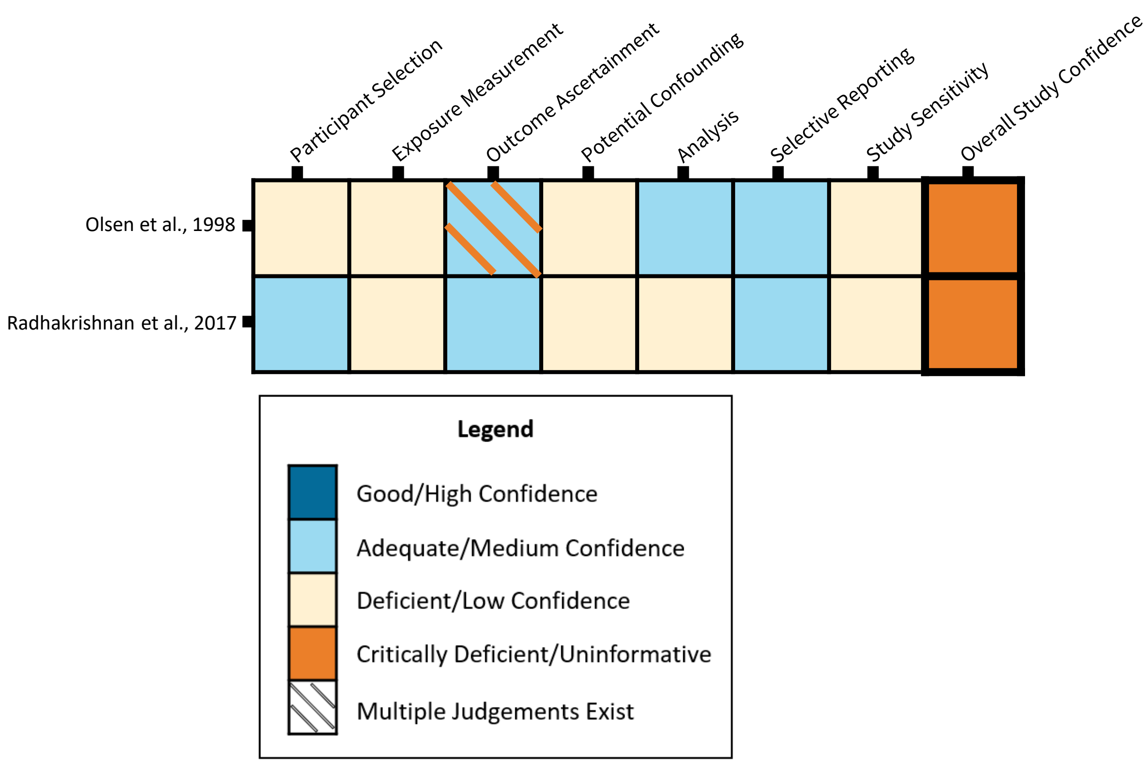


Figure 2-12. Study Quality Evaluations for Epidemiology Studies of Jet Fuel Exposure and Dermal Health Outcomes.

Table 2- below summarizes the number of studies with acute (e.g., measurement taken within 6 months of jet fuel exposure) dermal health outcomes. The review identified no studies with primary data on the association between jet fuel exposure and long-term dermal health outcomes. Additional information is provided by four case reports (Contestable, 2017; Dever et al., 2012; Lombardi & Lurie, 1957; Long & Charles, 2018), one risk assessment (Kendall et al., 2001) and six reviews (B'Hymer, 2015; EASA, 2017; Karanikas et al., 2021; Leggat & Smith, 2006; Ritchie et al., 2003; Wang, 2004). Conclusions from reviews with results that overlap with the primary studies are summarized in Table D-8 in Appendix D on page 311 .

Table 2-25. Number of Studies Reporting on the Acute and Long-term Dermal Health Outcomes Following Jet Fuel Exposures.

Health Outcomes	Acute[a]	Long-term[b]	Total Unique Studies
Skin irritation[c]	2	0	2

[a]Acute health outcomes are considered those that were measured within 6 months of exposure.
[b]Long-term health outcomes are considered those that were measured at least 6 months after exposure.
[c]Skin irritation health outcomes include skin rashes, dry or itchy skin, skin sensitivity, contact dermatitis and history of atopy.

2.16.2. Acute Dermal Health Outcomes

2.16.2.1. Skin Irritation

Olsen et al. (1998) conducted a pilot study of 17 exposed and 18 unexposed active-duty and civilian personnel at the Hill Air Force Base, Utah (see Table C-12 in Appendix C on page 294). Exposure was assigned based on job group; F-16 ground crew, aircraft fuel distribution personnel, fuel system mechanics and sheet metal workers were considered highly exposed. Acute skin irritation symptoms were self-reported as part of a physical examination at a baseline exposure assessment (when JP-4 was in use) and two follow-up assessments at 6 and 18 months (when JP-8 was in use) to document effects of JP-4 and after the transition to use of JP-8. Exposed subjects reported dry, itchy skin or rashes more frequently than unexposed workers (31 times and 20 times, respectively). Participants attributed symptoms to JP-4 exposure 5 out of 9 times and to JP-8 exposure 9 out of 21 times. Two exposed participants reported severe rashes and swelling of knuckles after exposure to JP-8. The average frequency of symptoms was less than twice a month for both groups and there were no differences in the frequency or severity of symptoms between exposed and unexposed groups at any time point and there were no trends over time. The authors note that symptoms of dry or itchy skin and rashes could have been related to the dry climate in Utah (Olsen et al., 1998).

In a cross-sectional study of 109 Indian Air Force ground crew members directly exposed to aviation fuel, Radhakrishnan et al. (2017) reported that 18% of participants showed symptoms of itching, transient whitening of the skin, rash, or scaling (Table C-12 on page 294). A history of atopy was a predisposing factor for the symptoms, but there was no difference in the number of cases of allergic contact dermatitis between symptomatic and asymptomatic participants. Thus, exposure to aviation fuel resulted in mild irritant dermal health outcomes in this population (Radhakrishnan et al., 2017).

Reviews consistently summarized symptoms indicative of skin irritation or damage to the dermal barrier associated with prolonged JP-4, JP-5, JP-8 and Jet A fuel exposure (B'Hymer, 2015; EASA, 2017; Karanikas et al., 2021; Leggat & Smith, 2006; Ritchie et al., 2003; Wang, 2004). Ritchie et al. (2003) conducted a review, including a risk assessment of JP-8 (Kendall et al., 2001) and noted that skin symptoms were some of the most common effects reported among workers exposed to jet fuel, including itching, burning, redness, rash, dryness, dermatitis, lesions or weeping and sensitization.

A risk assessment of JP-8 conducted by the AFIOH reported on health care visits for 265 active-duty Air Force personnel and found that visits for skin diseases were similar among service personnel with high-, moderate- and low-exposure to JP-8 (Kendall et al., 2001). The AFIOH risk assessment also reported on another analysis of medical records of a sample of 5,706 active-duty Air Force personnel who were occupationally exposed to JP-8 and found no difference in health care visits for skin conditions among JP-8-exposed and unexposed occupations (Kendall et al., 2001). The risk assessment also reported an analysis of self-reported health symptoms among 328 active-duty Air Force personnel and noted significantly increased odds of itchy skin at least once in the last 6 months among personnel with high or moderate exposure and significantly increased odds of blisters on hands or arms at least once in the last 6 months among personnel with high or moderate exposure compared to those with low exposure. However, the authors noted that other occupational exposures may have influenced the results.

Case reports among military personnel occupationally exposed to jet fuel document otitis externa (inflammation of the external ear canal) after JP-8 fuel splashed into the ear (Long & Charles, 2018) and contact dermatitis with plaques, cracking, weeping and crusting on hands after direct contact with JP-5 (Contestable, 2017). In these cases, symptoms worsened for several days after accidental direct skin contact (such as a spill) but resolved with treatment. In a case series report of 12 Air Force personnel responsible for fuel cell repair, one reported their "skin becomes dry and peels when clothing becomes wet with fuel" (Lombardi & Lurie, 1957).

2.16.3. Long-term Dermal Health Outcomes

2.16.3.1. Skin Irritation

The review identified no primary data or secondary reviews that evaluated long-term dermal health outcomes associated with exposure to jet fuels.

One case report documented a Veteran who presented with allergic contact dermatitis related to the use of butylhydroxytoluene (BHT), a component in personal care products, such as deodorant and antifungal spray. The authors hypothesized that past exposure to F-76 and JP-5 fuels while on active duty sensitized him to BHT, which is a component of jet fuels (Dever et al., 2012).

2.16.4. Summary of Dermal Health Outcomes by Duration of Exposure

Neither Olsen et al. (1998) nor Radhakrishnan et al. (2017) assessed skin irritation in relationship to duration of exposure. Radhakrishnan et al. (2017) noted that it was not possible to correlate duration of exposure with health outcomes in this study because participants only had intermittent exposure across their years of service. Although case reports describe multiple years of service or working in highly exposed occupations, acute skin irritation is generally reported in association with instances of direct contact, such as spills (Contestable, 2017; Long & Charles, 2018).

2.16.5. Conclusion

The quantity and quality of studies describing skin irritation associated with recent jet fuel exposure is limited to two small studies in military populations that lack thorough assessment for confounding (see Table 2- on page 131) (Olsen et al., 1998; Radhakrishnan et al., 2017). The results of the studies are inconsistent with one study suggesting that skin irritation is associated with jet fuel exposure and the other finding no differences between exposed and unexposed groups. No studies provided information indicating that immediate dermatologic health outcomes were associated with an increased risk of subsequent dermatologic health outcomes. In addition, data were insufficient to assess the risks of adverse dermatologic health outcomes by duration of exposure.

Therefore, due to the lack of primary data of sufficient quality, the evidence for an association between dermal health outcomes and jet fuel exposure is considered indeterminate. Additional studies are needed to better understand long-term dermal health outcomes that are related to jet fuel exposure and how risk changes with duration of exposure.

However, other conclusions about the causal relationship between direct dermal exposure to jet fuel and acute skin irritation might be drawn. There is consistency across lower quality data, including case reports, supporting an association. Causality is further supported by the directness and temporality of the relationship between dermal exposure, often in specific instances of spills, and subsequent skin irritation soon after. The relationship is supported by the resolution of symptoms with reduced exposure and treatment as reported in case studies.

Table 2-26. Summary of Dermal Health Outcomes Associated with Jet Fuel Exposure.

Studies and Interpretation	Summary and Key Findings	Factors That Increase Certainty	Factors That Decrease Certainty	Summary Judgment
Acute Health Outcomes[a]				⊙⊙⊙ Indeterminate Two uninformative described acute skin irritation in jet fuel exposed military populations. No studies reported long-term health dermal outcomes.
Skin irritation 2 Uninformative studies	One USAF study observed no differences in number of reports or frequency of symptoms between exposed and unexposed groups. One Indian Air Force study observed symptoms in 18% of the participants.	• No factors noted	• Limited number of studies examining health outcome • Inconsistent direction of effects • Uninformative studies	

United States Air Force = USAF

[a]Acute health outcomes are considered those that were measured within 6 months of exposure.

2.17. Developmental Health Outcomes

2.17.1. Summary of Developmental Health Outcomes

Developmental health outcomes refer to the growth of fetuses, infants and young children. Commonly researched developmental health outcomes include birth defects, birth size (e.g., birth weight, birth length, small for gestational age), preterm birth and postnatal growth. Markers of development specific to single organ systems are considered system-specific (e.g., tests of cognitive development are considered nervous health outcomes). Sexual maturation health outcomes (e.g., indicators of pubertal development) are considered reproductive in nature.

The review identified no studies with primary or secondary data that assessed jet fuel exposure and developmental health outcomes.

2.17.2. Conclusion

Data are not available to assess possible immediate developmental health outcomes associated with an increased risk of subsequent developmental health outcomes nor to assess the risks of adverse developmental outcomes by duration of exposure. Due to the lack of primary and secondary data, the evidence for an association between developmental health outcomes and jet fuel exposure is considered indeterminate. Studies are needed to better understand how jet fuel exposure may impact developmental health outcomes.

2.18. Endocrine Health Outcomes

2.18.1. Summary of Endocrine Health Outcomes

Endocrine health outcomes refer to non-reproductive hormones in tissue or blood and stress-related factors in blood. Examples of endocrine health outcomes include thyroid-related hormones (e.g., T3, T4, TSH) and stress markers (e.g., glucocorticoids or other adrenal markers). Hormones related to sexual maturation and reproduction (e.g., estrogen, progesterone, testosterone, luteinizing hormone, follicular stimulating hormone) are considered reproductive in nature.

No studies with primary or secondary data that assessed jet fuel exposure and endocrine health outcomes were identified.

2.18.2. Conclusion

Data are not available to assess possible immediate endocrine health outcomes associated with an increased risk of subsequent endocrine health outcomes nor to assess the risks of adverse endocrine outcomes by duration of exposure. Due to the lack of primary and secondary data, the evidence for an association between endocrine outcomes and jet fuel exposure is considered indeterminate. Studies are needed to better understand how jet fuel exposure may impact endocrine health outcomes.

2.19. Musculoskeletal and Connective Tissue Health Outcomes

2.19.1. Summary of Musculoskeletal and Connective Tissue Health Outcomes

Musculoskeletal health pertains to the function of the bone, muscle and connective tissue, including tendons and ligaments, throughout the body. Adverse musculoskeletal conditions are typically diagnosed following reports of pain and limited mobility (WHO, 2022). Common musculoskeletal health measures include measures of bone mineral density; bone conditions, such as osteoporosis and osteoarthritis; measures of muscular function, such as muscle weakness; and measures of connective tissue function, such as tissue fibrosis, calcification or impacts to innate reflexes. Musculoskeletal health outcomes are of particular concern for occupational and military populations, as these populations are regularly exposed to physical factors at work that may adversely impact the musculoskeletal system (Armed Forces Health Surveillance Branch, 2021; Putz-Anderson et al., 1997).

No studies with primary data that assessed the association between jet fuel exposure and musculoskeletal and connective tissue health outcomes were identified. Three review articles (EASA, 2017; Kendall et al., 2001; Ritchie et al., 2001) and one case report (Spock et al., 2009) provided information on musculoskeletal disorders and alterations in reflexes.

2.19.2. Acute Musculoskeletal and Connective Tissue Health Outcomes

2.19.2.1. Musculoskeletal Disorders

A risk assessment (Kendall et al., 2001) and one review summarized studies examining jet fuel exposures and musculoskeletal weakness (Ritchie et al., 2001).

The AFIOH final risk assessment of exposure to JP-8, Kendall et al. (2001) observed increased general weakness with JP-8 exposure. Military personnel from six Air Force personnel were categorized into high-, moderate- and low-JP-8 exposure groups based on job classifications and were asked to report the frequency of general weakness experienced in the prior 6 months. There were significantly increased odds of self-reported general weakness in the moderate and high exposure groups compared to the low exposure group.

A review of the neurotoxic health outcomes of hydrocarbon fuels (Ritchie et al., 2001) summarized a case report of an Air Force pilot unintentionally exposed to JP-4 via inhalation due to an in-flight leak. During flight, the pilot began experiencing feelings of weakness and upon landing, the pilot displayed mild muscular weakness. Symptoms subsided after 36 hours (Ritchie et al., 2001).

2.19.2.2. Reflexes

The review by the EASA of aviation engine oil toxicities following pyrolysis (i.e., decomposition at high temperatures) included a case report of depressed reflexes following exposure during flight in a military C-130A aircraft (EASA, 2017). The pilot experienced depressed deep tendon reflexes after in-flight exposure to aerosolized or vaporized jet engine oil. The symptoms subsided after 24 hours.

2.19.3. Long-term Musculoskeletal and Connective Tissue Health Outcomes

2.19.3.1. Musculoskeletal Disorders

Spock et al. (2009) presented a case report of a Navy jet fuel loader frequently exposed to JP-5 and JP-8. The patient experienced fibrosis of the hands, which led to decreased fine motor movements of the fingers and a decreased ability to fully extend joints in the hands and elbow. Diagnostic imaging revealed soft tissue calcification in the hands, along with fibrosis and thickening of some connective tissues (Spock et al., 2009). The patient's hand fibrosis is considered a long-term health outcome because the case report notes the progression of symptoms over the course of 10 years, although there is no indication that jet fuel exposures ceased at any point.

2.19.4. Summary of Musculoskeletal and Connective Tissue Health Outcomes by Duration of Exposure

There is limited discussion of duration of exposure in the reviewed literature. The JP-8 final risk assessment of exposure to jet fuel conducted by the AFIOH summarized findings of a study that included exposed participants with at least 9 months of persistent exposure to jet fuels (Kendall et al., 2001). However, there was no further discussion of exposure duration, as the risk assessment focused on acute exposures. Other reviews and case reports (EASA, 2015; Ritchie et al., 2001; Spock et al., 2009) did not discuss duration of exposure and its potential impacts on musculoskeletal and connective tissue health outcomes.

2.19.5. Conclusion

No studies with primary data assessed jet fuel exposure with musculoskeletal and connective tissue health outcomes; thus, additional data are needed to draw conclusions about potential associations with jet fuel exposure. Due to the lack of primary data, there was no information indicating that immediate musculoskeletal and connective tissue health outcomes were associated with an increased risk of subsequent musculoskeletal or connective tissue health outcomes. In addition, data were insufficient to assess the risks of adverse musculoskeletal and connective tissue outcomes by duration of exposure.

Several secondary data sources reported on musculoskeletal and connective tissue health following jet fuel exposures. The USAF JP-8 risk assessment (Kendall et al., 2001) observed increases in self-reported muscle weakness with exposures to JP-8, which was also supported by a case report summarized in a review of jet fuel toxicities (Ritchie et al., 2001). Another review summarized a case report presenting an instance of depressed deep tendon reflexes following exposure (EASA, 2015). Each of these reports examined acute health outcomes, while one case report presented long-term hand fibrosis in a Navy jet fuel loader regularly exposed to jet fuels (Spock et al., 2009). No studies analyzed the potential for acute respiratory health outcomes to become chronic.

Due to the lack of primary data, the evidence for an association between musculoskeletal and connective tissue outcomes and jet fuel exposure is considered indeterminate. Additional studies are needed to better understand specific musculoskeletal health outcomes that are related to jet fuel exposure and how risk changes with duration of exposure.

2.20. Other Health Outcomes

2.20.1. Summary of Other Health Outcomes

One low confidence study and two secondary data sources provided information on non-specific health outcomes that do not fit within the specific health outcome categories described elsewhere in this report (hereafter referred to as "other" health outcomes).

The low confidence study (D'Este et al., 2008) examined mortality related to all health outcomes. This study, which examined all-cause mortality, employed adequate health outcome measures and analytic strategies. Sources of potential bias in this study include the use of different methods to recruit participants in the exposed versus unexposed groups; the use of administrative data to define exposed and unexposed groups with no quantitative exposure measurement; and the potential for residual confounding by factors, such as smoking, alcohol use and co-exposure to other occupational hazards. In addition, as this study did not involve quantitative exposure measurements, it is not possible to confirm whether there was sufficient contrast in exposure levels between exposed and unexposed groups (i.e., adequate study sensitivity) (see Figure 2-13 below).

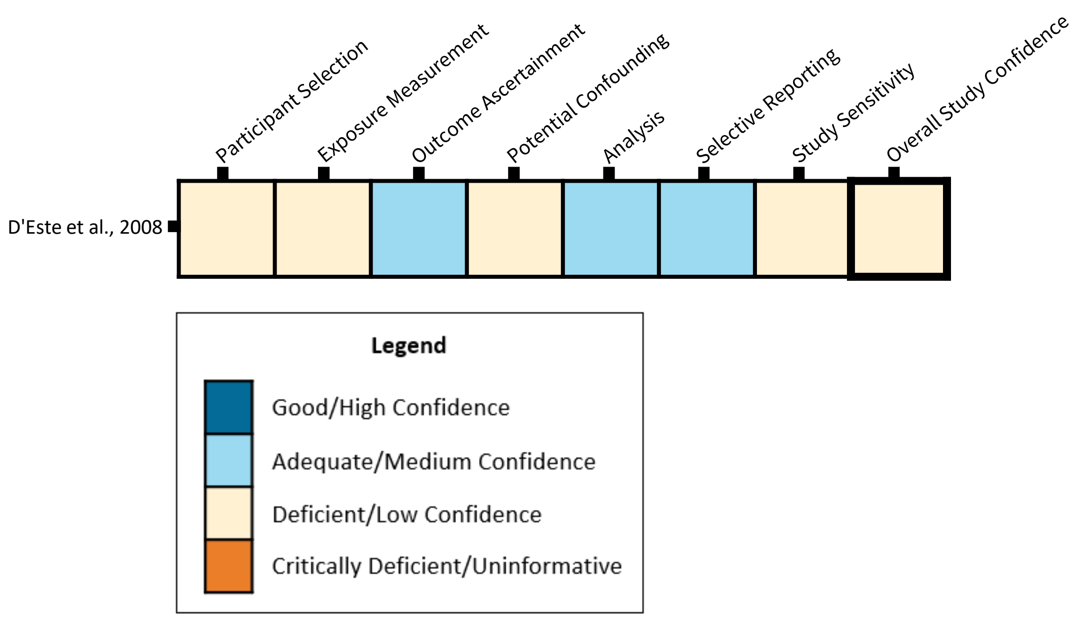


Figure 2-13. Study Quality Evaluations for Epidemiology Studies of Jet Fuel Exposure and Other Health Outcomes.

Table 2- below summarizes the number of primary studies with acute (i.e., measurement taken within 6 months of jet fuel exposure) and long-term (i.e., measurement taken after at least 6 months of jet fuel exposure) other health outcomes. The low confidence study (D'Este et al., 2008) measured long-term mortality. No primary epidemiologic studies measured acute other health outcomes.

Two secondary data sources provided additional information. A 1996 NRC report provided information on mortality (NRC, 1996). In addition, the 2001 JP-8 Final Risk Assessment (Kendall et al., 2001) provided information on health care encounters due to any cause assessed concurrently with jet fuel exposure. No studies with primary data assessed this health outcome.

Table 2-27. Number of Studies Reporting on the Acute and Long-term Other Health Outcomes Following Jet Fuel Exposures.

Health Outcomes	Acute[a]	Long-term[b]	Total Unique Studies
Mortality[c]	0	1	1

[a]Acute health outcomes are considered those that were measured within 6 months of exposure.
[b]Long-term health outcomes are considered those that were measured at least 6 months after exposure.
[c]Mortality includes all-cause mortality.

2.20.2. Acute Other Health Outcomes

2.20.2.1. All-Cause Health Care Encounters

A risk assessment of JP-8 provided information on rates of health care encounters due to any illness or injury over a period of 1 year among active-duty Air Force personnel while exposure to jet fuel was ongoing (Kendall et al., 2001). This risk assessment found that personnel performing duties involving routine JP-8 contact had similar rates of health care encounters to those performing duties with low to no contact.

2.20.3. Long-term Other Health Outcomes

2.20.3.1. All-Cause Mortality

One low confidence cohort study examined mortality among RAAF personnel involved in F-111 aircraft deseal/reseal (DSRS) fuel tank maintenance programs at RAAF Base Amberley compared to two unexposed groups (D'Este et al., 2008). Exposure was defined as participation in the fuel tank maintenance program, during which exposure to jet fuels, including JP-4, may have occurred and unexposed groups consisted of personnel at the same base who were not involved in technical jobs, as well as personnel working in technical jobs at a different RAAF base (RAAF Base Richmond). The study found that exposed personnel had significantly lower all-cause mortality rates compared to both groups of unexposed personnel (D'Este et al., 2008). The authors emphasize that these results should be interpreted with caution because it was not possible to identify personnel who worked on the fuel tank maintenance program but who died prior to the start of the study, potentially resulting in artificially lower death rates in the exposed group.

One secondary data source (NRC, 1996) described lower all-cause mortality rates among a cohort of workers with varying levels of exposure to MC77 or MC75 jet fuels (equivalent to JP-4 or Jet A-1) on a military base in Sweden when compared to an unspecified reference population.

2.20.4. Summary of Other Health Outcomes by Duration of Exposure

No studies reported data on duration of exposure.

2.20.5. Conclusion

One low confidence study examined a long-term health outcome that does not fit within the specific health outcome categories described elsewhere in this report (see Table 2- on page 138). This study (D'Este et al., 2008) found that military personnel exposed to jet fuel had significantly lower death rates than two comparison populations. This finding should be interpreted with caution due to potential for bias in this study. No primary studies examined acute health outcomes that do not fit within the specific health outcome categories described elsewhere in this report. Data were not available to assess the risks of such health outcomes by duration of exposure. In summary, the evidence for an association between adverse health outcomes not classified elsewhere (i.e., all-cause mortality) and jet fuel exposure is indeterminate, due largely to the very limited number of studies examining other health outcomes.

Table 2-28. Summary of Other Health Outcomes Associated With Jet Fuel Exposure.

Studies and Interpretation	Summary and Key Findings	Factors That Increase Certainty	Factors That Decrease Certainty	Summary Judgment
Long-term Health Outcomes[a]				⊙⊙⊙ Indeterminate
All-cause mortality 1 Low confidence study	One low confidence study in Australian Air Force personnel observed significantly lower mortality rates among those with duties involving exposure to jet fuel.	• No factors noted	• Limited number of studies examining this health outcome • Low confidence study	Evidence was limited to one low confidence study reporting lower mortality rates among military personnel with duties involving jet fuel exposure.

[a]Long-term health outcomes are considered those that were measured at least 6 months after exposure.

2.21. Cancerous Health Outcomes

2.21.1. Summary of Cancerous Health Outcomes

Jet fuel exposure may contribute to the development of various types of cancers as a result of dermal, inhalation or oral exposures. Data on cancer that can be used to estimate rates of incidence (i.e., number of newly diagnosed cases in a given population at a specific time) and mortality (i.e., number of deaths) are generally recorded in medical records and tumor registries. Cancers include leukemia, multiple myeloma, lymphoma, as well as organ-specific cancers such as bladder cancer, colorectal cancer, kidney cancer and lung cancer.

Of the eight studies with primary data examining the association between jet fuel exposure and cancer, one was considered medium confidence (Parent et al., 2000) and the remaining seven were considered low confidence (Blair et al., 1998; D'Este et al., 2008; D'Mello & Yamane, 2007; Radican et al., 2008; Reed et al., 2020; Siemiatycki, Dewar, et al., 1987; Spirtas et al., 1991) (see Figure 2-14 on page 138).

The medium confidence study (Parent et al., 2000) employed adequate outcome ascertainment and appropriately accounted for important confounders. Limitations included the exposure assessment method and low sensitivity due to a small number of individuals exposed to jet fuels.

Among the seven studies rated low confidence, sources of potential bias included exposure measurement methods (Blair et al., 1998; D'Este et al., 2008; D'Mello & Yamane, 2007; Radican et al., 2008; Reed et al., 2020; Siemiatycki, Dewar, et al., 1987; Spirtas et al., 1991), potential for residual confounding (Blair et al., 1998; D'Este et al., 2008; D'Mello & Yamane, 2007; Radican et al., 2008; Reed et al., 2020; Spirtas et al., 1991), limited study sensitivity (Blair et al., 1998; D'Este et al., 2008; Radican et al., 2008; Reed et al., 2020; Spirtas et al., 1991) and participant selection approach (D'Este et al., 2008).

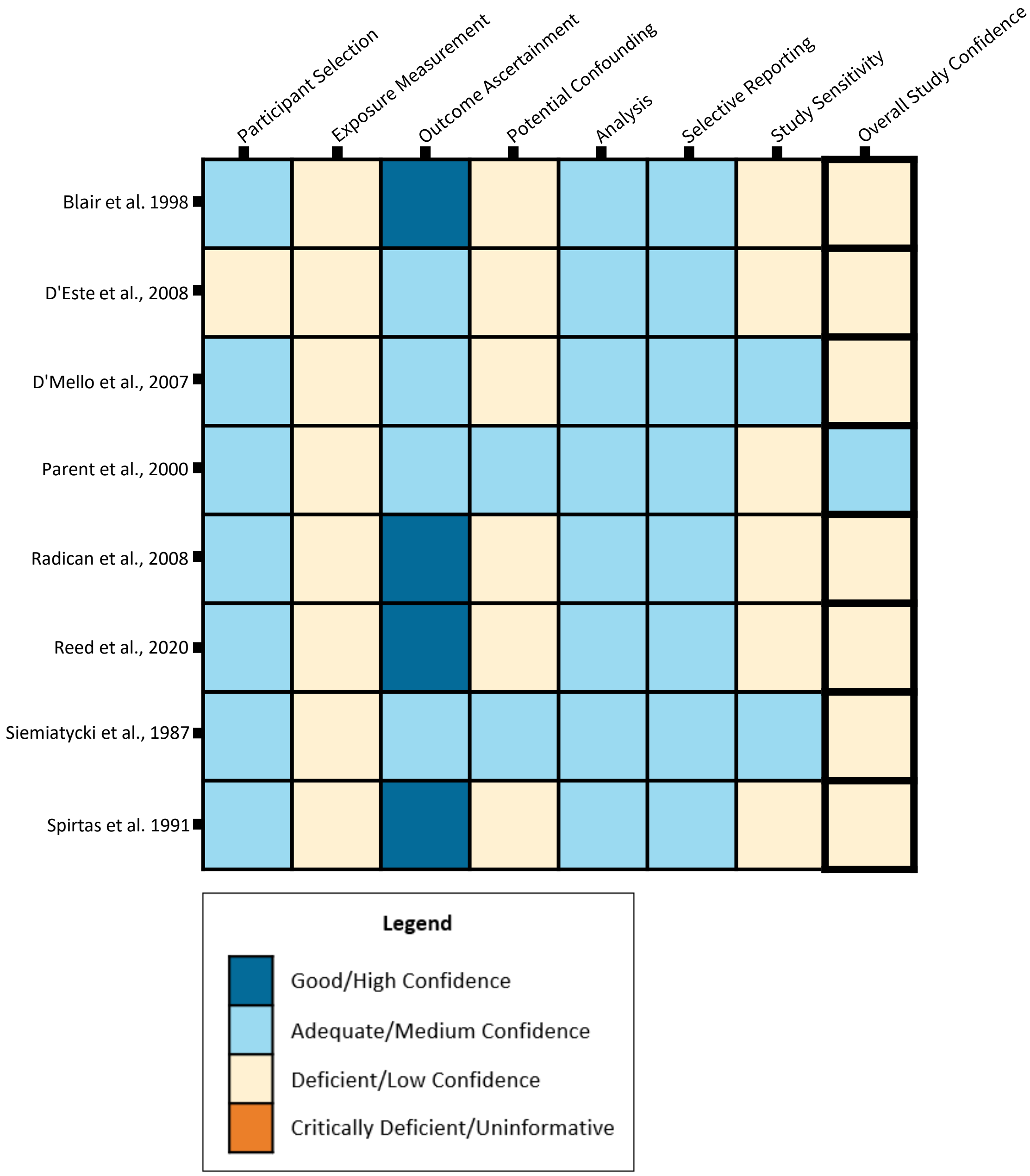


Figure 2-14. Study Quality Evaluations for Epidemiology Studies of Jet Fuel Exposure and Cancerous Health Outcomes.

Table 2- on page 141 summarizes numbers of studies by type of cancerous health outcome. Five studies evaluated the association between jet fuel exposure and cancer incidence and three studies evaluated cancer mortality.

Five studies (Blair et al., 1998; D'Mello & Yamane, 2007; Radican et al., 2008; Siemiatycki, Dewar, et al., 1987; Spirtas et al., 1991) examined lymphoma, including non-Hodgkin's and Hodgkin's lymphoma. Four of these studies also examined multiple myeloma (Blair et al., 1998; D'Mello & Yamane, 2007; Radican et al., 2008; Spirtas et al., 1991) and one considered leukemia, including acute and chronic lymphocytic leukemia and acute and chronic myeloid leukemia (D'Mello & Yamane, 2007).

Nine organ-specific cancers were assessed. Three studies examined bladder cancer (D'Mello & Yamane, 2007; Reed et al., 2020; Siemiatycki, Dewar, et al., 1987), three studies considered breast cancer (Blair et al., 1998; D'Mello & Yamane, 2007; Radican et al., 2008), three studies examined kidney cancer (D'Mello & Yamane, 2007; Parent et al., 2000; Siemiatycki, Dewar, et al., 1987) and two studies assessed lung cancer (D'Mello & Yamane, 2007; Siemiatycki, Dewar, et al., 1987). Only one study examined colorectal cancer (including cancers of the colon, rectum, intestine and rectosigmoid) (Siemiatycki, Dewar, et al., 1987), oropharyngeal cancer (including cancers of the buccal cavity and pharynx) (Spirtas et al., 1991), pancreatic cancer (Radican et al., 2008), prostate cancer (Siemiatycki, Dewar, et al., 1987) and stomach cancer (Siemiatycki, Dewar, et al., 1987).

Four secondary sources (Karanikas et al., 2021; NRC, 1996; NRC, 2003; Ritchie et al., 2003) provided information on the association between jet fuel exposure and cancers, including melanoma, a skin cancer that was not included in any of the studies with primary data. In addition, one case report (Helmers et al., 2004) observed epithelioid sarcoma, a soft-tissue cancer, which was also not considered in any study with primary data.

Table 2-29. Number of Studies Reporting on the Cancerous Health Outcomes Following Jet Fuel Exposures.

Health Outcomes	Incidence	Mortality	Total Studies
Bladder Cancer	3	0	3
Breast Cancer	1	2	3
Cancer (any or unspecified)	2	1	3
Colorectal Cancer[a]	1	0	1
Kidney Cancer	3	0	3
Leukemia[b]	1	0	1
Lung Cancer	2	0	2
Lymphoma[c]	2	3	5
Multiple Myeloma	1	3	4
Oropharyngeal Cancer[d]	0	1	1
Pancreatic Cancer	0	1	1
Prostate Cancer	1	0	1
Stomach Cancer	1	0	1

[a]Colorectal cancer includes cancers of the colon, rectum, intestine and rectosigmoid.
[b]Leukemia includes acute and chronic lymphocytic leukemia and acute and chronic myeloid leukemia.
[c]Lymphoma includes non-Hodgkin's and Hodgkin's lymphoma.
[d]Oropharyngeal cancer includes buccal cavity and pharynx cancer.

2.21.2. *Incidence*

Five studies examined the association between jet fuel exposure and incident cases of any type of cancer (D'Este et al., 2008; D'Mello & Yamane, 2007) and organ-specific cancers (D'Mello & Yamane, 2007; Parent et al., 2000; Reed et al., 2020; Siemiatycki, Dewar, et al., 1987). Results were mixed or no associations were observed. Jet fuel exposure was based on job duties reported via questionnaire or collected from occupational records.

In a cohort study of male F-111 fuel tank DSRS program workers at the RAAF Base Amberley, D'Este et al. (2008) observed increased incidence of any cancer (excluding non-melanocytic skin cancer) in exposed workers compared to two groups of unexposed RAAF personnel from different base locations. One unexposed group was recruited from Base Amberley and included personnel without aircraft maintenance work. The other unexposed group of workers were recruited from RAAF Base Richmond and had similar technical duties but did not participate in the DSRS program. Exposure status was assigned based on self-reported involvement with fuel tank DSRS activities. Incident rate ratios were consistently around 1.5 in the exposed group when compared with both unexposed groups and when comparing by first job posting or most recent job posting (D'Este et al., 2008) (see Table C-14 in Appendix C on page 297). However, a nested case-control study of active-duty USAF personnel with at least 1 year of active-duty service in the 16-year period between January 1, 1988 and December 31, 2003, observed no association between occupational jet fuel exposure and any invasive cancer occurrence when comparing personnel with moderate and high levels of exposure based on job duties to those with low levels of exposure (D'Mello & Yamane, 2007). These findings remained consistent in sex-stratified analyses. The timeframe of the study included a portion of the period during which the USAF converted from JP-4 to JP-8, but the study design prevented differential assessment of each fuel. (Table C-14 on page 296). The apparent conflicting results from the two studies might be explained by the fact that workers engaged in DSRS activities are predominantly exposed to various chemicals used in the desealing process and to the new sealant, in addition to fuel from fuel leaks.

Three case-control studies considered the effect of jet fuel exposure on incident kidney cancer (D'Mello & Yamane, 2007; Parent et al., 2000; Siemiatycki, Dewar, et al., 1987). Two studies examined cancer cases from the same population of male cancer patients aged 35-70 years old recruited from 19 hospitals in Montreal, Canada and both observed a positive association (Parent et al., 2000; Siemiatycki, Dewar, et al., 1987). Among the male cancer patients, a reference group was selected from among the other (non-kidney) cancer patients interviewed. Subjects self-reported occupational history, which was then coded by chemists and industrial hygienists into likely occupational exposure categories, including jet fuel exposure and aviation gasoline (Parent et al., 2000; Siemiatycki, Dewar, et al., 1987). Siemiatycki, Wacholder, et al. (1987) reported significantly increased odds of kidney cancer in patients exposed to jet fuel and aviation gasoline compared to the reference group (Table C-14 on page 296). Using a reference group that included population controls in addition to the other cancer patients, (Parent et al., 2000) also observed significantly increased odds of renal cell cancer in patients exposed to aviation gasoline and jet fuel and no difference in patients who were exposed to jet fuel engine emissions or who had worked as an aircraft mechanic (Parent et al., 2000) (Table C-14 on page 296). In contrast to the results from Parent et al. (2000) and Siemiatycki, Wacholder, et al. (1987), a nested case-control study of male and female USAF active-duty personnel observed that job duties with moderate- and high-levels of occupational jet fuel exposure were not associated with renal cell cancer occurrence compared to job duties not involving jet fuel contact (Table C-14 on page 296) (D'Mello & Yamane, 2007).

Three studies examined incident cases of bladder cancer, and results were mixed (D'Mello & Yamane, 2007; Reed et al., 2020; Siemiatycki, Dewar, et al., 1987). Studies of active-duty USAF personnel (D'Mello & Yamane, 2007) and male cancer patients aged 35-70 years old in Montreal (Siemiatycki, Dewar, et al., 1987) observed no association between jet fuel exposure and bladder cancer (Table C-14 on page 296). In contrast, a cross-sectional study of patients newly diagnosed with bladder cancer at a hospital in the United Kingdom observed a significantly higher prevalence of high-grade (i.e., more aggressive) bladder cancer compared to low-grade (i.e., less aggressive) bladder cancer in patients self-reporting work involving exposure to aircraft fuel (Reed et al., 2020) (Table C-14 on page 296).

One study examined the occurrence of colorectal cancer in relation to jet fuel exposure (Siemiatycki, Dewar, et al., 1987). In male cancer patients aged 35-70 years old in Montreal, there was no difference in the odds of colon cancer and rectum cancer when comparing patients with exposures to jet fuel and aviation gasoline to those without exposure (Siemiatycki, Dewar, et al., 1987) (Table C-14 on page 296).

There were no associations observed for other types of cancer considered by D'Mello and Yamane (2007) in a population of active-duty USAF personnel and Siemiatycki, Wacholder, et al. (1987) in a population of male cancer patients. Neither study observed an association between occupational jet fuel exposure and non-Hodgkin’s lymphoma or lung cancer (D'Mello & Yamane, 2007; Siemiatycki, Dewar, et al., 1987). In addition, Siemiatycki, Wacholder, et al. (1987) did not observe associations with prostate cancer or stomach cancer. Several reported effect estimates were likely imprecise due to the small number of exposed cases in the study (Siemiatycki, Dewar, et al., 1987). D'Mello and Yamane (2007) did not observe an association between jet fuel exposure and breast cancer, Hodgkin’s lymphoma, leukemia or multiple myeloma (Table C-14 on page 296).

A review emphasized the limited body of evidence examining associations between incident cancers and jet fuel exposures. Ritchie et al. (2003) noted that, despite there being limited epidemiological evidence for jet fuel-induced cancers, further study is justified, as jet fuel-exposed workers self-report large numbers of health complaints (Ritchie et al., 2003).

A case report described the development of epithelioid sarcoma in the thumb of a patient of a patient with several years of occupational history refueling tactical jet aircraft (Helmers et al., 2004).

2.21.3. *Mortality*

Three cohort studies examined the association between JP-4 jet fuel exposure and cancer mortality (Blair et al., 1998; Radican et al., 2008; Spirtas et al., 1991). All three studies examined the same cohort of former civilian workers at the Hill Air Force Base, enrolled between 1952 and 1956, but assessed different durations of follow-up. Exposure to JP-4 jet fuel was estimated qualitatively (yes/no) by two industrial hygienists based on the combination of job titles and department codes obtained from personnel records (Table C-14 on page 296). Radican et al. (2008) followed the cohort through 2000, the longest follow-up period, and observed significantly increased all-cancer mortality in male workers with JP-4 exposure compared to male workers without exposure. In addition, JP-4 exposure was significantly associated with increased pancreatic cancer mortality in exposed female workers compared to unexposed female workers. Spirtas et al. (1991) followed the cohort through 1982, the shortest follow-up period, and observed a significant positive association between JP-4 exposure in female workers and oropharyngeal cancer mortality.

Across the three studies, no associations were observed between JP-4 exposure and mortality from multiple myeloma or non-Hodgkin's lymphoma (Blair et al., 1998; Radican et al., 2008; Spirtas et al., 1991). In addition, there was no association between JP-4 jet fuel exposure and breast cancer mortality in women (Blair et al., 1998; Radican et al., 2008)(Table C-14 on page 296).

2.21.4. *Summary of Cancerous Health Outcomes by Duration of Exposure*

Few studies considered how the duration of jet fuel exposure may impact cancerous health outcomes. One case-control study (Siemiatycki, Dewar, et al., 1987) considered non-substantial and substantial exposure subgroups in analyses. To determine these subgroups, experts examined self-reported occupational history and combined the estimated level and duration of exposure into a cumulative estimate. Odds of kidney cancer in groups with substantial exposures to aviation gasoline and to jet fuel had greater magnitude and significance of effect compared to groups with non-substantial exposures to aviation gasoline and jet fuel. Further categorization of exposure into short- and long-term exposure (based on a 10-year cut point) and low and high exposure were not possible due to the limited number of cancer cases exposed to jet fuels and aviation gasoline (Siemiatycki, Dewar, et al., 1987). Another case-control study in the same population of cancer patients considered any duration of occupational jet fuel exposure rather than substantial and non-substantial subgroups, as there were fewer than four renal cell cancer cases exposed for over 10 years (Parent et al., 2000). Similarly, one cohort study collected data on length of employment in jet fuel exposed work (<9 months; 9 to 30 months; more than 30 months); however, the number of cancer cases was too low to conduct any meaningful analysis by this proxy for exposure duration (D'Este et al., 2008).

2.21.5. *Conclusion*

Overall, there is slight evidence that jet fuel exposure influences cancer in humans, particularly kidney and bladder cancer (see Table 2- on page 146). While there is evidence of an increased incidence of any cancer in male workers involved in F-111 fuel tank DSRS activities (D'Este et al., 2008), no such association was observed in active-duty USAF personnel (D'Mello & Yamane, 2007). This apparent lack of consistency might be explained by the fact that workers engaged in DSRS activities are predominantly exposed to various chemicals used in the desealing process and to the new sealant, in addition to fuel from fuel leaks.

The evidence for kidney cancer is supported by two case-control studies in the same population of Montreal cancer patients (Parent et al., 2000; Siemiatycki, Dewar, et al., 1987) that showed elevated risk of renal cell cancer in patients exposed to aviation gasoline and jet fuel, but not in patients who were exposed to jet fuel engine emissions or who had worked as an aircraft mechanic, suggesting that jet fuel might be an important factor for kidney carcinomas. However, the nested case-control study in active-duty USAF personnel found no evidence of elevated renal cell cancer when comparing personnel with moderate and high levels of exposure to those with low levels of exposure (D'Mello & Yamane, 2007).

The evidence for bladder cancer is supported by one cross-sectional study in newly diagnosed United Kingdom patients that observed higher prevalence of high-grade bladder cancer compared to low-grade bladder cancer in patients self-reporting work involving exposure to aircraft fuel (Reed et al., 2020). However, the number of cases was very small. Two studies of active-duty USAF personnel (D'Mello & Yamane, 2007) and male cancer patients in Montreal (Siemiatycki, Dewar, et al., 1987) observed no association between jet fuel exposure and bladder cancer.

The evidence for other specific cancers is lacking and there is little coherence across studies to establish a pattern of association given that studies only reported on one type of cancer and there were small numbers of cancer cases observed in each study.

The evidence for cancer mortality is supported by studies in the cohort of former civilian workers at the Hill Air Force Base exposed to JP-8 (Blair et al., 1998; Radican et al., 2008; Spirtas et al., 1991) that showed elevated all-cause cancer mortality in men and elevated pancreatic and oropharyngeal cancer mortality in women.

Because most cancer types are generally less common and require long follow-up to be detected, the number of studies examining these associations with respect to jet fuel exposure is limited. In addition, aside from one medium confidence study, all studies of cancer incidence and cancer mortality were considered low confidence due to concerns about the exposure measurement methods, potential for residual confounding and limited study sensitivity. Additional studies are needed to better understand specific types of cancer that are related to jet fuel exposure and how risks change with duration of exposure.

No data indicated the ascertainment of immediate cancer-related symptoms (such as precancerous lesions); therefore, progression from pre-cancerous lesions to subsequent development of cancer-related health outcomes could not be determined. In addition, data were not available to assess risks of cancer-related health outcomes by length of exposure.

Table 2-30. Summary of Cancerous Health Outcomes Associated With Jet Fuel Exposure.

Studies and Interpretation	Summary and Key Findings[a]	Factors That Increase Certainty	Factors That Decrease Certainty	Summary Judgment
Long-term Health Outcomes[b]				
Kidney Cancer 1 Medium confidence study of Incidence 2 Low confidence studies of Incidence	One medium confidence study and one low confidence study observed significantly increased occurrence of kidney cancer with exposures to jet fuels and aviation gasoline in male cancer patients in Montreal, Canada (2/3). One low confidence study of USAF personnel observed no association between occupational jet fuel exposure and renal cell cancer.	• Medium confidence study • Large magnitude of effect	• Low confidence studies	⊕⊙⊙ Slight One medium confidence study and five low confidence studies reported positive associations between jet fuel exposure and incident kidney, bladder and any cancer and all cancer mortality in men and pancreatic and oropharyngeal cancer mortality in women. Uncertainties remain due to the limited number of quality studies examining cancer.
Bladder Cancer 3 Low confidence studies of Incidence	One low confidence study reported that high-grade bladder cancer was more common than low-grade bladder cancer in workers exposed to aircraft fuel (1/3). Two low confidence case-control studies observed no significant associations.	• No factors noted.	• Low confidence studies	
Oropharyngeal Cancer 1 Low confidence study of Mortality	One low confidence cohort study found significantly increased mortality from buccal cavity and pharynx cancers in former civilian female workers exposed to JP-4 at Hill Air Force Base (Utah) (1/1).	• No factors noted.	• Low confidence study • Limited number of studies examining health outcome	
Pancreatic Cancer 1 Low confidence study of Mortality	One low confidence cohort study observed significantly increased mortality from pancreatic cancer in former civilian female workers exposed to JP-4 at Hill Air Force Base (Utah) (1/1).	• No factors noted.	• Low confidence study • Limited number of studies examining health outcome	

Studies and Interpretation	Summary and Key Findings[a]	Factors That Increase Certainty	Factors That Decrease Certainty	Summary Judgment
Cancer (any or unspecified) 2 Low confidence studies of Incidence 1 Low confidence study of Mortality	One low confidence occupational cohort study observed significantly increased cancer incidence in aircraft maintenance workers at RAAF bases compared to other unexposed personnel (1/3). One low confidence case-control study of USAF personnel observed no association between invasive cancer occurrence and occupational jet fuel exposure (1/3). One low confidence cohort study of former civilian workers at Hill Air Force Base (Utah) observed significantly increased all cancers mortality in males exposed to JP-4 gasoline compared to males with no chemical exposure (1/3).	• No factors noted.	• Low confidence studies	
Breast Cancer 2 Low confidence studies of Mortality 1 Low confidence study of Incidence	Two low confidence cohort studies observed no association between JP-4 exposure and breast cancer mortality among former civilian workers at Hill Air Force Base (Utah) (2/3). One low confidence case-control study observed non-significant decreases in breast cancer occurrence in the total study population and in women (1/3).	• No factors noted.	• Low confidence studies	
Colorectal Cancer 1 Low confidence study of Incidence	One low confidence case-control study observed non-significant increased odds of colon cancer and rectum cancer with exposures to jet fuel and aviation gasoline; No associations were observed for rectosigmoid cancer (1/1).	• No factors noted.	• Low confidence study • Limited number of studies examining health outcome	

Studies and Interpretation	Summary and Key Findings[a]	Factors That Increase Certainty	Factors That Decrease Certainty	Summary Judgment
Leukemia 1 Low confidence study of Incidence	One low confidence case-control study of USAF personnel observed no association between occupational jet fuel exposure and any type of leukemia (1/1).	• No factors noted.	• Low confidence study • Limited number of studies examining health outcome	
Lung Cancer 2 Low confidence studies of Incidence	Two low confidence case-control studies, one of USAF personnel and one of male cancer patients in Canada, observed no associations between jet fuel exposure and any type of lung cancer (2/2).	• No factors noted.	• Low confidence studies • Limited number of studies examining health outcome	
Lymphoma 2 Low confidence studies of Incidence 3 Low confidence studies of Mortality	Two low confidence case-control studies, one of USAF personnel and one of male cancer patients in Canada, observed no associations between jet fuel exposure and lymphoma. (2/5) Three low confidence cohort studies observed no associations between JP-4 exposure and lymphoma mortality among former civilian workers at Hill Air Force Base (Utah). Results of analyses were non-significant and mixed when stratified by sex (3/5).	• No factors noted.	• Low confidence studies • Inconsistent direction of effect in analyses stratified by sex.	
Multiple Myeloma 3 Low confidence studies of Mortality	One low confidence case-control study of USAF personnel observed no association between jet fuel exposure and multiple myeloma (1/4). Three low confidence cohort studies of former civilian male workers at Hill Air Force Base (Utah) observed non-	• No factors noted.	• Low confidence studies	

Studies and Interpretation	Summary and Key Findings[a]	Factors That Increase Certainty	Factors That Decrease Certainty	Summary Judgment
1 Low confidence study of Incidence	significantly increased multiple myeloma mortality with JP-4 exposure. Similar results were observed in analyses of female workers (3/4).			
Prostate Cancer 1 Low confidence study of Incidence	One low confidence case-control study of male cancer patients in Montreal, Canada, observed no association between incidence of prostate cancer and jet fuel or aviation gasoline exposure (1/1).	• No factors noted.	• Low confidence study • Limited number of studies examining health outcome	
Stomach Cancer 1 Low confidence study of Incidence	One low confidence case-control study of male cancer patients in Montreal, Canada, observed no association between incidence of stomach cancer and jet fuel or aviation gasoline exposure (1/1).	• No factors noted.	• Low confidence study • Limited number of studies examining health outcome	

Royal Australian Air Force = RAAF; United States Air Force = USAF

[a]Health outcomes are summarized in this column by a ratio of (number of studies that found a significant association for that health outcome/the number of studies reporting on that health outcome).

[b]Long-term health outcomes are considered those that were measured at least 6 months after exposure.

2.22. Summary and Conclusions

This review relied on 28 epidemiological studies with primary data, supported by case studies and reviews, to reach conclusions about evidence of associations between exposure to jet fuels and health outcomes in military and civilian occupational populations. The 28 primary studies reported on a range of outcomes across 14 health systems. Most of the studies (17) reported on military populations. Overall, there is slight evidence of associations between jet fuel exposure and nervous, respiratory, mental health and cancer health outcomes. While there are other health effect categories with some primary studies (<5 studies/category), the evidence for an association with jet fuel exposures is considered indeterminate for all other outcome categories. There was no primary data available for developmental, endocrine, metabolic or musculoskeletal outcomes.

Box 2-1. Summary of Conclusions Describing Evidence of Associations Between Health Effects and Jet Fuel Exposure.

- ***Robust*** **(⊕⊕⊕) (N = 0)**
- ***Moderate*** **(⊕⊕⊙) (N = 0)**
- ***Slight*** **(⊕⊙⊙) (N = 4)**
  - Cancer
  - Mental Health
  - Nervous
  - Respiratory
- ***Indeterminate*** **(⊙⊙⊙) (N = 14)**
  - Cardiovascular
  - Dermal
  - Developmental
  - Digestive
  - Endocrine
  - Hematologic
  - Hepatic
  - Immune
  - Metabolic
  - Musculoskeletal
  - Other
  - Renal
  - Reproductive (Female)
  - Reproductive (Male)
- ***Compelling evidence of no effect*** **(– – –) (N = 0)**

Several factors limit the ability to establish stronger conclusions based on this evidence. Most health effect categories have primary data available for either acute or long-term effects, but usually not both, and no health effect categories have primary data available on acute effects or symptoms predicting long-term outcomes. Exposure is often assessed concurrently with outcomes, with few studies reporting outcome data collected over time. Because the available studies rarely followed participants for several years, evidence of long-term effects is especially sparse. Many studies include only active workers, thereby excluding those who are too sick to work, those who may have changed jobs to avoid becoming sicker from jet fuel exposure, or those that may no longer be working in jet fuel-related occupations for other reasons (e.g., retirement, separation from military service). This leaves only the "healthy" workers to study, limiting the ability to detect true associations between exposures to jet fuels and potential health effects. In addition, many health outcome categories have one or more case studies observing effects of high-intensity, short duration jet fuel exposures (e.g., being soaked by a fuel spill). While informative from a clinical standpoint, these case studies are not generalizable to a wider military or civilian occupational population.

2.22.1. Nervous System Health Outcomes

There is slight evidence that jet fuel exposure negatively impacts neurological health, leading to adverse outcomes, including hearing impairment, memory impairment and ocular conditions. The evidence comes from 13 studies with primary data, considered medium (4), low (6) or uninformative (3) confidence studies. There was limited discussion about neurologic outcomes associated with duration of exposure. No primary studies assessed acute or immediate symptoms of neurologic outcomes as precursors to future risk of neurologic symptoms or diseases. Heaton et al. (2017) evaluated performance on motor and memory tests over the course of a week in active-duty USAF personnel with an average active-duty service length of 5.8 years. Years of Air Force service was not a significant predictor of any test. Study authors note that study day (i.e., Day 2, Day 4 or Day 6) was a significant predictor for multiple test outcomes, which suggests a practice effect from repeated testing rather than potential impact of pre-shift concentrations of urinary 1- and 2-naphthol. Maule et al. (2013) evaluated the relationship between exposure to JP-8 fuel and pre- and post-shift performance on a postural sway test in active-duty USAF personnel. Pre-shift performance and demographic data, rather than urinary 1- and 2-naphthol levels, explained most of the variance in post-shift performance. Olsen et al. (1998) examined neurological symptoms in exposed and unexposed active duty and civilian workers at Hill Air Force Base at the transition from JP-4 to JP-8 (baseline) and at 6 and 18 months of JP-8 use. For tests of memory, there was a significant increase in scores between baseline and 18 months in the exposed and unexposed groups, but these increases were similar between groups and attributed to a practice effect from repeated testing.

In a case study on a high-intensity, short-duration exposure, Shah and Wise (2015) reported on an aircraft mechanic with hearing loss the day after accidental JP-8 exposure, which had resolved after 2 weeks. Porter (1990) reported on two aviators with acute intoxication with JP-5 vapors during a training flight, who developed headache, worsened eye-hand coordination and “wobbly walk,” symptoms that resolved over the next 4 days. These case reports indicate that some immediate neurological symptoms following high-intensity exposures, such as hearing loss and headache, are reversible and less likely to result in long-term sequelae. However, a study of noise-exposed workers at a military installation showed evidence of increased acute hearing impairment and persistent hearing loss due to JP-4 exposure (Kaufman et al., 2005). Persistent hearing loss was elevated even under conditions of minimal noise exposure, with significant odds at 12 years and as the number of years of fuel exposure increased. Although the study design precluded the ability to determine whether workers with temporary hearing loss go on to develop persistent hearing loss, it is plausible for certain workers, especially with the added contribution of noise exposure.

Studies in civilian subjects provided evidence of increased neurological symptoms, self-reported symptoms of polyneuropathy and memory impairment, but these studies were frequently limited by ill-defined outcome assessment. Studies in military personnel frequently utilized standardized test instruments, which improved the quality of outcome assessment by limiting subjective interpretations. Medium confidence studies also suggested apparent improvements among jet fuel-exposed workers for vestibular function and motor function; however, study authors noted these findings may have been influenced by practice effects from repeated testing and/or exceptional performance of fit, young military personnel. Practice effects and exceptional performance may make it more difficult to observe associations due to jet fuel exposure in these populations.

2.22.2. Mental Health Outcomes

There is *slight* evidence that jet fuel exposure negatively impacts mental health, leading to certain adverse outcomes such as decrements in attention, cognitive function, visual-spatial performance, social-emotional behavior and regulation and depression. The evidence comes from five studies with primary data, considered medium (1), low (3) or uninformative (1) confidence studies. A case report (Porter, 1990), a case series (Lombardi & Lurie, 1957) and seven secondary data sources (ATSDR, 2017; B'Hymer, 2015; EASA, 2017; Karanikas et al., 2021; Kendall et al., 2001; NRC, 2003; Ritchie et al., 2001) also provided information on the association between jet fuel exposure and mental health outcomes. All studies reporting primary data evaluated long-term mental health outcomes, but determining acute changes in mental health responses in these studies was challenging given that the eligibility criteria for occupational studies frequently required more than 6 months of employment. Results were largely consistent across different aspects of mental health, demonstrating negative impacts of jet fuel exposure. Standardized mental health outcome assessment instruments were used in one study, but outcomes from other studies were less well-defined, resulting in some uncertainty.

There was limited discussion about long-term mental health outcomes and duration of exposure. Heaton et al. (2017) evaluated performance on attention, executive function, or visuospatial performance tests over the course of a week in active-duty USAF personnel with an average active-duty service length of 5.8 years. Years of Air Force service was not a significant predictor of attention, executive function or visuospatial performance scores. Apparent improvement in executive function over time may have been influenced by practice effects from repeated testing rather than exposure effect. Duration of exposure was considered in the study on active-duty and civilian workers at Hill Air Force Base at the transition from JP-4 to JP-8 and at 6 and 18 months of JP-8 use (Olsen et al., 1998). At 6 months, there were significantly faster reaction times in unexposed subjects compared to exposed subjects, but no difference in information processing speed or general cognitive function between the two groups.

Information from case reports and reviews also supported observations of detrimental effects of jet fuel exposure to attention, cognitive function, executive function and social-emotional behavior and regulation.

2.22.3. Respiratory Health Outcomes

There is *slight* evidence that jet fuel exposure negatively impacts respiratory health leading to acute adverse respiratory symptoms (such as dyspnea, cough with phlegm and runny nose), chronic cough and respiratory disease mortality. The evidence comes from seven primary studies, considered *medium* (1), *low* (3) or *uninformative* (3) confidence studies. There was limited discussion about acute or long-term respiratory health outcomes and duration of exposure. No primary studies assessed acute or immediate respiratory health outcomes as precursors to chronic symptoms or diseases; however, one case report described an aircraft mechanic with acute wheezing after being exposed to jet fuel, which worsened over the course of 4 years leading to an asthma diagnosis (Makker & Ayres, 1999). Olsen et al. (1998) examined respiratory symptoms in exposed and unexposed active-duty and civilian workers at Hill Air Force Base at the transition from JP-4 to JP-8 and at 6 and 18 months of JP-8 use but reported no statistical comparisons of exposure duration specifically. In a case study on a high-intensity, short-duration exposure, Aboudara and Yun (2006) reported on a military corporal who presented with acute pneumonitis following accidental aspiration of JP-8. The authors noted that the long-term implications of acute pneumonitis are uncertain.

While there were several primary and secondary studies on respiratory outcomes, most studies examined exposures and outcomes concurrently, limiting the ability to draw conclusions about relationships between jet fuel exposures and respiratory outcomes, especially those that are long term. Further, subjects in most studies were active workers, excluding subjects who have left the workforce because of illness or death, which if related to jet fuel exposure, would limit the ability to detect associations. Of the seven studies identified in this review, most included male civilians, with only one in active-duty personnel, thus limiting the ability to generalize about the impact of jet fuel exposures on military populations.

2.22.4. Cancer

There is *slight* evidence that jet fuel exposure is associated with cancer in humans, particularly kidney and bladder cancer. The evidence comes from eight studies, with one considered *medium* confidence and seven considered *low* confidence.

The evidence for kidney cancer is supported by two case-control studies in the same population of Montreal cancer patients (Parent et al., 2000; Siemiatycki, Dewar, et al., 1987) that reported an elevated risk of renal cell cancer in those exposed to aviation gasoline and jet fuel. The evidence for bladder cancer is supported by one cross-sectional study in newly diagnosed United Kingdom patients that observed a higher prevalence of high-grade bladder cancer compared to low-grade bladder cancer in patients self-reporting work involving exposure to aircraft fuel (Reed et al., 2020). In addition, there is evidence for increased cancer mortality supported by studies in a cohort of former civilian workers at the Hill Air Force Base, Utah, exposed to JP-8, enrolled between 1952 and 1956 and followed through the year 2000 (Blair et al., 1998; Radican et al., 2008; Spirtas et al., 1991) that showed elevated all-cause cancer mortality in men and elevated pancreatic and oropharyngeal cancer mortality in women.

The evidence for other specific cancers does not indicate associations with jet fuel exposures as some types of cancer were only studied in one type of cancer and the small number of cases observed.

Because most cancer types are generally less common, have long latencies and require long-term follow-up, the number of studies examining these associations with respect to jet fuel exposure is limited. Additional studies are needed to better understand specific types of cancers that are related to jet fuel exposure, precursors of these cancers and how risks change with duration of exposure.

2.22.5. *Health Outcomes with Indeterminate Evidence*

There is *indeterminate* evidence that jet fuel exposure is related to other health outcomes in humans. For cardiovascular, dermal, digestive, hematologic, hepatic, immune, renal, reproductive and other outcomes, little primary data were available, each with four or fewer studies with primary data. The results of these studies were inconsistent. For these health outcomes, no references discussed the risks of long-term health outcomes associated with immediate symptoms or health outcomes associated with duration of exposure.

- Cardiovascular health outcomes were reported in one *uninformative* study (Knave et al., 1978), three secondary reports (Kendall et al., 2001; NRC, 2003; Ritchie et al., 2003) and two case reports (Alsuwaida, 2010; Porter, 1990). These outcomes included acute cardiovascular symptoms, such as palpitations, thoracic oppression and elevated blood pressure among exposed workers and Service members; however, frequency of health care encounters did not reflect any differences related to exposure to jet fuels.

- Dermal health outcomes were reported in two *uninformative* studies (Olsen et al., 1998; Radhakrishnan et al., 2017), with additional information provided by four case reports (Contestable, 2017; Dever et al., 2012; Lombardi & Lurie, 1957; Long & Charles, 2018), one risk assessment (Kendall et al., 2001) and six reviews (B'Hymer, 2015; EASA, 2017; Karanikas et al., 2021; Leggat & Smith, 2006; Ritchie et al., 2003; Wang, 2004). These references reported on acute skin irritation including dry skin, itchy skin, rashes, scaling, transient whitening of the skin, burning sensation, redness, lesions or weeping and sensitization. None of the references discussed risks of long-term health outcomes.

- Digestive health outcomes were reported in one low confidence (Yang et al., 2003) and three uninformative studies (Knave et al., 1978; Knave et al., 1976; Olsen et al., 1998) as well as several secondary reports and case studies (EASA, 2017; Karanikas et al., 2021; Lombardi & Lurie, 1957; NRC, 1996; Porter, 1990; Ritchie et al., 2003; Salam et al., 2020; Wang, 2004). Symptoms reported included nausea, gastritis, vomiting and diarrhea, but none were associated with jet fuels in primary studies.

- Hematologic health outcomes were reported in one *low* confidence study (Olsen et al., 1998) and one case report (Salam et al., 2020), including markers of anemia and blood chemistry parameters, with no observed associations.

- Hepatic health outcomes, measured by liver enzymes as indicators of liver function, were reported in two *low* confidence studies (Olsen et al., 1998; Tu et al., 2004) and two secondary reports (Kendall et al., 2001; NRC, 2003). Neither primary study observed associations between liver enzyme levels and jet fuel exposure.

- Immune health outcomes, represented by measures of immune function and immune hypersensitivity, were reported in one *medium* confidence study

(Rhodes et al., 2003), one *low* confidence study (Olsen et al., 1998) and one *uninformative* study (Tunnicliffe et al., 1999), as well as four secondary reports (Kendall et al., 2001; NRC, 2003; Ritchie et al., 2003; Touri et al., 2013). Findings for immune system function were inconsistent across studies and no significant associations were observed for immune hypersensitivity with jet fuel exposure.

- Renal health outcomes, including acute renal failure and measures of serum or urinary biomarkers of kidney function, were reported in two *low* confidence studies (Olsen et al., 1998; Tu et al., 2004), three secondary reports (Kendall et al., 2001; NRC, 1996; NRC, 2003) and two case reports (Alsuwaida, 2010; Salam et al., 2020). Neither primary study observed significant associations between renal health outcomes and jet fuel exposure.

- Female reproductive health outcomes, including levels of reproductive hormones and menstrual cycle characteristics, were reported in one *medium* confidence study (Reutman et al., 2002) and one *low* confidence study (Gordley et al., 2000) in the same population and two reviews (ATSDR, 1995; Van Dyke, 2010). While a significant decrease in one reproductive hormone was observed in one study, no differences were observed for other hormones, nor for menstrual cycle characteristics analyzed in the other study, constituting inconsistent results.

- Other health outcomes described health outcomes that did not fit within the other categories. One *low* confidence study (D'Este et al., 2008) and a secondary review (NRC, 1996) reported on all-cause mortality, while a secondary report described rates of health care encounters due to any cause (Kendall et al., 2001). While the primary study and the secondary review reported lower mortality with jet fuel exposure, the limited number of studies and concerns for bias prevent a stronger overall determination.

No primary data were available for developmental, endocrine, metabolic and musculoskeletal outcomes. However, secondary data sources, including one risk assessment (Kendall et al., 2001), two reviews (EASA, 2017; Ritchie et al., 2001) and one case report (Spock et al., 2009) provided information on musculoskeletal disorders and alterations in reflexes. There was no information on developmental or endocrine outcomes.

2.22.6. Immediate Symptoms and Future Health Risks

This review was not able to directly assess the association between jet fuel exposures and acute symptoms that might be indicative of future health risks. Few of the primary studies or reviews, and almost none of the case reports, directly assessed acute symptoms (e.g., skin irritation, chest tightness, blurred vision, nausea) that persisted over a long period of time or progressed to more serious health conditions. A study of noise-exposed workers at a military installation showed evidence of increased temporary hearing impairment and of persistent hearing loss due to JP-4 jet fuel exposure (Kaufman et al., 2005). Persistent hearing loss was elevated even under conditions of minimal noise exposure, with significant loss at 12 years and as the number of years of fuel exposure increased. Although the study design precluded the ability to determine whether workers with acute hearing loss go on to develop persistent hearing loss, it is plausible that it could occur in certain workers, especially with the added contribution of noise exposure. One case report described acute respiratory symptoms (wheezing) that developed into asthma (Makker & Ayres, 1999). Primary epidemiologic studies generally measured exposures and health outcomes at the same timepoint in a cross-sectional fashion. For example, a study of active-duty Service members does not follow subjects over time, includes a single point of measurement of exposure and outcomes, and cannot examine changes in health over time or the persistence of symptoms after exposure. Notably, the case studies and case series often relate acute symptoms attributed to recent, high-intensity exposures, like accidental spills or inhaling vapors in confined spaces and symptoms that resolve with medical treatment within days or weeks, if follow-up is reported at all.

Furthermore, this review did not find ample evidence of future health risks (i.e., long-term health outcomes). With more information about long-term effects, it would be possible to determine early symptoms or precursors to disease from a broader knowledge base about a condition and then monitor for these conditions.

2.22.7. Effects by Length of Exposure

Only a handful of primary studies assessed risk of health effects by length of exposure (Andersen et al., 2021; Heaton et al., 2017; Knave et al., 1978; Knave et al., 1976; Lemasters et al., 1999; Maule et al., 2013; Olsen et al., 1998; Rhodes et al., 2003). Some studies that did so used years of service as a proxy for exposure duration or reported employment duration among exposed and unexposed groups as part of their analyses but did not analyze the impact of employment duration differences explicitly. Heaton et al. (2017) found that years of Air Force service was not a predictor of neurocognitive test performance. Olsen et al. (1998) reported health outcomes at the transition of JP-4 to JP-8 and then at 3, 6 and 18 months afterwards, finding differences among those exposed for 6 months to JP-8 compared to those unexposed for some mental health and nervous system outcomes and no differences in other outcomes (i.e., digestive, dermal, hematologic, renal, respiratory and hepatic). Andersen et al. (2021) found that exposed workers had significantly more years of experience, yet there was no difference between the groups with respect to lung function.

Some studies assessed outcomes at exposure intervals that might reflect an effect of cumulative exposure over time. Maule et al. (2013) investigated pre- and post-shift changes and found mixed relationships with balance testing. Lemasters et al. (1999) assessed outcomes upon beginning a jet fuel exposure job and again at 15 and 30 weeks and found a significant increase in sperm concentrations over time. While these approaches may be useful for long-term exposures via inhalation, one study noted that it was not possible to correlate duration of exposure with dermal exposures in their design since they were intermittent over many years of service (Radhakrishnan et al., 2017), posing a challenge in accurately assessing exposures for health analyses.

Furthermore, effects of various types of fuels by length of exposure could not be assessed given the limited available evidence in military and occupational settings as called for by section (b)(1). Studies included in this review predominantly assessed populations exposed to JP-8. The jet fuel that individuals were exposed to was not specified in some studies (n = 9). In addition, none of the studies included in this review conducted thorough exposure assessments to identify other exposures typically present in military and occupational studies, such as use of industrial solvents, nor did they conduct the subsequent analyses that allow for effects to be attributed to specific types of jet fuel. Therefore, it is not possible to tease apart the effect of one type of jet fuel from another within this body of literature.

While there may be limited analyses on duration of exposure, there are numerous case studies and series detailing high-intensity, short-duration exposure events (e.g., being soaked by a fuel spill) for nearly every health outcome category. By their nature, these studies assess acute outcomes that are present shortly after exposure, lasting a short time and usually resolving within days or weeks without evidence of leading to long-term disease. While these may be relatively common, they may not be useful beyond a clinical capacity or as a direction for future study. The impacts of short-term, high-intensity exposures point to the necessity of considering the magnitude of exposures on effects in addition to duration. For example, health outcomes related to very high exposure levels over a short time may lead to different health outcomes than low-level exposures over a long time.

2.22.8. Limitations

Several factors limit the ability to draw stronger conclusions based on the available epidemiologic evidence. The body of literature lacks prospective cohort studies with reliable exposure assessment and sufficient follow-up time to collect data on health outcomes with long latency periods (e.g., cancer) or that tend to develop later in life (e.g., chronic obstructive pulmonary disease [COPD]). Without such studies, it is difficult to discern what risk factors may promote disease development. With limited follow-up, studies are unable to observe whether acute outcomes or symptoms are precursors to long-term effects. Another limitation is that many studies examined exposures and outcomes concurrently, reducing the ability to draw causal determinations between jet fuel exposures and long-term health outcomes. Further, subjects in the available studies were active workers or service personnel, likely a healthier part of the population, which might be limiting the ability to detect true associations. Observational studies of occupational exposures are prone to healthy worker bias when workers previously exposed may have changed jobs due to health outcomes, retired, or died and, thus, are absent from the study population. The workers that are included in the occupational studies in this review often tended to be male, thus reducing the generalizability of findings. In addition, many health outcome categories have one or more case studies observing effects of high-intensity, short-duration jet fuel exposures (e.g., being soaked by a fuel spill). While informative from a clinical standpoint, these case studies are not generalizable to a wider population.

Although four health outcomes categories have sufficient evidence to draw conclusions on the relationship with jet fuel exposures, most health outcomes do not, with some areas being practically unstudied (e.g., endocrine and developmental outcomes). While certain topics may be more difficult to study for any number of reasons (e.g., developmental outcomes in babies born to mothers exposed to jet fuel during pregnancy), it does not make them any less important to assess. The lack of data from primary epidemiological studies identified as part of this review reflects the defined scope, which was limited to military and occupational populations. Additional information from other types of evidence streams of research, including jet fuel exposures among other populations or other exposure routes, considerations of co-morbidities and co-exposures, and data from toxicological research (i.e., animal and mechanistic data), can be useful to support the understanding of outcomes with little human data. Finally, there are no high confidence studies in this body of literature. While this is partly due to limitations already discussed, it is an indicator of areas of focus for future research priorities.

Part 3: Gaps and Next Steps

The literature review presented in Part 2 describes the availability and quality of epidemiological evidence available to support conclusions about associations between:

- Jet fuel exposure and health outcomes.
- Immediate symptoms, acute health outcomes and future health risks, or long-term health outcomes.
- Duration of exposure and health outcomes.

The review identified 28 unique primary epidemiological studies, 19 reviews and 14 case reports or case series that specifically investigated or described adverse health effects associated with jet fuel exposure among military or civilian occupational populations. There is slight evidence of associations between jet fuel exposure and certain organ system-level health outcomes, including the nervous system (e.g., decreased performance on motor and memory tests, as well as hearing impairment), mental health (e.g., decrements in attention, cognitive function, social-emotional behavior and regulation, visual-spatial performance and depression), the respiratory system (e.g., respiratory symptoms, such as dyspnea, cough with phlegm and runny nose, chronic cough and respiratory disease mortality) and cancers (e.g., kidney and bladder cancer). There is indeterminate evidence for all other health outcome categories.

3.1. Gaps in the Evidence

The body of evidence regarding health outcomes associated with jet fuel exposure in human occupational cohorts lacks high quality studies. The review identified no high confidence studies and eight medium confidence studies. The medium confidence studies reported on several health outcomes; one study reported on each of the following outcomes: mental health, respiratory, immune, female reproductive and neoplastic. Neurological outcomes are the only category informed by multiple (four) medium confidence studies. For neurological, mental health, respiratory and neoplastic outcomes, for which there is slight evidence of an association with jet fuel exposure, additional research or supporting evidence is needed to confirm possible associations and to show consistency, specificity, temporality, biological gradient, plausibility and coherence of the associations and, ultimately, to increase the ability to make causal determinations.

The other health outcome categories relied only on low or uninformative studies, which had methodological limitations that left their results open to the influence of bias or questionable reliability. No primary epidemiological studies in occupational cohorts reported metabolic, developmental, endocrine or musculoskeletal and connective tissue effects. Additional research is needed to further explore whether there are health outcomes of concern among these categories.

Another important gap in the available evidence is that few studies included adequate follow-up to observe long-term health outcomes many months or years after exposure began; most studies assessed health outcomes among current workers who were actively working and exposed to jet fuels. Most of the case studies and case series reviewed indicate resolution of symptoms with treatment or removal of exposure, rather than long-term, irreversible damage. Therefore, the persistence of these health outcomes after exposure has ceased and development of long-term effects is not well understood.

Results from the reviewed studies require further consideration to be generalizable to the broader Veteran population. Impacts of jet fuel exposure were investigated among military personnel or at military bases in 17 studies and among occupational (non-military) populations in 10 studies. Study populations were located primarily in the United States (15) but also in Australia, Canada, Denmark, India, Sweden, Taiwan and the United Kingdom. There is a lack of data describing outcomes in female Service members and workers. In addition, important characteristics that might be associated with exposures and health outcomes, such as race/ethnicity, lifestyle factors (e.g., diet, alcohol consumption) and co-morbidities, were rarely reported in this body of literature.

The ability to draw conclusions about associations between jet fuel exposure and health outcomes is limited by the availability and quality of epidemiological data. As this review focused on evidence among military and civilian occupational populations only, other streams of evidence, including other kinds of human exposure (such as environmental exposure to jet fuels), toxicological data from animal studies and mechanistic data can be useful to fill some of the gaps in the epidemiological data. These additional evidence streams can provide support for evidence seen in the military and occupational populations, enhance the understanding of the relationship between jet fuel exposure and health outcomes (i.e., provide coherence) and potentially show a biological gradient (i.e., dose-response). Previous authoritative reviews relied on toxicological evidence to inform risk-based estimates of jet fuel exposure (ATSDR, 2017; NRC, 2003). A systematic review of such data will be conducted and included in the follow-up report due in 5 years.

3.1.1. Evidence Informing the Association Between Health Effects and Length of Exposure

There are no studies that examined health effects by length of exposure. Although studies reported contextual information, such as average duration of employment, statistical analyses or qualitative comparisons to distinguish between shorter and longer durations were not reported. Furthermore, the role of magnitude of exposure was often not reported, but it was evident across case reports and case series, wherein effects were generally associated with short-term, high-intensity exposures.

3.1.2. Evidence Informing the Association Between Immediate Symptoms and Future Health Risks

None of the primary studies provided direct evidence regarding whether immediate symptoms or acute effects resulting from jet fuel exposure developed into more severe and/or chronic health risks. Early signs and symptoms indicative of future health risks (i.e., long-term health outcomes) could be identified from the broader knowledge of specific health conditions. However, there was not enough evidence of adequate quality to reach reliable conclusions about whether jet fuel exposure was associated with risks of any future long-term health outcomes. In the absence of an understanding about long-term health outcomes, it is not possible to determine early symptoms or signs that would predict future health risks.

Evidence showing a temporal relationship between exposure, early symptoms or signs and later disease requires prospective studies with sufficient follow-up to allow for disease progression and clinical diagnosis. While cross-sectional studies can collect retrospective information about symptoms and exposure, potential for recall bias may affect the accuracy of such information.

3.1.3. Approaches to Address Evidence Gaps

Gathering or generating evidence to fill the gaps identified above can be accomplished through additional epidemiological studies and literature reviews.

Additional literature reviews and synthesis of available information:

- Expand the scope of the evidence review to include non-occupationally exposed populations, if available, such as those unintentionally exposed through environmental releases or spills.
- Review the toxicological literature, including animal studies and mechanistic data, to provide supporting evidence and further develop the understanding of potential health outcomes in humans.

Types of research to pursue:

High confidence studies of neurological, mental health, respiratory and cancer outcomes, for which there is currently slight evidence of an association with jet fuel exposure, to confirm those associations and to show consistency, specificity, temporality, biological gradient, plausibility and coherence of the associations and, potentially, enable causality determinations.

- Studies that explore associations between jet fuel exposure and health outcomes that are not well studied.
- Studies that make statistical comparisons based on duration of exposure to jet fuel.
- Studies with adequate follow-up after the onset of exposure to observe long-term health outcomes.
- Studies that follow participants over time to observe the natural history of jet fuel-related health effects and the resolution, persistence or progression of immediate symptoms.
- Studies in populations from underrepresented groups, such as women and racial/ethnic minorities.

- Studies that also consider co-morbidities and potential impact of co-exposures which might act as effect modifiers of the associations between exposures to jet fuels and health outcomes.

- Studies that integrate epidemiological methods with biological endpoints to elucidate mechanisms of toxicity in jet fuel-exposed Service members and Veterans.

VA intends to conduct research to address these gaps where feasible, including conducting additional epidemiological studies (outlined below) that will add to the available evidence base. VA also plans to conduct a more comprehensive systematic review that includes toxicological data and mechanistic data as part of the follow up to this report, due to Congress in 5 years.

3.2. VA Studies Currently in Progress

It is documented that exposure to jet fuels can cause acute adverse effects (ATSDR, 2017; NRC, 2003); however, long-term, chronic health outcomes have not been well studied in military populations. To address this issue, HOME and the U.S. Air Force School of Aerospace Medicine (USAFSAM) conducted a pilot study in 2018 using Military Occupational Specialty (MOS) codes as a surrogate for jet fuel exposure. This study suggested that those with potential occupational exposure to jet fuel during service in the Air Force may have increased risks of disease in several organ systems. HOME, in collaboration with USAFSAM, the Defense Centers for Public Health—Aberdeen and Portsmouth and the Uniformed Services University of the Health Sciences, is currently conducting a larger, retrospective study using administrative data collected by DoD and VA databases, exposure monitoring data, health care data, disability compensation claims data and mortality data to investigate the long-term health effects of occupational jet fuel exposure (studies 1 through 3 below) (Irons et al., 2019; Samuel et al., 2022; Vincent, 2019).

Although, as described below, this research will rely on occupation as a proxy for jet fuel exposure and time spent under a fuel-exposed job code as a proxy for exposure duration, it will also incorporate monitoring data to characterize exposure intensity. Furthermore, it will contribute the largest cohort studied for adverse effects of jet fuel exposure during service in the U.S. military, with sufficient follow-up to account for latencies of certain health outcomes and adequate statistical power to evaluate conditions in all body systems, including rare conditions. Results of the initial analyses are expected in early 2024.

In addition, a complementary biomarkers study (study 4) is being planned that will use serum samples of Millennium Cohort Study participants that are banked in the DoD Serum Repository to validate exposure to jet fuels. This effort is a collaboration with the Naval Health Research Center and is slated to begin in fall 2023.

3.2.1. Assembly of Cohorts and Exposure Characterization

HOME will explore different methods of characterizing exposure using MOS codes and duty history. Industrial health personnel from all branches have provided two sets of

MOS codes: one set wherein jet fuel exposure is likely (e.g., fuel handlers, mechanics) and one set of control codes for which no exposure to jet fuel is expected (e.g., administrative jobs). The study population is restricted to those: (1) with the specified MOS codes at any point in their service, (2) who started in 1995 or later, (3) who served in active duty only, (4) who served in only one branch, %5) who had served at least 2 years and (6) who had separated from the military. Analyses to make statistical comparisons based on duration of exposure to jet fuel will be conducted. Duration of fuel exposure will be generated by assessing the total amount of time spent serving under a fuel-exposed MOS code for all individuals in the exposed group. Cumulative exposure estimates will also be calculated using the exposure duration and frequency and intensity of exposure associated with the exposed MOS codes based on monitoring data from the Defense Occupational and Environmental Health Readiness System—Industrial Hygiene database. Major strengths of these studies include a large population (i.e., the ability to analyze most outcomes) and the incorporation of comprehensive records on military history (e.g., MOS codes, changes in rank, deployments). A limiting factor is the use of MOS/monitoring data as a proxy for exposure since individual exposure measurements are not available.

3.2.1.1. Study 1: Health Care Encounters

The aim of this study is to determine whether occupational exposure to jet fuel increases the risk of adverse health outcomes among Veterans who served in the U.S. military. DoD TRICARE claims and VHA health care utilization data (ICD-9/10 diagnosis codes related to inpatient, outpatient or fee-for-service visits) were obtained for all individuals in the cohort who used TRICARE or VA for health care after separation. Outcomes will be assessed based on condition categories by organ system and subcategories within categories. Retrospective analyses will be conducted for all outcomes using the start of active duty as the index date for outcome occurrence. Models will be adjusted for race, sex, rank, length of service, age at separation and deployment. Sub-analyses may also consider other confounders, such as smoking and alcohol/drug abuse. Health care encounter data represent up to 25 years of surveillance for this study population, which provides adequate follow-up after the onset of exposure to observe long-term health outcomes, such as cancer.

3.2.1.2. Study 2: Mortality

The aim of this study is to assess the relationship between all-cause mortality and jet fuel exposure in Veterans and Service members with previous occupational exposure to jet fuels. Data were obtained from the VA Mortality Data Repository. The study objective is to assess the effects of jet fuel exposure and duration of exposure on mortality and, In addition, to assess the impact of deployment on jet fuel exposure and duration on mortality. Models will be adjusted for age, gender, race/ethnicity, rank and length of service. Individuals with deaths related to operations of war and sequelae will be excluded from the analyses. Future analyses will include comparisons of specific causes of mortality (e.g., cancers, neurological, respiratory, cardiovascular and mental health outcomes) in exposed vs. unexposed Veterans and Service members.

3.2.1.3. Study 3: Disability Compensation Claims

The aim of this study is to assess the association between occupational jet fuel exposure and disability compensation claims in individuals from the cohort identified above who had filed a claim for disability compensation with the Veterans Benefits Administration. Selected claims data for chronic health conditions will be retrieved for these individuals. Disability compensation claims for health conditions that are considered unrelated to jet fuel exposure, such as orthopedic or traumatic injuries, will be excluded from all analyses. Models will analyze several claims-related variables, including but not limited to the rate of compensation claims filed and granted and the disability rating percentage (adjusting for the same variables mentioned above). Initial analyses will explore comparisons between exposed and unexposed populations for system-level outcome categories and sub-analyses will include analyses of claims data for specific diagnoses. While this study has the same strengths as the other records-based studies in this portfolio, it is worth noting that the analysis of compensation claims data for this purpose has significant limitations because there are several other factors (besides exposure to jet fuels) that may impact (1) a Veteran's decision to seek disability compensation and (2) the adjudication of compensation claims. Thus, the findings of this study will serve as supporting information to be considered with the results of the encounters and mortality studies.

3.2.1.4. Study 4: Exposure Validation Study

The objective of this study is to conduct an analysis of fuels biomarkers measured in serum collected from Service members with certain MOS codes enrolled in the Millennium Cohort Study. Existing serum specimens from the DoD Serum Repository will be analyzed at the Military and Veteran Microbiome Consortium for Research and Education (MVM CoRE) in VA's Rocky Mountain Mental Illness Research, Education and Clinical Center (MIRECC) in Aurora, Colorado, using a validated method to quantify miRNAs and other markers. Profiles of miRNAs will be measured, and associations between military characteristics (e.g., occupation, time-in-job, deployment) and fuel biomarker concentrations will be analyzed. Exploratory analyses will examine associations between biomarkers of exposure to fuel and biomarkers predictive of long-term health outcomes, including cancers and respiratory and neurological effects, thus providing some insight into the mechanistic underpinnings of these diseases in exposed personnel. An additional exploratory analysis will investigate the association between military occupations, including those involving the handling of fuels and health outcomes ascertained from Millennium Cohort Study surveys, as well as Military Health System and VHA health care utilization data. This study will be critical for establishing biomarkers to track exposure and potential long-term health outcomes among military personnel, particularly those in fuel-handling occupations.

3.2.2. Conclusion

VA has submitted this report regarding the health effects of jet fuels used by the Armed Forces as required by section 510 of the PACT Act. In completing the report, VA has included a discussion of the effect of various different types of jet fuels used by the Armed Forces on the health of individuals by length of exposure, an identification of the immediate symptoms of jet fuel exposure that may indicate future health risks, a chronology of health safeguards implemented by the Armed Forces intended to reduce the exposure of members of the Armed Forces to jet fuel and an identification of any areas relating to jet fuel exposure about which new research needs to be conducted. While the health effects related to certain individual components of jet fuels are documented, factors related to how these individual components combine to impact long-term health have not been established. VA is actively investigating the implications of occupational jet fuel exposure in the military and looks forward to providing a follow-up report to Congress in 5 years.

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Table A-1. DoD-wide Policies and Guidance Regarding Jet Fuel Safeguards.

Policy Name	Issue Date	Document Name	Prior Versions
Aircraft Refueling Handbooks for Navy/Marine Corps Aircraft	12/3/2003	MIL-HDBK-844A (AS), Department of Defense Handbook	MIL-HDBK-844 dated October 20, 1992
Occupational and Environmental Health	11/8/2008	DoDI 6055.05	
DoD Safety and Occupational Health Program	10/14/2014	DoDI 6055.01	
Identification Methods for Bulk Petroleum Products and Systems including Hydrocarbon Missile	9/30/2015	MIL-STD 161-H	MIL-STD 161-F and G dated January 6, 1972
Joint Bulk Petroleum and Water Doctrine	1/11/2016	Joint Publication 4-03	
Petroleum Fuel Systems Maintenance	11/10/2017	UFC 3-460-03	
Petroleum Fuel Facilities	7/16/2019	UFC 3-460-01	USD (AT and L) Memorandum dated May 29, 2002
DoD Hazard Communication Program	2/26/2019	DoDI 6050.05	
Occupational Medical Examinations: Medical Surveillance and Medical Qualification	7/27/2022	DoD Manual 6055.05	

DoD = Department of Defense; DoDI = DoD Instruction; MIL-HDBK = Military Handbook; MIL-STD = Military Standard; UFC = Unified Facilities Criteria; USD (AT and L) = Under Secretaries of Defense, Acquisition, Technology and Logistics

Table A-2. Army-Wide Policies and Guidance Regarding Jet Fuel Safeguards.

Policy Name	Issue Date	Document Name	Prior Versions
Medical Surveillance Exams of Army Personnel Exposed to Fuel	Unknown	Army Public Health Center Fact Sheet No. 65-052-0918	
Operator's Manual for HEMMT Tanker Aviation Refueling System (NSN 4930-01-269-2273) Model Number 50-0051	3/10/1989	TM 5-4930-237-10	
Aviation Unit Maintenance and Aviation Intermediate Maintenance for General Aircraft Maintenance (Maintenance Practices for Fuel and Oil Systems) Volume 3	7/31/1992	TM 1-1500-204-23-3	
Environmental Protection and Enhancement	12/13/2007	AR 200-1	
Army Aviation Accident Prevention Program	8/27/2007	DA PAM 385-90	
Army Facilities Management	11/2/2007	AR 420-1	
The Army Safety Program	5/23/2008	DA PAM 385-10	
Soldier Training Publication 10-92F15-SM-TG	5/20/2010	STP 10-92F15-SM-TG	
Environmental Health Risk Assessment and Chemical Exposure Guidelines for Deployed Military Personne	2013	USAPHC-TG 230	
Army Industrial Hygiene Program	4/2/2013	DA PAM 40-503	
Risk Management	12/2/2014	DA PAM 385-30	
Firefighting	4/23/2015	TM 3-34.30	
Environmental Considerations	8/10/2015	ATP 3-34.5 MCRP 3-40B.2	
Army Emergency Management Program	3/29/2016	AR 525-27	

Policy Name	Issue Date	Document Name	Prior Versions
The Environment and Deployment: Tactical Risk and Spill Response Procedures	4/30/2016	GTA 05-08-017	
Army Safety Program	2/24/2017	AR 385-10	
Toxic Chemicals Agent Safety Standards	11/1/2018	DA PAM 385-61	
Techniques for Forward Arming and Refueling Points	6/30/2018	ATP 3-04.17	
Airfield Operations	2/28/2020	TC 3-04.16	
Army Public Health Program	5/18/2020	DAPAM 40-11	
Army Emergency Management Program	7/17/2020	DA PAM 525-27	
Hazardous Material Spill Response Procedures for Vehicle Operators	7/31/2020	GTA 05-08-003	
Petroleum Supply Operations	4/18/2022	ATP 4-43	
Fuels and Lubricants	5/6/2022	AR) 70-12	

ATP = Army Techniques Publication; AR = Army Regulation; DAPAM = Department of the Army Pamphlet; GTA = Graphic Training Aid; HEMMT = Heavy Expanded Mobility Tactical Truck; JP = Jet Petroleum; STP = Soldier Training Program; TC = Training Circular; TM = Technical Manual.

Table A-3. Air Force-Wide Policies and Guidance Regarding Jet Fuel Safeguards.

Policy Name	Issue Date	Document Name	Prior Versions
Jet Fuel Health Hazard Training	Unknown	711th Human Performance Wing/United States Air Force School of Aerospace Medicine	
Health Risk Assessment Information for Alternative to F-24/JP-8 Jet Fuels	Undated	711th Human Performance Wing/United States Air Force School of Aerospace Medicine	
Interim Base-Level Guide for Exposure to Jet Fuel and Additives	12/31/2011	AFRL-SA-WP-SR-2012-0002	
Fact Sheet Jet A and Jet A-1 Fuel	1/12/2016	711th Human Performance Wing/United States Air Force School of Aerospace Medicine	
Fact Sheet Jet Fuel Vapor Sampling and Information	1/12/2016	711th Human Performance Wing/United States Air Force School of Aerospace Medicine	
United States Air Force School of Aerospace Medicine and Laboratory Sampling and Analysis Guide	11/30/2016	AFRL-SA-WP-SR-2016-0023	
Management of Bulk Petroleum and Related Products	8/2/2017	AFPD 23-2	
Environmental Safety and Occupational Health Management and Risk Management	12/23/2019	AFPD 90-8	
Fuels Management	9/9/2021	AFI 23-201	
Occupational and Environmental Health	9/22/2022	AFI 48-145	AFI 48-145 dated July 11, 2018
Occupational Health Program Management	12/1/2022	Air Force Manual 48-146	

AFI = Air Force Instruction; AFPD = Air Force Policy Directive; AFRL = Air Force Research Lab; JP = Jet Petroleum.

Table A-4. Navy-Wide Policies and Guidance Regarding Jet Fuel Safeguards.

Policy Name	Issue Date	Document Name	Prior Versions
Fuel Management Ashore	12/31/1994	NAVSUP Publication 558	Prior publication dated January 1987
Bulk Liquids Operations	8/29/1996	MCWP 4-25.5	
Underway Replenishment	8/31/1996	NWP 4-01.4	NWP 14 (Revision E) "Replenishment at Sea" dated 1987
Petroleum and Water Logistics Operations	6/19/2005	MCWP 4-11.6	MCWP 4-11.6, dated August 19, 1996
Marine Corps Occupational Safety and Health Program Manual	5/15/2006	NAVMC DIR 5100.8	
Gasoline and JP-5 Fuel Systems	7/1/2010	Naval Ships' Technical Manual S9086-SP-STM-010	Revision 4, dated January 15, 2008
Navy Safety and Occupational Health Program Manual for Forces Afloat	5/5/2019	OPNAVINST 5100.19F	OPNAVINST 5100.19E, dated May 30, 2007
Navy Safety and Occupational Health Program	6/5/2020	OPNAVINST 5100.23H	OPNAVINST 5100.23G
Aircraft Refueling Naval Air Training and Operating Procedures Standardization Manual	10/15/2022	NAVAIR 00-80T-109	NATOPS Manual dated May 30, 1999

JP = Jet Petroleum; MCWP= Marine Corps Warfighting Publication; NAVAIR = Naval Air Systems Command; NAVMC DIR = Navy and Marine Corps Directive; NAVSUP = Naval Supply Systems; NWP= Naval Warfare Publication; OPNAVINST = Operational Naval Instruction.

Appendix B: Systematic Review Protocol for Jet Fuels

Jet fuel, one of the single largest sources of chemical exposures to military personnel, is a heterogeneous mixture that consists of aromatic and aliphatic hydrocarbons and non-hydrocarbon performance additives, with kerosene being the primary component (>98%). Toxic hydrocarbons, such as benzene, toluene and naphthalene, are minor constituents of bulk fuel, but their volatility is such that there is high potential for inhalation among military personnel working with fuels. Exposures in occupational settings can also occur via dermal absorption and incidental ingestion. Previous studies have reported acute health outcomes associated with exposure to the constituents of jet fuels, including hematological and neurological effects; however, less is known about long-term, chronic health outcomes. VA's HOME is currently collaborating with DoD on an investigation of the long-term health outcomes in Veterans that have experienced occupational exposure to jet fuels.

This review was designed to follow a systematic literature review methodology to ensure consistency and transparency regarding the evidence that was considered and how it was evaluated. However, the approach was tailored to suit VA's priorities. The review methods were derived and adapted from those used by the U.S. EPA (the IRIS Handbook) to conduct comprehensive assessment of the scientific evidence and support evaluation of the effects of chemical agents (U.S. EPA, 2022b). EPA's approach is well accepted for its support of scientific decision-making. EPA's approach provides guidance for conducting an assessment, including developing PECO (Populations, Exposures, Comparators and Outcomes) criteria, evaluating study quality, extracting data and synthesizing evidence using a weight of the evidence approach to reach conclusions.

The ability to reach conclusions about associations between exposures to jet fuels and certain health outcomes was determined by the availability of epidemiologic evidence (i.e., quantity of studies) and certainty in the results (i.e., degree of confidence that results are valid, replicable and not due to chance), also known as a weight-of-the-evidence assessment. Where evidence was lacking, for example, for health outcome categories for which there were no epidemiologic studies of sufficient quality or health outcomes, gaps in the evidence base were identified.

B.1. Scope and Populations, Exposures, Comparators and Outcomes Criteria

B.1.1. Scope

The scope of this review is limited by population and exposure to ensure that conclusions are specific to Veterans who have had jet fuel exposure. VA's goal is to support the health and wellbeing of Veterans who were exposed to jet fuels as part of their military duties. Therefore, the systematic literature review focused on effects in exposed military populations. Occupational exposures such as workers at commercial airports were also included to ensure a robust evidence base that is specific to working adults. Studies of the general population exposed through other means were not included because such studies include heterogenous populations (such as children, the elderly or susceptible populations) and exposures (such as contaminated ground water or residential use of kerosene) with unknown relevance to Veterans.

The health impacts of jet fuels can be informed by the broader evidence base regarding jet fuel components such as kerosene, individual chemical constituents (such as particulate matter, naphthalene or benzene) or jet fuel additives (chemicals added to enhance performance and impart anti corrosive or anti-icing properties). However, the understanding of how the effects of those individual components combine to cause health effects is an area of ongoing research. To account for the effects of all components of jet fuels as a mixture and reflect the real-world context of Veteran exposures, this review concentrated on exposure to jet fuels only. In addition, this review included instances where epidemiological studies measured components or constituents as a surrogate for jet fuel exposure.

Because of the specificity of the scope, this review took a broad view of the types of evidence to consider. Case reports or case series (documentation of effects in one or a few people with no comparison to unexposed people) are included in the discussion as supporting information. Reviews are also included in this review, including comprehensive reviews that do not use systematic methodology. Although case reports, case series and reviews provide less reliable evidence to support conclusions, they are discussed as part of the synthesis of the evidence as supporting information and context for gaps in the existing body of evidence and noted as secondary references.

B.1.2. PECO Criteria

This section describes the PECO criteria that were developed and used for this assessment. As described in the IRIS Handbook (EPA, 2022b), the PECO criteria provide the framework for literature search strategies and are the inclusion/exclusion criteria by which literature search results will be screened for relevancy to identify epidemiological evidence that addresses the aims of the assessment. The PECO criteria were used to screen results of the literature searches to identify and prioritize the primary epidemiological literature by categorizing (“tagging”) studies of jet fuel exposure related health effects for further evaluation. Animal toxicological, mechanistic and other supplemental studies captured in the literature search were not tagged or considered further in this assessment.

Table B-1 on page 183 describes the PECO criteria used to screen the results of the literature search (the literature search is described in Section Literature Search Strategies of this appendix).

Table B-1. PECO Criteria for a Systematic Review on the Health Effects From Exposure to Jet Fuel.

PECO Element	Inclusion Criteria
Population	Any military or occupationally exposed population (not limited by country).
Exposure	**Relevant forms:** Jet Fuels Other names: Kerosene, jet exhaust, jet engine exhaust, aircraft exhaust, aircraft engine exhaust, aircraft fuel, aviation fuel, aviation turbine fuel, jet propellant, aviation propellant, aircraft propellant, jet A fuel, jet A-1 fuel, Jet B fuel, TS-1 fuel, JP-1 fuel, JP1 fuel, JP-2 fuel, JP2 fuel, JP-3 fuel, JP3 fuel, JP-4 fuel, JP4 fuel, JP-5 fuel, JP5 fuel, JP-6 Fuel, JP6 Fuel, JP-7 Fuel, JP7 Fuel, JP-8 fuel, JP8 fuel, JP-9 fuel, JP9 fuel, JP-10 fuel, JP10 fuel, JPTS fuel, zip fuel, JP5 jet fuel, S-8 fuel, JP8 aviation fuel, JP4 aviation fuel Any exposure to jet fuels, listed above, via any exposure route (e.g., oral, dermal, inhalation or unknown/multiple routes).
Comparator	A comparison or referent population not exposed, or exposed to lower levels, of jet fuels.
Outcome	All health outcomes (cancer and non-cancer, see Table B-2: Health Effect Categories Considered for Epidemiological Studies). Epidemiological studies with self-reported diagnosed disease and self-reported symptoms are included

Table B-2 below was generated to supplement the Outcome criteria described in the PECO and is referenced throughout the systematic review steps.

Table B-2. Health Effect Categories Considered for Epidemiological Studies.

Health Effect Category	Example Health Outcomes	Notes
Cancers	Benign Tumors Malignant Tumors Precancerous lesions (e.g., dysplasia)	Includes multiple myeloma, myelodysplastic syndrome, lymphomas
Cardiovascular	Atherosclerosis Blood pressure Clotting factors and functional tests (e.g., tissue factor, fibrinogen) Coronary heart disease Hypertension Other cardiovascular disease Serum lipids (e.g., cholesterol, LDL, HDL, triglycerides) Stroke	–
Dental	Dental caries/cavities	–

Health Effect Category	Example Health Outcomes	Notes
Dermal	Acne Skin sensitivity, irritation Immune: o Scleroderma o Atopic dermatitis/eczema	
Developmental	Birth defects Birth size (e.g., birth weight, birth length, small for gestational age) Preterm birth Postnatal growth Sex ratio	Markers of development specific to other systems are organ/system-specific (e.g., tests of sensory maturation are considered ***Nervous*** outcomes) Sexual maturation is considered a ***Reproductive*** outcome Pubertal development is considered a ***Reproductive*** outcome
Digestive	Symptoms of the stomach and intestines (e.g., diarrhea, nausea, vomiting, abdominal pain, cramps) Immune: o Ulcerative colitis o Crohn's disease o Celiac disease o Inflammatory bowel disease	Cytokine measurements (e.g., Interleukin-6 [IL-6]) are considered ***Mechanistic*** outcomes Serum globulin levels are considered an ***Immune*** outcome Serum glucose levels are considered a ***Metabolic*** outcome
Endocrine	Hormonal measures in any tissue or blood (non-reproductive) Stress-related factors in blood (e.g., glucocorticoids or other adrenal markers) Thyroid-related hormones (e.g., T3, T4, TSH)	Reproductive hormones (e.g., estrogen, progesterone, testosterone, luteinizing hormone (LH), follicular stimulating hormone (FSH), FSH) are considered ***Reproductive*** outcomes
Hematologic	Anemia Blood biochemical measurements (e.g., sodium, calcium, phosphorus, Vitamin D) Blood count Blood platelets or reticulocytes Corpuscular volume	Serum lipids are considered ***Cardiovascular*** outcomes Serum liver markers (e.g., ALT, AST) are considered ***Hepatic*** outcomes White blood cell counts and globulin are considered ***Immune*** outcomes

Health Effect Category	Example Health Outcomes	Notes
	Hematocrit or hemoglobin Red blood cells	
Hepatic	Albumin Albumin/globulin ratio Bile acids/salts Bilirubin Hepatic steatosis/fatty liver Liver disease Liver enzymes (e.g., Alanine transaminase; aspartate transferase; alkaline phosphatase) Liver-specific serum biochemistry markers (e.g., gamma-glutamyl transferase, sorbitol dehydrogenase)	
Immune	Allergy Autoimmune diseases (e.g., multiple sclerosis, lupus, rheumatoid arthritis) General immune assays (e.g., white blood cell counts) Hypersensitivity Immunoglobulins (e.g., IgE, IgG, IgM) Infectious diseases Serum globulin levels Vaccine response White blood cell activity assays	Red blood cells are considered a ***Hematological*** outcome Cytokine measurements (e.g., Interleukin-6 [IL-6]) are considered ***Mechanistic*** outcomes
Mental Health	Anxiety Attention (ADHD) Autism Behavior/behavioral tests Cognition Depression Post-traumatic stress disorder (PTSD/PTSS) Suicide Other mental health disorders	–
Metabolic	Adiponectin and leptin levels Adiposity Body Mass Index (BMI; e.g., BMI standard deviation score, BMI z-scores)	Gestational weight gain and adult weight change are included here

Health Effect Category	Example Health Outcomes	Notes
	Body mass measurements Diabetes (including gestational diabetes) Glucose measurements (e.g., serum glucose levels, glucose intolerance tests) Insulin measurements (e.g., HOMA-IR, insulin resistance, serum insulin levels) Metabolic syndrome Obesity Ponderal index Resting metabolic rate Waist circumference	
Musculoskeletal/Connective Tissue	Bone density Bone health Muscle weakness or fatigue Osteoarthritis Osteoporosis	–
Nervous	Ataxia Communication Eye disease Eye irritation Headache Hearing impairment or loss Memory tests Migraine Motor function tests Neurotransmitter levels Neurodevelopmental Neurodegenerative disorders Other neurobehavioral conditions Parkinson's Disease, parkinsonism TBI (traumatic brain injury) Tinnitus Vision changes	–
Renal	Creatine End Stage Renal Disease (ESRD) Glomerular filtration rate Gout Kidney disease	–

Health Effect Category	Example Health Outcomes	Notes
	Nephropathy Renal function Uric acid Urinary measures (e.g., protein; volume; pH; specific gravity; BUN; ammonia) Other renal conditions	
Reproductive, female	Anogenital distance (females) Breastfeeding Endometriosis Fecundity Fertility index Length of gestation Menopause Menstrual cycle characteristics Polycystic ovarian syndrome (PCOS) Pubertal development Reproductive hormones Spontaneous abortion (e.g., miscarriage, stillbirths)	If data indicate altered birth parameters are likely attributable to female fertility, these data may be discussed under **Female Reproductive**
Reproductive, male	Anogenital distance (males) Pubertal development Reproductive hormones Semen parameters Sexual maturation Sperm DNA damage	–
Respiratory	Bronchitis Pulmonary function tests (e.g., FEV1, FVC, lung capacity) Rhinitis Sleep apnea Sinusitis Immune: o Asthma o Lower/upper respiratory tract infections o Wheeze	–
Other	Select this category if the outcome does not fit in any of the above categories, including multi-system syndromes (e.g., chronic fatigue syndrome) and	–

Health Effect Category	Example Health Outcomes	Notes
	non-specific symptoms or diseases (e.g., fatigue)	

ADHD = attention-deficit/hyperactivity disorder; ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate aminotransferase; BMI = body mass index; BUN = blood urea nitrogen; DNA = deoxyribonucleic acid; ESRD = end stage renal disease; FEV1 = forced expiratory volume in one second; FSH = follicular stimulating hormone; FVC = forced vital capacity; GFR = glomerular filtration rate; HDL = high-density lipoprotein; HOMA-IR = homeostatic model assessment of insulin resistance; IgE = immunoglobulin E; IgG = immunoglobulin G; IgM = immunoglobulin M; IL-6 = interleukin 6; LDL = low-density lipoprotein; LH = luteinizing hormone; PBPK = physiologically-based pharmacokinetic; PCOS = polycystic ovary syndrome; PK = pharmacokinetic; PTSD = post-traumatic stress disorder; PTSS = post-traumatic stress syndrome; T3 = triiodothyronine; T4 = thyroxine; TBI = traumatic brain injury; TSH = thyroid stimulating hormone.

B.2. Literature Search

VA conducted a broad search of epidemiological studies for this health assessment based on four data streams:

- Literature identified via searches of scientific literature databases (PubMed and EBSCOhost) with no date restrictions,
- Literature identified via a search of the gray literature, or publications produced outside of traditional scientific publishing avenues, including reports from government agencies and authoritative bodies not generally available in databases of published literature,
- Expert identified publications and reports identified by VA, DoD or other subject matter experts; and
- A review of references cited in five identified secondary reviews to ensure a comprehensive body of literature.

B.2.1. Literature Search Strategies

The following sections describe literature search strategies used for databases and for additional sources. The literature search strategy included searches within core literature databases (e.g., PubMed) as well as relevant domestic and international non-periodical “gray” literature, such as technical reports, monographs and conference and symposium proceedings prepared by select committees or bodies (e.g., those convened by the National Academy of Sciences or the World Health Organization [WHO]).

B.2.2. Database Searches

The database literature searches for this review focused only on the chemical name (jet fuels) of only epidemiological (human) data with no limitations on health outcomes. The health effects search strings applied to the database searches were developed as a generic filter that would remove studies outside of the broad topic areas of Health, Epidemiology and Toxicology. As such, there are many terms used that will not be relevant for a given research topic. This filter is intended to restrict the scope of search results while being broad enough to not remove relevant studies.

These searches comprised all literature related to health effects in humans resulting from acute, subchronic and chronic exposure durations and from all exposure pathway (e.g., inhalation, oral, dermal and injection) studies.

PubMed (National Library of Medicine) and EBSCOhost were searched for literature containing the search strings identified in Table B below and Table B-4 on page 192, respectively. These terms searched in Title and Abstract fields, unless otherwise noted. The literature search was conducted on January 10, 2023 with no date limit on the search.

Table B-3. Search String for PubMed Search (January 10, 2023).

String Name	Search String	Results
Jet Fuel	Jet Fuel* OR aircraft fuel* OR aviation fuel* OR aviation turbine fuel* OR Jet propellant* OR aviation propellant* OR aircraft propellant* OR "Jet A fuel"[tiab] OR "Jet A-1 fuel"[tiab] OR "Jet B fuel"[tiab] OR "TS-1 Fuel"[tiab] OR "JP-1 Fuel"[tiab] OR "JP1 Fuel"[tiab] OR "JP-2 Fuel"[tiab] OR "JP2 Fuel"[tiab] OR "JP-3 Fuel"[tiab] OR "JP3 Fuel"[tiab] OR "JP-4 Fuel"[tiab] OR "JP4 Fuel"[tiab] OR "JP-5 Fuel"[tiab] OR "JP5 Fuel"[tiab] OR "JP-6 Fuel"[tiab] OR "JP6 Fuel"[tiab] OR "JP-7 Fuel"[tiab] OR "JP7 Fuel"[tiab] OR "JP-8 Fuel"[tiab] OR "JP8 Fuel"[tiab] OR "JP-9 Fuel"[tiab] OR "JP9 Fuel"[tiab] OR "JP-10 Fuel"[tiab] OR "JP10 Fuel"[tiab] OR "JPTS Fuel"[tiab] OR "Zip fuel"[tiab] OR "JP5 jet fuel"[Supplementary Concept] OR "S-8 fuel"[Supplementary Concept] OR "JP8 aviation fuel"[Supplementary Concept] OR "JP4 aviation fuel" [Supplementary Concept] OR Kerosene OR Kerosene[mh] OR "Jet Exhaust" OR “Jet Engine Exhaust” OR “Aircraft Engine Exhaust” OR “Aircraft Exhaust”	3,535
Health Effects	(Health OR health[mh] OR Epidemiol* OR "Epidemiology"[mh] OR Risk OR "Risk Assessment"[Mesh] OR Safety OR Hazard OR Outcome OR Effect OR "Cardiovascular Diseases" OR "Congenital Diseases" OR "Congenital Abnormalities" OR "Hereditary Diseases" OR "Hereditary Abnormalities" OR "Neonatal Diseases" OR "Neonatal Abnormalities" OR "Digestive System Diseases" OR "Disorders of Environmental Origin" OR "Environmental Disorders" OR "Endocrine System Diseases" OR "Eye Diseases" OR "Urogenital Diseases" OR "Pregnancy Complications" OR "Hemic Diseases" OR "Lymphatic Diseases" OR "Immune System Diseases" OR "Immune Diseases" OR "mental disorders" OR "Musculoskeletal Diseases" OR "Neoplasms" OR "Cancer" OR "Nervous System Diseases" OR "Nutritional Diseases" OR "Metabolic Diseases" OR "Otorhinolaryngologic Diseases" OR "Pathological Conditions" OR "Pathological Signs" OR "Pathological Symptoms" OR "Respiratory Tract Diseases" OR "Stomatognathic Diseases" OR	21,287,752

String Name	Search String	Results
	"Skin Diseases" OR "Connective Tissue Diseases" OR "Liver injury" OR drug-induced abnormalities OR occupational accidents OR adverse drug reaction reporting systems OR Drug-Induced Akathisia OR Amino Acids, Peptides and Proteins/adverse effects[Mesh] OR Animal Diseases/chemically induced[Mesh] OR poisonous animals OR Background Radiation OR biohazard release OR Biological Factors/adverse effects[Mesh] OR Biomedical and Dental Materials/adverse effects[Mesh] OR birth weight/drug effects[Mesh] OR chemical burns OR Carbohydrates/adverse effects[Mesh] OR carcinogen* OR Carcinogenesis OR cardiotox* OR Cardiotoxicity OR Cardiovascular Diseases/chemically induced[Mesh] OR Chemical Actions and Uses/adverse effects[Mesh] OR Chemical and Drug Induced Liver Injury OR chemical hazard release OR chemical terrorism OR Chemically-Induced Disorders OR Climate Change OR Clin Toxicol Phila[TA] OR Colony Collapse OR Complex Mixtures/adverse effects[Mesh] OR Congenital, Hereditary and Neonatal Diseases and Abnormalities/chemically induced[Mesh] OR Crit Rev Toxicol[TA] OR Digestive System Diseases/chemically induced[Mesh] OR Disorders of Environmental Origin/chemically induced[Mesh] OR Drug Interactions OR Drug Recalls OR drug therapy/adverse effects[Mesh] OR Drug-Induced Dyskinesia OR ecotox* OR Ecotoxicology OR Endocrine System Diseases/chemically induced[Mesh] OR Environ Health Perspect[TA] OR Environ Toxicol Chem[TA] OR Environ Toxicol Pharmacol[TA] OR Environment and Public Health/adverse effects[Mesh] OR Environmental Health OR environmental illness OR environmental monitoring OR environmental pollutants OR environmental pollution OR Environmental Restoration and Remediation OR Enzymes and Coenzymes/adverse effects[Mesh] OR Extreme Environments OR Eye Diseases/chemically induced[Mesh] OR Female Urogenital Diseases and Pregnancy Complications/chemically induced[Mesh] OR Fetal Alcohol Spectrum Disorders OR food and beverages/adverse effects[Mesh] OR forensic toxicology OR Genetic Phenomena/drug effects[Mesh] OR Global Warming OR hazardous substances OR Hemic and Lymphatic Diseases/chemically induced[Mesh] OR hepatotox* OR Heterocyclic Compounds/adverse effects[Mesh] OR Hormones, Hormone Substitutes and Hormone Antagonists/adverse effects[Mesh] OR household products/adverse effects[Mesh] OR Hum Exp Toxicol[TA] OR Immune System Diseases/chemically induced[Mesh] OR immunotox* OR Metabolic Inactivation OR Inorganic Chemicals/adverse effects[Mesh] OR Integumentary System Physiological Phenomena/drug effects[Mesh] OR J Toxicol Environ Health[TA] OR J Toxicol Sci[TA] OR LC50 OR Lipids/adverse effects[Mesh] OR Macromolecular	

String Name	Search String	Results
	Substances/adverse effects[Mesh] OR Male Urogenital Diseases/chemically induced[Mesh] OR manufactured materials/adverse effects[Mesh] OR Material Safety Data Sheets OR mental disorders/chemically induced[Mesh] OR Musculoskeletal Diseases/chemically induced[Mesh] OR mutagen* OR mutagenesis OR nanostructures OR Neoplasms/chemically induced[Mesh] OR nephrotox* OR Nervous System Diseases/chemically induced[Mesh] OR neurotox* OR noxae OR Nuclear Power Plants OR Nucleic Acids, Nucleotides and Nucleosides/adverse effects[Mesh] OR Nutritional and Metabolic Diseases/chemically induced[Mesh] OR occupational diseases OR Ocular Physiological Phenomena/drug effects[Mesh] OR Organic Chemicals/adverse effects[Mesh] OR Otorhinolaryngologic Diseases/chemically induced[Mesh] OR Pathological Conditions, Signs and Symptoms/chemically induced[Mesh] OR persian gulf syndrome OR pesticides/toxicity[Mesh] OR Pharmaceutical Preparations/adverse effects[Mesh] OR Phytochemicals/adverse effects[Mesh] OR plants, medicinal/adverse effects[Mesh] OR toxic plants OR poison* OR poisoning OR Polycyclic Compounds/adverse effects[Mesh] OR substance-induced psychoses OR radiation injuries OR Radiation Monitoring OR radiation-induced abnormalities OR Radioactive Hazard Release OR Radioactive Pollutants OR radiotherapy/adverse effects[Mesh] OR Regul Toxicol Pharmacol[TA] OR Reproductive and Urinary Physiological Phenomena/drug effects[Mesh] OR Respiratory Tract Diseases/chemically induced[Mesh] OR Safety-Based Drug Withdrawals OR Skin and Connective Tissue Diseases/chemically induced[Mesh] OR Stomatognathic Diseases/chemically induced[Mesh] OR substance-related disorders OR terata* OR terato* OR Teratogenesis OR Drug Therapeutic Index OR Toxic Actions OR toxic OR toxicity tests OR Toxicokinetics OR Toxicol Appl Pharmacol[TA] OR Toxicological Phenomena OR toxicology OR Toxicology[TA] OR toxif* OR toxig* OR Toxin-Antitoxin Systems OR venoms/toxicity[Mesh])	
Human Only	NOT ("Animals"[mesh] NOT "Humans"[mesh])	N/A
Combined	**Jet Fuel AND Health Effects AND Human Only**	**2,354**

Table B-4. Search String for EBSCOhost Search (January 10, 2023).

String Name	Search String	Results
Jet Fuel	Jet Fuel* OR aircraft fuel* OR aviation fuel* OR aviation turbine fuel* OR Jet propellant* OR aviation propellant* OR aircraft propellant* OR "Jet A fuel" OR "Jet A-1 fuel" OR "Jet B fuel" OR "TS-1 Fuel" OR "JP-1 Fuel" OR "JP1 Fuel" OR "JP-2 Fuel" OR "JP2 Fuel" OR "JP-3 Fuel" OR "JP3 Fuel" OR "JP-4 Fuel" OR "JP4 Fuel" OR "JP-5 Fuel" OR "JP5 Fuel" OR "JP-6 Fuel" OR "JP6 Fuel" OR "JP-7 Fuel" OR "JP7 Fuel" OR "JP-8 Fuel" OR "JP8 Fuel" OR "JP-9 Fuel" OR "JP9 Fuel" OR "JP-10 Fuel" OR "JP10 Fuel" OR "JPTS Fuel" OR "Zip fuel" OR "S-8 fuel" OR Kerosene OR "Jet Exhaust" OR “Jet Engine Exhaust” OR “Aircraft Engine Exhaust” OR “Aircraft Exhaust”	48,227
Health Effects	(Health OR Epidemiol* OR Risk OR Safety OR Hazard OR Outcome OR Effect OR "Cardiovascular Diseases" OR "Congenital Diseases" OR "Congenital Abnormalities" OR "Hereditary Diseases" OR "Hereditary Abnormalities" OR "Neonatal Diseases" OR "Neonatal Abnormalities" OR "Digestive System Diseases" OR "Disorders of Environmental Origin" OR "Environmental Disorders" OR "Endocrine System Diseases" OR "Eye Diseases" OR "Urogenital Diseases" OR "Pregnancy Complications" OR "Hemic Diseases" OR "Lymphatic Diseases" OR "Immune System Diseases" OR "Immune Diseases" OR "mental disorders" OR "Musculoskeletal Diseases" OR "Neoplasms" OR "Cancer" OR "Nervous System Diseases" OR "Nutritional Diseases" OR "Metabolic Diseases" OR "Otorhinolaryngologic Diseases" OR "Pathological Conditions" OR "Pathological Signs" OR "Pathological Symptoms" OR "Respiratory Tract Diseases" OR "Stomatognathic Diseases" OR "Skin Diseases" OR "Connective Tissue Diseases" OR "Liver injury" OR (“adverse effects” AND (“Amino Acids, Peptides and Proteins “ OR “Biological Factors “ OR “Biomedical Materials” OR “Dental Materials” OR Carbohydrates OR “Chemical Actions” OR “Chemical Uses” OR “Complex Mixtures” OR “drug therapy” OR “Environment Health” OR “Public Health” OR Enzymes OR Coenzymes OR food OR beverages OR Hormones OR “Hormone Substitutes” OR “Hormone Antagonists” OR “Heterocyclic Compounds” OR “household products” OR Lipids OR “Macromolecular Substances” OR “Nucleic Acids” OR Nucleotides OR Nucleosides “Pharmaceutical Preparations” OR Phytochemicals OR “Polycyclic Compounds” OR radiotherapy)) OR ((“chemically induced” OR “chemical induced”) AND (“Animal Diseases” OR “Cardiovascular Diseases” OR “Congenital Diseases” OR “Congenital Abnormalities” OR “Hereditary Diseases” OR “Hereditary Abnormalities” OR “Neonatal Diseases” OR “Neonatal Abnormalities” OR “Digestive System Diseases” OR “Disorders of Environmental Origin” OR “Environmental Disorders” OR “Endocrine System Diseases” OR “Eye Diseases” OR “Urogenital Diseases” OR “Pregnancy	30,517,654

String Name	Search String	Results
	Complications" OR "Hemic Diseases" OR "Lymphatic Diseases" OR "Immune System Diseases" OR "Immune Diseases" OR "mental disorders" OR "Musculoskeletal Diseases" OR "Neoplasms" OR "Cancer" OR "Nervous System Diseases" OR "Nutritional Diseases" OR "Metabolic Diseases" OR "Otorhinolaryngologic Diseases" OR "Pathological Conditions" OR "Pathological Signs" OR "Pathological Symptoms" OR "Respiratory Tract Diseases" OR "Stomatognathic Diseases" OR "Skin Diseases" OR "Connective Tissue Diseases" OR "Liver injury")) OR (("drug effects" OR "drug induced") AND ("birth weight" OR "Genetic Phenomena" OR "Integumentary System Physiological Phenomena" OR "Ocular Physiological Phenomena" OR "Reproductive Physiological Phenomena" OR "Urinary Physiological Phenomena" OR "liver injury")) OR "drug-induced abnormalities" OR "occupational accidents" OR "adverse drug reaction reporting systems" OR "Drug-Induced Akathisia" OR "biohazard release" OR "chemical burns" OR carcinogen* OR Carcinogenesis OR cardiotox* OR Cardiotoxicity OR "chemical hazard release" OR "chemical terrorism" OR "Chemically-Induced Disorders" OR "chemical induced disorders" OR "Colony Collapse" OR "Drug Interactions" OR "Drug Recalls" OR "Drug-Induced Dyskinesia" OR ecotox* OR Ecotoxicology OR "Environmental Health" OR "environmental illness" OR "environmental monitoring" OR "environmental pollutants" OR "environmental pollution" OR "Environmental Restoration" OR "Environmental Remediation" OR "Fetal Alcohol Spectrum" OR "forensic toxicology" OR "hazardous substances" OR hepatotox* OR immunotox* OR "Metabolic Inactivation" OR "LC50" OR "Material Safety Data Sheets" OR mutagen* OR mutagenesis OR nephrotox* OR neurotox* OR noxae OR "occupational diseases" OR "persian gulf syndrome" OR Pesticides OR poison* OR poisoning OR "substance-induced psychoses" OR terata* OR terato* OR Teratogenesis OR "Toxic Actions" OR toxic OR "toxicity tests" OR Toxicokinetics OR "Toxicological Phenomena" OR toxicology OR toxif* OR toxig* OR "Toxin-Antitoxin Systems")	
Human Only	All Fields(Human* OR people* OR person* OR Epidemiol* OR veteran* OR soldier* OR patient* OR man OR men OR woman OR women OR worker* OR employee* OR child* OR infant* OR boy OR girl)	75,880,733
Additional Limits	Limit results to Academic Journals Only	N/A
Combined	**Jet Fuel AND Health Effects AND Human Only**	2,309

The "Human Only" search string appears different in the above EBSCOhost search as compared to PubMed due to the lack of consistent keyword tagging across the many databases contained within EBSCOhost. Therefore, a broad general string is used is the place of the specific limiting string used in PubMed.

Deduplication across databases resulted in 2,830 unique results, as summarized in Table B-55 below.

Table B-5. Boolean Search Summary (January 10, 2023).

Database	Raw Result Counts	Unique Result Counts
PubMed	2,354	2,340
EbscoHost	2,309	490
Total	**4,663**	**2,830**

B.2.3. Gray Literature Searches

Gray literature was searched using an ICF-developed webscraper tool to pull results from Google into an Excel spreadsheet. The webscraper tool is a Python executable that allows a user to specify keyword search strings, URL source domains to be searched, target date ranges and desired file types to download (PDF, docx, xlsx). Using these specifications, the tool executes a series of searches in Google. For each search, the scraper tool copies and pastes each search result and search result URL into an Excel spreadsheet. The tool also downloads any specified files while copying and pasting the search results.

Keyword Search String:

(Health OR Epidemiology OR Safety OR Hazard OR "adverse effects") AND (Jet Fuel* OR aircraft fuel* OR aviation fuel* OR aviation turbine fuel* OR Jet propellant* OR aviation propellant* OR aircraft propellant* OR "Jet A fuel" OR "Jet A-1 fuel" OR "Jet B fuel" OR "TS-1 Fuel" OR "JP-1 Fuel" OR "JP1 Fuel" OR "JP-2 Fuel" OR "JP2 Fuel" OR "JP-3 Fuel" OR "JP3 Fuel" OR "JP-4 Fuel" OR "JP4 Fuel" OR "JP-5 Fuel" OR "JP5 Fuel" OR "JP-6 Fuel" OR "JP6 Fuel" OR "JP-7 Fuel" OR "JP7 Fuel" OR "JP-8 Fuel" OR "JP8 Fuel" OR "JP-9 Fuel" OR "JP9 Fuel" OR "JP-10 Fuel" OR "JP10 Fuel" OR "JPTS Fuel" OR "Zip fuel" OR "S-8 fuel" OR Kerosene OR "Jet Exhaust" OR “Jet Engine Exhaust” OR “Aircraft Engine Exhaust” OR “Aircraft Exhaust”)

Source List:

- Defense Technical Information Center—Dtic.mil
- Defense Health Agency—health.mil
- Army Public Health Command—phc.amedd.army.mil
- Navy Medical Research Center—med.navy.mil
- Airforce Research Laboratory—Afrl.af.mil
- National Technical Reports Library—Ntrl.ntis.gov
- Occupational Safety and Health Administration—Osha.gov

- Agency for Toxic Substance and Disease Registry—Atsdr.cdc.gov
- National Institute for Environmental Health and Safety—Niehs.nih.gov
- Federal Aviation Administration—faa.gov
- Australia Airforce—airforce.gov.au
- European Aviation Safety Authority—easa.europa.eu
- National Academies—nationalacademies.org
- European Chemicals Agency—echa.europa.eu
- U.S. Environmental Protection Agency—epa.gov
- International Agency for Research on Cancer—iarc.who.int
- World Health Organization—who.int

Date Range: None

These searches yielded 235 references.

B.2.4. Additional Sources

The literature search strategies used were designed to be broad; however, like any search strategy, studies may be missed (e.g., if the chemical of interest is not mentioned in title, abstract or keyword content; or if gray literature is not indexed in the databases that were searched). Thus, additional sources were reviewed to identify studies that could have been missed in the database searches. Reviews of additional sources included expert-identified publications and reports identified by VA, DoD or other subject matter experts; and references cited in five identified secondary reviews.

The five secondary reviews chosen for a crosswalk review were:

- Agency for Toxic Substances and Disease Registry. 2017. Toxicological Profile for JP-5, JP-8 and Jet A Fuels. https://www.atsdr.cdc.gov › ToxProfiles › tp121-c4.
- National Research Council. 2003. Toxicologic Assessment of Jet-Propulsion Fuel 8. Toxicologic Assessment of Jet-Propulsion Fuel 8. Washington (DC). 10.17226/10578
- Ritchie, G, Still, K, Rossi, J, 3rd, et al. 2003. Biological and health effects of exposure to kerosene-based jet fuels and performance additives. J Toxicol Environ Health B Crit Rev 6:357-451.
- Warner, R, Fuente, A, Hickson, L. 2015. Jet Fuel, Noise and the Central Auditory Nervous System: A Literature Review. Mil Med 180:950-955.

- Bendtsen, KM, Bengtsen, E, Saber, AT, et al. 2021. A Review of Health Effects Associated with Exposure to Jet Engine Emissions in and Around Airports. Environ Health 20:10.

The objective of the reference crosswalk was to document all studies that were referenced within PECO-relevant secondary data reviews captured in the initial literature search. The crosswalk determined if studies referenced within the five reviews were already screened at the Title/Abstract level. If reviewed references are found to not have been screened at the Title/Abstract level, they were evaluated for PECO relevance. This process was completed to ensure the most comprehensive literature review.

Expert identification yielded 74 additional references and the crosswalk yielded 141 additional references.

B.3. Literature Screening Process to Identify Relevant Studies

This section summarizes the methods used to screen the literature to identify which references are potentially relevant for further assessment. Briefly, the PECO statement described above established the criteria used to screen all references identified in the search. Literature search results were screened at Title/Abstract and Full-Text levels. These screening steps are described further below.

The PECO criteria used to screen the literature search results are the same as those used to frame the initial literature search (Table B-1 on page 183 and Table B-2 on page 183).

Following de-duplication, literature search results were imported into litstream® (https://icf-litstream.com) software and were screened against the PECO criteria at the title and abstract level to identify PECO-relevant studies. Following completion of Title/Abstract screening (described further in Section B.4.1), the literature search results were re-screened, except at the Full-Text level (described further in Section B.4.2). Studies identified as not relevant following Title/Abstract or Full-Text screening did not undergo study evaluation or data extraction steps.

The Title/Abstract and Full-Text level screenings were performed by two independent reviewers using structured forms in litstream®, with a process for conflict resolution.

B.3.1. Title/Abstract Screening Questions

Studies identified from the literature search and review efforts were imported into litstream® software for Title/Abstract screening. For each study, screeners reviewed the title and abstract and completed the litstream® form to assess PECO relevance. Table B-66 on page 197 lists the prompts within the litstream® forms used for Title/Abstract screening and the response options for each prompt.

Table B-6. Litstream® Form for Title Abstract Screening.

Response Options	Explanation
Relevant	Select when all PECO elements are clearly met or alluded to. Select all child tags that apply, or none.
Meta-Analysis	The study design of the reference appears to be meta-analysis.
Case study, case report or case series	The study design of the reference appears to be case study, case report or case series.
Unclear	Select if unsure about application to PECO. Select all child tags that apply (i.e., which element/s are unclear).
Human (military/occupational)	It is unclear if the reference includes a human military or occupational population of interest.
Jet Fuels	It is unclear if the reference includes a jet fuel exposure of interest.
Health outcomes	It is unclear if the reference reports any health outcomes for a relevant population and exposure.
Not relevant	Select when one or more of the PECO elements are clearly NOT met. Select ALL child tags that apply (i.e., which element/s are not met).
Human (not military/occupational)	The population of interest is clearly not military or occupational.
Not jet fuels	The exposure of interest is clearly not jet fuels.
No health outcomes	The reference clearly does not report health outcomes for a relevant population and exposure.

B.3.2. Full-Text Screening Questions

All studies identified as PECO-relevant from Title/Abstract screening advanced to Full-Text screening, which was performed in litstream®. Screeners reviewed each full study report and any supplemental study materials and completed the litstream® form to assess PECO relevance and whether certain jet fuels were evaluated. Table B-77 below lists the prompts and response options that were used for Full-Text screening.

Table B-7. Litstream® Form for Full-Text Screening.

Response Options	Explanation
Relevant	Select when all PECO elements are met. Select all child tags that apply.
Meta-Analysis	The study design of the reference is meta-analysis.
Case study, case report or case series	The study design of the reference is case study, case report or case series.

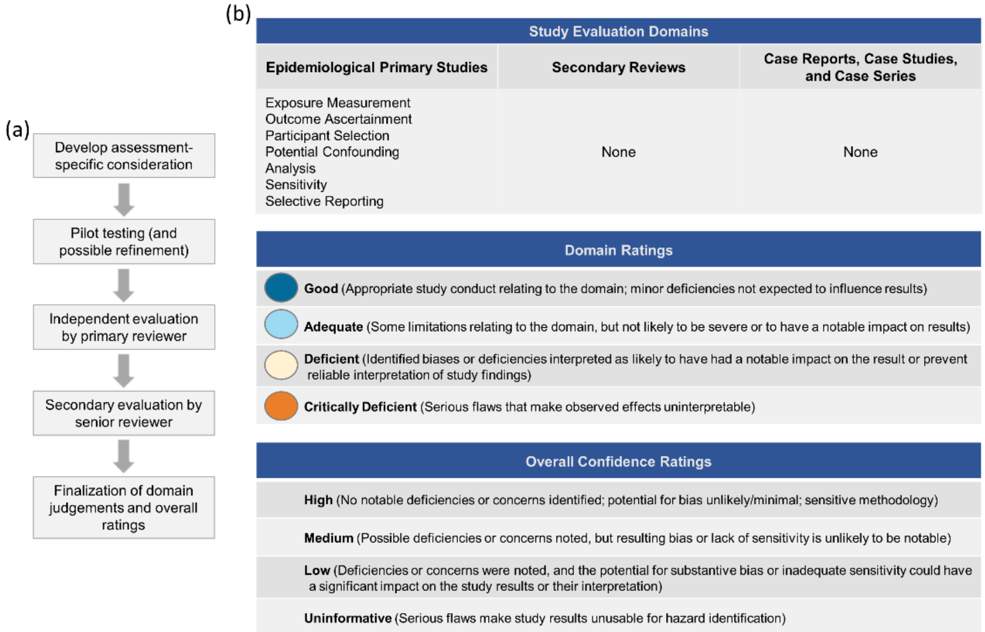
Response Options	Explanation
JP 4, JP 5, JP 8, Jet A	At least one of the exposures of interest in the reference is included in this list.
Other or unknown jet fuel	At least one of the exposures of interest in the reference is a jet fuel not captured in the above list.
Not relevant	Select when one or more of the PECO elements are NOT met. Select ALL child tags that apply (i.e., which element/s are not met).
Human (not military/occupational)	The population of interest is not military or occupational.
Not jet fuels	The exposure of interest is not jet fuels.
No health outcomes	The reference does not report health outcomes for a relevant population and exposure.

B.3.3. Overlapping References

In some cases, multiple references reported on the same epidemiologic study. In such cases, the process for designating the "parent" references included several considerations: the peer-reviewed reference, or the reference with the largest number of participants, the most accurate outcome measures, or the most comprehensive reporting was given preference and was assigned as the "parent" reference while the others were assigned as "child" references for a given study. The parent reference underwent study evaluation and data extraction and is represented in tables. However, parent and child references are cited together in the discussion and documented as unique references reporting overlapping data from the same study. This approach avoids misinterpretation about the quantity of evidence available for a given health outcome.

B.4. Study Evaluation Overview

After literature search results were screened at the Title/Abstract and Full-Text level, epidemiological studies that met PECO criteria underwent study evaluation to assess each study's validity and utility. As outlined in the IRIS Handbook (EPA, 2022b), the key concerns during the review of epidemiological studies are potential sources of bias (factors that affect the magnitude or direction of an effect in either direction) and sensitivity (factors that limit the ability of a study to detect a true effect; low sensitivity is a bias toward the null when an effect exists). Study evaluations produce overall judgments about confidence in the reliability of study results. The general approach for study evaluation is outlined in Figure B-1 on page 196, which has been adapted from Figure 4-1 in the IRIS Handbook (EPA, 2022b). Study evaluations were performed for primary studies using structured forms housed within litstream®.



(a) An overview of the study quality evaluation process; (b) Evaluation domains and ratings definitions (i.e., domain ratings and overall confidence ratings, performed on an outcome-specific basis as applicable).

Figure B-1. Overview of Study Evaluation Approach.

In brief, a primary reviewer independently judged the reliability of the study results according to multiple study quality evaluation domains similar to those presented in the IRIS Handbook. Domain-specific core and prompting questions are provided to guide the reviewer in assessing different aspects of study design and conduct related to reporting, risk of bias and study sensitivity. For each domain, each reviewer assigned a rating of good, adequate, deficient (or "not reported," which carried the same functional interpretation as deficient) or critically deficient (see Figure B-1 above and Figure B-2 on page 198). A secondary reviewer revised the evaluations from the primary reviewer as needed and made a final determination reflected as study confidence ratings (see Figure B-1 above and Figure B-2. Possible Domain Ratings for Study Quality Evaluation.

on page 198). Any discrepancies were discussed with a subject matter expert.

Study quality evaluation metrics (including domain ratings and overall confidence rating) were assessed and rated for each individual health outcomes analyzed by the study. A study that reported on multiple health outcomes may have received varying ratings in a given domain, impacting the overall confidence rating for each health outcome, resulting in a mixed confidence classification for the study. For example, the study may be considered medium confidence for health outcomes determined by a validated test (adequate Outcome Ascertainment) but uninformative for health outcomes collected by self-report only (critically deficient Outcome Ascertainment). Variation in any domain had the potential to result in mixed overall confidence ratings. In addition, the magnitude of difference in overall ratings depended on the ratings in all domains. For example, the difference in Outcome Ascertainment described above may have only made the difference between low confidence and uninformative if the ratings of the other domains did not support a higher overall confidence rating.

The overall confidence rating should, to the extent possible, reflect interpretations of the potential influence on the results (including the direction and/or magnitude of influence) across all domains. The rationale supporting the overall confidence rating is documented clearly and consistently and includes a brief description of any important study strengths and/or limitations and their potential impact(s) on the overall confidence.

The specific study limitations identified during study quality evaluation were carried forward to inform the synthesis of findings within each body of evidence for a given health effect (i.e., study confidence determinations were not used to inform judgments in isolation).

Case reports, case studies, case series, secondary reviews and overlapping ‘child’ references did not undergo study evaluation.

Good	Intended to represent a judgment that there was appropriate study conduct relating to the domain (as defined by consideration of the criteria listed below) and any minor deficiencies that were noted would not be expected to influence interpretation of the study findings.
Adequate	Indicates a judgment that there were study design limitations relating to the domain (as defined by consideration of the criteria listed below), but that those limitations are not likely to be severe and are expected to have minimal impact on interpretation of the study findings.
Deficient	Denotes identified biases or limitations that are interpreted as likely to have had a substantial impact on the results or that prevent reliable interpretation of the study findings. **Note: Not reported** indicates that the information necessary to evaluate the domain was not available in the study. Generally, this term carries the same functional interpretation as **Deficient** for the purposes of the study confidence classification.
Critically Deficient	Reflects a judgment that the study design limitations relating to the domain introduced a flaw so serious that the study should not be used without exceptional justification (e.g., it is the only study of its kind and may highlight possible research gaps). This judgment should only be used if there is an interpretation that the limitation(s) would be the primary driver of any observed effect(s), or if it makes the study findings uninterpretable.

Figure B-2. Possible Domain Ratings for Study Quality Evaluation.

High Confidence	No notable concerns were identified (e.g., most or all domains rated **Good**).
Medium Confidence	Some concerns are identified but expected to have minimal impact on the interpretation of the results (e.g., most domains rated **Adequate** or **Good**; may include studies with **Deficient** ratings if concerns are not expected to strongly impact the magnitude or direction of the results). Any important concerns should be carried forward to evidence synthesis.
Low Confidence	Identified concerns are expected to significantly impact the study results or their interpretation (e.g., generally, **Deficient** ratings for one or more domains). The concerns leading to this confidence judgment must be carried forward to evidence synthesis.
Uninformative	Serious flaw(s) make the study results unusable for informing hazard identification (e.g., generally, **Critically Deficient** rating in any domain; many **Deficient** ratings).

Figure B-3. Overall Study Confidence Classifications.

Study quality evaluation domains for assessing risk of bias and sensitivity are participant selection, exposure measurement, outcome ascertainment, potential confounding, analysis, selective reporting and study sensitivity. As noted in the IRIS Handbook, this framework is adapted from the Risk Of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool (https://methods.cochrane.org/methods-cochrane/robins-i-tool), modified by IRIS for use with the types of studies more typically encountered in EPA's work.

The tables presented in the following sections describe the epidemiological study quality evaluation domains and the prompting questions and considerations for assessing study quality in relation to each domain.

B.4.1. Participant Selection

The aim of study quality evaluation for this domain is to ascertain whether the reported information indicates that selection in or out of the study (or analysis sample) and participation was not likely to be biased (i.e., the exposure-outcome distribution of the participants is likely representative of the exposure-outcome distribution in the overall population of eligible persons) (see Table B-88 below).

Table B-8. Study Quality Evaluation Considerations for Participant Selection.

Core Question: Is there evidence that selection into or out of the study (or analysis sample) was jointly related to exposure and to outcome?			
Prompting Questions	**Follow-Up Questions**	**Suggested Considerations**	
For longitudinal cohort: Did participants volunteer for the cohort based on knowledge of exposure and/or preclinical disease symptoms? Was entry into the cohort or continuation in the cohort related to exposure and outcome? ***For occupational cohort:*** Did entry into the cohort begin with the start of the exposure? Was follow-up or outcome assessment incomplete and if so, was follow-up related to exposure and outcome status? Could exposure produce symptoms that would result in a change in work assignment/work status ("healthy worker survivor effect")? ***For case-control study:***	Were differences in participant enrollment and follow-up evaluated to assess the potential for bias? If there is a concern about the potential for bias, what is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)? Were appropriate analyses performed to address changing exposures over time in relation to symptoms?	**Good**	Minimal concern for selection bias based on description of recruitment process (e.g., selection of comparison population, population-based random sample selection, recruitment from sampling frame including current and previous employees) such that study participants were unlikely to differ from a larger cohort based on recruitment or enrollment methods (or data provided to confirm a lack of difference). Exclusion and inclusion criteria specified and would not be likely to induce bias. Participation rate is reported at all steps of study (e.g., initial enrollment, follow-up, selection into analysis sample). If the rate is not high, there is an appropriate rationale for why it is unlikely to be related to exposure (e.g., comparison between participants and nonparticipants or other available information indicates differential selection is not likely). Comparison groups are similar with respect to factors expected to influence exposure-outcome

Core Question: Is there evidence that selection into or out of the study (or analysis sample) was jointly related to exposure and to outcome?			
Were controls representative of population and time periods from which cases were drawn? Are hospital controls selected from a group whose reason for admission is independent of exposure? Could recruitment strategies, eligibility criteria or participation rates result in differential participation relating to disease and exposure? ***For population based-survey:*** Was recruitment based on advertisement to people with knowledge of exposure, outcome and hypothesis?	Is there a comparison of participants and nonparticipants to address whether differential selection is likely?		relationship (confounders, effect measure modifiers).
		Adequate	Enough of a description of the recruitment process (i.e., recruitment strategy, participant selection or case ascertainment) to be comfortable that there is no serious risk of bias. Inclusion and exclusion criteria specified and would not induce bias. Participation rate is incompletely reported for some steps of the study, but available information indicates participation is unlikely to be related to exposure. Comparison groups are largely similar with respect to factors expected to influence exposure-outcome relationship (confounders, effect measure modifiers) or these are mostly accounted for in the study analysis.
		Deficient	Little information on recruitment process, selection strategy, sampling framework and/or participation OR aspects of these processes raises the likelihood of bias (e.g., healthy worker effect, survivor bias). *<u>Example</u>: Enrollment of "cases" from a specific clinic setting (e.g., diagnosed autism), which could be biased by referral practices and services availability, without consideration of similar selection forces affecting recruitment of controls.*

Core Question: Is there evidence that selection into or out of the study (or analysis sample) was jointly related to exposure and to outcome?		
	Critically Deficient	Aspects of the processes for recruitment, selection strategy, sampling framework, or participation result in concern that the likelihood of selection bias is high (e.g., convenience sample with no information about recruitment and selection, cases and controls are recruited from different sources with different likelihood of exposure, recruitment materials stated outcome of interest and potential participants are aware of or are concerned about specific exposures). Convenience sample and recruitment and selection not described. Case report, case series or other study designs lacking a comparison group (these should be excluded if they do not meet assessment PECO criteria).

B.4.2. Exposure Measurement

This domain may need to be evaluated multiple times for a single study if more than one measurement of exposure is assessed. Therefore, different sets of criteria may be applied for different exposure assessments in the same study. Table B-99 on page 206 outlines criteria that apply across exposure assessments (first row) and specific additional criteria for specific types of exposure assessments (e.g., biomarkers, occupational) in subsequent rows.

Table B-9. Study Quality Evaluation Considerations for Exposure Measurement.

Core Question: Does the exposure measure reliably distinguish between levels of exposure in a time window considered most relevant for a causal effect with respect to the development of the outcome?			
Prompting Questions	**Follow-Up Questions**	**Suggested Considerations**	
Does the exposure measure capture the variability in exposure among the participants, considering intensity, frequency and duration of exposure? Does the exposure measure reflect a relevant time window? If not, can the relationship between measures in this time and the relevant time window be estimated reliably? Was the exposure measurement likely to be affected by a knowledge of the outcome? Was the exposure measurement likely to be affected by the presence of the outcome (i.e., reverse causality)?	Is the degree of exposure misclassification likely to vary by exposure level? If the correlation between exposure measurements is of concern, is there an adequate statistical approach to ameliorate variability in measurements? If there is a concern about the potential for bias, what is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)?	**Good**	Valid exposure assessment methods used, which represent the etiologically relevant time period for reported effects (e.g., exposure during a critical developmental window or exposure preceding the evaluation of the outcome). Exposure misclassification is expected to be minimal.
		Adequate	Valid exposure assessment methods used, which represent the etiologically relevant time period of interest. Exposure misclassification may exist but is not expected to greatly impact the effect estimate.
		Deficient	Specific knowledge about the exposure and outcome raises concerns about reverse causality, but there is uncertainty whether it is influencing the effect estimate. Exposed groups are expected to contain a notable proportion of unexposed or minimally exposed individuals, the method did not capture important temporal or spatial variation, or there is other evidence of exposure misclassification that would be expected to notably change the effect estimate.
		Critically Deficient	Exposure measurement does not characterize the etiologically relevant time period of exposure or is not valid. There is evidence that reverse causality is very likely to account for the observed association. Exposure measurement was not independent of outcome status.

Core Question: Does the exposure measure reliably distinguish between levels of exposure in a time window considered most relevant for a causal effect with respect to the development of the outcome?		
Additional prompting questions for biomarkers of exposure: Is a standard assay used? What are the intra- and inter-assay coefficients of variation? Is the assay likely to be affected by contamination? Are values less than the limit of detection dealt with adequately? What exposure time period is reflected by the biomarker? If the half-life is short, what is the correlation between serial measurements of exposure?	***Additional suggested considerations for biomarkers of exposure (should be evaluated in addition to the general considerations above):***	
	Good	Use of appropriate analytic method such as [specific gold standard exposure assessment method for the exposure of interest].
	Adequate	Use of appropriate (but not gold standard) analytic method.
	Deficient	Did not identify analytical methods used to measure exposure. Failure to report LOD, percentage less than LOD and methods used to account for values below the LOD. Failure to report QA/QC measures and results.
	Critically Deficient	Use of inappropriate analytical method or use of an appropriate method with measurement issues that are likely to impact the interpretation of results.
Additional prompting questions for case-control studies of occupational exposures: Is exposure based on a comprehensive job history describing tasks, setting, time period and use of specific materials?	***Additional suggested considerations for occupational exposures (should be evaluated in addition to the general considerations above):***	
	Good	Describes the use of personal protective equipment. Confirmed contrast in exposure between groups using biomarker measurements. Expert assessment method based on a detailed lifetime occupational history and using a high-quality, validated job exposure matrix (JEM) or a JEM that incorporates industry, time period, population/country, tasks and material used.
	Adequate	Describes the use of personal protective equipment.

Core Question: Does the exposure measure reliably distinguish between levels of exposure in a time window considered most relevant for a causal effect with respect to the development of the outcome?			
			Confirmed contrast in exposure between groups using biomarker measurements.
		Deficient	Expert assessment method based on incomplete occupational history information (lacking job titles, employers, industries, start and finish years, number of hours worked per day, number of days worked per week, tasks performed, or materials used)—may be Critically Deficient, depending on severity of this limitation.
		Critically Deficient	JEM with data indicating it cannot differentiate between exposure levels over time, area or between individuals.

JEM = job exposure matrix; LOD = limit of detection; QA/QC = quality assurance/quality control.

B.4.3. Outcome Ascertainment

This domain may need to be evaluated multiple times for a single study if more than one PECO-relevant outcome is reported. Therefore, different sets of criteria may be applied for different outcomes in the same study. Table B-10 below presents criteria that apply across outcomes.

Table B-10. Study Quality Evaluation Considerations for Outcome Ascertainment.

Core Question: Does the outcome measure reliably distinguish the presence or absence (or degree of severity) of the outcome?			
Prompting Questions	**Follow-Up Questions**	**Suggested Considerations**	
Is outcome ascertainment likely to be affected by knowledge of, or presence of, exposure (e.g., consider access to health care, if based on self-reported history of diagnosis)? ***For case-control studies:*** Is the comparison group without the outcome (e.g., controls in a case-control study) based on objective criteria with little or no likelihood of inclusion of people with the disease? ***For mortality measures:*** How well does cause of death data reflect occurrence of the disease in an individual? How well do mortality data reflect incidence of the disease? ***For diagnosis of disease measures:*** Is the diagnosis based on standard clinical criteria? If it is based on self-report of the diagnosis, what is the validity of this measure?	Is there a concern that any outcome misclassification is nondifferential, differential, or both? What is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)?	**Good**	High certainty in the outcome definition (i.e., specificity and sensitivity), minimal concerns with respect to misclassification. Assessment instrument was validated in a population comparable to the one from which the study group was selected.

Core Question: Does the outcome measure reliably distinguish the presence or absence (or degree of severity) of the outcome?		
For laboratory-based measures (e.g., hormone levels): Is a standard assay used? Does the assay have an acceptable level of inter-assay variability? Is the sensitivity of the assay appropriate for the outcome measure in this study population? Were quality assurance and quality control (QA/QC) measures and results reported?		
	Adequate	Moderate confidence that outcome definition was specific and sensitive, some uncertainty with respect to misclassification but not expected to greatly change the effect estimate. Assessment instrument was validated but not necessarily in a population comparable to the study group.
	Deficient	Outcome definition was not specific or sensitive. Uncertainty regarding validity of assessment instrument.
	Critically Deficient	Invalid/insensitive marker of outcome. Outcome ascertainment is very likely to be affected by knowledge of, or presence of, exposure. **Note:** Lack of blinding should not be automatically construed to be ***Critically Deficient***.

B.4.4. Potential Confounding

The aim of evaluating this domain is to ascertain whether confounding of the relationship between the exposure and health outcome of interest is likely to exist and if so, what the direction and magnitude of the effect of the confounder might be and whether it was considered in the design and/or analysis of the study (see Table B-1 below).

Table B-11. Study Quality Evaluation Considerations for Confounding.

Core Question: Is confounding of the effect of the exposure likely?			
Prompting Questions	**Follow-Up Questions**	**Suggested Considerations**	
Is confounding adequately addressed by considerations in: Participant selection (matching or restriction)? Accurate information on potential confounders and statistical adjustment procedures? Lack of association between confounder and outcome, or confounder and exposure in the study? Information from other sources? Is the assessment of confounders based on a thoughtful review of published literature, potential relationships (e.g., as can be gained through directed acyclic graphing) and minimizing potential overcontrol (e.g., inclusion of a variable on the pathway between exposure and outcome)?	If there is a concern about the potential for bias, what is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)?	**Good**	Conveys strategy for identifying key confounders. This may include a priori biological considerations, published literature, causal diagrams or statistical analyses; with recognition that not all "risk factors" are confounders. Inclusion of potential confounders in statistical models not based solely on statistical significance criteria (e.g., $p < 0.05$ from stepwise regression). Does not include variables in the models that are likely to be influential colliders or intermediates on the causal pathway. Key confounders are evaluated appropriately and considered to be unlikely sources of substantial confounding. This often will include: ○ Presenting the distribution of potential confounders by levels of the exposure of interest and/or the outcomes of interest (with amount of missing data noted); ○ Consideration that potential confounders were rare among the study population, or were expected to be poorly correlated with exposure of interest; ○ Consideration of the most relevant functional forms of potential confounders;

Core Question: Is confounding of the effect of the exposure likely?		
		○ Examination of the potential impact of measurement error or missing data on confounder adjustment; ○ Presenting a progression of model results with adjustments for different potential confounders, if warranted.
	Adequate	Similar to **Good** but may not have considered all potential confounders (though all key confounders were considered), or less detail may be available on the evaluation of confounders (e.g., sub-bullets in **Good**). It is possible that residual confounding could explain part of the observed effect, but concern is minimal.
	Deficient	All key confounders were not considered by design or in the statistical analysis. Assessed an outcome based on report of medical diagnosis that would have required access to a health professional (e.g., autism, ADHD, depression) and failed to consider some marker of socioeconomic status (e.g., maternal education, household income, marital status, crowding, poverty, job status) as a potential confounder. Does not include variables in the models that are likely to be influential colliders or intermediates on the causal pathway. **And any of the following:** The potential for bias to explain some of the results is high based on an inability to rule out residual confounding, such as a lack of demonstration that key confounders of the exposure-outcome relationships were considered; Descriptive information on key confounders (e.g., their relationship relative to the outcomes and exposure levels) is not presented; or

Core Question: Is confounding of the effect of the exposure likely?		
		Strategy of evaluating confounding is unclear or is not recommended (e.g., only based on statistical significance criteria or stepwise regression (forward or backward elimination)).
	Critically Deficient	Includes variables in the models that are colliders and/or intermediates in the causal pathway, indicating that substantial bias is likely from this adjustment; or Substantial confounding is likely present and not accounted for, such that all the results were most likely due to bias. If confounders not considered by design or in the analysis (e.g., only simple correlations presented).

ADHD = attention deficit hyperactivity disorder.

B.4.5. Analysis

Information relevant to evaluation of analysis includes, but is not limited to, the extent (and if applicable, treatment) of missing data for exposure, outcome and confounders, approach to modeling, classification of exposure and outcome variables (continuous vs. categorical), testing of assumptions, sample size for specific analyses and relevant sensitivity analyses (see Table B-2 below).

Table B-12. Study Quality Evaluation Considerations for Analysis.

Core Question: Does the analysis strategy and presentation convey the necessary familiarity with the data and assumptions?			
Prompting Questions	**Follow-Up Questions**	**Suggested Considerations**	
Are missing outcome, exposure and covariate data recognized and if necessary, accounted for in the analysis? Does the analysis appropriately consider variable distributions and modeling assumptions? Does the analysis appropriately consider subgroups of interest (e.g., based on variability in exposure level or duration or susceptibility)? Is an appropriate analysis used for the study design? Is effect modification considered, based on considerations developed a priori? Does the study include additional analyses addressing potential biases or limitations (i.e., sensitivity analyses)?	If there is a concern about the potential for bias, what is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)?	**Good**	Use of an optimal characterization of the outcome variable. Quantitative results presented (effect estimates and confidence limits or variability in estimates (e.g., standard error, standard deviation); i.e., not presented only as a p-value or “significant”/“not significant”). Descriptive information about outcome and exposure provided (where applicable). Amount of missing data noted and addressed appropriately (discussion of selection issues—missing at random vs. differential). Where applicable, for exposure, includes LOD (and percentage below the LOD) and decision to use log transformation. Includes analyses that address robustness of findings, e.g., examination of exposure-response (explicit consideration of nonlinear possibilities, quadratic, spline or threshold/ceiling effects included, when feasible); relevant sensitivity analyses; effect modification examined based only on a priori rationale with sufficient numbers.

Core Question: Does the analysis strategy and presentation convey the necessary familiarity with the data and assumptions?		
		No deficiencies in analysis evident. Discussion of some details may be absent (e.g., examination of outliers).
	Adequate	Same as Good, except: Descriptive information about exposure provided (where applicable) but may be incomplete; might not have discussed missing data, cut points or shape of distribution. Includes analyses that address robustness of findings (examples in Good), but some important analyses are not performed.
	Deficient	Descriptive information about exposure levels not provided (where applicable). Effect estimate and p-value presented, without standard error or confidence interval (where applicable). Results presented as statistically "significant"/"not significant."
	Critically Deficient	Results of analyses of effect modification examined without clear a priori rationale and without providing main/principal effects (e.g., presentation only of statistically significant interactions that were not hypothesis driven). Analysis methods are not appropriate for design or data of the study.

LOD = limit of detection.

B.4.6. Selective Reporting

This domain concerns the potential for misleading results that can arise from selective reporting (e.g., of only a subset of the measures or analyses that were conducted). The concept of selective reporting involves the selection of results from among multiple outcome measures, multiple analyses or different subgroups, based on the direction or magnitude of these results (e.g., presenting "positive" results) (see Table B-13 below).

Table B-13. Study Quality Evaluation Considerations for Selective Reporting.

Core Question: Is there reason to be concerned about selective reporting?			
Prompting Questions	**Follow-Up Questions**	**Suggested Considerations**	
Were results provided for all the primary analyses described in the methods section? Is there appropriate justification for restricting the amount and type of results that are shown? Are only statistically significant results presented?	If there is a concern about the potential for bias, what is the predicted direction or distortion of the bias on the effect estimate (if there is enough information)?	**Good**	The results reported by study authors are consistent with the primary and secondary analyses described in a registered protocol or methods paper.
		Adequate	The authors described their primary (and secondary) analyses in the methods section and results were reported for all primary analyses.
		Deficient	Concerns were raised based on previous publications, a methods paper or a registered protocol indicating that analyses were planned or conducted that were not reported, or that hypotheses originally considered to be secondary were represented as primary in the reviewed paper. Only subgroup analyses were reported; results for the entire group were omitted without any

Core Question: Is there reason to be concerned about selective reporting?			
			justification (e.g., to address effect measure modification). Of the PECO-relevant outcomes examined, only statistically significant results were reported.

B.4.7. Study Sensitivity

The aim of evaluation of this domain is to determine if there are features of the study that affect its ability to detect a true association (see Table B-4 below). Some of the study features that can affect study sensitivity may have already been included in the outcome, exposure or other categories, such as the validity of a method used to ascertain an outcome, the ability to characterize exposure in a relevant time period for the outcome under consideration, selection of affected individuals out of the study population, or inappropriate inclusion of intermediaries in a model.

Other features may not have been addressed and so should be included here. Examples include the exposure range (e.g., the contrast between the "low" and "high" exposure groups within a study), the level or duration of exposure and the length of follow-up. In some cases (for very rare outcomes), sample size or number of observed cases may also be considered within this "sensitivity" category.

Table B-14. Study Quality Evaluation Considerations for Study Sensitivity.

Core Question: Is there a concern that sensitivity of the study is not adequate to detect an effect?			
Prompting Questions	**Follow-Up Questions**	**Suggested Considerations**	
Is the exposure range/contrast adequate to detect associations that are present? Was the appropriate (at risk) population included? Was the length of follow-up adequate? Is the time/age of outcome ascertainment optimal given the interval of exposure and the health outcome?	–	**Good**	There is sufficient variability/contrast in exposure to evaluate primary hypotheses. The study population was sensitive to the development of the outcomes of interest (e.g., ages, life stage, sex). The timing of outcome ascertainment was appropriate given the expected latency for outcome development (i.e., adequate follow-up interval). The study was considered adequately powered to detect an effect (based on factors such as sample

Core Question: Is there a concern that sensitivity of the study is not adequate to detect an effect?		
Are there other aspects related to risk of bias or otherwise that raise concerns about sensitivity?		size (overall and across subgroups), precision, prevalence of outcome, number of covariates in model). The main effects and stratified analyses were fairly precise (relatively small confidence bounds) No other notable concerns raised regarding study sensitivity.
	Adequate	Same considerations as **Good**, but there might be issues identified that could reduce sensitivity, but they are considered unlikely to substantially impact the overall findings of the study.
	Deficient	Concerns were raised about the issues described for ***Good*** that are expected to notably decrease the sensitivity of the study to detect associations for the outcome.
	Critically Deficient	Severe concerns were raised about the considerations described for Good such that a true association is unlikely to be detected (i.e., null results cannot be interpreted as a lack of association). Sample size only should not be used to reach this rating.

B.4.8. Overall Confidence

Once individual domains were rated, reviewers also assigned overall study confidence ratings. The identified strengths and limitations were considered to reach an overall classification of High, Medium, Low or Uninformative for each PECO-relevant endpoint evaluated in the study.

Table B-15. Study Quality Evaluation Considerations for Overall Study Confidence.

<table>
<tr><th colspan="3">Provide judgment and rationale for each endpoint or groups of endpoints. The overall confidence rating considers the likely impact of the noted concerns (i.e., limitations or uncertainties) in reporting, bias and sensitivity on the results. Evaluation Core Question: Considering the identified strengths and limitations, what is the overall confidence rating for the endpoint(s)/outcome(s) of interest?</th></tr>
<tr><th>Prompting Questions</th><th colspan="2">Suggested Considerations</th></tr>
<tr><td rowspan="4">For each endpoint/outcome or grouping of endpoints/outcomes in a study:

Were concerns (i.e., limitations or uncertainties) related to the reporting quality, risk of bias or sensitivity identified?

If yes, what is their expected impact on the overall interpretation of the reliability and validity of the study results, including (when possible) interpretations of impacts on the magnitude or direction of the reported effects?

NOTE: Reviewers should mark studies that are rated lower than high confidence only due to low sensitivity (i.e., bias towards the null) for additional consideration during evidence synthesis. If the study is otherwise well-conducted and an effect is observed, confidence may be increased.</td><td>High Confidence</td><td>No notable concerns are identified (e.g., most or all domains rated Good).</td></tr>
<tr><td>Medium Confidence</td><td>Some concerns are identified but expected to have minimal impact on the interpretation of the results. (e.g., most domains rated Adequate or Good; may include studies with Deficient ratings if concerns are not expected to strongly impact the magnitude or direction of the results). Any important concerns should be carried forward to evidence synthesis.</td></tr>
<tr><td>Low Confidence</td><td>Identified concerns are expected to significantly impact on the study results or their interpretation (e.g., generally, Deficient ratings for one or more domains). The concerns leading to this confidence judgment must be carried forward to evidence synthesis (see note).</td></tr>
<tr><td>Uninformative</td><td>Serious flaw(s) that make the study results unusable for informing hazard identification (e.g., generally, Critically Deficient rating in any domain; many Deficient ratings). Uninformative studies are not considered further in the synthesis and integration of evidence.</td></tr>
</table>

B.5. Data Extraction

All studies identified as PECO-relevant after full-text screening were considered eligible for data extraction. As noted in the IRIS Handbook (EPA, 2022b), during data extraction, relevant results from each study are extracted to facilitate organization, visualization, comparison and analysis of findings and results. All health outcomes were considered for extraction, regardless of the magnitude or statistical significance of effect, or quality of the study. The level of detail in data extractions for different health outcomes within a study could differ based on how the data were presented for each health outcome (i.e., ranging from qualitative information to a full extraction of dose-response effect size information). Case studies/reports and secondary reviews only had qualitative information extracted.

Information extracted from epidemiology studies included population description, study design, year of enrollment in military, length of employment, life stage information, exposure details, health outcomes measured, results reported as qualitative data or quantitative data from statistical models. Data values extracted from statistical models reported in the studies included the result metric, covariates, sample size in the analysis, effect estimate, statistical significance and model comments.

Data extraction of epidemiological studies was carried out using a set of structured forms in litstream®. Data extraction was performed by one reviewer and then independently verified by at least one other reviewer for quality control. Any conflicts or discrepancies related to data extraction were resolved by discussion and confirmation within the evaluation team.

Data extracted was used to categorize studies, complete summary tables (Appendix B) and provide summary data for figures throughout the report.

B.5.1. Study Design Definitions

Studies were included without restriction by study design. The study design definitions shown in Table B-6 below were used throughout full-text screening and data extraction.

Table B-16. Study Design Definitions.

	Study Design	Description
Observational	Cross-sectional	Exposure and outcome are examined at the same point in time in a defined study population. Cannot determine if exposure came before or after outcome.
	Cohort	A group of people is examined over time to observe a health outcome. Everyone belongs to the same population (e.g., general U.S. population; an occupational group; cancer survivors). All cohort studies (prospective or retrospective) consider exposure data from before the occurrence of the health outcome.

	Study Design	Description
	Case-control	Cases (people with the health outcome) and controls (people without the health outcome) are selected at the start of a study. Exposure is determined and compared between the two groups. A case-control study can be nested within a cohort.
	Ecological	The unit of observation is at the group level (e.g., zip code; census tract), rather than the individual level. Ecological studies are often used to measure prevalence and incidence of disease. Cannot make inferences about an individual's risk based on an ecological study.
	Meta-analysis	Quantitative analysis combining the results of several observational studies, in order to synthesize data and provide a quantitative (pooled) estimate of the risk. Not every review or systematic review includes a meta-analysis.
	Case study or case report	Descriptive study, discussing in detail the experience of a patient's symptom, diagnosis and treatment.
	Case series	Descriptive study, several study participants or patients with similar experiences are grouped.
Experimental	Controlled Trial	Exposure is assigned to subject and then outcome is measured.
	Clinical Trial	Experimental human study to study the effect of an intervention over a placebo (e.g., drug safety trial, efficacy trials).

B.6. Evidence Synthesis

Evidence synthesis refers to the process of analyzing the results of the available studies (including their strengths and weaknesses) for consistency and coherence, often by health outcome. Generally, in evidence integration, the evidence across streams (e.g., human or animal) is considered together and integrated to develop judgments (for each health outcome) about whether the chemical in question poses a hazard to human health; however, this assessment does not consider animal streams of evidence and so evidence integration was not performed in this work.

For each assessed health outcome, the evidence synthesis tables provide a summary discussion of the body of evidence considered in the review, considering the conclusions from the individual study quality evaluations. Given the small body of literature in this field, all data were presented regardless of overall confidence level including results from uninformative studies. Syntheses of the evidence for human health outcomes were organized by presenting high and medium confidence studies first if available; low confidence and uninformative results were given less weight compared to high or medium confidence results during evidence synthesis and integration. In certain instances (i.e., for health outcomes for which few or no studies with higher confidence are available), low confidence and uninformative studies were used to help evaluate consistency, or to address gaps and uncertainties provided by the available high or medium confidence studies.

Strength-of-evidence judgments were made for each health outcome using standard terminology (i.e., robust, moderate, slight, indeterminate) and definitions according to the framework described in the IRIS Handbook and outlined in Table B-7 below.

Table B-17. Framework for Strength-of-Evidence Judgments.[a]

Strength-of-Evidence Judgment	Description
Robust (⊕⊕⊕)	A set of high or medium confidence studies reporting an association between the exposure and the health outcome, with reasonable confidence that alternative explanations, including chance, bias and confounding, can be ruled out across studies. The set of studies is primarily consistent, with reasonable explanations when results differ; and an exposure response gradient is demonstrated. Supporting evidence, such as associations with biologically related endpoints in human studies (coherence) or large estimates of risk or severity of the response, may help to rule out alternative explanations. Similarly, mechanistic evidence from exposed humans may serve to address uncertainties relating to exposure-response, temporality, coherence and biological plausibility (i.e., providing evidence consistent with an explanation for how exposure could cause the health effect based on current biological knowledge) such that the totality of human evidence supports this judgment.
Moderate (⊕⊕⊙)	Multiple studies showing generally consistent findings, including at least one high or medium confidence study and supporting evidence, but with some residual uncertainty due to potential chance, bias or confounding (e.g., effect estimates of low magnitude or small effect sizes given what is known about the endpoint; uninterpretable patterns with respect to exposure levels). Associations with related endpoints, including mechanistic evidence from exposed humans, can address uncertainties relating to exposure response, temporality, coherence and biological plausibility and any conflicting evidence is not from a comparable body of higher confidence, sensitive studies. A single high or medium confidence study demonstrating an effect with one or more factors that increase evidence strength, such as: a large magnitude or severity of the effect, a dose-response gradient, unique exposure or outcome scenario (e.g., a natural experiment), or supporting coherent evidence, including mechanistic evidence from exposed humans. There are no comparable studies of similar confidence and sensitivity providing conflicting evidence, or if there are, the differences can be reasonably explained (e.g., by the population or exposure levels studied)
Slight (⊕⊙⊙)	One or more studies reporting an association between exposure and the health outcome, where considerable uncertainty exists: A body of evidence, including scenarios with one or more high or medium confidence studies reporting an association between exposure and the health outcome, where either (1) conflicting evidence exists in studies of similar confidence and sensitivity (including mechanistic evidence contradicting the biological plausibility of the reported effects), a (2) a single study without a factor that increases evidence strength (factors described in moderate), OR (3) considerable methodological uncertainties remain across the body of evidence (typically related to exposure or outcome ascertainment, including

Strength-of-Evidence Judgment	Description
	temporality) and there is no supporting coherent evidence that increases the overall evidence strength. A set of only low confidence studies that are largely consistent. Strong mechanistic evidence in well-conducted studies of exposed humans (medium or high confidence) or human cells, in the absence of other substantive data, where an informed evaluation has determined that the data are reliable for assessing the health effect of interest and the mechanistic events have been reasonably linked to the development of that health effect.
Indeterminate (⊙⊙⊙)	No studies in humans or well-conducted studies of human cells. Situations when the evidence is highly inconsistent and primarily of low confidence. May include situations with medium or high confidence studies, but unexplained heterogeneity exists (in studies of similar confidence and sensitivity) and there are additional outstanding concerns such as effect estimates of low magnitude, uninterpretable patterns with respect to exposure levels, or uncertainties or methodological limitations that result in an inability to discern effects from exposure. A set of largely null studies that does not meet the criteria for compelling evidence of no effect, including evidence bases with inadequate testing of susceptible populations and life stages.
Compelling evidence of no effect (– – –)	Several high confidence studies showing null results (for example, an odds ratio of 1.0), ruling out alternative explanations including chance, bias and confounding with reasonable confidence. Each of the studies should have used an optimal outcome and exposure assessment and adequate sample size (specifically for higher exposure groups and for susceptible populations). The set as a whole should include the full range of levels of exposures that human beings are known to encounter, an evaluation of an exposure response gradient and an examination of at-risk populations and life stages.

[a] Table adapted from Table 11-3 in the IRIS Handbook.

Appendix C: Study Results Summaries

C.1. Results by Health System—Noncancerous Health Outcomes

C.1.1. Nervous System Health Outcomes

Table C-1. Associations Between Jet Fuel Exposure and Nervous System Health Outcomes in Epidemiologic Studies.

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
Acute Health Outcomes[d]						
Kaufman et al., 2005 Cross-sectional Medium	United States[f]	Noise-exposed workers at a military installation who were exposed or unexposed to jet fuel Exposed: 42.8 years Unexposed: 40.8 years N = 138	Jet fuel type: JP-4 Assessment method: Job exposure matrix, measured from personal or area monitors Exposure duration: 10.6 years Length of employment: Exposed: 15.8 years Unexposed: 15.6 years	Hearing impairment Assessment method: Medical professional or test, medical records Time since exposure of outcome assessment: Concurrent	Odds ratio Unexposed used as reference group	Hearing loss Full model Cumulative exposure: No significant associations observed Full model Exposure duration: 1.13 (0.96, 1.33) Full model **First 12 years of exposure: 8.25 (1.67, 55.6)** **Full model with dichotomized age: 1.89 (1.24, 2.89)**
	Confounding: Tinnitus, drank alcohol regularly exposed to loud noise in the military, longest duration of noise-hazardous leisure activity, hearing protection worn during noisy leisure activities, cigarettes smoked, noise and smoking interaction, jet fuel and smoking interaction, jet fuel and alcohol interaction, hearing protection and smoking interaction					

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
	Additional confounding for full models of cumulative exposure, exposure duration and first 12 years of exposure: Age, jet fuel, noise interaction Additional confounding for full model with dichotomized age: Age					
Dreisbach et al., 2022 Cross-sectional Low	United States, MCAS Miramar[f]	MCAS bulk fuel specialists with varying degrees of exposure to concurrent JP-5) and noise and military personnel whose occupations did not involve exposure to jet fuel Exposed: 22.5 years, Unexposed: 23.8 years N = 48	Jet fuel type: JP-5 Assessment method: Administrative data Exposure duration: 13.6 months Years of service: Unclear	Hearing impairment Assessment method: Medical professional or test Time since exposure of outcome assessment: Unclear	Differences between groups	Hearing impairment Non-significant differences between groups were observed
	Confounding: None reported					
Knave et al., 1978 Cross-sectional Low	Sweden[f]	Male jet motor factory workers (fuel system testers, engine testers, mechanics and unexposed workers) Exposed: 46.4 years,	Jet fuel type: Unspecified Assessment method: Measured from personal or area monitors Exposure duration: 17.1 years	Neurological pain or discomfort, ocular conditions Assessment method: Self-report, medical professional or test Time since	Number of subjects who experienced symptoms	Neurological pain or discomfort Acute headache Exposed: 7 out of 30 Ocular conditions Symptoms of eye irritation **Exposed: 9 out of 30** **Unexposed: 1 out of 30, p = 0.015**

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
		Unexposed: 46.2 years N = 60	Length of employment: Exposed: 17.7 years, Control: 19.8 years	exposure of outcome assessment: Concurrent		
	Confounding: Age					
Olsen et al., 1998 Cohort Low	United States, Hill Air Force Base, Utah, 1995	Active duty and civilian personnel exposed or unexposed to JP-4 and JP-8 Exposed: 32.8 years, Unexposed: 32.3 years N = 30	Jet fuel type: JP-4, JP-8 Assessment method: Administrative data, personal or area monitors Exposure duration: Unclear Years of service: ≥6 months	Neurological pain or discomfort, neurological, ocular conditions Assessment method: Self-report Time since exposure of outcome assessment: Baseline (JP-4), 6 months (JP-8), 18 months (JP-8)	Mean frequency of symptoms scale Outcome frequency scale groups: 0 = never happens; 1 = 1–2 times per month; 2 = 3–4 times per month; 3 = 5–9 times per month; 4 = ≥10 times per month; 5 = every day	Neurological pain or discomfort Headache (exposed; unexposed) Baseline, JP-4: 1.0; 0.5 6 months, JP-8: 1.6; 0.9 18 months, JP-8: 1.2; 0.8 Ocular conditions Eye irritation (exposed; unexposed) Baseline, JP-4: 1.2; 0.6 6 months, JP-8: 1.5; 1.6 18 months, JP-8: 1.7; 1.0
	Confounding: Age, sex					
Yang et al., 2003 Cross-sectional Low	Taiwan, 2000–2001	Male airport workers at Kaohsiung International Airport (Exposed: jet fuel handlers, baggage handlers, operational engineers,	Jet fuel type: Unspecified Assessment method: Administrative data Exposure Duration: Unclear	Neurological pain or discomfort, ocular conditions Assessment method: Questionnaire Time since exposure of outcome	Odds ratio Unexposed workers used as reference group	Headache: 1.27 (0.64, 2.51) Eye irritation: 1.27 (0.46, 3.54)

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
		marshallers, airport hands, fitters and engineering technicians; Unexposed: security staff, airfield operation managers, clerks, accountants, maintenance personnel and terminal and other office workers) ≥40 years: Exposed = 50.9% Unexposed = 14.8% N = 411	Length of employment, ≥10 years; Exposed = 68.9% Unexposed = 6.6%	assessment: Concurrent		
	Confounding: Age, marital status, education, duration of employment, smoking status, previous occupational dust or fume exposures					
Knave et al., 1976 Cohort Uninformative	Sweden, 1975	Aircraft factory workers exposed to jet fuels Heavily exposed: 54.2 years Less heavily exposed: 46.3 years	Jet fuel type: Unspecified Assessment method: Administrative data Exposure	Neurological pain or discomfort Assessment method: Self-reported questionnaire	Number of subjects who experienced symptoms	Headache Heavily exposed: 3 out of 13 Less heavily exposed: 5 out of 16

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
		N = 29	duration: ≥5 years; Heavily exposed: Continuous high concentration exposures for several hours daily or intermittent exposure of 20–30 min to high concentrations; Less heavily exposed: Less frequent intermittent exposure Length of employment: ≥5 years	Time since exposure of outcome assessment: Concurrent		
	Confounding: None reported					
Bell et al., 2005 Controlled Trial Medium	United States[f]	Gulf War Veterans N = 89	Jet fuel type: JP-8 Assessment method: Controlled exposure via nasal cannula Exposure duration: 7 minutes, weekly for 3 weeks	Neurological symptoms Assessment method: Medical professional or test Time since exposure of outcome assessment: Same day	Mean (SD)	Central reaction time (exposed; unexposed): Unhealthy Veterans with chemical intolerance: Session 1 1.02 (0.40); 0.76 (0.46) Session 2 0.96 (0.59); 0.93 (0.59) Session 3 1.07 (0.74); 0.90 (0.58) Unhealthy Veterans without chemical intolerance:

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
			Years of service: Unclear			Session 1 0.67 (0.53); 0.69 (0.29) Session 2 0.68 (0.48); 0.72 (0.33) Session 3 0.82 (0.36); 0.74 (0.36) Healthy Gulf War Veterans: Session 1 0.70 (0.37); 0.66 (0.15) Session 2 0.71 (0.37); 0.61 (0.24) Session 3 0.69 (0.35); 0.59 (0.22) Healthy Gulf War-era Veterans: Session 1 0.59 (0.31); 0.66 (0.38) Session 2 0.65 (0.35); 0.81 (0.48) Session 3 0.57 (0.41); 0.58 (0.28) Peripheral reaction time: Unhealthy Veterans with chemical intolerance: Session 1 1.30 (0.37); 1.19 (0.19) Session 2 1.27 (0.38); 1.18 (0.21) Session 3 1.21 (0.38); 1.22 (0.26) Unhealthy Veterans without chemical intolerance: Session 1

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						1.26 (0.24); 1.04 (0.18) Session 2 1.15 (0.20); 1.05 (0.17) Session 3 1.12 (0.19); 1.13 (0.23) Healthy Gulf War Veterans: Session 1 1.10 (0.24); 1.22 (0.25) Session 2 1.09 (0.25): 1.08 (0.24) Session 3 1.03 (0.18); 1.10 (0.31) Healthy Gulf War-era Veterans: Session 1 1.13 (0.18); 1.04 (0.33) Session 2 1.04 (0.19); 0.96 (0.26) Session 3 1.02 (0.26); 0.99 (0.27)
	Confounding: None reported					
Long-term Health Outcomes[e]						
Kaufman et al., 2005 Cross-sectional Medium	United States[f]	Noise-exposed workers at a military installation who were exposed or unexposed to jet fuel Exposed: 42.8 years Unexposed: 40.8 years	Jet fuel type: JP-4 Assessment method: Job exposure matrix, measured from personal or area monitors Exposure duration: 10.6 years	Hearing impairment Assessment method: Medical professional or test, medical records Time since exposure of outcome	Odds ratio Unexposed used as a reference group	Persistent hearing loss Full model Cumulative exposure: **Exposure duration: 1.23 (1.05, 1.44)** **First 3 years of exposure: 1.70 (1.14, 2.30)** **First 12 years of exposure: 2.41 (1.04, 5.57)**

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
		N = 138	Length of employment: Exposed: 15.8 years Unexposed: 15.6 years	assessment: Concurrent		Full model without jet fuel and noise interaction: 1.01 (0.96, 1.06)
	Confounding: Age, tinnitus, alcohol consumption, exposure to loud noise in the military, longest duration of noise-hazardous leisure activity, hearing protection worn during noisy leisure activities, cigarettes smoked, noise and smoking interaction, jet fuel and smoking interaction, jet fuel and alcohol interaction, hearing protection and smoking interaction Additional confounding for exposure duration, first 3 years of exposure, first 12 years of exposure: Jet fuel and noise interaction					
Dreisbach et al., 2022 Cross-sectional Low	United States, MCAS Miramar[f]	MCAS bulk fuel specialists with varying degrees of exposure to concurrent JP-5 and noise and military personnel whose occupations did not involve exposure to jet fuel Exposed: 22.5 years, Unexposed: 23.8 years N = 48	Jet fuel type: JP-5 Assessment method: Administrative data Average exposure duration: At Miramar: 13.6 months Away from Miramar: 15.2 months Years of service: Unclear	Hearing impairment Assessment method: Questionnaire Time since exposure of outcome assessment: Concurrent	Mean differences	Hearing impairment Non-statistically significant difference between the jet-fuel and noise exposed group compared to the noise exposed group
	Confounding: None reported					
Fuente et al., 2019 Cross-sectional	Australia[f]	Personnel from a RAAF base in Queensland with exposure to jet fuels	Jet fuel type: JP-8 Assessment method:	Hearing impairment Assessment method: Medical	Mean	Hearing impairment Audiometric hearing threshold (Low, Moderate or High Exposure) 1 kHz

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
Low		Low exposure: 42.3 years, Moderate exposure: 37.8 years, High exposure: 38.7 years N = 57	Administrative data Exposure duration: Unclear Years of service: Low exposure: 17.8 years, Moderate exposure: 14.8 years, High exposure: 19.7 years	professional or test Time since exposure of outcome assessment: Minimum of 2 weeks		Right ear Low: 5.51 (1.84, 9.19) Moderate: 7.00 (2.61, 11.40) High: 4.40 (1.89, 6.91) Left ear Low: 4.40 (0.36, 8.43) Moderate: 4.10 (–0.18, 8.37) High: 5.60 (2.06, 9.14) 2 kHz Right ear Low: 2.22 (–1.49, 5.93) Moderate: 6.48 (1.42, 11.55) High: 7.20 (2.78, 11.61) Left ear Low: 4.91 (1.34, 8.50) Moderate: 8.52 (3.94, 13.10) High: 6.40 (3.17, 9.64) 3 kHz Right ear Low: 3.80 (–0.20, 7.81) Moderate: 8.34 (0.72, 15.96) High: 11.73 (7.15, 16.30) Left ear Low: 6.39 (1.60, 11.19) Moderate: 11.73 (5.37, 18.08) High: 14.96 (9.24, 20.68) 4 kHz Right ear Low: 5.85 (1.44, 10.25) **Moderate: 15.80 (8.41, 23.20)** **High: 16.99 (11.05, 22.92)** Left ear Low: 7.88 (2.92, 12.85) **Moderate: 24.04 (13.66, 34.42)**

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						High: 19.27 (12.82, 25.72) 6 kHz Right ear Low: 11.07 (5.30, 16.84) Moderate: 19.92 (11.29, 28.55) High: 16.54 (10.84, 22.25) Left ear Low: 10.60 (4.97, 16.23) Moderate: 23.29 (12.09, 34.50) High: 21.45 (13.90, 29.01) 8 kHz Right ear Low: 6.98 (1.86, 12.10) Moderate: 20.59 (9.81, 31.36) High: 15.65 (9.35, 21.95) Left ear Low: 9.68 (3.13, 16.23) Moderate: 21.59 (12.16, 31.03) High: 20.91 (13.46, 28.36) 10 kHz Right ear Low: 14.18 (6.71, 21.66) Moderate: 28.33 (18.69, 37.97) High: 21.45 (14.67, 28.23) Left ear Low: 13.18 (5.15, 21.20) Moderate: 27.92 (18.27, 37.58) High: 25.37 (18.32, 23.43) 12 kHz Right ear Low: 24.94 (17.29, 32.60) Medium: 33.58 (25.44, 41.72) High: 32.39 (24.14, 40.63)

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						Left ear Low: 24.84 (15.43, 34.25) Moderate: 32.91 (24.26, 41.57) High: 36.01 (27.37, 44.64) Audiometric hearing threshold, better ear 1–8 kHz Low: 4.70 (1.39, 8.01) **Moderate: 12.10 (6.35, 17.80)** **High: 11.57 (7.49, 15.65)** 10–12 kHz Low: 15.93 (8.48, 23.39) Moderate: 28.97 (20.17, 37.78) High: 25.25 (18.49, 32.02) DPOAE 2 kHz Right ear Low: 13.20 (8.93, 17.47) Moderate: 8.11 (3.90, 12.32) High: 10.67 (6.17, 15.17) Left ear Low: 15.56 (12.13, 19.00) Moderate: 12.97 (9.52, 16.42) High: 12.55 (9.61, 15.48) 2.8 kHz Right ear Low: 15.15 (12.01, 18.28) Moderate: 9.24 (4.65, 13.83) High: 11.79 (8.07, 15.51) Left ear Low: 16.02 (13.43, 18.62) **Moderate: 9.71 (5.68, 13.73)** **High: 9.92 (6.17, 13.67)**

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						4 kHz Right ear Low: 15.52 (12.90, 18.14) **Moderate: 8.57 (5.12, 12.02)** **High: 11.26 (7.31, 15.22)** Left ear Low: 16.68 (14.19, 19.16) **Moderate: 7.67 (3.18, 12.16)** **High: 8.79 (4.92, 12.67)** 6 kHz Right ear Low: 12.22 (8.10, 16.34) Moderate: 5.37 (1.25, 9.49) High: 8.60 (4.76, 12.43) Left ear Low: 13.59 (10.64, 16.54) **Moderate: 5.37 (–0.05, 10.79)** **High: 6.03 (2.28, 9.77)** 8 kHz Right ear Low: 0.89 (–5.29, 7.08) Moderate: –7.35 (–12.02, –2.68) High: –6.69 (–9.80, –3.58) Left ear Low: –5.31 (–9.80, –0.82) Moderate: –7.68 (–10.99, –4.37) High: –7.85 (–10.47, –5.24) Auditory brainstem response Wave I Right ear Low: 1.47 (1.36, 1.59) Moderate: 1.57 (1.48, 1.68) High: 1.59 (1.52, 1.67)

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						Left Ear Low: 1.46 (1.34, 1.57) Moderate: 1.59 (1.51, 1.67) High: 1.59 (1.53, 1.65) Wave III Right ear Low: 3.65 (3.49, 3.80) Moderate: 3.76 (3.64, 3.88) High: 3.82 (3.73, 3.90) Left ear Low: 3.59 (3.40, 3.78) Moderate: 3.96 (3.76, 4.16) High: 3.84 (3.72, 3.96) Wave V Right ear Low: 5.08 (4.79, 5.37) **Moderate: 5.63 (5.43, 5.82)** **High: 5.65 (5.44, 5.86)** Left ear Low: 5.27 (4.99, 5.54) Moderate: 5.65 (5.40, 5.91) High: 5.55 (5.41, 5.69) Inter-peak latency, I-V Right ear Low: 3.61 (3.34, 3.87) Moderate: 4.06 (3.87, 4.26) High: 4.05 (3.81, 4.29) Left ear Low: 3.82 (3.58, 4.07) Moderate: 4.06 (3.79, 4.33) High: 3.94 (3.81, 4.06) Inter-peak latency, I-III Right ear

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						Low: 2.17 (2.02, 2.32) Moderate: 2.20 (2.06, 2.33) High: 2.22 (2.11, 2.34) Left ear Low: 2.15 (1.97, 2.33) Moderate: 2.37 (2.13, 2.60) High: 2.22 (2.11, 2.33) Inter-peak latency, III-V Right ear Low: 1.44 (1.11, 1.76) Moderate: 1.86 (1.60, 2.13) High: 1.83 (1.64, 2.02) Left ear Low: 1.67 (1.39, 1.96) Moderate: 1.69 (1.49, 1.89) High: 1.71 (1.58, 1.85) Central auditory function Compressed speech Low: 51.80 (47.14, 56.46) **Moderate: 42.07 (36.95, 47.20)** **High: 45.60 (41.52, 49.69)** Words-in-noise Low: 5.99 (5.24, 6.74) **Moderate: 7.40 (6.55, 8.25)** **High: 7.28 (6.43, 8.13)** Dichotic digits Low: 92.67 (87.80, 97.54) Moderate: 89.69 (87.08, 92.31) High: 87.23 (81.93, 92.53) Pitch pattern sequence Low: 100.0 (98.16, 100.0) Moderate: 97.28 (94.50, 100.0)

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						High: 94.13 (89.97, 98.30) Duration pattern sequence Low: 99.50 (98.08, 100.0) Moderate: 98.42 (97.00, 99.84) High: 96.82 (93.53, 100.0) Auditory test of temporal resolution Within channel Low: 3.51 (2.31, 4.71) Moderate: 3.28 (2.46, 4.10) High: 5.24 (2.91, 7.56) Across channel Low: 48.63 (34.90, 62.35) Moderate: 41.65 (29.40, 53.90) High: 46.53 (33.98, 59.09)
	Confounding: Age, noise exposure levels					
Odkvist et al., 1987 Cohort Uninformative	Sweden[f]	Three groups of workers with long-term (5–41 years) occupational exposures to various industrial solvents, including one group exposed to jet fuels Group A: 56 years Group B: 51 years Group C: 51 years N = 31	Jet fuel type: Not specified Assessment method: Administrative data Exposure duration: 25 years Length of employment: Group A: 27 years, Group B: 21 years, Group C: 25 years	Hearing impairment, motor deficits, ocular conditions Assessment method: Medical professional or test Time since exposure of outcome assessment: Unclear	Incidence of significant abnormality, percent	Hearing Impairment Auditory brainstem response Group A: 1/11, 9% Group B: 1/7, 14% Group C: 0/8, 0% Speech reception threshold Group A: 0/11, 0% Group B: 0/7, 0% Group C: 0/8, 0% Speech discrimination Group A: 1/11, 9% Group B: 0/7, 0% Group C: 0/8, 0% Speech discrimination, interrupted Group A: 7/11, 64% Group B: 3/7, 43%

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						Group C: 3/8, 38% Cortical response Group A: 7/11, 64% Group B: 3/7, 43% Group C: 4/8, 50% Motor Deficits Co-ordination Group A: 6/16, 31% Group B: 2/7, 29% Group C: 0/8, 0% Romberg's test Group A: 7/16, 43% Group B: 1/7, 14% Group C: 1/8, 13% Ocular Conditions Broad frequency rotatory test Group A: not tested Group B: not tested Group C: 4/8, 50% Broad frequency smooth pursuit test Group A: not tested Group B: not tested Group C: 4/8, 50% ENG Group A: 12/16, 75% Group B: 3/7, 43% Group C: 1/8, 13% Saccade test

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						Group A: 9/16, 56% Group B: 2/7, 29% Group C: 1/8, 13%
	Confounding: None reported					
Heaton et al., 2017 Cross-sectional Low	United States 2009–2010	Male and female participants recruited from three U.S. Air Force bases with a range of JP-8 exposures based on their primary job activities 18.6–43 years N = 73	Jet fuel type: JP-8 Assessment method: Administrative data, biomonitoring, measured from personal or area monitors, Exposure duration: Unclear Years of service: 0.5–20.0 years	Memory impairment, motor deficits Assessment method: Medical professional or test Time since exposure of outcome assessment: Same day	Regression coefficient per μg/m^3 increase in average daily air sample of NAP Regression coefficient per μg/m^3 increase in average daily air sample of THC Regression coefficient per μg/g creatinine increase in urinary 1-NAP Regression coefficient per μg/g creatinine increase in urinary 2-NAP	NAP: Auditory consonant trigrams, # correct, 35s delay: 0.14 (–0.4, 0.7) Auditory consonant trigrams, total # correct: 0.40 (–0.8, 1.6) Finger tapping, dominant hand, # taps: 0.17 (–1.2, 1.5) Finger tapping, non-dominant hand, # taps: 0.17 (–1.2, 1.5) Grooved pegboard, dominant hand, mean time to complete: –1.26 (–2.9, 0.3) **Grooved pegboard, non-dominant hand, mean time to complete: –2.32 (–4.2, 0.5)** Hopkins Verbal Learning Test-Revised, total recall: –0.29 (–0.9, 0.4) Hopkins Verbal Learning Test-Revised, retention (%): –1.71 (–3.6, 0.1) Hopkins Verbal Learning Test-Revised, Recognition Discrimination Index: 0.03 (–0.2, 0.3) Simple reaction time, throughput: 2.22 (–2.0, 6.5)

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						THC: Auditory consonant trigrams, # correct, 35s delay: 0.10 (–0.4, 0.6) Auditory consonant trigrams, total # correct: 0.47 (–0.8, 1.7) Finger tapping, dominant hand, # taps: –0.15 (–1.5, 1.2) Finger tapping, non-dominant hand, # taps: 0.12 (–1.2, 1.5) Grooved pegboard, dominant hand, mean time to complete: –1.34 (–3.0, 0.3) **Grooved pegboard, non-dominant hand, mean time to complete: –2.13 (–4.0, –0.2)** Hopkins Verbal Learning Test-Revised, total recall: –0.19 (–0.8, 0.4) Hopkins Verbal Learning Test-Revised, retention, %: –1.16 (–3.0, 0.7) Hopkins Verbal Learning Test-Revised, Recognition Discrimination Index: 0.08 (–0.2, 0.3) Simple reaction time, throughput: 1.87 (–2.4, 6.2) Urinary 1-NAP: Auditory consonant trigrams, # correct, 35s delay: –0.07 (–0.2, 0.1)

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						Auditory consonant trigrams, total # correct: –0.11 (–0.4, 0.2) Finger tapping, dominant hand, # taps: –0.20 (–0.5, 0.1) Finger tapping, non-dominant hand, # taps: –0.13 (–0.4, 0.1) Grooved pegboard, dominant hand, mean time to complete: 0.16 (–0.2, 0.5) Grooved pegboard, non-dominant hand, mean time to complete: 0.11 (–0.2, 0.5) Simple reaction time, throughput: 0.02 (–1.2, 1.2) Urinary 2-NAP: Auditory consonant trigrams, # correct, 35s delay: –0.01 (–0.1, 0.1) Auditory consonant trigrams, total # correct: 0.06 (–0.1, 0.3) Finger tapping, dominant hand, # taps: 0.14 (–0.02, 0.3) Finger tapping, non-dominant hand, # taps: –0.03 (–0.2, 0.1) Grooved pegboard, dominant hand, mean time to complete: –0.09 (–0.3, 0.2) Grooved pegboard, non-dominant hand, mean time to complete: 0.07 (–0.2, 0.4)

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						Simple reaction time, throughput: 0.11 (–0.6, 0.9)
	Confounding: Sex, Shipley scale summary score (general intelligence), years of Air Force service					
Knave et al., 1978 Cross-sectional Low	Sweden[f]	Male jet motor factory workers (fuel system testers, engine testers, mechanics and unexposed workers) Exposed: 46.4 years, Unexposed: 46.2 years N = 60	Jet fuel type: Not specified Assessment method: Measured from personal or area monitors Exposure duration: 17.1 years Length of employment: Exposed: 17.7 years, Unexposed: 19.8 years	Memory impairment, motor deficits, neurological pain or discomfort, neurological symptoms, peripheral nervous system Assessment method: Self-report Time since exposure of outcome assessment: Concurrent	Number of subjects who experienced symptoms Mean (SD)	Memory impairment Verbal recall Recognition Exposed: 29.5 (2.9) Unexposed: 28.7 (4.0) Reproduction criterion 1a Exposed: 8.0 (3.3) Unexposed: 8.2 (3.7) Reproduction criterion 1b Exposed: 53.8 (10.2) Unexposed: 54.6 (10.3) Motor deficits Manual dexterity Right Exposed: 49.1 (7.9) Unexposed: 48.0 (6.8) Left Exposed: 47.0 (7.4) Unexposed: 45.2 (6.1) Coordination Exposed: 31.6 (8.4) Unexposed: 31.3 (7.5) Neurological pain or discomfort Headache Exposed: 5 out of 30

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						Unexposed: 1 out of 30 p = 0.20 Neurological symptoms Dizziness Exposed: 10 out of 30 Unexposed: 2 out of 30 p = 0.024 Fatigue Exposed: 13 out of 30 Unexposed: 1 out of 30 p = 0.0008 Sleep disturbance Exposed: 9 out of 30 Unexposed: 2 out of 30 p = 0.046 Irritability Exposed: 4 out of 30 Unexposed: 1 out of 30 p = 0.35 Excess sweating Exposed: 3 out of 30 Unexposed: 2 out of 30 Peripheral nervous system Symptoms of polyneuropathy Exposed: 12 out of 30 Unexposed: 5 out of 30 p = 0.086 Signs of polyneuropathy

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						Exposed: 18 out of 30 Unexposed: 15 out of 30
	Confounding: None reported					
Olsen et al., 1998 Cohort Low	United States, Hill Air Force Base, Utah, 1995	Active duty and civilian personnel exposed or unexposed to JP-4 and JP-8 Exposed: 32.8 years, Unexposed: 32.3 years N = 30	Jet fuel type: JP-4, JP-8 Assessment method: Administrative data, personal area monitors Exposure duration: Unclear Years of service: ≥6 months	Memory impairment, peripheral nervous system, neurological symptoms Assessment method: Medical professional or test, self-report Time since exposure of outcome assessment: Baseline (JP-4), 6 months (JP-8), 18 months (JP-8)	Mean (SD) Mean frequency of symptoms scale Outcome frequency scale groups: 0 = never happens; 1 = 1–2 times per month; 2 = 3–4 times per month; 3 = 5–9 times per month; 4 = ≥10 times per month; 5 = every day	Memory impairment Memory (exposed; unexposed) Baseline, JP-4: 100.9 (16.7); 104.9 (14.6) 6 months, JP-8: 104.1 (12.1); 105.6 (10.6) 18 months, JP-8: 111.3 (12.2); 111.8 (10.9) Peripheral nervous system Numbness/tingling of hands or feet (exposed; unexposed) Baseline, JP-4: 1.2; 1.2 6 months, JP-8: 1.4; 1.5 18 months, JP-8: 1.4; 1.6 Neurological symptoms Dizziness (exposed; unexposed) Baseline, JP-4: 1.6; 1.3 6 months, JP-8: 1.3; 1.9 18 months, JP-8: 1.2; 1.4 Fatigue (exposed; unexposed) Baseline, JP-4: 0.9; 0.5 6 months, JP-8: 0.7; 1.3 18 months, JP-8: 1.2; 1.1
	Confounding: None reported					

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
Knave et al., 1976 Cohort Uninformative	Sweden, 1975	Aircraft workers exposed to jet fuels Heavily exposed: 54.2 years Less exposed: 46.3 years N = 29	Jet fuel type: Not specified Assessment method: Administrative data Exposure duration: ≥5 years; Heavily exposed: Continuous high concentration exposures for several hours daily or intermittent exposure of 20–30 min to high concentrations; Less heavily exposed: Less frequent intermittent exposure Length of employment: ≥5 years	Memory impairment, neurological pain or discomfort, peripheral nervous system Assessment method: Medical professional or test, self-report, questionnaire Time since exposure of outcome assessment: >5 years employment at workplace	Number of subjects who experienced symptoms	Memory impairment Heavily exposed: 2 out of 13 Less heavily exposed: 2 out of 16 Neurological pain or discomfort Headache Heavily exposed: 4 out of 13 Less heavily exposed: 5 out of 16 Neurological Symptoms Dizziness Heavily exposed: 10 out of 13 Less heavily exposed: 3 out of 16 Peripheral nervous system Polyneuropathy symptoms Heavily exposed: 11 out of 13 Less heavily exposed: 6 out of 16
	Confounding: Age					
Tunnicliffe et al., 1999 Cross-sectional	United Kingdom[f]	Employees of Birmingham International Airport who lived locally and	Jet fuel type: Not specified Assessment method:	Ocular conditions Assessment method: Self-	Odds ratio Medium exposure group	Watering eyes 0.8 (0.32, 1.86)

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
Low		commuted to work daily (High exposure: baggage handlers, airport hands, marshallers, operational engineers, fitters and engineering technicians; Medium exposure: security staff, fire fighters and airfield operations managers; Low exposure: terminal and office workers) 38.6 years N = 222	Administrative data Exposure duration: Unclear Average length of employment: 7.6 years	report, questionnaire Time since exposure of outcome assessment: Concurrent	used as reference group	
	Confounding: Age, smoking, self-reported history of hay fever					
Maule et al., 2013 Cross-sectional Medium	United States[f]	Male and female active-duty AF personnel with high or low JP-8 fuel exposure in current job tasks 26.8 years	Jet fuel type: JP-8 Assessment method: Biomonitoring, administrative data, measured	Vestibular function Assessment method: Medical professional or test Time since	Regression coefficient per mg/m³ increase in TWA THC or per µg/m³ increase in TWA NAP or per µg/g creatinine	Vestibular function Postural sway 8-h TWA for THC Mean path velocity EO: –0.002 (–0.006, 0.003) EC: 0.002 (–0.004, 0.007) F, EO: 0.001 (–0.005, 0.007) F, EC: –0.001 (–0.006, 0.003)

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
		N = 37	from personal or area monitors Exposure duration: Unclear Years of service: 5.8 years	exposure of outcome assessment: Same day	increase in 1-NAP	Total angular area EO: –0.006 (–0.016, 0.004) EC: 0.002 (–0.010, 0.015) F, EO: –0.008 (–0.020, 0.004) F, EC: –0.004 (–0.017, 0.008) 8-hours TWA for NAP Mean path velocity EO: –0.004 (–0.011, 0.003) EC: 0.003 (–0.005, 0.012) F, EO: 0 (–0.009, 0.010) F, EC: –0.003 (–0.010, 0.004) Total angular area EO: –0.009 (–0.025, 0.007) EC: 0.007 (–0.012, 0.026) F, EO: –0.012 (–0.031, 0.006) F, EC: –0.005 (–0.024, 0.014) 1-NAP Urine Mean path velocity EO: –0.004 (–0.011, 0.003) EC: –0.003 (–0.011, 0.006) F, EO: –0.007 (–0.015, 0.002) F, EC: –0.005 (–0.012, 0.001) Total angular area EO: –0.001 (–0.016, 0.014) EC: –0.008 (–0.027, 0.010) F, EO: –0.020 (–0.037, –0.003) F, EC: –0.018 (–0.036, –0.001) 2-NAP Urine Mean path velocity EO: –0.005 (–0.017, 0.006) EC: –0.009 (–0.022, 0.005)

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						F, EO: –0.009 (–0.024, 0.005) F, EC: –0.004 (–0.015, 0.006) Total angular area EO: 0.004 (–0.020, 0.028) EC: –0.025 (–0.056, 0.005) F, EO: –0.024 (–0.052, 0.003) F, EC: –0.021 (–0.049, 0.007)
	Confounding: Preshift postural sway variables Confounding for 8-hour TWA THC mean path velocity: EO: current smoking, age; EC: current smoking, BMI, age; F, EO: none; F, EC: age Confounding for 8-hour TWA THC total angular area: EO: age; EC: current smoking; F, EO: age; F, EC: age Confounding for 8-hour TWA NAP mean path velocity: EO: current smoking, age; EC: current smoking, BMI, age; F, EO: None; F, EC: age Confounding for 8-hour TWA NAP total angular area: EO: age; EC: current smoking; F, EO: age; F, EC: age Confounding for 1-NAP mean path velocity: EO: current smoking, age; EC: current smoking, BMI, age; F, EO: current smoking; F, EC: age Confounding for 1-NAP total angular area: EO: age; EC: current smoking; F, EO: age; F, EC: age Confounding for 2-NAP mean path velocity: EO: current smoking, age; EC: current smoking, BMI, age; F, EO: current smoking; F, EC: age Confounding for 2-NAP total angular area: EO: age; EC: current smoking; F, EO: age; F, EC: age					
Smith et al., 1997 Cross-sectional Low	United States[f]	USAF employees and volunteers from the military, university and other sources Exposed: 37.5 years Unexposed: 34.0 years N = 52	Jet fuel type: JP-8 Assessment method: Measured from personal or area monitors, administrative data Exposure duration: Unclear	Vestibular function Assessment method: Medical professional or test Time since exposure of outcome assessment: Unclear	Regression coefficient per ppm increase in cumulative JP-8 benzene (SE) Percent change, exposed vs. unexposed R-squared	Vestibular function Regression coefficient per ppm increase in cumulative JP-8 benzene (SE) Postural sway area EO: 0.02 (0.01), p = 0.08 **EC: 0.03 (0.01), p = 0.01** F, EO: 0.013 (0.01), p=0.13 F, EC: 0.016 (0.01), p=0.08 **Postural sway length** **EO: 0.01 (0.004), p = 0.01** **EC: 0.02 (0.01), p = 0.0005**

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
			Years of service: 12.0 years			**F, EO: 0.01 (0.004), p = 0.009** **F, EC: 0.014 (0.006), p = 0.009** Percent change EO: Postural sway area: 0.40; Postural sway length: –0.02, $p < 0.06$ R-squared Postural sway area F, EC, TWA JP-8 benzene: $p < 0.05$ F, EC, all JP-8 benzene: $p < 0.05$ Postural sway length F, EO, TWA JP-8 benzene: $p < 0.05$ F, EC, TWA JP-8 benzene: $p < 0.05$
	Confounding: EO, EC and F, EC sway area: None reported EO sway length and F, EO sway area: Weight-to-height ratio EC sway length: Gender, caffeine F, EO and F, EC sway length: Age, weight-to-height ratio					

MCAS = Marine Corps Air Station; SD = standard deviation; RAAF = Royal Australian Air Force; kHz = kilohertz; DPOAE = distortion product otoacoustic emissions; ENG = electronystagmography; U.S. = United States; THC = total hydrocarbon; NAP = naphthalene; 1-NAP = 1-naphthol; 2-NAP = 2-naphthol; TWA = time-weighted average; EO = eyes open; EC = eyes closed; F, EO = eyes open, on foam support; F, EC = eyes closed, on foam support; BMI = body mass index; USAF = United States Air Force; ppm = parts per million; SE = standard error.

[a]Data reported as mean, unless otherwise noted.
[b]Results reported as effect estimate (95% confidence interval), unless otherwise noted.
[c]Bolded results are statistically significant at 0.05 level.
[d]Acute health outcomes are considered those that were measured within 6 months of exposure.
[e]Long-term health outcomes are considered those that were measured at least 6 months after exposure.
[f]The years the study was conducted were not reported for this publication.

C.1.2. Mental Health Outcomes

Table C-2. Associations Between Jet Fuel Exposure and Mental Health Outcomes in Epidemiologic Studies.

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
Long-term Health Outcomes[d]						
Heaton et al., 2017 Cross-sectional Medium	United States, 2009–2010	Male and female participants recruited from three U.S. Air Force bases with a range of JP-8 exposures based on their primary job activities 18.6–43 years N = 73	Jet fuel type: JP-8 Assessment method: Administrative data, personal air monitoring and biomonitoring Exposure Duration: Unclear Years of Service: 0.5–20.0 years	Attention, executive function, visuospatial performance Assessment method: Medical professional or test Time since exposure of outcome assessment: Concurrent	Mean (SD) Regression coefficient per μg/m^3 naphthalene, or per mg/m^3 THC or per μg/g creatinine 1- or 2-NAP, or for higher vs. lower exposure groups	Attention Continuous Performance Test Response time, (Day 2, Day 4, Day 6) Mean (SD): 397.64 (62.7), 403.6 (44.9), 420.11 (46.5) **Mean reaction time, Day 6 compared to Day 2, Naphthalene model: 22.59 (10.6, 34.6)** **THC: 22.85 (11.1, 34.6)** Naphthalene: 2.39 (–8.4, 13.2) Urinary 1-naphthol: 0.21 (–1.5, 1.9) Executive function WAIS III Digit Span Forward (Day 2, Day 4, Day 6) Mean (SD): 10.86 (2.1), 11.30 (2.0), 11.46 (2.3) WAIS III Digit Span Forward, Naphthalene: 0.31 (–0.02, 0.7) THC: 0.28 (–0.1, 0.6) WAIS III Digit Span Backward (Day 2, Day 4, Day 6) Mean (SD): 6.85 (2.0), 7.78 (2.2), 7.86 (2.2)

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						WAIS III Digit Span Backward, Naphthalene: 0.17 (–0.2, 0.5) THC: 0.21 (–0.1, 0.5) Visuospatial performance ANAM4—Matching 2 Sample, Naphthalene: –0.29 (–2.1, 1.5) Urinary 1-NAP: 0.07 (–0.4, 0.5) Urinary 2-NAP: −0.05 (–0.3,0.2) Hooper Test Naphthalene: –0.21 (–0.5, 0.1) Higher vs. lower exposure: –0.92 ($p<0.05$)
	Confounding: Sex, Shipley scale summary score (general intelligence), years of Air Force service					
Olsen et al., 1998 Cohort Low	United States, Hill Air Force Base, 1995	Active duty and civilian personnel exposed or unexposed to JP-4 and JP-8 Exposed = 32.8 years; Unexposed = 32.3 years N = 35	Jet fuel type: JP-8, JP4 Assessment method: Administrative data Exposure Duration: Unclear Years of service: ≥6 months Length of Employment: Unclear	Attention, cognitive function, executive function, visuospatial performance Assessment method: Medical professional or test, test administered using computer Time since exposure of outcome assessment: Baseline, 6	Mean (SD)	Attention Attention/Mental Control (exposed, unexposed) JP-4: 94.7 (21.0), 100.4 (14.7) JP-8, 6-months: 96.7 (17.0), 100.6 (9.8) JP-8, 18 months: 100.3 (13.6), 106.1 (13.1) Difficulties concentrating JP-4: 1.3, 0.9 JP-8, 6-months: 1.6, 1.2 JP-8, 18 months: 1.4, 1.2 Reaction time JP-4: 105.5 (10.1), 106.3 (9.7) **JP-8, 6-months: 105.3 (12.2), 112.1 (6.4)** JP-8, 18 months: 107.2 (9.5), 108.2 (6.7) Cognitive function

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
				months and 18 months		Reasoning/Calculation JP-4: 95.4 (14.7), 97.3 (11.5) JP-8, 6-months: 98.4 (13.5), 98.0 (13.2) JP-8, 18 months: 102.5 (15.6), 04.4 (17.3) General cognitive functioning JP-4: 94.2 (16.9), 97.8 (13.1) JP-8, 6-months: 98.6 (12.1), 99.7 (9.9) JP-8, 18 months: 104.9 (14.6), 106.4 (12.1) General Proficiency JP-4: 90.1 (12.4), 97.1 (10.8) JP-8, 6-months: 94.3 (10.5), 98.0 (8.2) JP-8, 18 months: 99.4 (14.4), 103.3 (12.8) Executive function Information processing speed JP-4: 94.8 (11.5), 98.5 (15.3) JP-8, 6-months: 100.0 (8.5), 103.3 (12.1) JP-8, 18 months: 99.4 (15.3), 103.8 (14.8) Information processing accuracy JP-4: 95.9 (18.2), 97.7 (12.5) JP-8, 6-months: 97.7 (14.7), 96.3 (15.9) JP-8, 18 months: 107.9 (14.7), 105.8 (8.7) Visuospatial function

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
	Confounding: Education, age					Spatial processing JP-4: 100.9 (14.8), 103.4 (11.9) JP-8, 6-months: 105.5 (7.4), 106.4 (8.5) JP-8, 18 months: 105.3 (11.9), 105.6 (10.8)
Tu et al., 2004 Cross-sectional Low	United States, Warfield ANG Base, Essex, MD, 2001	ANG members either likely or less likely to be exposed to JP-8 by their job (Likely exposed: Fuel cell workers, crew chiefs, mechanics, fuel specialists; Less likely exposed: incidental subjects); Age- and education-matched controls Exposed: 41 years Unexposed: 41 years N = 113	Jet fuel type: JP-8 Assessment method: Biomonitoring Exposure duration: Unclear Years of service: 10–16 years[e]	Attention, cognition, executive function, visuospatial performance Assessment method: Medical professional or test Time since exposure of outcome assessment: Same day	Mean (SD)	Attention (Group differences: crew chiefs, fuel workers, mechanics, incidental subjects) **Divided attention test immediate recall speed:** **Group differences: 0.38 (0.05)**, 0.34 (0.09), 0.36 (0.08), **0.31 (0.08)** **Warfield group, controls:** 0.37 (0.19), **0.47 (0.11)** **Divided attention test delayed recall speed:** Group differences: 0.70 (0.19), 0.82 (0.24), 0.84 (0.50), 0.69 (0.35) **Warfield group, controls:** 0.74 (0.33), **0.81 (0.20)** **Divided attention test premature responses:** **Group differences: 4 (2), 4 (2), 4 (3), 7 (4)** **Warfield group, controls: 5 (3)**, 3 (2) **Shifting attention test discovery rule:** Group differences: 3 (3), 5 (3), 5 (3), 4 (3)

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						Warfield group, controls: 4 (3), 7 (3) Cognition (Group differences: crew chiefs, fuel workers, mechanics, incidental subjects) **Math speed:** Group differences: 34.5 (15.1), 35.2 (15.7), 34.1 (12.9), 29.5 (11.5) **Warfield group, controls: 32.3 (13.3)**, 24.2 (6.0) **Sequence comparison speed:** **Group differences:** 2.49 (0.97), **2.81 (0.84)**, 2.38 (0.68), **2.21 (0.59)** Warfield group, controls: 2.41 (0.76), 2.13 (0.49) **Auditory sequence comparison speed:** **Group differences: 0.72 (0.17)**, 0.77 (0.16), **0.88 (0.12)**, 0.78 (0.78) Warfield group, controls: 0.78 (0.16), 0.74 (0.24) **Pathfinder number speed:** Group differences: 0.97 (0.15), 1.03 (0.25), 1.01 (0.23), 1.01 (0.27) **Warfield group, controls: 1.07 (0.58)**, 0.72 (0.18) **Pathfinder letter speed:** Group differences: 0.87 (0.14), 0.94 (0.23), 0.93 (0.22), 0.92 (0.21) **Warfield group, controls: 0.92 (0.20)**, 0.64 (0.18)

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						Pathfinder combined speed: Group differences: 1.21 (0.27), 1.93 (1.57), 1.59 (0.65), 1.42 (0.45) **Warfield group, controls: 1.50 (0.81)**, 1.08 (0.32) **Arrow direction speed:** Group differences: 0.70 (0.16), 0.69 (0.10), 0.70 (0.08), 0.68 (0.10) **Warfield group, controls: 0.69 (0.11)**, 0.55 (0.1) **Arrow color speed:** Group differences: 0.77 (0.11), 0.72 (0.07), 0.78 (0.14), 0.74 (0.12) **Warfield group, controls: 0.75 (0.12)**, 0.53 (0.09) **Instruction speed:** **Group differences:** 0.92 (0.16), **0.89 (0.20)**, **1.11 (0.47)**, **0.93 (0.18)** **Warfield group, controls: 0.95 (0.25)**, 0.71 (0.12) **Discovery speed:** Group differences: 1.18 (0.49), 1.24 (0.46), 1.13 (0.19), 1.12 (0.23) **Warfield group, controls: 1.16 (0.34)**, 0.78 (0.2) **Dual tasking test previous number alone speed:**

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						Group differences: 0.59 (0.28), 0.76 (0.37), **0.99 (0.59)**, **0.58 (0.34)** **Warfield group, controls: 0.68 (0.40)**, 0.47 (0.24) Dual tasking test previous number dual speed: Group differences: 0.67 (0.33), 0.80 (0.24), 0.82 (0.45), 0.72 (0.34) Warfield group, controls: 0.74 (0.34), 0.67 (0.24) Dual tasking test alone error: Group differences: 16 (12), 14 (13), 23 (16), 25 (19) Warfield group, controls: 21 (16), 23 (17) **Dual tasking test dual error:** Group differences: 70 (25), 62 (24), 73 (24), 69 (26) **Warfield group, controls: 69 (25)**, 51 (23) **Math accuracy:** Group differences: 49 (31), 48 (38), 64 (34), 65 (25) **Warfield group, controls: 58 (31)**, 81 (22) **Symbol digit coding accuracy:** **Group differences:** 99 (2), **98 (3)**, 100 (1), **99 (1)** **Warfield group, controls:** 99 (2), **98 (4)**

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						Symbol digit coding immediate recall accuracy: Group differences: 86 (23), 72 (35), 75 (28), 73 (30) Warfield group, controls: 76 (29), 82 (25) Sequence comparison accuracy: Group differences: 90 (15), 94 (9), 86 (15), 88 (11) Warfield group, controls: 89 (12), 89 (7) Auditory sequence comparison accuracy: Group differences: 92 (7), 93 (8), 90 (9), 89 (10) Warfield group, controls: 90 (9), 88 (8) **Pathfinder number accuracy:** **Group differences: 94 (14)**, **100 (1)**, 100 (1), **100 (0)** Warfield group, controls: 99 (7), 100 (1) Pathfinder letter accuracy: Group differences: 99 (2), 99 (2), 99 (2), 99 (1) Warfield group, controls: 99 (2), 100 (2) **Pathfinder combined accuracy:** **Group differences: 97 (8)**, **88 (16)**, 91 (16), **96 (5)** Warfield group, controls: 84 (11), 98 (3)

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						Symbol digit coding delayed recall accuracy: Group differences: 73 (34), 58 (39), 65 (36), 64 (33) Warfield group, controls: 65 (34), 75 (2) Arrow direction accuracy: Group differences: 97 (4), 99 (3), 98 (3), 98 (5) Warfield group, controls: 98 (4), 99 (3) Arrow color accuracy: Group differences: 99 (5), 99 (2), 99 (3), 100 (0) Warfield group, controls: 99 (3), 99 (3) Instruction accuracy: Group differences: 96 (4), 91 (19), 87 (15), 93 (11) Warfield group, controls: 92 (13), 96 (8) **Discovery accuracy:** Group differences: 54 (12), 57 (20), 58 (11), 54 (15) **Warfield group, controls: 55 (15)**, 66 (14) **Dual tasking test previous number alone accuracy:** **Group differences: 88 (14), 87 (13), 72 (20), 90 (12)**

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						Warfield group, controls: 86 (15), 92 (9) **Dual tasking test previous number dual accuracy:** Group differences: 79 (11), 74 (17), 67 (29), 79 (19) **Warfield group, controls: 76 (20)**, 84 (13) Dual tasking test alone boundary hits: Group differences: 1 (2), 2 (2), 2 (2), 3 (4) Warfield group, controls: 2 (3), 1 (2) **Dual tasking test dual boundary hits:** Group differences: 6 (5), 5 (5), 6 (6), 6 (5) **Warfield group, controls: 6 (5)**, 3 (4) Sequency comparison thruput: Group differences: 24.4 (9.1), 21.4 (6.0), 22.4 (4.4), 25.3 (6.5) Warfield group, controls: 23.9 (6.8), 26.2 (5.9) **Auditory sequence comparison thruput:** **Group differences: 80.4 (18.6)**, 75.3 (16.7), **62.6 (13.4)**, 71.5 (19.4) Warfield group, controls: 72.6 (18.3) 78.9 (27.8)

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						Pathfinder number thruput: Group differences: 62.3 (9.6), 61.1 (13.0), 61.3 (10.9), 63.2 (14.8) Warfield group, controls: 61.4 (14.5), 89.2 (23.5) **Pathfinder combined thruput:** **Group differences: 50.7 (13.4)**, **36.8 (17.3)**, 39.1 (14.7), 44.4 (13.0) Warfield group, controls: 43.5 (14.5), 59.6 (18.4) **Dual tasking test previous number alone thruput:** **Group differences:** 112.4 (52.6), 82.8 (32.6), **73.7 (67.2)**, **123.5 (72.3)** Warfield group, controls: 105.6 (64.3), 145.7 (74.7) Executive function (Group differences: crew chiefs, fuel workers, mechanics, incidental subjects) **Visual sequence comparison speed:** **Group differences:** 2.64 (0.71), 2.91 (0.61), **3.16 (0.91)**, **2.57 (0.68)** **Warfield group, controls: 2.74 (0.73)**, 2.27 (0.67) **Matching to sample speed:**

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						Group differences: 1.45 (0.28), 1.43 (0.25), 1.40 (0.23), 1.44 (0.27) **Warfield group, controls: 1.43 (0.26)**, 2.13 (0.49) **Backward digit span accuracy:** Group differences: 68 (19), 76 (20), 72 (19), 72 (20) **Warfield group, controls: 72 (20)**, 79 (21) Visual sequence comparison accuracy: Group differences: 97 (5), 96 (4), 97 (4), 96 (5) Warfield group, controls: 96 (5), 98(3) Matching to sample accuracy: Group differences: 93 (8), 93 (10), 94 (6), 93 (6) Warfield group, controls: 93 (7), 94 (5) Visuospatial performance (Group differences: crew chiefs, fuel workers, mechanics, incidental subjects) Manikin speed: Group differences: 2.05 (0.41), 2.12 (0.51), 1.92 (0.56), 1.92 (0.58) Warfield group, controls: 1.98 (0.53), 1.84 (0.42)

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						Manikin accuracy: Group differences: 89 (14), 92 (9), 82 (20), 85 (21) Warfield group, controls: 87 (18), 89 (13)
	Confounding: None reported					
Knave et al., 1978 Cross-sectional Low	Sweden, 1974	Male jet motor factory workers (fuel system testers, engine testers, mechanics and unexposed workers) Exposed: 46.4 years, Unexposed: 46.2 years N = 60	Jet fuel type: Unspecified Assessment method: Personal air monitors Exposure Duration: Unclear Length of Employment: Exposed: 17.7 years, Control: 19.8 years	Attention, cognitive function, depression, executive function, social emotional behavior Assessment method: Self-reported, medical professional or test Time since exposure of outcome assessment: Concurrent	Mean (SD) Incidence	Attention Simple reaction time Speed: 275 (44), 270 (31) Regularity: 19 (9), 19 (13) Reaction time addition Speed: 3.0 (1), 2.8 (1) Regularity: 1.2 (0.4), 1.0 (0.4) Cognitive function **Mental symptoms (exposed, unexposed): 8.6, 5.6** Depression **Depressed mood: 10/30, 1/30 p = 0.0076** Executive function Perceptual speed: 14.0 (2.5), 12.8 (2.1) Social-emotional behavior Irritability: 4/30,1/30

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						Neurasthenia, anxiety and/or depression **Standardized interview: 24/30, 10/30, p = 0.0008** **Medical records: 23, 10, p = 0.0018** **Diagnosed and treated by physician—standardized interview:19, 7, p = 0.004** **Diagnosed and treated by physician—medical records: 23/30,10/30, p = 0.0018** **On several occasions—standardized interview: 14, 4, p = 0.011** **On several occasions—medical records: 19/30, 6/30, p = 0.0017** Anxiety and/or depression Standardized interview: 3/30, 3/30 Medical records: 4/30, 4/30
	Confounding: None reported					
Knave et al., 1976 Cohort Uninformative	Sweden, 1975	Aircraft workers exposed to jet fuels Median Age: heavily exposed = 56.5 years, less heavily expose = 45.0 years N = 29	Jet fuel type: Unspecified Assessment method: Administrative data Exposure Duration: ≥5 years; Heavily exposed: Continuous high	Depression Assessment method: Self-reported Time since exposure of outcome assessment: Following 5 years of employment with exposure	Incidence	Self-reported depression/anxiety Heavily exposed: 8 out of 13 Less heavily exposed: 4 out of 16

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
			concentration exposures for several hours daily or intermittent exposure of 20–30 min to high concentrations; Less heavily exposed: Less frequent intermittent exposure Length of Employment: ≥5 years			
	Confounding: None reported					

U.S. = United States; SD = standard deviation; THC = total hydrocarbon; 1-NAP = 1-naphthol; 2-NAP = 2-naphthol; WAIS III = Wechsler Adult Intelligence Scale--Third Edition; ANG = Air National Guard

[a]Data reported as mean, unless otherwise noted.

[b]Results reported as effect estimate (95% confidence interval), unless otherwise noted.

[c]Bolded results are statistically significant at 0.05 level.

[d]Long-term health outcomes are considered those that were measured at least 6 months after exposure.

[e]Years of service represents a range of mean years reported across all job titles.

C.1.3. Respiratory Health Outcomes

Table C-3. Associations Between Jet Fuel Exposure and Respiratory Health Outcomes in Epidemiologic Studies.

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
Acute Health Outcomes[d]						
Andersen et al., 2021 Cross-sectional Medium	Denmark, 2018	Ground crew personnel (crew chiefs, aircraft engineers, fuel operators, munition specialists, office workers, avionics) at a Danish Air Force base 46.9 years N = 79	Jet fuel type: JP-8 Assessment method: Measured from personal or area monitors, biomonitoring, administrative data Exposure Duration: Unclear Length of employment: Exposed: 1–10 years = 43%; >10 years = 57%, Unexposed: 1–10 years = 24%; >10 years = 76%	Lung function measures Assessment method: Medical professional or test Time since exposure of outcome assessment: Concurrent	Regression coefficient (SE) Unexposed workers used as reference group	Lung function measures FEV_1: –3.689 (3.538), p = 0.301 FVC : –4.226 (3.192), p = 0.191 PEF : –0.121 (4.770), p = 0.980
	Confounding: Age, sex, body mass index, health history (asthma), smoking history, height					
Tunnicliffe et al., 1999 Cross-sectional Low	United Kingdom[f]	Employees of Birmingham International Airport, who lived locally and commuted to work daily (High exposure: baggage handlers, airport hands, marshallers, operational engineers,	Jet fuel type: Unspecified Assessment method: Administrative data Exposure Duration: Unclear	Lung function measures, respiratory hypersensitivity (males only), respiratory symptoms (males only) Assessment	Mean differences (SD) Odds ratio Medium exposure group used as reference group	Lung function measures FEV_1 (low, medium, high exposure groups): Never smokers: 101 (12), 102 (12), 100 (12)

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
		fitters and engineering technicians; Medium exposure: security staff, fire fighters and airfield operations managers; Low exposure: terminal and office workers) 38.6 years N = 222	Length of employment: 7.6 years	method: Medical professional or test, self-reported questionnaire Time since exposure of outcome assessment: Concurrent		Ex-smokers: 97 (15), 102 (15), 99 (11) Current smokers: 94 (16), 100 (12), 93 (11) FVC (low, medium, high exposure groups): Never smokers: 107 (14), 108 (12), 106 (11) Ex-smokers: 107 (12), 109 (17), 106 (11) Current smokers: 108 (18), 109 (12), 104 (11) FEV_1/FVC (low, medium, high exposure groups): Never smokers: 81 (14), 78 (16), 78 (16) Ex-smokers: 77 (15), 78 (11), 77 (10) Current smokers: 76 (15), 77 (9), 74 (12) Respiratory hypersensitivity (males) Wheeze or whistling in chest: 0.8 (0.31, 2.73) Respiratory symptoms (males)

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						Cough: 2.2 (0.94, 5.26) **Cough with phlegm: 3.5 (1.23, 9.74)** Stuffy nose: 1.4 (0.49, 2.81) **Runny nose: 2.9 (1.32, 6.40)** Shortness of breath: 0.9 (0.34, 2.52)
	Confounding: Age, smoking, self-reported asthma (for wheeze or whistling in chest and shortness of breath), self-reported hay fever (for stuffy nose and runny nose)					
Yang et al., 2003 Cross-sectional Low	Taiwan, 2000–2001	Male airport workers at Kaohsiung International Airport (Exposed: jet fuel handlers, baggage handlers, operational engineers, marshallers, airport hands, fitters and engineering technicians; Unexposed: security staff, airfield operation managers, clerks, accountants, maintenance personnel and terminal and other office workers) ≥40 years: Exposed = 50.9% Unexposed = 14.8%	Jet fuel type: Unspecified Assessment method: Administrative data Exposure Duration: Unclear Length of employment, ≥10 years: Exposed = 68.9% Unexposed = 6.6%	Respiratory symptoms Assessment method: Questionnaire Time since exposure of outcome assessment: Concurrent	Odds ratio Unexposed used as reference group	Respiratory symptoms **Dyspnea: 2.34 (1.05, 5.18)** Nose irritation: 1.14 (0.60, 2.15) Throat irritation: 1.55 (0.75, 3.21)

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
		N = 411				
	Confounding: Age, education, marriage status, duration of employment, smoking status, previous occupational dust or fume exposure					
Knave et al., 1976 Cohort Uninformative	Sweden[f]	Aircraft workers exposed to jet fuels Heavily exposed: 54.2 years, less heavily exposed: 46.3 years N = 29	Jet fuel type: Unspecified Assessment method: Administrative data Exposure Duration: ≥ 5 years; Heavily exposed: Continuous high concentration exposures for several hours daily; Less heavily exposed: Heavy intermittent exposure of 20–30 min Length of employment: ≥5 years	Respiratory symptoms Assessment method: self-report questionnaire Time since exposure of outcome assessment: Concurrent	Number of subjects who experienced symptoms	Respiratory symptoms Acute respiratory tract symptoms: Heavily exposed: 6 out of 13 Less heavily exposed: 3 out of 16
	Confounding: None reported					
Knave et al., 1978 Cross-sectional Uninformative	Sweden[f]	Male jet motor factory workers (fuel system testers, engine testers, mechanics and unexposed workers) Exposed: 46.4 years, Unexposed: 46.2 years N = 60	Jet fuel type: Unspecified Assessment method: Measured from personal or area monitors Exposure Duration: 17.1 years Length of employment:	Respiratory symptoms Assessment method: Self-report Time since exposure of outcome assessment: Concurrent	Number of subjects who experienced symptoms	Respiratory symptoms Exposed: 3 out of 30 Unexposed: 2 out of 30

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
			Exposed: 17.7 years, Unexposed: 19.8 years			
	Confounding: None reported					
Olsen et al., 1998 Cohort Uninformative	United States, Hill Air Force Base, 1995	Active duty and civilian personnel exposed or unexposed to JP-4 and JP-8 Exposed: 32.8 years, Unexposed: 32.3 years N = 35	Jet fuel type : JP-4, JP-8 Assessment method: Measured from personal or area monitors, administrative data Exposure Duration: Unclear Length of employment: ≥6 months	Respiratory symptoms Assessment method: Self-reported Time since exposure of outcome assessment: Concurrent at baseline, 6 months and 18 months	Mean frequency of symptoms scale Outcome frequency scale groups: 0 = never happens; 1 = 1–2 times per month; 2 = 3–4 times per month; 3 = 5–9 times per month; 4 = ≥10 times per month; 5 = every day	Respiratory symptoms Nose irritation (exposed, unexposed): JP-4: 1.6, 0.8 JP-8, 6 months: 1.8, 1.6 JP-8, 18 months: 1.8, 1.0 Throat irritation (exposed, unexposed): JP-4: 1.0, 0.6 JP-8, 6 months: 1.4, 1.2 JP-8, 18 months: 1.3, 1.0 Cough (exposed, unexposed): JP-4: 1.0, 0.8 JP-8, 6 months: 1.2, 1.7 JP-8, 18 months: 1.6, 0.3 Shortness of breath (exposed, unexposed):

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						JP-4: 1.1, 0.7 JP-8, 6 months: 0.8, 1.3 JP-8, 18 months: 1.4, 0.0
	Confounding: Age, sex					
Long-term Health Outcomes[e]						
Radican et al., 2008 Cohort Low	United States, Hill Air Force Base, 1952–2000	Civilian workers at an aircraft maintenance facility For remaining subjects alive in 2000 (n = 5,875): 75 years N = 14,455	Jet fuel type: JP-4 Assessment method: Administrative data Exposure Duration: ≥1 year Length of employment: ≥1 year	Obstructive disease Assessment method: Medical records, registry Time since exposure of outcome assessment: 30 years	Hazard ratio Unexposed workers used as reference group	Obstructive disease Non-malignant respiratory disease: **Men: 1.31 (1.01, 1.69)** Women: 0.80 (0.57, 1.14) Emphysema (women): 3.99 (1.00, 15.96)
	Confounding: Age, race					
Yang et al., 2003 Cross-sectional Low	Taiwan, 2000–2001	Male airport workers at Kaohsiung International Airport (Exposed: jet fuel handlers, baggage handlers, operational engineers, marshallers, airport hands, fitters and engineering technicians; Unexposed: security staff, airfield operation	Jet fuel type: Unspecified Assessment method: administrative data Exposure Duration: Unclear Length of employment, ≥10 years: Exposed = 68.9%,	Obstructive disease, respiratory symptoms experienced for ≥3 months in the past year Assessment method: Questionnaire	Odds ratio Unexposed workers used as reference group	Obstructive disease Chronic bronchitis: 1.50 (0.50, 4.54) Respiratory symptoms **Cough: 3.41 (1.26, 9.28)**

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
		managers, clerks, accountants, maintenance personnel and terminal and other office workers) ≥40 years: Exposed = 50.9%, Unexposed = 14.8% N = 411	Unexposed = 6.6%	Time since exposure of outcome assessment: Concurrent		Phlegm: 1.46 (0.39, 5.41)
	Confounding: Age, education, marriage status, duration of employment, smoking status, previous occupational dust or fume exposure					

SE = standard error; FEV_1 = forced expiratory volume in the first second; FVC = forced vital capacity; PEF = peak expiratory flow; SD = standard deviation

[a]Data reported as mean, unless otherwise noted.
[b]Results reported as effect estimate (95% confidence interval), unless otherwise noted.
[c]Bolded results are statistically significant at 0.05 level.
[d]Acute health outcomes are considered those that were measured within 6 months of exposure.
[e]Long-term outcomes are considered those that were measured at least 6 months after exposure.
[f]The years the study was conducted were not reported for this publication.

C.1.4. Immune Health Outcomes

Table C-4. Associations Between Jet Fuel Exposure and Immune Health Outcomes in Epidemiologic Studies.

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
Acute Health Outcomes[d]						
Rhodes et al., 2003 Cross sectional Medium	United States[e]	USAF personnel from three bases in the Southeastern United States (High exposure: fuel system maintenance personnel; Low exposure: personnel in non-fuel related jobs, e.g., mechanics, information managers) High exposure = 23.87 years Low/no exposure = 27.14 years N = 123	Jet Fuel Type: JP-8 Assessment method: Measured from personal or area monitors, biomonitoring, administrative data Exposure Duration: High exposure: ≥9 months); Low/no exposure: Unclear Length of employment: High exposure: 47.20 months; Low/no exposure: 50.04 months	Immune system function Assessment method: Peripheral blood analyzed by flow cytometry Time since exposure of outcome assessment: Concurrent	Coefficient of determination Low/no exposure group used as reference group	Immune system function **WBC: r^2 = 0.15, p = 0.001** **Neutrophils: r^2 = 0.20, p = 0.05** **Monocytes: r^2 = 0.22, p = 0.02** Lymphocyte, eosinophil, basophil, T-cell, T-helper cell, T-suppressor cell, natural killer cell or B-cell counts: non-significant differences in mean counts between groups
	Confounding: Smoking, race, age, gender, BMI					
Olsen et al., 1998 Cohort	United States, Hill Air Force Base, Utah, 1995	Active duty and civilian personnel exposed or unexposed to JP-4 and JP-8	Jet fuel type: JP-4, JP-8 Assessment method: Administrative data,	Immune system function Assessment method: Medical professional or test	Mean (SD)	Immune system function WBC, neutrophils, lymphocytes,

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
Low		Exposed: 32.8 years, Unexposed: 32.3 years N = 35	personal or area monitors, Exposure duration: Unclear Years of service: ≥6 months	Time since exposure of outcome assessment: Baseline, 3, 6 and 18 months		monocytes, eosinophils, basophils: no significant differences in mean counts between groups
	Confounding: Smoking, age, sex					
Tunnicliffe et al., 1999 Cross-sectional Uninformative	United Kingdom[e]	Employees of Birmingham International Airport, (High exposure: baggage handlers, airport hands, marshallers, operational engineers, fitters and engineering technicians; Medium exposure: security staff, fire fighters and airfield operations managers; Low exposure: terminal and office workers) 38.6 years N = 222	Jet fuel type: Unspecified Assessment method: Administrative data Exposure Duration: Unclear Length of employment: 7.6 years	Immune hypersensitivity Assessment method: Medical professional or test Time since exposure of outcome assessment: Concurrent	Number (%) of subjects who experienced symptoms	Immune hypersensitivity Dermal atopy: All: 111/216 (51) Low exposure: 40/83 (48) Medium exposure: 42/81 (52) High exposure: 29/52 (56)
	Confounding: None reported					

WBC = white blood cells; BMI = body mass index; SD = standard deviation
[a]Data reported as mean, unless otherwise noted.

[b]Results reported as effect estimate (95% confidence interval), unless otherwise noted.
[c]Bolded results are statistically significant at 0.05 level.
[d]Acute health outcomes are considered those that were measured within 6 months of exposure.
[e]The years the study was conducted were not reported for this publication.

C.1.5. Female Reproductive Health Outcomes

Table C-5. Associations Between Jet Fuel Exposure and Female Reproductive Health Outcomes in Epidemiologic Studies.

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
Acute Health Outcomes[d]						
Reutman et al., 2002 Cross-sectional Medium	United States[e] Davis Monthan, Hill, Langley, Luke, Moody, Nellis, Pope, Warner-Robins, Seymour Johnson and Shaw Military Bases	Military and civilian female employees from 10 Air Force Bases 30.9 years N = 100	Jet fuel type: JP-8 (represented by aliphatic hydrocarbons and BTEX) Assessment method: Biomonitoring samples of exhaled breath Exposure duration: Unclear	Female reproductive hormones: preovulatory LH, follicular Pd3G, midluteal Pd3G, midluteal E_13G Assessment method: Self-reported questionnaire Time since exposure of outcome assessment: Concurrent	Regression coefficient (SE) Low exposure group used as reference group	Female reproductive hormones **Preovulatory LH:** **Aliphatic hydrocarbons:** **–7.34 (2.60), p = 0.007** BTEX: –4.61 (2.59), p = 0.10 Follicular Pd3G: Aliphatic hydrocarbons: 0.04 (0.20), p = 0.89 BTEX: –0.10 (0.20), p = 0.34 Midluteal Pd3G: Aliphatic hydrocarbons: 1.04 (1.79), p = 0.51 BTEX: –3.59 (1.79), p = 0.08 Midluteal E_13G: Aliphatic hydrocarbons: –2.79 (3.18), p = 0.34 BTEX: –2.73 (3.38), p = 0.32 No other significant association observed
	Confounding: Age, maximum job strain, illness or fever >101°F, alcoholic beverages, race group					

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
Gordley et al., 2000 Cross-sectional Low	United States[e] Davis Monthan, Hill, Langley, Luke, Moody, Nellis, Pope, Warner-Robins, Seymour Johnson and Shaw Military Bases	Military and civilian female employees from 10 Air Force Bases 29.4 years N = 170	Jet fuel type: JP-8 Assessment method: Fuel-handling based on self-reported questionnaire Exposure duration: Unclear	Menstrual cycle characteristics: Dysmenorrhea, abnormal cycle length Assessment method: Self-reported questionnaire Time since exposure of outcome assessment: Concurrent	Odds ratio Non-fuel handling group used as reference group	Menstrual cycle characteristics Dysmenorrhea: 1.83 (0.90, 3.70), $p < 0.10$ Abnormal cycle length: 0.29 (0.08, 1.06), $p < 0.10$
	Confounding: Job strain, life events, non-work activities, race, age, education level, military employee, BMI, smoking status, passive smoke exposure					

BTEX = benzene, toluene, ethylbenzene and xylene; LH = luteinizing hormone; Pd3G = pregnanediol 3-glucuronide; E13G = estrone 3-glucuronide; SE = standard error; BMI = body mass index

[a]Data reported as mean, unless otherwise noted.

[b]Results reported as effect estimate (95% confidence interval), unless otherwise noted.

[c]Bolded results are statistically significant at 0.05 level.

[d]Acute health outcomes are considered those that were measured within 6 months of exposure.

[e]The years the study was conducted were not reported for this publication.

C.1.6. Male Reproductive Health Outcomes

Table C-6. Associations Between Jet Fuel Exposure and Male Reproductive Health Outcomes in Epidemiologic Studies.

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
Acute Health Outcomes[d]						
Lemasters et al., 1999 Cohort Low	United States[f]	Civilian or active-duty military personnel 26.5 years N = 58	Jet fuel type: JP-4 Assessment method: Administrative data (employment or deployment records) Exposure duration: 15 weeks	Semen parameters Assessment method: Medical professional or test Time since exposure of outcome assessment: Concurrent measured at 15 weeks of employment	Percent change Baseline outcome measures used as the reference	Semen parameters at 15 weeks Sperm concentration: Unexposed: 1.4 Jet fuel workers: 9.7 **Flight line workers: 34.0, p = 0.01** Sperm length: **Unexposed: –2.5, p = 0.01** Jet fuel workers: 1.5 Flight line workers: –0.3 Sperm width/length: Unexposed: –1.5 Jet fuel workers: 1.1 Flight line workers: –0.4 Percent motile sperm: Unexposed: 15.9 Jet fuel workers: –2.1 Flight line workers: 2.9 Straight line velocity: Unexposed: –5.7 Jet fuel workers: 3.0 Flight line workers: 1.2

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						Linearity: Unexposed: –5.1 Jet fuel workers: 0.2 Flight line workers: –4.3
	Confounding: Age, race, smoking, having a STD, alcohol consumption, hot baths, season of sample collection					
Long-term Health Outcomes[e]						
Lemasters et al., 1999 Cohort Low	United States[f]	Civilian or active-duty military personnel 26.5 years N = 58	Jet fuel type: JP-4 Assessment method: Administrative data (employment or deployment records) Exposure duration: 30 weeks	Semen parameters Assessment method: Medical professional or test Time since exposure of outcome assessment: Concurrent measured at 30 weeks of employment	Percent change Baseline outcome measures used as the reference	Semen parameters at 30 weeks Sperm concentration: Unexposed: 23.7 Jet fuel workers: 9.0 **Flight line workers: 32.9, p = 0.02** Sperm length: Unexposed: –1.1 Jet fuel workers: 0.8 Flight line workers: –1.6 Sperm width/length: **Unexposed: –3.1, p = 0.05** Jet fuel workers: 0.1 Flight line workers: –1.2 Percent motile sperm: Unexposed: 8.1 Jet fuel workers: –6.2 Flight line workers: 7.2 Straight line velocity: Unexposed: 0.7 Jet fuel workers: –7.8 Flight line workers: 2.6

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						Linearity: Unexposed: –3.9 **Jet fuel workers: –7.7, p = 0.02** Flight line workers: 0.0
Confounding: Age, race, smoking, having a STD, alcohol consumption, hot baths, season of sample collection						

STD = sexually transmitted disease
[a]Data reported as mean, unless otherwise noted.
[b]Results reported as effect estimate (95% confidence interval), unless otherwise noted.
[c]Bolded results are statistically significant at 0.05 level.
[d]Acute health outcomes are considered those that were measured within 6 months of exposure.
[e]Long-term health outcomes are considered those that were measured at least 6 months after exposure.
[f]The years the study was conducted were not reported for this publication.

C.1.7. Renal Health Outcomes

Table C-7. Associations Between Jet Fuel Exposure and Renal Health Outcomes in Epidemiologic Studies.

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
Acute Health Outcomes[d]						
Olsen et al., 1998 Cohort Low	United States, Hill Air Force Base, Utah, 1995	Active duty and civilian personnel exposed or unexposed to JP-4 and JP-8 Exposed: 32.8 years, Unexposed: 32.3 years N = 35	Jet fuel type: JP-4, JP-8 Assessment method: Administrative data, personal or area monitors, Exposure duration: Unclear Years of service: ≥6 months	Kidney function, as measured by serum or urinary markers: BUN, creatinine Assessment method: Medical professional or test Time since exposure of outcome assessment: Concurrent at baseline (JP-4); 3, 6 and 18 months (JP-8)	Mean (SD)	BUN (exposed; unexposed): Baseline: 11.889 (2.742); 13.778 (3.021) 3 months: 11.389 (2.973); 13.158 (2.949) 6 months: 10.222 (3.318); 10.211 (2.780) 18 months: 12.176 (3.557); 13.000 (2.160) Creatinine (exposed; unexposed): Baseline: 1.028 (0.136); 1.039 (0.146) 3 months: 1.000 (0.153); 0.995 (0.127) 6 months: 1.072 (0.336); 0.963 (0.121) 18 months: 1.024 (0.168); 1.008 (0.150)
	Confounding: Smoking, age, sex					
Tu et al., 2004 Cross-sectional Low	United States, Warfield ANG Base, Essex, MD, 2001	ANG members either likely or less likely to be exposed to JP-8 by their job (Likely exposed: Fuel cell workers, crew chiefs, mechanics, fuel specialists;	Jet fuel type: JP-8 Assessment method: Biomonitoring Exposure duration: Unclear	Kidney function, as measured by serum or urinary markers Assessment method: Medical professional or test	Not specified	Serum and urinary biomarkers (color, appearance, pH, ketone bodies, bilirubin, glucose and hemoglobin) No statistically significant associations

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
		Less likely exposed: incidental subjects); Age- and education-matched controls Exposed: 41 years Unexposed: 41 years N = 113	Years of service: 10–16 years[e]	Time since exposure of outcome assessment: Same day		
	Confounding: Age, education					

BUN = blood urea nitrogen; SD = standard deviation; ANG = Air National Guard

[a]Data reported as mean, unless otherwise noted.

[b]Results reported as effect estimate (95% confidence interval), unless otherwise noted.

[c]Bolded results are statistically significant at 0.05 level.

[d]Acute health outcomes are considered those that were measured within 6 months of exposure.

[e]Years of service represents a range of mean years reported across all job titles.

C.1.8. Cardiovascular Health Outcomes

Table C-8. Associations Between Jet Fuel Exposure and Cardiovascular Health Outcomes in Epidemiologic Studies.

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcomes Characteristics	Comparison	Select Results[b,c]
Acute Health Outcomes[d]						
Knave et al., 1978 Cross-sectional Uninformative	Sweden[e]	Male jet motor factory workers (fuel system testers, engine testers, mechanics and unexposed workers) Exposed: 46.4 years, Unexposed: 46.2 years N = 60	Jet fuel type: Unspecified Assessment method: Measured from personal or area monitors Exposure Duration: 17.1 years Length of employment: Exposed: 17.7 years, Unexposed: 19.8 years	Palpitations or thoracic pressure Assessment method: Self-report Time since exposure of outcome assessment: Concurrent	Number of subjects who experienced symptoms	Palpitations or thoracic pressure **Exposed: 9 out of 30** **Unexposed: 1 out of 30, p = 0.015**
	Confounding: Age					

[a]Data reported as mean, unless otherwise noted.
[b]Results reported as effect estimate (95% confidence interval), unless otherwise noted.
[c]Bolded results are statistically significant at 0.05 level.
[d]Acute health outcomes are considered those that were measured within 6 months of exposure.
[e]The years the study was conducted were not reported for this publication.

C.1.9. Digestive Health Outcomes

Table C-9 Associations Between Jet Fuel Exposure and Digestive Health Outcomes in Epidemiologic Studies.

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
Acute Health Outcome[d]						
Yang et al., 2003 Cross-sectional Low	Taiwan, 2000–2001	Male airport workers at Kaohsiung International Airport (Exposed: jet fuel handlers, baggage handlers, operational engineers, marshallers, airport hands, fitters and engineering technicians; Unexposed: security staff, airfield operation managers, clerks, accountants, maintenance personnel and terminal and other office workers) ≥40 years: Exposed = 50.9%,	Jet fuel type: Unspecified Assessment method: Administrative data Exposure duration: Unclear Length of employment: ≥10 years; Exposed = 68.9% Unexposed = 6.6%	Nausea and gastrointestinal symptoms Assessment method: Questionnaire Time since exposure of outcome assessment: Concurrent	Odds ratio Unexposed workers used as reference group	Nausea and gastrointestinal symptoms Nausea: 0.87 (0.16, 4.65)

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
		Unexposed = 14.8% N = 411				
	Confounding: Age, education, marriage status, duration of employment, smoking status, previous occupational dust or fume exposure					
Knave et al., 1976 Cohort Uninformative	Sweden, 1975	Aircraft factory workers exposed to jet fuels Heavily exposed: 54.2 years Less heavily exposed: 46.3 years N = 29	Jet fuel type: Unspecified Assessment method: Administrative data Exposure duration: ≥5 years; Heavily exposed: continuous high concentration exposures for several hours a day; Less heavily exposed: Heavy intermittent exposure of 20–30 minutes Length of employment: ≥5 years	Nausea and gastrointestinal symptoms Assessment method: Self-reported Time since exposure of outcome assessment: Concurrent	Number of subjects who experienced symptoms	Nausea and gastrointestinal symptoms Nausea: Heavily exposed: 4 out of 13 Less heavily exposed: 2 out of 16
	Confounding: None reported					
Knave et al., 1978 Cross-sectional Uninformative	Sweden[e]	Male jet motor factory workers (fuel system testers, engine testers, mechanics and unexposed workers)	Jet fuel type: Unspecified Assessment method: Measured from personal or area monitors	Nausea and gastrointestinal symptoms Assessment method: Self-reported and factory physician's notes	Number of subjects who experienced symptoms	Nausea and gastrointestinal symptoms Nausea (self-reported) Total exposed workers: 4 out of 30

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
		Exposed: 46.4 years Unexposed: 46.2 years N = 60	Exposure duration: 17.1 years Length of employment: Exposed: 17.7 years Unexposed: 19.8 years	Time since exposure of outcome assessment: Concurrent		Fuel system testers (exposed workers only): 1 out of 15 Motor engine testers (exposed workers only): 3 out of 15 Gastritis (self-reported): Exposed: 15 out of 30 Unexposed: 10 out of 30 Gastritis (physician notes): Exposed: 22 out of 30 Unexposed: 15 out of 30
	Confounding: None reported					

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
Olsen et al., 1998 Cohort Uninformative	United States, Hill Air Force Base, 1995	Active duty and civilian personnel exposed or unexposed to JP-4 and JP-8 Exposed: 32.8 years Unexposed: 32.3 years N = 35	Jet fuel type: JP-4, JP-8 Assessment method: Measured from personal or area monitors, administrative data Exposure duration: Unclear Length of employment: ≥6 months	Diarrhea and vomiting Assessment method: Self-reported Time since exposure of outcome assessment: Concurrent at baseline, 6 months and 18 months	Mean frequency of symptoms scale Outcome frequency scale groups: 0 = never happens; 1 = 1–2 times per month; 2 = 3–4 times per month; 3 = 5–9 times per month; 4 = ≥10 times per month; 5 = every day.	Diarrhea and vomiting Nausea and vomiting (exposed, unexposed): JP-4: 0.4, 0.2 JP-8, 6 months: 0.8, 0.5 JP-8, 18 months: 0.3, 0.4
	Confounding: Age, sex					

[a]Data reported as mean, unless otherwise noted.
[b]Results reported as effect estimate (95% confidence interval), unless otherwise noted.
[c]Bolded results are statistically significant at 0.05 level.
[d]Acute health outcomes are considered those that were measured within 6 months of exposure.
[e]The years the study was conducted were not reported for this publication.

C.1.10. *Hepatic Health Outcomes*

Table C-10. Associations Between Jet Fuel Exposure and Hepatic Outcomes in Epidemiologic Studies.

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
			Acute Outcomes[d]			
Olsen et al., 1998 Cohort Low	United States, Hill Air Force Base, Utah, 1995	Active duty and civilian personnel exposed or unexposed to JP-4 and JP-8 Exposed: 32.8 years, Unexposed: 32.3 years N = 35	Jet fuel type: JP-4, JP-8 Assessment method: Administrative data, personal or area monitors, Exposure duration: Unclear Years of service: ≥6 months	Liver enzymes: ALT, AST, ALP[e] Assessment method: Medical professional or test Time since exposure of outcome assessment: Baseline (JP-4), 3 (JP-8), 6 (JP-8) and 18 months (JP-8)	Mean (SD)	Liver enzymes AST (IU/L) (exposed; unexposed): Baseline, JP-4: 27.2 (11.7); 26.6 (8.0) 3 months, JP-8: 27.2 (9.1); 29.3 (10.4) 6 months, JP-8: 26.1 (8.2); 29.9 (17.3) 18 months, JP-8: 28.2 (9.2); 27.0 (7.8) ALT (IU/L) (exposed; unexposed): Baseline, JP-4: 36.8 (28.3); 37.1 (18.8)

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						3 months, JP-8: 30.5 (23.9); 33.1 (26.0) 6 months, JP-8: 30.1 (15.9); 33.2 (21.5) 18 months, JP-8: 37.1 (18.2); 33.5 (15.4) ALP (IU/L) (exposed; unexposed) Baseline, JP-4: 88.3 (20.0); 83.3 (19.2) 3 months, JP-8: 78.4 (15.5); 76.5 (20.5) 6 months, JP-8: 64.2 (13.4); 64.8 (17.7) 18 months, JP-8: 82.3 (15.5); 81.5 (29.6).
	Confounding: Age, sex					
Tu et al., 2004 Cross-sectional Low	United States, Warfield ANG Base, Essex, MD, 2001	ANG members either likely or less likely to be exposed to JP-8 by their job (Likely exposed:	Jet fuel type: JP-8 Assessment method: Biomonitoring	Liver enzymes: ALT, AST, GGT Assessment method: Medical	Not specified	Liver enzymes No statistically significant associations

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
		Fuel cell workers, crew chiefs, mechanics, fuel specialists; Less likely exposed: incidental subjects); Age- and education-matched controls Exposed: 41 years Unexposed: 41 years N = 113	Exposure duration: Unclear Years of service: 10–16 years[f]	professional or test Time since exposure of outcome assessment: Same day		
	Confounding: Age, education					

AST = aspartate transferase; ALT = alanine transaminase; ALP = alkaline phosphatase; SD = standard deviation; IU/L= international units per liter; ANG = Air National Guard; GGT = gamma-glutamyl transferase

[a]Data reported as means, unless otherwise noted. N exposed/unexposed varied over time: 18/18, 18/19, 18/19 and 17/13.

[b]Results reported as effect estimate (95% confidence interval), unless otherwise noted.

[c]Bolded results are statistically significant at 0.05 level.

[d]Acute health outcomes are considered those that were measured within 6 months of exposure.

[e]Cleveland Clinic reference ranges vary by laboratory. Common ranges: AST 8 to 33; ALT 7 to 56; ALP 44 to 147. The study did not report changes over time in any factors that could affect enzyme levels (e.g., infections).

[f]Years of service represents a range of mean years reported across all job titles.

C.1.11. Hematologic Health Outcomes

Table C-11. Associations Between Jet Fuel Exposure and Hematologic Health Outcomes in Epidemiologic Studies.

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
Acute Health Outcomes[d]						
Olsen et al., 1998 Cohort Low	United States, Hill Air Force Base, Utah, 1995	Active duty and civilian personnel exposed or unexposed to JP-4 and JP-8 Exposed: 32.8 years, Unexposed: 32.3 years N = 35	Jet fuel type: JP-4, JP-8 Assessment method: Administrative data, personal or area monitors, Exposure duration: Unclear Years of service: ≥6 months	MCH, MCHC MCV, hemoglobin, red blood cells, hematocrit, platelet count Assessment method: Medical professional or test Time since exposure of outcome assessment: Baseline, 3, 6 and 18 months	Mean (SD)	MCH (exposed; unexposed): Baseline, JP-4: 30.2 (1.2); 31.1 (0.9) 3 months, JP-8: 31.0 (1.1); 32.0 (1.3) 6 months, JP-8: 31.3 (1.2); 32.0 (1.2) 18 months, JP-8: 29.7 (1.6); 30.3 (1.2) MCHC (exposed; unexposed): Baseline, JP-4: 34.2 (0.7); 34.2 (0.7) 3 months, JP-8: 35.3 (0.7); 35.0 (0.8) 6 months, JP-8:

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
Acute Health Outcomes[d]						
						35.0 (0.5); 34.6 (1.0) 18 months, JP-8: 33.4 (0.7); 32.6 (0.7) MCV (exposed; unexposed) Baseline, JP-4: 88.1 (3.4); 91.0 (3.0) 3 months, JP-8: 88.1 (2.9); 91.5 (3.3) 6 months, JP-8: 89.4 (3.2); 92.4 (3.4) 18 months, JP-8: 87.8 (7.2); 92.9 (4.0) Hemoglobin, red blood cells, hematocrit, platelet counts: no differences between exposed and unexposed, at any time point
	Confounding: Age, sex					

MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; SD = standard deviation
[a]Data reported as mean, unless otherwise noted.

[b]Results reported as effect estimate (95% confidence interval), unless otherwise noted.
[c]Bolded results are statistically significant at 0.05 level.
[d]Acute health outcomes are considered those that were measured within 6 months of exposure.

C.1.12. Dermal Health Outcomes

Table C-12. Associations Between Jet Fuel Exposure and Dermal Health Outcomes in Epidemiologic Studies.

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
Acute Health Outcomes[d]						
Olsen et al., 1998 Cohort Uninformative	United States, Hill Air Force Base, Utah, 1995	Active duty and civilian personnel exposed or unexposed to JP-4 and JP-8 Exposed: 32.8 years Unexposed: 32.3 years N = 35	Jet fuel type: JP-4, JP-8 Assessment method: Measured from personal or area monitors, administrative data Exposure duration: Unclear Length of employment: ≥6 months	Skin irritation Assessment method: Self-reported and physical exam Time since exposure of outcome assessment: Concurrent at baseline, 6 months and 18 months	Number of times symptoms were reported Mean frequency of symptoms scale Outcome frequency scale groups: 0 = never happens; 1 = 1–2 times per month; 2 = 3–4 times per month; 3 = 5–9 times per month; 4 = ≥10 times per month; 5 = every day	Skin irritation Dry itchy skin or rashes: Exposed: 31 times Unexposed: 20 times Skin rashes Symptom frequency (exposed, unexposed): JP-4: 0.3, 0.3 JP-8, 6 months: 0.7, 0.1 JP-8, 18 months: 0.3, 0.5 Dry itchy skin, Symptom frequency (exposed, unexposed): JP-4: 1.7, 1.6 JP-8, 6 months: 1.8, 1.5 JP-8, 18 months: 1.7, 1.7

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
	Confounding: Age, sex					
Radhakrishnan et al., 2017 Cross-sectional Uninformative	India, 2013	Ground crew members of three Indian Air Force flying stations exposed to ATF K-50 and lubricants 34.57 years N = 109	Jet fuel type: ATF K-50 Assessment method: Administrative data Exposure duration: Unclear Length of service: 16.65 years	Skin irritation Assessment method: Physical exam Time since exposure of outcome assessment: Concurrent	Number and percentage of symptomatic personnel by trade or overall Number and/or percentage of asymptomatic personnel	Skin irritation Mild irritant contact dermatitis by trade: Weapon fitter: 66.6% Electrical fitter: 12.5% **Mild irritant contact dermatitis: 20 out of 109 personnel (18.35%)** Allergic contact dermatitis: 0 out of 109 personnel (0%) History of atopy in symptomatic personnel: 13 out of 20 (65%) History of atopy in asymptomatic personnel: 9 out of 89 (10.11%)
	Confounding: None reported					

ATF = aviation turbine fuel
[a]Data reported as mean, unless otherwise noted.
[b]Results reported as effect estimate (95% confidence interval), unless otherwise noted.
[c]Bolded results are statistically significant at 0.05 level.
[d]Acute health outcomes are considered those that were measured within 6 months of exposure.

C.1.13. Other Health Outcomes

Table C-13. Associations Between Jet Fuel Exposure and Other Health Outcomes in Epidemiologic Studies.

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
Long-term Health Outcomes[d]						
D'Este et al., 2008 Retrospective Cohort Low	Australia, RAAF Base Amberely and Richmond, 1975–1999	Male personnel involved and uninvolved in F-111 fuel tank deseal/reseal activities at two Royal Australian Air Force bases Age range: 20–75 years N = 17,858	Jet fuel type: JP-4 Assessment method: Administrative data Exposure duration: Unclear Years of service: 1975-1999	Mortality Assessment method: Record linkage to the National Death Index Time since exposure of outcome assessment: <25 years	Mortality rate ratio RAAF Base Amberley comparison group ('same base, different job') and RAAF Base Richmond comparison group ('similar job, different base') used as reference groups	Mortality—first posting **Amberley comparison group: 0.44 (0.20, 0.85)** **Richmond comparison group: 0.42 (0.19, 0.82)** Mortality—last posting **Amberley comparison group: 0.35 (0.16, 0.67)** **Richmond comparison group: 0.33 (0.15, 0.63)**
	Confounding: Age, job posting, posting period					

[a]Data reported as mean, unless otherwise noted.
[b]Results reported as effect estimate (95% confidence interval), unless otherwise noted.
[c]Bolded results are statistically significant at 0.05 level.
[d]Long-term health outcomes are considered those that were measured at least 6 months after exposure.
[e]The years the study was conducted were not reported for this publication.

C.2. Results by Health System—Cancerous Health Outcomes

C.2.1. Cancerous Health Outcomes

Table C-14. Associations Between Jet Fuel Exposure and Cancerous Health Outcomes in Epidemiologic Studies.

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
D'Este et al., 2008 Cohort Low	Australia, RAAF Base Amberely and Richmond, 1975–1999	Male personnel involved and uninvolved in F-111 fuel tank deseal/reseal activities at two RAAF bases 20–75 years N = 17,858	Jet fuel type: JP-4 Assessment method: Administrative data Exposure Duration: <9 months, 9—<30 months and ≥30 months Years of service: 1975–1999 Length of employment: <9 months, 9—<30 months and ≥30 months	Cancer incidence Assessment method: Registry Time since exposure of outcome assessment: Concurrent	Incidence rate ratio RAAF Base Amberley comparison group ('same base, different job') and RAAF Base Richmond comparison group ('similar job, different base') used as reference groups Standardized incidence ratio Australian population used as reference group	**All cancer—last posting: Amberley comparison group 1.62 (1.03, 2.47) Richmond comparison group 1.60 (1.02, 2.41)** All cancer—first posting: Amberley comparison group 1.51 (0.96, 2.29) Richmond comparison group 1.45 (0.93, 2.18) Standardized incidence ratios Exposed group 148 (98, 216), Amberley comparison group 100.1 (86.4, 115.2) Richmond comparison group 94.6 (81.9, 109.3)
	Confounding: Person years at risk, age, period of exposure or posting, service rank					
D'Mello et al., 2007 Case-control	United States, 1988–2003	U.S. Air Force Personnel with >1 year of active duty	Jet fuel type: Unspecified Assessment	Cancer incidence Assessment method: Registry	Odds ratio Low exposure	Invasive cancer (moderate exposure, high exposure): 0.84 (0.65, 1.09) p = 0.19, 0.73 (0.32, 1.64) p = 0.44

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
Low		Median age at diagnosis: 37 years N = 13,770	method: Job exposure matrix Exposure Duration: >1 year Years of service: 1988–2003 Length of employment: >1 year	Time since exposure of outcome assessment: Concurrent	used as reference group	Invasive cancer—males (moderate exposure, high exposure): 0.85 (0.64, 1.11) p = 0.23, 0.70 (0.29, 1.67) p = 0.42 Invasive cancer—females (moderate exposure, high exposure):0.83 (0.42, 1.65) p = 0.60, 1.00 (0.11, 8.95) p = 1.00 Acute myeloid leukemia: 0.48 (0.06, 4.01) p = 0.50 Acute leukemia :0.35 (0.05, 2.79) = 0.32 Acute and chronic leukemia :0.32 (0.04, 2.53) p = 0.34 All leukemias: 0.55 (0.12, 2.52) p = 0.45 Bladder cancer: 0.70 (0.10, 5.07) p = 0.73 Breast cancer: 0.49 (0.11, 2.17) p = 0.35 Breast cancer—females: 0.53 (0.12, 2.33) p = 0.40 Hodgkin's lymphoma: 0.44 (0.10, 1.91) p = 0.27

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						Lung cancer: 0.79 (0.09, 7.28) p = 0.83 Multiple myeloma: 1.33 (0.14, 12.82) p = 0.80 Non-Hodgkin's lymphoma: 1.00 (0.33, 3.03) p = 1.00 Renal cell cancer: 0.83 (0.21, 3.32) p = 0.79
	Confounding: None reported					
Siemiatycki et al., 1987 Case-control Low	Canada, 1979–1985	Men diagnosed with cancer (multiple types) in 19 participating hospitals in Montreal, Quebec, Canada 35–70 years N = 3,726	Jet fuel type: Unspecified Assessment method: Administrative data Exposure Duration: Unclear Length of employment: Unclear	Cancer incidence Assessment method: Medical professional or test Time since exposure of outcome assessment: Unclear	Odds ratio Unexposed used as reference group	**Kidney cancer** **Jet fuel:** **Screening analysis: 2.5 (1.1, 5.4)** **Any vs. no exposure: 3.1 (1.5, 6.6)** **Non-substantial vs. no exposure: 2.1 (0.3, 12.7)** **Substantial vs. no exposure: 3.4 (1.5, 7.6)** **Aviation gasoline:** **Screening analysis: 2.6 (1.2, 5.8)** **Any vs. no exposure: 3.1 (1.5, 6.5)** **Non-substantial vs. no exposure: 1.5 (0.3, 8.6)** **Substantial vs. no exposure: 3.9 (1.7, 8.8)**

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						Jet fuel, screening analysis Stomach cancer: 0.2 (0.0, 1.7) Colon cancer: 2.1 (0.9, 5.1) Rectosigmoid cancer: 0.8 (0.2, 3.8) Rectum cancer: 2.1 (0.6, 7.4) Lung cancer (oat cell): 1.3 (0.2, 7.0) Lung cancer (squamous cell): 0.2 (0.0, 2.4) Lung cancer (adenocarcinoma cell): 1.2 (0.2, 6.6) Lung cancer (other and unknown cell): 0.6 (0.1, 6.0) Prostate cancer: 0.7(0.2, 2.1) Bladder cancer: 0.7 (0.3, 1.8) Non-Hodgkin’s lymphoma cancer: 0.7 (0.2, 3.2) Aviation gasoline, screening analysis

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
						Stomach cancer: 0.8 (0.3, 2.7) Colon cancer: 1.7 (0.7, 3.6) Rectosigmoid cancer: 0.8 (0.2, 2.7) Rectum cancer: 2.5 (0.6, 10.3) Lung cancer (oat cell): 0.4 (0.1, 3.2) Lung cancer (squamous cell): 0.4 (0.1, 1.6) Lung cancer (adenocarcinoma cell): 0.9 (0.2, 3.8) Lung cancer (other and unknown cell): 0.4 (0.1, 3.1) Prostate cancer: 0.9 (0.4, 2.0) Bladder cancer: 1.0 (0.5, 2.2) Non-Hodgkin's lymphoma cancer: 0.4 (0.1, 2.5)
	Confounding: Age, ethnic group, socioeconomic status, smoking, blue/white-collar job history					
Parent et al., 2000	Canada, 1979–1985	Men diagnosed with cancer (multiple types) in 19	Jet fuel type: Unspecified	Cancer incidence Assessment	Odds ratio Unexposed	**Renal cell cancer**

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
Case-control Medium		participating hospitals in Montreal, Quebec, Canada and population controls selected using random digit dialing 35–70 years N = 2,575	Assessment method: Job exposure matrix Exposure Duration: 0–5 years Length of employment: Unclear	method: Medical record, hospital admission, medical professional or test Time since exposure of outcome assessment: Unclear	used as reference group	**Aircraft mechanics: 2.8 (1.0, 8.4)** **Jet fuel: 3.5 (1.4, 8.7)** **Aviation gasoline: 3.5 (1.4, 8.6)** Jet fuel engine emissions: 2.7 (0.9, 8.1)
	Confounding: Respondent status, age, smoking, BMI, hydrogen sulphide					
Reed et al., 2020 Cohort Low	United Kingdom, 2010–2012	Patients with bladder cancer treated at the Royal Hallamshire Hospital, Sheffield, South Yorkshire, UK Males: 67 years Females: 66.4 years N = 454	Jet fuel type: Unspecified Assessment method: Self-reported Exposure Duration: Unclear Length of employment: >1 year	Cancer incidence Assessment method: Medical professional or test, medical records, hospital admission Time since exposure of outcome assessment: Unclear	Number of cases exposed to aircraft fuel Grade of bladder cancer	**Bladder cancer** **Grade 1 tumor: n = 1;** **Grade 2 tumor: n = 2;** **Grade 3 tumor: n = 7** **Low grade 11.1%, High grade 77.7% p = 0.05**[d]
	Confounding: None reported					
Spirtas et al., 1991 Cohort Low	United States, Hill Air Force Base 1952–1982	Civilians employed at Hill Air Force Base (Utah) for at least 1 year between January 1, 1952 and December 31, 1956 Age: ≥18 years	Jet fuel type: JP-4 Assessment method: Administrative data	Cancer mortality Assessment method: Medical records Time since exposure of	Standardized mortality ratio Unexposed used as reference group	**Mortality from cancer of buccal cavity and pharynx, women: 853 (103, 3079)** Multiple myeloma mortality, men: 106 (13, 382)

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
		N = 14,457	Exposure Duration: Unclear Length of employment: ≥1 year	outcome assessment: Unclear		Non-Hodgkin's lymphoma mortality, men: 114 (37, 227) Non-Hodgkin's lymphoma mortality, women: 184 (5, 1022)
	Confounding: Age, calendar period					
Blair et al. 1998 Cohort Low	United States, Hill Air Force Base 1952–1990	Civilians employed at Hill Air Force Base (Utah) for at least 1 year between January 1, 1952 and December 31, 1956 N = 14,457	Jet fuel type: JP-4, Assessment method: Administrative data Exposure duration: Unclear Length of employment: >1 year	Cancer mortality Assessment method: Medical records Time since exposure of outcome assessment: Unclear	Rate ratio Unexposed used as reference group	Non-Hodgkin's lymphoma Mortality in men: 1.7 (0.6, 5.1) Non-Hodgkin's lymphoma Mortality in women: 2.7 (0.4, 16.1) Multiple myeloma mortality in men: 1.4 (0.4, 5.2) Breast cancer mortality in women: 1.0 (0.4, 2.7)
	Confounding: Date of birth, calendar year of death					
Radican et al., 2008 Cohort Low	United States, Hill Air Force Base, 1952–2000	Civilian workers at an aircraft maintenance facility For remaining subjects alive in 2000 (n = 5,875): 75 years N = 14,455	Jet fuel type: JP-4 Assessment method: Administrative Data Exposure Duration: ≥1 year Length of	Cancer mortality Assessment method: Medical records, registry Time since exposure of outcome assessment: Unclear	Hazard ratio Unexposed workers used as reference group	**All cancers mortality—men: 1.21 (1.02, 1.43)** **Pancreatic cancer mortality—women: 3.31 (1.01, 10.84)** Breast cancer mortality—women: 1.06 (0.51, 2.21) Non-Hodgkin's lymphoma mortality

Reference, Study Design, Confidence	Location, Years Study was Conducted	Population, Ages[a], N	Exposure Characteristics[a]	Outcome Characteristics	Comparison	Select Results[b,c]
			employment: ≥ 1 year			Men: 1.71 (0.74, 3.95) Women: 0.70 (0.16, 3.15) Multiple myeloma mortality Men: 1.29 (0.47, 3.53) Women: 1.98 (0.36, 10.82)
	Confounding: Age, race					

RAAF = Royal Australian Air Force; U.S. = United States
[a]Data reported as mean, unless otherwise noted.
[b]Results reported as effect estimate (95% confidence interval), unless otherwise noted.
[c]Bolded results are statistically significant at 0.05 level for all studies except for Siemiatycki et al. (1987) which used a 0.10 level.
[d]Low-grade tumors are characterized by papillary growth patterns, few genetic alterations and an indolent behavior. High-grade bladder cancer is an aggressive disease with genetic and epigenetic instability and multiple mutation.

Appendix D: Overlapping Review Articles

Table D-1. Review Articles Citing Nervous System Health Outcome Conclusions Reported on by Primary Epidemiological References.

Review Article Reference(s)	Primary Epidemiological Reference(s)	Overall Conclusion
Karanikas et al. (2021); Morata et al. (2021); Warner et al. (2015)	Kaufman et al. (2005)	Jet fuel exposure status was not associated with hearing loss. However, duration of jet fuel exposure was associated with a non-significant increase in the odds of hearing loss.
B'Hymer (2015); NRC (1996)	Knave et al. (1978)	Reports of headache symptoms were reported in jet fuel-exposed workers. Reports were lower among heavily exposed workers (n = 3 of 13) than less heavily exposed workers (n = 5 of 16). However, no statistical comparison was conducted.
Ritchie et al. (2001)	Olsen et al. (1998)	The mean frequency of each symptom was assessed on a scale from zero to five ranging from "never happens" to "every day." An increased mean frequency of headache symptoms was observed in the exposed group at JP-4 baseline (mean exposed = 1.0; mean unexposed = 0.5), 6 months after JP-8 transition (mean exposed = 1.6; mean unexposed = 0.9) and 18 months after JP-8 transition (mean exposed = 1.2; mean unexposed = 0.8).
Karanikas et al. (2021); Morata et al. (2019)	Fuente et al. (2019)	Statistically significant increases of mean audiometric hearing thresholds were observed in both ears at 4 kHz and in the right ear at 8 kHz with increased jet fuel exposure, indicating diminished hearing ability. A statistically significant increase was observed in audiometric hearing threshold in the better ear at 1-8 kHz with increased jet fuel exposure. Statistically significant increases of mean audiometric hearing thresholds were reported in both ears at 4 kHz and in the right ear at 8 kHz with increased jet fuel exposure. The study reported a statistically significant decrease in distortion product otoacoustic emissions with increased jet fuel exposure at 4 kHz in both ears and at 2.8 and 6 kHz in the left ear, indicating greater hearing impairment. The study reported a statistically significant increase in mean ABR latency with the absolute latency of wave V in the right ear with increased jet fuel exposure, indicating greater hearing impairment. The authors reported a statistically significant increase in mean score for the words-in-noise test and a statistically significant decrease in mean score for the compressed speech test with increased jet fuel exposure, indicating greater hearing impairment. There were no differences in other auditory measures. The study observed no association with auditory test of temporal resolution, dichotic digits and duration pattern sequence with increased jet fuel exposure.
Ritchie et al. (2003)	Odkvist et al. (1987)	The study notes that cortical responses to frequency glides are sensitive to cerebellopontine angle tumors and lesions, which can affect hearing and speech

Review Article Reference(s)	Primary Epidemiological Reference(s)	Overall Conclusion
		discrimination. No abnormalities were observed in this group in speech reception threshold, speech discrimination, interrupted speech discrimination and auditory brainstem responses.
Ritchie et al. (2001)	Knave et al. (1978)	No statistically significant differences in performance on a verbal recall task. However, memory impairment was reported in standardized interviews by jet-fuel exposed workers (n = 5 of 30) and not observed (n = 0 of 30) in unexposed workers. Findings should be interpreted with caution because details on the verbal recall task design and each exposure group were minimal and there was some concern for potential residual confounding for covariates, such as alcohol use.
NRC (1996)	Knave et al. (1978)	Jet fuel-exposed workers (n = 5 of 30) reported more chronic headaches due to neurasthenia in comparison to the control group (n = 1 of 30).
B'Hymer (2015)	Knave et al. (1978)	Higher frequency of fatigue, dizziness, sleep disturbances were reported in jet fuel-exposed workers compared to unexposed workers.
NRC (1996); NRC (2003); B'Hymer (2015)	Knave et al. (1978)	Jet fuel-exposed workers reported a higher incidence of self-reported symptoms of polyneuropathy (i.e., the dysfunction of multiple peripheral nerves) (n = 12) compared to unexposed workers (n = 5). However, when physical examinations for early signs of polyneuropathy were conducted, the difference between exposed (n = 18) and unexposed (n = 15) workers exhibiting signs was reduced. Descriptions of the workers in the unexposed group were minimal and the difference between symptoms and signs was not clear.
B'Hymer (2015); Ritchie et al. (2003); ATSDR (2015)	Smith et al. (1997)	Greater postural sway among exposed subjects compared to unexposed subjects. Cumulative exposure to JP-8, assessed by personal monitoring of benzene concentrations, was significantly associated with greater sway length. Results for other exposures (quantified by other JP-8 components such as toluene and xylene) were mixed and inconsistent.

Table D-2. Review Articles Citing Mental Health Outcome Conclusions Reported on by Primary Epidemiological References.

Review Article Reference(s)	Primary Epidemiological Reference(s)	Overall Conclusion
NRC (2003)	Knave et al. (1978)	A cross-sectional study in Swedish jet-engine factory workers evaluated various measures of reaction time to assess attention. The workers had an average duration of employment of 17 years (range: 2 to 32 years). There were no significant differences in attention between the group of workers exposed to an unspecified type of jet fuel compared to the unexposed age-matched group.
Karanikas et al. (2021)	Heaton et al. (2017)	WAIS-III performance was statistically significantly better for forward and backward digit spans in high exposure personnel compared to low exposure personnel. No significant associations were observed between naphthalene or THC concentrations, or years of Air Force service and performance on WAIS-III Digit Span scores. No significant association was observed in models using pre-shift urinary markers of exposure. Performance statistically significantly improved between test days, suggesting a practice effect. Study authors noted that despite a statistically significant difference in exposure concentrations between high (mean 8-hr time weighted average (TWA) THC = 7.62 mg/m^3) and low (mean 8-hr TWA THC = 1.19 mg/m^3) exposure groups, both mean exposure concentrations were considerably lower than the Air Force guideline for THC (200 mg/m^3).
Karanikas et al. (2021)	Heaton et al. (2017)	In the population of active-duty USAF personnel from three different Air Force bases, visuospatial performance was measured with the Hooper Visual Organization test and the ANAM4 Matching 2 Sample test. No significant differences were observed between the high and low exposure groups on the first day of testing. Generalized linear models compared performance on the Hooper Visual Organization test in high exposure personnel to low exposure personnel across the study period and observed that performance was statistically significantly decreased in high exposure personnel. Non-significant inverse associations for mean correct responses on the Hooper Visual Organization test in models evaluating average daily naphthalene or THC exposure concentrations were observed, suggesting reduced visuospatial ability in the exposed group. Results from models evaluating the relationship between years of Air Force service and test performance were not significant. No significant associations were observed for the Matching 2 Sample test.

Table D-3. Review Articles Citing Respiratory Health Outcome Conclusions Reported on by Primary Epidemiological References.

Review Article Reference(s)	Primary Epidemiological Reference(s)	Overall Conclusion
NRC (2003)	Tunnicliffe et al. (1999)	In a cross-sectional study of current workers at the Birmingham International Airport in the United Kingdom, no differences in lung function were observed as measured by for mean forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) or FEV_1/FVC across groups of low, medium and high exposure aircraft fuel or jet stream exhaust. The high exposure workers consisted of baggage handlers, airport hands, marshallers, operational engineers, fitters and engineering technicians. The medium exposure group consisted of security staff, fire fighters and airfield operations managers who would expect to spend some of their working time on the airport apron, some in reasonable proximity to aircraft and some within the terminal buildings. The low exposure group consisted of terminal and office workers.
NRC (2003); Touri et al. (2013)	Tunnicliffe et al. (1999)	The cross-sectional study of workers at the Birmingham International Airport evaluated self-reported wheeze or whistling in the chest in the past 12 months. There were non-statistically significant decreased odds of wheeze or whistling in the chest in men in the high exposure group when compared with men in the medium exposure group. Analyses were restricted to male participants, thus data on wheeze among female workers were not available.
Merzenich et al. (2021)	Yang et al. (2003)	In a cross-sectional study of male workers at the Kaohsiung International Airport in Taiwan, statistically significantly increased odds of self-reported dyspnea were observed in workers exposed to unspecified jet fuel compared to unexposed workers. There were no differences in nose irritation and throat irritation in exposed and unexposed workers.
Merzenich et al. (2021)	Yang et al. (2003)	In the cross-sectional study of male workers at the Kaohsiung International Airport, statistically significantly increased odds of chronic cough in workers exposed to unspecified jet fuels compared to unexposed workers was observed. The study also reported no differences in phlegm production in exposed workers compared to unexposed workers. Chronic cough and phlegm production were defined as those experienced for a partial or full day for at least 3 months within a year, thus these health outcomes are considered long-term despite the cross-sectional study design and concurrent nature of exposure and health outcome assessment.
NRC (1996)	Knave et al. (1976)	In a cohort study of aircraft factory workers, higher numbers of self-reported acute respiratory tract symptoms (e.g., “pain upon inhalation,” “feelings of suffocation,” “slight cough”) were reported among those highly exposed to unspecified jet fuel compared to those with low exposure, but statistical tests were not conducted. Six subjects from the highly exposed group also reported feelings of suffocation, which the authors considered chronic respiratory tract symptoms.

Table D-4. Review Articles Citing Immune Health Outcome Conclusions Reported on by Primary Epidemiological References.

Review Article Reference(s)	Primary Epidemiological Reference(s)	Overall Conclusion
NRC (2003); Ritchie et al. (2003)	Rhodes et al. (2003)	A cross-sectional study of 123 Air Force personnel at three bases across the Southeastern United States observed statistically significant increases in total white blood cell, neutrophil and monocyte counts in the high exposure to JP-8 group compared to a group with low or no exposure. However, all counts of immune system cells were within normal clinical ranges. No statistically significant differences were observed for lymphocyte, eosinophil, basophil, T-cell, T-helper cell, T-suppressor cell, natural killer cell or B-cell counts. Air Force personnel were assigned to exposure levels by job title, with fuel system maintenance workers categorized as high exposure and personnel in jobs unrelated to jet fuels categorized as low or no exposure. Air sampling measures of naphthalene, a major component of JP-8, were collected for all workers with sampling monitors worn outside of any personal protective equipment. Breath sample analyses for naphthalene 30 minutes before and after work assignments were also conducted. Personnel in the high exposure group had statistically significantly higher levels of exposure to naphthalene compared to low or no exposure group in personal air sampling and post-breath analysis. Workers wore personal protective equipment. Thus, the higher levels of naphthalene in the high exposure group workers suggest evidence of either dermal exposure and/or poor respiratory protection. However, these measured concentrations were not used in statistical analyses of immune health outcomes. The authors note that a possible explanation for the significantly elevated levels of certain immune system cells may be microbial colonization of jet fuel.
Touri et al. (2013)	Tunnicliffe et al. (1999)	In a cross-sectional study among 432 airport workers at the Birmingham International Airport in the United Kingdom, no differences were observed in the incidence of allergic reactions across groups of low, medium and high exposure aircraft fuel or jet stream exhaust. The study measured allergic reactions as dermal atopy, defined as at least one positive skin test to an allergen (including *Dermatophagoides pteronyssinus*, cat, grass, mixed tree and *Aspergillus fumigatus* allergen solutions). The percentages of participants with dermal atopy were 48%, 52% and 56% for the low, medium and high exposure groups, respectively. Exposure groups were determined based on official job titles, with employees classified as high exposure if they were determined to spend a considerable portion of their working day close to service aircraft (e.g., baggage handlers, airport hands, marshallers, operational engineers, fitters and engineering technicians), medium exposure if they were expected to spend "some" of their working time near service aircraft and low exposure if they were terminal or office workers. The cross-sectional design of this study precludes establishing temporality between exposure to jet fuels and health outcome measurement.

Table D-5. Review Articles Citing Female Reproductive Health Outcome Conclusions Reported on by Primary Epidemiological References.

Review Article Reference(s)	Primary Epidemiological Reference(s)	Overall Conclusion
ATSDR (2015); Van Dyke (2010)	Reutman et al. (2002)	One cross-sectional study examined urinary reproductive hormone levels following jet fuel exposures in 100 female civilian and active military personnel at 10 U.S. Air Force bases. Those hormones were selected a priori because they were predictive of conceptive menstrual cycles as subclinical markers of female reproductive dysfunction. Exposures to JP-8 constituents including aliphatic hydrocarbons and aromatic hydrocarbons (i.e., benzene, toluene, ethylbenzene and *m,p,o*-xylenes; also referred to as BTEX) were assessed using exhaled breath samples. Personnel were assigned to high and low exposure groups based on median levels of aliphatic and BTEX levels. Personnel in the high exposure group for aliphatic hydrocarbons had statistically significantly lower preovulatory luteinizing hormone levels compared to those in the lower exposure group. There were no differences in levels of midluteal estrone 3-glucuronide or midluteal pregnanediol 3-glucuronide (PD3G) levels between the aliphatic hydrocarbon or BTEX to exposure groups.

Table D-6. Review Articles Citing Male Reproductive Health Outcome Conclusions Reported on by Primary Epidemiological References.

Review Article Reference(s)	Primary Epidemiological Reference(s)	Overall Conclusion
NRC, 2003; Ritchie et al. (2003)	Lemasters et al. (1999)	In a cohort study of male aircraft maintenance workers at an Air Force installation in the United States, job categories were used as a proxy for exposure to JP-4. Exposed flight line workers had statistically significantly increased sperm concentrations at 15 weeks of employment compared to baseline. No differences were observed in exposed and unexposed groups for other acute sperm parameters, including sperm length, sperm width/length, percent motile sperm, straight line velocity and linearity, at 15 weeks of employment compared to baseline.

Table D-7. Review Articles Citing Digestive Health Outcome Conclusions Reported on by Primary Epidemiological References.

Review Article Reference(s)	Primary Epidemiological Reference(s)	Overall Conclusion
Karanakis et al. (2021); NRC (1996)	Knave et al. (1976)	The association between unspecified jet fuel exposure and self-reported gastritis was assessed among 30 workers exposed to jet fuel, 15/30 self-reported gastritis and 22/30 had a record of gastritis in plant physician journals. The proportion of workers with gastritis was lower among a control group of 30 unexposed workers (10/30 self-reported, 15/30 recorded in plant physician journals). There was no statistical evaluation of the differences in the number of symptoms between these groups.

Table D-8. Review Articles Citing Dermal Health Outcome Conclusions Reported on by Primary Epidemiological References.

Review Article Reference(s)	Primary Epidemiological Reference(s)	Overall Conclusion
Ritchie et al. (2003)	Knave et al. (1976)	A pilot study of 18 exposed and 18 unexposed active duty and civilian personnel was conducted at the Hill Air Force Base in Utah. Exposure was assigned based on job group; F-16 ground crew, aircraft fuel distribution personnel, fuel system mechanics and sheet metal workers were considered highly exposed. Acute skin irritation symptoms were self-reported as part of a physical examination at a baseline exposure assessment (when JP-4 was in use) and two follow-up assessments at 6 and 18 months (when JP-8 was in use) to document effects of JP-4 and after the transition to use of JP-8. Exposed subjects reported dry, itchy skin or rashes more frequently than unexposed workers (31 times and 20 times, respectively). Participants attributed symptoms to JP-4 exposure 5 out of 9 times and to JP-8 exposure 9 out of 21 times. Two exposed participants reported severe rashes and swelling of knuckles after exposure to JP-8. The average frequency of symptoms was less than twice a month for both groups and there were no differences in the frequency or severity of symptoms between exposed and unexposed groups at any time point and there were no trends over time. The authors note that symptoms of dry or itchy skin and rashes could be related to the dry climate in Utah.