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BIOLOGICAL AND HEALTH EFFECTS OF EXPOSURE TO KEROSENE-BASED JET FUELS AND PERFORMANCE ADDITIVES

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Over 2 million military and civilian personnel per year (over 1 million in the United States) are occupationally exposed, respectively, to jet propulsion fuel-8 (JP-8), JP-8+100 or JP-5, or to the civil aviation equivalents Jet A or Jet A-1. Approximately 60 billion gallons of these kerosene-based jet fuels are annually consumed worldwide (26 billion gallons in the United States), including over 5 billion gallons of JP-8 by the militaries of the United States and other NATO countries. JP-8, for example, represents the largest single chemical exposure in the U.S. military (2.53 billion gallons in 2000), while Jet A and A-1 are among the most common sources of nonmilitary occupational chemical exposure. Although more recent figures were not available, approximately 4.06 billion gallons of kerosene per se were consumed in the United States in 1990 (IARC, 1992). These exposures may occur repeatedly to raw fuel, vapor phase, aerosol phase, or fuel combustion exhaust by dermal absorption, pulmonary inhalation, or oral ingestion routes. Additionally, the public may be repeatedly exposed to lower levels of jet fuel vapor/aerosol or to fuel combustion products through atmospheric contamination, or to raw fuel constituents by contact with contaminated groundwater or soil. Kerosene-based hydrocarbon fuels are complex mixtures of up to 260+ aliphatic and aromatic hydrocarbon compounds (C_6–C_{17+}; possibly 2000+ isomeric forms), including varying concentrations of potential toxicants such as benzene, n-hexane, toluene, xylenes, trimethylpentane, methoxyethanol, naphthalenes (including polycyclic aromatic hydrocarbons [PAHs], and certain other C_9–C_{12} fractions (i.e., n-propylbenzene, trimethylbenzene isomers). While hydrocarbon fuel exposures occur typically at concentrations below current permissible exposure limits (PELs) for the parent fuel or its constituent chemicals, it is unknown whether additive or synergistic interactions among hydrocarbon constituents, up to six performance additives, and other environmental exposure factors may result in unpredicted toxicity. While there is little epidemiological evidence for fuel-induced death, cancer, or other serious organic disease in fuel-exposed workers, large numbers of self-reported health complaints in this cohort appear to justify study of more subtle health consequences. A number of recently published studies reported acute or persisting biological or health effects from acute, subchronic, or chronic exposure of humans or animals to kerosene-based hydrocarbon fuels, to

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14. ABSTRACT

Over 2 million military and civilian personnel per year (over 1 million in the United States) are occupationally exposed, respectively, to jet propulsion fuel-8 (JP-8), JP-8 + 100 or JP-5, or to the civil aviation equivalents Jet A or Jet A-1. Approximately 60 billion gallons of these kerosene- based jet fuels are annually consumed worldwide (26 billion gallons in the United States), including over 5 billion gallons of JP-8 by the militaries of the United States and other NATO countries. JP-8, for example, represents the largest single chemical exposure in the U.S. military (2.53 billion gallons in 2000), while Jet A and A-1 are among the most common sources of nonmilitary occupational chemical exposure. Although more recent figures were not available, approximately 4.06 billion gallons of kerosene per se were consumed in the United States in 1990 (IARC, 1992). These exposures may occur repeatedly to raw fuel, vapor phase, aerosol phase, or fuel combustion exhaust by dermal absorption, pulmonary inhalation, or oral ingestion routes. Additionally, the public may be repeatedly exposed to lower levels of jet fuel vapor/aerosol or to fuel combustion products through atmospheric contamination, or to raw fuel constituents by contact with contaminated groundwater or soil. Kerosene-based hydrocarbon fuels are complex mixtures of up to 260+ aliphatic and aromatic hydrocarbon compounds (C6?C17+ possibly 2000+ isomeric forms), including varying concentrations of potential toxicants such as benzene, n-hexane, toluene, xylenes, trimethylpentane, methoxyethanol, naphthalenes (including polycyclic aromatic hydrocarbons [PAHs], and certain other C9?C12 fractions (i.e., n-propylbenzene, trimethylbenzene isomers). While hydrocarbon fuel exposures occur typically at concentrations below current permissible exposure limits (PELs) for the parent fuel or its constituent chemicals it is unknown whether additive or synergistic interactions among hydrocarbon constituents, up to six performance additives, and other environmental exposure factors may result in unpredicted toxicity. While there is little epidemiological evidence for fuel-induced death, cancer, or other serious organic disease in fuel-exposed workers, large numbers of self-reported health complaints in this cohort appear to justify study of more subtle health consequences. A number of recently published studies reported acute or persisting biological or health effects from acute, subchronic, or chronic exposure of humans or animals to kerosene-based hydrocarbon fuels, to constituent chemicals of these fuels, or to fuel combustion products. This review provides an in-depth summary of human, animal, and in vitro studies of biological or health effects from exposure to JP-8, JP-8 + 100, JP-5, Jet A, Jet A-1, or kerosene.

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constituent chemicals of these fuels, or to fuel combustion products. This review provides an in-depth summary of human, animal, and in vitro studies of biological or health effects from exposure to JP-8, JP-8 + 100, JP-5, Jet A, Jet A-1, or kerosene.

RISK ASSESSMENT ISSUES

Although some kerosene-based jet fuels (Jet A, Jet A-1) have been used for as long as 55 yr, there was remarkably little published research on human health effects. Particularly since the U.S. Air Force (USAF) and U.S. Army transitions (1991–1996) from the predominant use of JP-4 (50–60% unleaded gasoline, 40–50% kerosene), or JP-4, diesel fuel (DF), and unleaded gasoline (MOGAS), respectively, to the nearly exclusive use of JP-8 and/or JP-8+100, an increasing number of self-reported and medically diagnosed symptoms have been documented from fuel-exposed workers. Additionally, the U.S. Navy, which has used (lower volatility) kerosene-based JP-5 since approximately 1952 to power carrier-based aircraft, is proposing transition by 2008 to exclusive use of JP-8/JP-8+100 to meet implementation requirements for the Joint Strike Fighter (JSF) aircraft. Indeed, the Department of Defense (DoD) is planning to completely replace use of unleaded gasoline with use of JP-8/JP-8+100 by 2010 for vehicle and equipment powering (Maurice et al., 2000). Consequently, it is expected that by 2010 over 95% of all U.S. military aircraft, land vehicles, and power equipment, as well as all domestic and commercial aircraft, will utilize kerosene-based jet fuels.

In response to JP-8–related health reports and concerns, the Centers for Disease Control and Prevention, Agency for Toxic Substances and Disease Registry (CDC-ATSDR), prepared an extensive document, the Toxicology Profile for Jet Fuels (JP-5 and JP-8) (ATSDR, 1998). This report concluded that possible jet fuel toxicity and underlying physiological mechanisms are not well defined or understood. More recently, the U.S. Environmental Protection Agency (EPA), Office of Pollution Prevention and Toxics, National Advisory Committee for Acute Exposure Guidelines for Hazardous Substances (NAC-AEGL), officially recognized significant data gaps in the toxicology profiles submitted by the ATSDR. In addition, a 1996 report by the National Research Council, Committee on Toxicology, Subcommittee on Permissible Exposure Levels for Military Fuels, further identified major data gaps in human occupational studies of possible JP-8 toxicity (NRC, 1996). In 1998, the USAF sponsored the first International Conference on Environment, Health, and Safety of Jet Fuels (San Antonio, TX). In response to data presented at this conference, the military Tri-Service (USAF, U.S. Army, and U.S. Navy) sponsored a meeting (Edgewood Proving Grounds, MD) to evaluate data gaps in JP-8 toxicology research. In 2000, an American Conference of Governmental Industrial Hygienists (ACGIH) Draft Notice of Intended Changes (NIC) was filed to recommend reduction of the current 8-h threshold limit value (TLV)–time-weighted average (TWA) standards for both kerosene and diesel fuel, from 350 mg/m^3 to 100 mg/m^3. In 1997, the Worldwide Aircraft Fuels Systems Conference (San Antonio, TX) responded to reports from various USAF Biomedical Engineering offices concerning elevated benzene levels detected during maintenance operations on JP-8–fueled aircraft

(Zelnick, 1998). The USAF Office of the Surgeon General tasked the AF Institute for Environment, Safety, and Occupational Health Risk Analysis (AFIERA) and the Air Force Research Laboratory (AFRL) to develop appropriate research strategies to examine possible JP-8 toxicity. These organizations appointed the USAF JP-8 Environmental, Safety, and Occupational Health Integrated Process Team (IPT) to address JP-8 risk assessment issues. Since 1996, this organization has funded a large number of animal and in vitro studies of JP-8 toxicity, in collaboration with the National Institute for Occupational Safety and Health (NIOSH), the U.S. EPA National Exposure Research Laboratory (NERL), the National Institute for Environmental Health Sciences (NIEHS), and a number of academic institutions. Recognizing a further need for human occupational evaluation of possible jet fuel toxicity, AFIERA funded from 2000 to 2001 a major epidemiological and health effects evaluation of approximately 340 jet-fuel-exposed military personnel and matched controls at six environmentally diverse, domestic USAF bases (Davis Montham AFB, AZ; Seymour Johnson AFB, NC; Langley AFB, VA; Pope AFB, NC; Little Rock AFB, AR; and Hurlbert Field, FL). Subchronically and chronically JP-8–exposed (worst-case scenario) subjects and low-exposure controls were compared on a large number of medical, neurobehavioral, biochemical, and physiological tests both before and immediately following daily occupational assignment. Preliminary results of this study were presented at the AFIERA International Conference on JP-8 Jet Fuel, San Antonio, TX (AFIERA, 2001), and are summarized in this article. Most recently, the National Academies, Committee on Toxicology (COT), convened an expert panel to review existing occupational JP-8 exposure standards (generally, 8-h PEL=350 mg/m^3; 15-min, short-term exposure limit [STEL]=1000 mg/m^3). The findings of this panel were recently published in book format, and represent the most comprehensive investigation of JP-8 toxicity available (National Research Council, 2003). In general, the NRC panel concluded that the currect interim PEL (350 mg/m^3) may be "too high to be protective of human health."

EXPOSURE SCENARIOS

Since 1996, there is increasing concern for possible health effects in individuals living near military bases at which JP-8 is used, and near commercial airports using Jet A or Jet A-1. Atmospheric exposure to vaporized or aerosolized jet fuel from leakage, spillage, engine cold starts, and high-altitude aircraft fuel jettisoning, or to combustion exhaust, and exposure to soil and groundwater contamination with raw fuels are being critically examined.

Direct exposure to kerosene-based jet fuels occurs in military and civilian avionics, aircraft maintenance, and fuel manufacturing/handling personnel through (1) dermal contact with raw fuel and/or aerosol; (2) dermal contact with clothing and gloves saturated with fuel; (3) respiratory exposure to fuel or exhaust in vapor or aerosol phase; or (4) occasional oral exposure to aerosol or to fuel contaminated food or water (Harris et al., 1997a; Pleil et al., 2000; Ritchie, Still et al., 2001). Exposure of military personnel to JP-8 or JP-5 can also occur through fuel applications unrelated to aircraft fueling, including fueling of land

vehicles and equipment, fueling of heaters and lighting sources, use as a coolant (heat sink) in aircraft, aerosolization/combustion of JP-8 for use as a combat obscurant, use of JP-8 to suppress environmental sand or dust, decontamination of military vehicles and equipment with JP-8, or use of JP-8 as a carrier for herbicide applications (Ritchie, Still et al., 2001). With the increasing number of females involved occupationally with jet fuels, there is mounting concern for possible health effects from intrauterine exposures.

Exposure of individuals not involved occupationally with jet fuel occurs through atmospheric, soil, or groundwater contamination with jet fuels or their combustion products, or through off-gassing from the skin and clothing of fuel-exposed personnel (Ritchie, Still et al., 2001). Major identified sources of atmospheric and groundwater contamination with jet fuels include: (1) unavoidable leakage or accidental spillage from manufacturing facilities, transportation, and storage systems (including pipelines); (2) fueling/defueling/maintenance operations, as well as aircraft and vehicle operation (including cold start-up of engines); and (3) atmospheric jettisoning (usually above 6000 ft) of fuels during emergency aircraft landing (Pfeiffer, 1994).

Studying perhaps the worst-case jet-fuel-exposure scenario, Carlton and Smith (2000) measured JP-8 and benzene exposures during aircraft fuel tank (foam-filled) entry and repair at 12 USAF bases. Breathing-zone samples were collected on the fuel handlers during occupational assignments, while instantaneous samples were taken at various workplace locations during the procedures with stainless steel (SUMMA) canisters and subsequent analysis by mass spectrometry. The highest 8-h TWA was 1.3 g/m^3; the highest short-term (15-min average) exposure was 10.3 g/m^3. The instantaneous sampling results indicated benzene exposures during fuel tank repair up to 49.1 mg/m^3. These readings occurred within aircraft fuel tanks (cells), from which foam blocks soaked with JP-8 were inspected and removed. Workers entering the tanks are required to wear self-contained breathing apparatus (SCBA) and chemically resistant gloves and boots, but only cotton jumpsuits, allowing potential extensive dermal exposure. Personnel working outside the fuel tanks (attendants), but assisting in removal of the foam blocks, do not typically wear SCBAs, allowing both extensive dermal and respiratory exposure to JP-8 (Pleil et al., 2000).

Kerosene is the primary fuel used for personal heating, cooking, and illumination applications in a number of Third World countries, allowing extensive opportunity for repeated exposure to raw fuel, vapor/aerosol, or combustion products. Oral ingestion of kerosene by children is a major source of poisoning in a number of African and Asian countries (Majeed et al., 1981; Dutta et al., 1998). Additionally, use of kerosene as a carrier in a number of industrial/commercial products provides additional sources of exposure.

CHEMICAL AND PHYSICAL PROPERTIES OF FUELS, INCLUDING ADDITIVES

As determined by gas chromatography/mass spectrometry (GC/MS), kerosene-based jet fuels typically contain approximately 228 identifiable

hydrocarbon constituents (C_6–C_{17}+), although this number may exceed 2000 when all isomeric forms of these constituents are considered (Allen et al., 2001; Ritchie, Still et al., 2001). GC/MS analysis of JP-5, JP-8, or Jet A/A-1 provides unique constituent profiles or fingerprints, such that it cannot be assumed that toxicological effects from exposure to one of these fuels is necessarily generalized to the others. Additionally, hydrocarbon and nonhydrocarbon performance additive packages that differentiate JP-5, JP-8, JP-8+100, Jet A, Jet A-1, and neat kerosene further complicate toxicological profiling. Within any specific fuel formulation, the percentage of specific chemical components and various nonhydrocarbon contaminants (i.e., sulfur, copper, etc.) may vary substantially as a function of the fuel manufacturer, fuel lot, and targeted fuel performance objectives. The general specifications for military kerosene-based jet fuels are detailed in MIL-DTL-5624T (1998). The unique chemical and physical property signatures of JP-8, JP-8+100, JP-5, Jet A, Jet A-1, and desulfurized kerosene are presented next.

Jet Propulsion Fuel-8 (Also Known as JP-8, AVTUR, MIL-DTL-83133, NATO F-34)

Kerosene-based (98+%) type; 3–5 performance additives.

JP-8+100 (Also Known as JP-8[100])

Kerosene-based (98+%) type: high thermal stability; six performance additives; identical to JP-8, except for addition of thermal stability (TS) performance package.

Distillation temperature	366–626 °F
Physical state/appearance	Clear and bright, to light amber liquid
Odor description	Light hydrocarbon/kerosene/ether odor
Odor threshold	0.082 ppm (kerosene)
Molecular weight	180 (average)
Density	–0.082 g/ml
API gravity	44.07° API Min
Boiling point	302–527 °F
Viscosity	4.27 ± 0.69 cst
Lower explosive limit	0.7–0.9%
Upper explosive limit	5–6%
Autoignition temperature	>475 °F
Freezing point, maximum	–61.8 ± 7.9 °F
Flash point method	TCC
Flash point	120.6 ± 12.2 °F
Vapor pressure (mm Hg)	0.52 at 50 °F; 1.8 at 82 °F; 20 at 158 °F
Vapor density (air = 1)	4.5–5
Specific gravity (kg/L at 59 °F)	0.775–0.840
Heating value (BTU/lb)	18,400
Solubility in water	Negligible (<0.1%)
Conversion factors (at STP)	1 ppm = 8 mg/m^3; 1 mg/m^3 = 0.12 ppm
Composition (% v/v)	Range: C_6–C_{18} Aromatics: mean 17.37% Olefins: mean 1.15 ± 0.68%

(*Continued*)

Primary constituents in JP-8 (w/w%)	Dodecane (C_{12}) 22.54% Tetradecane (C_{14}) 16.87% Decane (C_{10}) 16.1% Hexadecane (C_{16}) 12.22% Trimethylbenzenes (C_9) <6.6% Butylbenzene (C_{10}) 4.72% Cyclo-octane (C_8) 4.3–4.4% Tetramethylbenzenes (C_{10}) 4.28% Tetralin (C_{10}) 4.14% *m*-Xylene (C_8) 3.95% Iso-octane (C_8) 3.7% Methylnaphthalene (C_{12}) 3.49% Naphthalene (C_{10}) 1.46 ± 0.65% Toluene (C_7) <1% Benzene (C_6) <0.8% *p-, o*-Xylenes (C_8) <1.4% *n*-Hexane (C_6) <0.1% PAHs <0.1% Sulfur 0.058 ± 0.049%
Performance additives JP-8	<0.5%
Required	1. Static dissipater 2. Corrosion inhibitor/lubricity improver 3. Icing inhibitor
Allowed	4. Metal deactivator 5. Antioxidant
Performance additives JP-8 + 100	<0.5% 1. Thermal stability package, including performance additives 1–5, above.
Applications JP-8	USAF, U.S. Army and some U.S. Navy/Marines turbo-jet and turbo-prop jet fuels; motor and equipment fuels; heating fuel; thermal heat sink; dust suppressant; vehicle for insecticides, herbicides, and pesticides
Applications JP-8 + 100	Generally, USAF light fighter (F-15, F-16, T-38) and helicopter fuel; thermal heat sink
Exposure limits	
8-h PEL (interim)	350 mg/m^3
15-min STEL (interim)	1000 mg/m^3

JP-8+100 Jet Fuel Military requirements (MIL-DTL-83133E) allowing for improved thermal stability (TS [higher safe fuel operating temperatures]) in JP-8 fuel formulations led recently to development of a new performance additive package. When this additive package, costing only several cents per gallon, is injected into JP-8 stock on the flight line, the resultant formulation is categorized as JP-8+100. The name JP-8+100 was selected because addition of the performance package increases the TS of JP-8 by 100°F (technical specifications, Heneghan et al., 1996a, 1996b; Kalt et al., 2001).

The additive package, known in the United States as Betz-Dearborn SPEC-AID 8Q462 (manufactured exclusively by Betz-Dearborn, Division of Hercules, Inc., Wilmington, DE), commercially as Turboline FS100/FS100C, or internationally as Aero-Shell PA101 (distributed by Shell Oil Aviation, United Kingdom) contains three additives and a solvent and is injected into JP-8 at 256 ppm (256 mg/L). SPEC-AID 8Q462, Turboline FS100/FS100C, or Aero-Shell PA101 contain: (1) 1 of 6 approved antioxidant formulations (presently butylated hydroxytoluene, or BHT), added at 25 ppm (25 mg/L); (2) the metal deactivator (MDA) *N,N*-disalycylidene-1,2-propanediamine, added at 2 ppm (2 mg/L); (3) the detergent/fuel stabilizer/dispersant Betz-Dearborn Dispersant (proprietary), added at 100 ppm (100 mg/L); and (4) a heavy aromatic naphtha solvent (6–10% naphthalene), added at 129 ppm (129 mg/L) (Heneghan et al., 1996a, 1996b; AFAL, 1996; Kalt et al., 2001; Kanikkannan, Burton et al., 2001; personal communication, Zabarnick; personal communication, Stonecipher). As a result of the improved TS, heat-sink capacity of the JP-8+100 formulation is increased by 50%, and fuel-induced engine coking and fouling in jet engine nozzles and afterburner spray assemblies are significantly reduced. There is some preliminary evidence that the thermal stability additive package in JP-8+100 may both significantly reduce the formation of particulate matter (aerosol content) and eliminate several classes of PAHs found normally in JP-8 exhaust (personal communication, Stonecipher; Maurice et al., 2000). JP-8+100 may, however, permanently disable current fuel-system water separators, possibly leading to plugging of fuel injectors, increased water in fuels, and increased growth of bacterial/fungal contamination.

The additive package chemical is commonly delivered to the flight line by the manufacturer (i.e., Betz-Dearborn or Shell Oil Aviation) in temporary 400-gal tanks (filled to 280 gal) or to permanent, free-standing, 560- to 2000-gal additive tanks. The additive may be injected into fuel, leaving a fuel truck to enter an aircraft fuel tank, or directly into the aircraft fuel tank itself. Excepting equipment failures, accidental spills, and unavoidable leaking, there is minimal opportunity for human flight line contact with the undiluted additive. Human contact with the diluted additive package, after addition to JP-8 stock, would appear to occur, as does human contact to the JP-8+100 or its combustion products. There are no published or otherwise available human toxicology data on possible health consequences from exposure to SPEC-AID 8Q462, Turboline FS100/FS100C, or Aero-Shell PA 101 (personal communication, Stonecipher). Several in vitro studies of JP-8+100 toxicity have been published and are further discussed in subsequent sections of this report (AFAL, 1996; Kabbur et al., 2001; Kanikkannan et al., 2000; Kanikkannan, Burton et al. 2001; Kanikkannan, Patel et al. 2001; Allen et al., 2000, 2001).

The SPEC-AID 8Q462, Turboline FS100/FS100C, or Aero-Shell PA 101 additive package combines with the following three additives found normally in JP-8 stock:

1. Stadis 450, an antistatic agent and conductivity improver added to JP-8 at <3 mg/L. Produced by several chemical manufacturers, Stadis 450 consists of 35–60% toluene, 5–20% solvent naphtha, <5% naphthalene, 1–10% dodecylbenzenesulfonic acid, <0.06% benzene, <5% isopropyl alcohol, 1–10% dinonylnaphthylsulfonic acid, and 1–10% proprietary chemical (MSDS, Stadis 450, 2000a). Depending upon concentration of Stadis 450 in fuels, conductivity measurement can be improved from 10 to 100% (personal communication, Stonecipher).
2. DCI-4A or Corrosion Inhibitor No. 4A (MSDS, DCI-4A, 2001), the corrosion inhibitor/lubricity improver added to JP-8 (0.85–11 mg/L) to protect ferrous metals from corrosion in jet fuel handling systems, including pipelines and fuel storage tanks, and to improve fuel lubricity. DCI-4A consists of 20–30% xylenes, 0–5% ethylbenzene, and 70–80% proprietary (organic acids) chemicals.
3. Diethylene glycol monomethyl ether (DiEGME or 2,2-methoxy ethoxy ethanol) and/or ethylene glycol monomethyl ether (EGME or 2-methoxy ethanol) (Hobson et al., 1986), anti-icing additives added to JP-8 to minimize formation of ice crystals in aircraft or vehicle fuel systems. Generally DiEGME, with less potential for dermal absorption than EGME (initially used in JP-5), is most commonly used for anti-icing applications, although EGME or combinations of EGME/DiEGME are still used at some U.S. military bases. EGME/DiEGME are water-soluble solvents that absorb oxygen content from fuels, additionally functioning as significant biocides for aerobic microorganisms in the fuel (Lee & Wong, 1979; personal communication, Stonecipher).

At present, approximately 125,000 gal/yr of Betz-Dearborn SPEC-AID 8Q462, Turboline FS100/FS100C, or Aero-Shell PA 101 are consumed per year (personal communication, Stonecipher). JP-8+100 is presently (October 2001) used to fuel the majority of domestic USAF fighters and trainers, a limited number of USAF helicopters, 50% of Air National Guard C-130 aircraft, and virtually all USAF Reserves C-130 aircraft and related ground vehicles and equipment (personal communication, Stonecipher). Because JP-8+100 may permanently disable water separators in vehicle fuel filters, resulting possibly in increased corrosion, seizure of fuel nozzles, and bacterial/fungal contamination of fuel, its use in ground vehicles is limited. JP-8+100 (injected with the Turboline FS100 package) is presently used in the majority of military aircraft and related equipment by the North Atlantic Treaty Organization (NATO) member country Sweden. At present, only three commercial aircraft (747 aircraft flown by KLM Royal Dutch Airlines) are fueled with Jet A or Jet A-1 to which SPEC-AID 8Q462 or Turboline FS100 was added. One civilian police department in Florida is presently adding SPEC-AID 8Q462 to its helicopter fuel (personal communication, Stonecipher).

Jet Propulsion Fuel-5 (JP-5; AVCAT; NATO F-44; MIL-DTL-5624T)

Kerosene-type; high flash point; 3–5 performance additives.

Distillation temperature	366–626 °F
Physical state/appearance	Clear, water-white to light amber liquid
Odor description	Light hydrocarbon/kerosene/ether odor
Odor threshold	0.082 ppm (kerosene)
Molecular weight	185 (average)
Density	–0.82 g/ml
API gravity	42.24° API Min
Boiling point	302–527 °F
Viscosity	5.51 cst
Lower explosive limit	0.6–1%
Upper explosive limit	4.6–7%
Autoignition temperature	>475 °F
Freezing point	–59.8 ± 8.1 °F
Flash point method	PMCC
Flash point (minimum)	145 ± 3.45 °F
Vapor pressure (mm Hg)	1–2 at 70 °F
Vapor density (air = 1)	4
Specific gravity (kg/L at 59 °F)	0.778–0.845
Heating value (BTU/lb)	18,300
Solubility in water	Negligible (<1%)
Conversion factors (at STP)	1 ppm = 8.3 mg/m^3; 1 mg/m^3 = 0.12 ppm
Major composition (% v/v)	Range: C_7–C_{17} Olefins 1.56 ± 0.78% Dodecane 22.54% Tetradecane 16.87% Hexadecane 12.22% Decane 16.08% Butylbenzene 4.72% Cyclooctane 4.54% 1,2,4,5-Tetramethylbenzene 4.28% Tetralin 4.14% Aromatics: 17.45 ± 2.76% *m*-Xylene 3.95% Benzene <0.2% Toluene 0.1% *p*-, *o*-Xylenes 0.6% Trimethylbenzenes 1–2% Isooctane 3.66% Methylcyclohexane 3.51% 1-Methylnaphthalene 3.49% Naphthalene 0.4–3% Sulfur 0.061 ± 0.05% *n*-Hexane <0.1%
Performance additives	<0.5%
Required	1. Corrosion inhibitor/lubricity improver 2. Icing Inhibitor 3. Antioxidant
Allowed	4. Anti-static agent 5. Metal deactivator

(*Continued*)

Applications	U.S. Navy/Marines motor and jet fuels; occasional ship engine fuel; illuminating fuels; heating fuel; vehicle for insecticides and fungicides.
Exposure limits	
8-h PEL (interim)	350 mg/m^3
15-min STEL (interim)	1000 mg/m^3

Jet A (AVTUR; Aviation Fuel A; Turbine Fuel A; Military JP-1; NATO F-35; ASTM D 1655)

Kerosene-based (98+%) type; higher freezing point than Jet A-1; up to 5 additives.

Jet A-1 (AVTUR; Aviation Fuel A-1; Turbine Fuel A-1; NATO F-35; DEF STAN 91-91)

Kerosene-based (98+%) type; lower freezing point than Jet A; 1–5 additives.

Distillation temperature	400–572 °F
Physical state/appearance	Light yellow liquid
Odor description	Light hydrocarbon/kerosene odor
Odor threshold	0.082 ppm (kerosene)
Molecular weight	180 (average)
Boiling point	315–572 °F
Viscosity (–4 °F, mm^2/s)	8
Lower explosive limit	0.5%
Upper explosive limit	6%
Autoignition temperature	410–450 °F
Freezing point	
Jet A	–40 °F
Jet A-1	–53 °F
Flash point method	TCC
Flash point (minimum)	100–111 °F
Vapor pressure (mm Hg)	2–3 at 70 °F
Vapor density (air = 1)	4.5
Specific gravity (kg/L at 59 °F)	0.804
Heating value (BTU/lb)	N/A
Solubility in water	Negligible (<1%)
Conversion factors (at STP):	N/A
Major composition (% v/v)	Range: C_6–C_{16}
	Aromatics <25%
	Dodecane (C_{12}) 4.7%
	Tridecane (C_{13}) 4.4%
	Undecane (C_{11}) 4.1%
	p-, m-, o-Xylenes (C_8) 3.5%
	Tetradecane (C_{14}) 3%
	2,6-Dimethylundecane (C_{13}) 2.1%
	1-Methylnaphthalene (C_{11}) 1.8%
	Pentadecane (C_{15}) 1.6%
	2-Methylnaphthalene (C_{12}) 1.5%

(*Continued*)

	2,6-Dimethylnaphthalene (C_{11}) 1.3% 2-Methylundecane (C_{12}) 1.2% Heptylcyclohexane (C_{13}) 1% Naphthalene (C_{10}) 1.1% 1,2,3,4-Tetramethylbenzene (C_{10}) 1.1% Toluene (C_8) 0.8–0.9% Benzene (C_6) 0.5–0.8% Sulfur <0.30% *n*-Hexane (C_6) <0.1%
Performance additives	<0.5%
Required	None
Allowed	1. Antistatic agent (required Jet A-1) 2. Antioxidant 3. Corrosion inhibitor/lubricity improver 4. Metal deactivator 5. Biocide
Applications	Turbo-jet and turbo-prop commercial airline and general aviation aircraft; occasionally military aircraft; Jet A, generally U.S. domestic flights; Jet A-1, generally international flights
Exposure limits	
8-h PEL	N/A
15-min STEL	N/A

Kerosene (Kerosene, Fuel Oil #1, K-1; JP-1; Hydrodesulfurized Kerosene)

Additives	None
Human odor threshold	0.6 mg/m^3 or 0.09 ppm (range for 83% human detection = 0.2–2 mg/m^3)
Distillation temperature	340–572 °F
Physical state/appearance	White to light yellow liquid
Odor description	Light hydrocarbon odor
Molecular weight	171 (average)
Boiling range	302–572 °F
Density	–0.80 g/ml
Boiling point	300°–400 °F
Lower explosive limit	0.7%
Upper explosive limit	6%
Specific gravity (kg/L at 59 °F)	0.789
Flash point	176–190 °F
Conversion factors (at STP)	1 ppm = 6.99 mg/m^3; 1 mg/m^3 = 0.143 ppm Range: C_6–C_{16} Paraffins: 55.2% (w/w) Naphthenes: 40.9% (w/w) Aromatics: 3.9% (w/w) Aromatics: 17–25% (v/v) Benzene 0.1–1% Toluene 0.8–0.9% *p-, m-, o*-Xylenes 3.5% Trimethylbenzenes <2%

(*Continued*)

	Sulfur <0.05% *n*-Hexane <0.1% Naphthalene 1–3%
ACGIH 8-h PEL	100 mg/m^3
Applications	Heating, cooking, and illuminating fuel; tar, grease, and oil removal; pesticide vehicle; paint thinner; solvent in printing, auto repair, plastic and rubber products manufacture; distillation to JP-5, JP-8, Jet A, Jet A-1

Resources: Carpenter et al. (1976); Air Force (1991); ATSDR (1998); TPHCWG (1998); Chevron Products Corporation (1999); CONCAWE (1999); Riviere et al. (1999); White (1999); PQIS (2000, 2001). Current JP-8, JP-5, Jet A/A-1, or hydrodesulfurized kerosene MSDSs; Exxon/Mobil; Amoco; Pride Company; BP Oil; Shell Oil; Mapco Alaska Petroleum; Arco Products; Navajo Refining; Coastal; La Gloria Oil and Gas; Hunt Refining; Chevron Oil; Age Refining; Repsol Oil International, Ltd.; Diamond Shamrock Refining (http://msds.pdc.cornell.edu/msdssrch.asp).

HEALTH EFFECTS FROM EXPOSURE TO SELECTED CHEMICAL COMPONENTS OF KEROSENE-BASED JET FUELS

The following section contains descriptions of health effects known to occur from exposure to each of six well-researched chemical components common (in varying concentrations) to all hydrocarbon fuels discussed in this review. Possible health consequences from exposure to the remaining 200+ chemical components (2000+ isomeric forms) of the fuels discussed are not addressed, as there is either no scientific data available, minimal data, or data presenting conflicting results. It should, of course, be remembered that health effects discussed in this section occur typically to concentrations significantly higher than those encountered during "real-world" exposure to kerosene-based jet fuels. Even considering this limitation, it is important to note that some of the health effects observed during or following single-component exposures may mimic effects discussed in later sections that may occur from exposure to specific kerosene-based jet fuel formulations. Further, the possibility must be considered that possible synergistic (or antagonistic) effects from repeated, concurrent lower concentration exposures to all of the chemical components discussed may induce health effects that cannot be predicted additively from single component exposures data.

Polycyclic Aromatic Hydrocarbons (PAHs)

JP-8 raw fuel (0.29–3% v/v) and particularly exhaust (20–4000 ng/m^3) from JP-8 partial combustion contain PAHs and nitro-PAHs, predominated by naphthalenes, and including at least benzo[a]pyrene (BaP), fluoranthene, pyrene, phenathyrene, anthracene, and chrysene. A recent study detected more than 30 different PAHs in a 40-min analysis of jet fuel combustion (Bernabei et al., 2003). The addition of performance additives to hydrocarbon fuels can increase PAH levels in emissions (Mi et al., 1998), although preliminary data indicate that addition of the TS package to JP-8 (JP-8+100) may actually reduce PAH emissions in combustion exhaust (personal communication, Stonecipher).

PAHs are distributed in the air in vapor phase or in the particulate (aerosol) phase through adsorption or condensation on the surface of respirable particles (Childers et al., 2000), or from spills in fuel-contaminated soil and groundwater. Aislabie et al. (1999), for example, measured samples ranging from 41 to 8105 ng/g (dried soil) of naphthalene and other PAHs in samples collected at a spill site in Antarctica.

Acute inhalation exposure to bicyclic aromatic hydrocarbon naphthalenes was shown in mice or rats to result in damage to pulmonary epithelial cells, while repeated exposure may be associated with renal damage. Naphthalene is thought to be metabolized under the influence of cytochrome P-450 to toxic, electrophilic intermediates (i.e., 1,2-naphthalene oxide, 1,4-naphthoquinone) that mediate damage to nonciliated bronchiolar epithelial cells (Clara cells) and proximal renal tubules in mice (Kawabata & White, 1990). Whether this metabolism occurs strictly in liver hepatocytes and the metabolite is transported to other target organs, or whether metabolism also occurs within target organs containing P-450 (i.e., lung Clara cells, splenocytes, etc.) remains conjectural. Kawabata and White (1990) reported mild immune suppression in splenocyte cultures exposed to high concentrations (>200 μm) of naphthalene metabolites.

Knuckles et al. (2001) exposed male and female F-344 rats orally to BaP at concentrations of 0, 100, 600, or 1000 mg/kg/d for 14 d (acute group) or 0, 50, or 100 mg/kg/d for 90 d (subchronic group). In the acute study, white blood cells (WBCs) were significantly decreased and mean cell hemoglobin concentration was significantly increased in BaP-exposed males. Additionally, the liver/body weight ratio was increased up to 30% in both males and females. In the subchronic study, mean body weight was significantly decreased in exposed males while the liver/body weight ratio was significantly increased. In both male and female BaP-exposed groups, red blood cells (RBCs), hematocrit, and hemoglobin were all significantly decreased. The histopathological examination of selected tissues indicated significant abnormalities (i.e., tubular casts) in the kidneys of some BaP-exposed males.

Exposure to respirable PAHs is thought to represent a significant human cancer risk (Holland et al., 1981; U.S. Department of Health and Human Services, 1998), particularly for the oral surfaces, lung, skin, and possibly kidneys. BaP and fluoranthene, for example, have been ranked by the ASTDR (Ostrowski et al., 1999) as among the most hazardous substances in the environment.

Again, the carcinogenicity of PAHs is based on their bioactivation to yield carcinogenic intermediates that can penetrate cells. The glutathione *S*-transferase genes GSTM1 and GSTT1, cytochrome P-450 (particularly CYP1A, CYP1A1, and CYP1B1), and microsomal epoxide hydrolase have been identified in catalyzing the dihydrodiol epoxide (+)-(7*R*,8*S*)-dihydroxy-(9*S*,10*R*)-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene, the ultimate carcinogenic form of BaP (Vakharia et al., 2001). Related biomarkers for possible carcinogenicity include 7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene-DNA adducts or BaP metabolites in the urine (Hecht, 2001).

As is more fully discussed in a subsequent section, a percentage of jet fuel stores is contaminated with bacterial or fungal colonies. For example, Ferrari et al. (1998) detected bacterial or fungal contamination in each of 350 (fuel/water interface) samples from jet fuel storage systems (i.e., tanks, trucks, and pipelines). Eaton and Chapman (1992, 1995) hypothesized pathways by which highly specific bacterial strains can initiate the metabolism of PAHs to compounds with toxicity potential. For example, *Pseudomonas putida* can, through naphthalene 1,2-deoxygenase, initiate a metabolic cascade with possible end products of salicylate, then catechol. *Pseudomonas* and a number of other hydrocarbon-degrading strains commonly exist in jet-fuel-contaminated soils and groundwater.

Benzene

Although some relatively clear health effects of exposure to benzene have been identified, no definitive concentration response pattern was determined. The evidence suggests the major health problems possibly resulting from benzene exposure, aplastic anemia and acute myelocytic leukemia (AML), require more than a single exposure (Krewski et al., 2000). However, it is still unknown what levels and lengths of exposure result in increased risk. For instance, it has yet to be resolved whether or not there are risk differences associated with multiple lower concentration exposures over a long period of time, versus fewer high-concentration exposures over a shorter period of time (Kacew & Lemaire, 2000). Even so, recognition of the health effects of benzene exposure has a relatively long history, with reports as early as 1897 (Santesson) and 1916 (Selling) of illness and death in chronically exposed workers. A link between benzene exposure and leukemia was first reported in 1928 (Delore & Borgomano). Today it is widely accepted that the primary health effect of benzene exposure is a depression of bone marrow that may culminate in aplastic anemia or certain forms of leukemia (Snyder, 2000). A third health problem associated with benzene exposure is myelofibrosis, wherein bone marrow is replaced with fibrous tissue (Zoloth et al., 1986). Much recent research into the health effects of benzene exposure has concentrated on identifying the molecular mechanisms that underlie the decline in bone marrow function that is evidenced with benzene exposure.

Aoyoma (1986) exposed male BALB/*c* mice to benzene vapor at 50 or 200 ppm, 6 h/d for 7 or 14 d. Depression of leukocyte counts was found after at least a 14-d exposure to 50 ppm benzene vapor, consistent with thymic (reduction in thymocytes in the cortex and medulla of the thymus) and splenic atrophy (loss of small lymphocytes in lymphoid nodules in the spleen). Additionally, it was shown that all inhalation conditions resulted in reduced numbers of B and T lymphocytes in both the spleen and blood. The ability to form antibodies was suppressed by benzene in all exposure conditions, but contact sensitivity (to picryl chloride) was actually enhanced by the 200 ppm exposure for 14 d. It was concluded that acute benzene inhalation in mice induced selective toxicity in both B lymphocytes and suppressor T cells.

Pancytopenia, a reduction in RBCs, WBCs, and platelets, as a result of depressed bone marrow function, characterizes aplastic anemia. Epidemiological research suggests a connection between the development of the disease and benzene exposure (Aksoy et al., 1971; Yin et al., 1987, 1989). Similarly, epidemiological studies provide evidence for the link between benzene exposure and leukemia (Aksoy & Erdem, 1978; Infante et al., 1977a, 1977b; Ott et al., 1978; Rinsky et al., 1981, 1987; Bond et al., 1986; Yin et al., 1987, 1989). The onset of acute myelocytic leukemia (AML), related to benzene exposure, is often preceded by myelodysplastic syndrome (MDS) (Forni & Moreo, 1967, 1969; van den Berghe et al., 1979). It is proposed that benzene-related MDS is a precursor to the later developing AML (Le Beau et al., 1986; Irons & Stillman, 1996; Irons, 2000). All these conditions (aplastic anemia, MDS, AML) involve a compromised hematopoietic system that may be produced by benzene toxicity. It is posited that one major cause of the compromised bone marrow function is damage to the stromal cells responsible for normal bone marrow function (Garnett et al., 1983; Snyder, 2000). Benzene exposure detrimentally affects stromal cells (Gaido & Wierda, 1984, 1985; Chertkov et al., 1992) that are critical for establishing the hematopoietic environment necessary for the normal maturation of stem cells into blood cells. In addition to indirectly inhibiting the maturation of stem cells, there is evidence that benzene directly damages proliferating stem cells (Uyeki et al., 1977).

Although benzene may directly produce some of the health effects that have been discussed, more recent data suggest the majority of the problems are produced by benzene metabolites. Consequently, compounds that promote benzene metabolism have been demonstrated to increase its toxic effects (Gad-El-Karim et al., 1985, 1986), while an inhibition of benzene metabolism reduces the amount of cytotoxic damage (Tice et al., 1982; Morimoto et al., 1983). Indeed, it was reported that concurrent toluene exposure inhibits benzene metabolism and reduces benzene toxicity (Andrews et al., 1977), a significant factor in exposure to kerosene-based jet fuels that contain varying concentrations of both benzene and toluene. Hydroquinone is one metabolite that directly affects bone marrow and the immune system. It interferes with stromal cell activity (Gaido & Weirda, 1984, 1985, 1987; Renz & Kalf, 1991) that is necessary for proper hematopoietic functioning. Hydroquinone also suppresses nuclear factor kappa β, a transcription factor that regulates genes critical for normal T lymphocyte activation (Pyatt et al., 1998). Likewise, it also suppresses interleukin 2 (IL-2), a cytokine required for the proliferation of T cells (Pyatt et al., 1998). Although the data support the theory that benzene metabolites underlie the toxic effects of exposure, there is not sufficient evidence to clearly implicate a single metabolite or combination of metabolites responsible for benzene cytotoxicity (Ross, 2000). Indeed, it is likely that combinations of the different metabolites have synergistic toxic effects (Eastmond et al., 1987; Snyder et al., 1989; Guy et al., 1991).

To further support the evidence that benzene metabolism is a critical component of the observed health effects, animal research shows that genetic

factors controlling the metabolism of benzene correlate with benzene cytotoxicity. For instance, CYP2E1 is an enzyme important for benzene metabolism. In transgenic mice negative for the enzyme, the cytotoxic and genotoxic effects of benzene exposure were not observed, although they were found in mice of the control groups (Valentine et al., 1996). This finding was not supported in a study of benzene-exposed workers, where CYP2E1 expression was not correlated with incidence of benzene-related disease (Rothman et al., 1997). A second enzyme, NAD(P)H:quinone oxidoreductase (NQ01), is also important for benzene metabolism. It is a quinone reductase that acts to detoxify some benzene metabolites and appears to reduce the resulting cytotoxic insult (Cadenas et al., 1992; Smith, 1999; Wiemels et al., 1999). Reports from epidemiological studies suggest an increased susceptibility to benzene toxicity in people lacking the gene for NQ01 (Larson et al., 1999; Rothman et al., 1997, 1998).

In summary, the data suggest a link between benzene exposure and development of hematopoietic disorders such as aplastic anemia and nonlymphoblastic leukemia. The goal of current research is to determine the molecular mechanisms of benzene and its metabolites that contribute to such problems.

Toluene

Although there is often concomitant exposure to benzene and toluene in many occupational scenarios, the data suggest toluene is not a cause of the same blood disorders as benzene. It was proposed that a difference in chemical structure, an alkyl group attached to the benzene ring, is the reason toluene does not produce the myelotoxic effects observed with benzene (Gerarde, 1956.) In cases where toluene exposure is correlated with anemia and leukemia, it is likely that there was a combination exposure including benzene (Banfer, 1961; NIOSH, 1973; Tahti et al., 1981; Moszczynski & Lisiewicz, 1985). In a study where the exposure was toluene without benzene or xylene, rotogravure printers and assistants were occupationally exposed for about 3 yr while their blood constituents and bone marrow were consistently monitored (Banfer, 1961). No evidence of hematopoietic problems was observed. In contrast to the hematopoietic effects of benzene, toluene produces more neurological effects. The acute effects of a toluene exposure include a narcotic effect, as well as impairment of cognitive and neuromuscular functions that may persist beyond clearance of the drug and its metabolites from the body.

Two large literature reviews of toluene have been conducted (ATSDR, 1994; Low et al., 1988). The data for human health effects overall suggest the effects of toluene are primarily neurobehavioral effects. For instance, a 6-h exposure to 100 ppm toluene produced deficits in visual perception, the ability to discriminate colors, and the ability to perform multiplication calculations (Baelum et al., 1985). Similar exposures resulted in deficits in some, but not all, tests of short-term memory (Echeverria et al., 1991). In this study, no differences were reported for tasks of sensory motor skills such as reaction time, hand-eye coordination, finger tapping, or critical tracking. There were also no exposure effects on mood or vigilance. As documented in a NIOSH report on occupational

exposure to toluene (NIOSH, 1973), the most carefully controlled exposure to toluene was conducted with 3 volunteers who were exposed to different concentrations of toluene for 8 h, twice a week for 3 mo (von Oettingen, Neal & Donahue, 1942; von Oettingen, Neal, Donahue et al., 1942). No myelotoxic effects were observed in these volunteers; however, neurobehavioral effects were apparent. In general, the effects during exposure consisted of fatigue, headaches, incoordination, and muscle weakening, with a worsening of symptoms as the concentrations increased from 50 to 800 ppm. At the highest doses, neurobehavioral effects such as mental confusion, exhilaration, and lack of self-control were reported. There were no lasting effects at concentrations up to 100 ppm. However, lasting problems with fatigue, general confusion, headaches, insomnia, and skin paresthesia were evident following exposures at higher doses.

Less controlled studies of toluene effects have been conducted in cases of "huffing," where toluene is used as a drug of abuse and health effects are monitored in the abusers. It should be noted that in studies with abusers, hypoxia is a major confounding variable and should be considered when interpreting results. For instance, there are reports of atrophy in several locations throughout the brain (Fornazzari et al., 1983; Lazar et al., 1983; Rosenberg et al., 1988; Damasceno & de Capitani, 1994), oculo-motor deficits (Mass et al., 1991), and the emergence of personality disorders (Byrne & Zibin, 1991) in toluene abusers. Scores on neuropsychological evaluation tests show few deficits on simple tasks, such as reaction time or finger tapping, but there are deficits on more involved tests of short-term memory and spatial skills (Foo et al., 1990), or even more cognitively challenging tasks (Hanninen et al., 1976). A reduction in intelligence (IQ) scores from before versus after exposure has also been reported (Byrne et al., 1991). Evidence from animal models of neurobehavior following toluene exposure also suggest deficits with several different tests of cognitive processing (Ikeda & Miyake, 1978; Miyake et al., 1983; Taylor & Evans, 1985; Evans et al., 1985; Wada et al., 1988). No differences were reported in measures of open-field activity (i.e., spontaneous motor activity) or activity wheel (i.e., spontaneous motor activity, neuromuscular coordination, and motivation) tests (Ikeda & Miyake, 1978). Although these results suggest limited problems with the more basic brain functions, there is evidence to suggest a slowing in the rate of auditory information traveling to the brain for further processing (Abbate et al., 1993).

Toluene exposure also induces reproductive and teratological effects. LeMasters et al. (1997; LeMasters, Olsen et al., 1999; LeMasters, Lockey et al., 1999) reported a small but statistically significant increase in the frequency of sister chromatid exchanges, as well as in micronucleus frequency (MN) in the sperm of sheet metal workers or painters exposed to occupational toluene for up to 30 wk. In female toluene abusers, an absence of effects on menstruation variables was reported (Ng et al., 1992a), consistent with an increase in spontaneous abortions (Ng et al., 1992b). In males, hormonal changes were reported, although there was not a systematic analysis of the effects on fertility (Svensson, Nise, Erfurth et al., 1992; Svensson, Nise & Erfurth, 1992). The effects were

reductions in luteinizing hormone, follicular stimulating hormone (FSH), and testosterone. Infants of mothers who abuse toluene often have craniofacial features that resemble those of children with fetal alcohol syndrome, even if the mother did not consume alcohol during pregnancy (Toutant & Lippman, 1979; Hersh et al., 1985; Pearson et al., 1994). Other effects on the embryos and infants include digital hypoplasia, urinary tract anomalies, intrauterine growth retardation, prenatal microencephaly, and developmental delays (Goodwin, 1988; Hersh, 1989; Wilkins-Haug & Grabou, 1991; Pearson et al., 1994; Arnold et al., 1994).

Furman et al. (1998) implicated intraperitoneal (ip) exposure (125–375 mg/kg, 6 h/d, for up to 5 d) to toluene or its metabolites in modulation of mixed function oxidase (MFO) activity, in an organ- and isozyme-specific pattern. Exposure to the highest level of toluene, for example, produced significant inhibition of the activity of pulmonary aryl hydrocarbon hydroxylase (AHH), cytochrome P-4502B1 (CYP2B1), and CYP4B1 (but not CYP1A1) suggesting altered metabolic profiles of other xenobiotics in an organ-specific fashion.

Neghab and Stacey (1997) reported a reliable serum biomarker of exposure to toluene. These authors measured increased bile salts released from hepatocytes exposed to toluene vapor, and referenced several studies indicating obsevations of increases serum bile salts (SBA) in toluene-exposed humans and animals.

In summary, toluene exposure does not seem to induce significant hematopoietic problems; however, it does appear to possess neurotoxic and possibly developmental properties. Its acute effects are narcotic-like, while the persisting effects may include fatigue, as well as cognitive confusion and impaired motor coordination. With chronic exposures, detrimental effects related to permanent brain damage have been reported. A major consideration with repeated toluene exposure is persisting modulation of enzyme systems that are involved with metabolic reduction of other chemical toxicants.

Trimethylbenzenes

Trimethylbenzene (TMB) has three common isomers: 1,2,3-, 1,2,4-, and 1,3,5-TMB. The three isomers exhibit quantitatively different, and in a few cases qualitatively different, health effects. Rats exposed to 1,2,4-TMB at 123–1230 mg/m^3 showed low systemic toxicity, with no changes in body weight gain or organ/body weight ratio when compared to controls. However, at the highest concentration, a decrease in RBCs and increase in WBCs was noted (Korsak et al., 2000a). When rats were exposed to the same regimen of 1,2,3-TMB, a liver weight increase was noted in male rats at the highest exposure, in addition to the blood effects noted for 1,2,4-TMB (Korsak et al., 2000b). In a similar finding, exposure to 1,2,4-TMB for 90 d increased macrophages, polymorphonuclear leukocytes, and lymphocytes at all tested concentrations (Korsak et al., 1997).

Like many other hydrocarbons exposures, excessive exposure to TMB produces neurological and behavioral effects. In vitro exposure of rat neural synaptosomes to 1,2,4-TMB produced a dose-dependent increase in reactive oxygen species (ROS) and reactive nitrogen species (Myhre & Fonnum, 2001). Rats exposed

6 h/d, 5 d/wk to each of the 3 common isomers of TMB at 100 ppm exhibited significant effects in learning and spontaneous behavior 2 wk after exposure; however, rats exposed to 1,2,3-TMB had fewer effects (Gralewicz & Wiaderna, 2001). Single-dose oral exposure of rats increased spontaneous locomotor activity (Tomas et al., 1999) and inhibited brain activity (Tomas et al., 2000).

It is worth noting that exposure to TMB as a part of a hydrocarbon mixture does not appear to affect systemic or organ-specific uptake (Eide & Zahlsen, 1996); although, it does interfere with clearing the compound from the human system (Jarnberg et al., 1998). It is important, therefore, to consider TMB exposure in context.

All three common TMB isomers were tested for in vitro endpoints (Janik-Spiechowicz et al., 1998). Only the 1,2,3-isomer was positive in the Ames test, and that without S9 liver extract (tests with enzymatic transformation did not show increased mutation rates). All three isomers induced increased SCE in mouse bone marrow cells, with 1,2,3-TMB stimulating exchange at the lowest concentration. These tests provide incomplete evidence that all trimethylbenzenes are mutagens, with a higher likelihood for the 1,2,3-isomer.

Xylenes

Xylenes, or dimethylbenzenes (alkylbenzes or substituted benzenes) exist in three isomeric forms in jet fuels: *ortho*-xylene (*o*-xylene), *meta*-xylene (*m*-xylene), and *para*-xylene (*p*-xylene); ethylbenzene may also be commonly found in xylene mixtures. Xylenes are of moderate to low toxicity via the oral route, with LD_{50} values in rats ranging from 3.5–7.7 g/kg (Carpenter et al., 1975; Low et al., 1989).

While absorbable by inhalation > oral ingestion > dermal exposure, the biotransformation of xylene occurs in the liver or lungs. Of the xylene absorbed, about 95% is metabolized in the liver to methylhippuric acid (MHA) and 70–80% of metabolites are excreted in the urine within 24 h. Xylene induces liver cytochrome P-450, responsible for the oxidation of the methyl group side chain to form toluic acids (methylbenzoic acids). Second, the toluic acids are conjugated with glycine to form toluric acids (methylhippuric acids), which are rapidly excreted in the urine (2–18 h). Additional primary metabolites of xylene are dimethylphenol (DMP) and methylbenzyl alcohol (MBA).

Chronic occupational exposure to xylenes was associated with anemia, thrombocytopenia, leukopenia, chest pain with electrocardiogram (ECG) abnormalities, dyspnea, and cyanosis, in addition to central nervous system (CNS) symptoms (Langman, 1994; Ritchie, Still et al., 2001). In humans, mixed xylene exposures from 100–690 ppm for 15 min have been shown to result in eye irritancy, as well as mild dizziness and lightheadedness without a loss of postural equilibrium (Carpenter et al., 1975). Irritancy effects from xylene exposures, as a function of dose, were reported to range from turbidity and irritation of the ocular conjunctiva, to irritation of the upper airways, to severe lung congestion, and to pulmonary edema and hemorrhages (Reese & Kimbrough, 1993). Human occupational exposure, monitored by personal diffusive sampling, to

a mean of 21 ppm xylene demonstrated no toxicity to hematopoietic organs, liver, or kidneys (Uchida et al., 1993). There was, however, an increased number of subjective symptoms in these personnel, as well as eye, nose, and throat irritation. In a series of 12 chronic and subchronic animal exposures, no substantial or consistent effects were seen in blood, liver, kidneys, or lungs (Low et al., 1989).

Increased reaction time, reduced short-term memory, and impaired postural equilibrium have been documented at xylene exposure levels ranging from 100 to 200 ppm, but not at 70 ppm (reaction time and memory reproduction only) (Olson et al., 1985). Savolainen et al. (1980, 1984) reported deficits in reaction time, manual dexterity, body balance, and electroencephalograph (EEG) following acute exposure to 90 ppm *m*-xylene, while exposure to 300 ppm mixed xylene resulted in deficits on memory span, critical flicker fusion, and reaction time (Gamberale et al., 1978). Seppalainen et al. (1989), exposing human subjects acutely to 135–400 ppm *m*-xylene, reported modulations of visual evoked potentials (VEP) to a pattern reversal stimulus (pattern VEP) and to a light flash (flash VEP), and brainstem auditory evoked potential (BAEP) to a click stimulus. Accidental human xylene exposures estimated at up to 10,000 ppm were reported to result in epileptic seizures, complete amnesia, cerebral hemorrhage, and unconsciousness, as well as ventricular fibrillation related possibly to cardiac epinephrine sensitization (Low et al., 1989).

Epidemiological studies in humans suggest that even significant occupational exposure to xylenes is not carcinogenic. A 20-yr study of several thousand Finnish workers with occupational exposure showed no evidence of increased cancer risk (Anttila et al., 1998). A Montreal study of 3370 cancer patients of 15 types (nonleukemia) found no evidence of excess risk associated with exposure to xylene for most cancer sites; there was limited evidence that suggested a possible link with colorectal cancer (Gerin et al., 1998). Recent evidence, however, indicates that *o*-xylene exposure in rats alters mixed-function oxidase (MFO) activity in an organ- and isozyme-specific pattern following ip administration. These MFO alterations shifted the metabolism of the carcinogen benzo[a]pyrene (BaP) toward formation of toxic metabolites in lung. The major BaP-DNA adduct, BaP diol epoxide-N^2-deoxyguanosine , was increased in lung but decreased in liver microsomes from *o*-xylene–exposed rats (Park & Schatz, 1999).

Carpenter et al. (1975) exposed rats to mixed xylenes at 580–9900 ppm for 4 h, with an LD_{50} of 6700 ppm; 4 cats that inhaled 9500 ppm died within 2 h. Exposed animals exhibited salivation, ataxia, loss of coordination, tonic-clonic spasms, and unconsciousness, followed in some cases by death. Additionally, Carpenter et al. (1975) exposed rats and beagle dogs for 13 wk to mixed xylenes from 180–810 ppm, with no changes in body weight gain observed relative to controls, and no xylene-related alterations in histopathology. Jenkins et al. (1970) exposed rats, guinea pigs, dogs, and monkeys to 3.35 g/m^3 *o*-xylene either for 8 h/d, 5 d/wk, for 6 wk, or for 90 or 127 d continuously, reporting no

effects seen on body weight gain, hematological parameters, blood chemistry, or tissue histology, although several dogs exhibited repeated tremors. Several studies of xylene exposure in rats have, however, reported hypertrophy of the liver following repeated exposures at 220 mg/m^3 or above (Toftgard et al., 1981; Toftgard & Nilsen, 1982). In rats exposed to 3500 ppm *o*-xylene for 6 wk, hepatomegaly and ultrastructurally evident proliferation of smooth endoplasmic reticulum were noted (Tatrai & Ungvary, 1980). Foy et al. (1996) reported that a single 6-h ip exposure to *m*-xylene resulted in the inhibition of aryl hydrocarbon hydroxylase (AHH) activity in the lung without changing the activity of AHH in the liver. CYP2B1 activity, responsible for the metabolism of benzo[a]pyrene (BaP) to relatively nontoxic metabolites, was decreased in lung but not in liver by *m*-xylene exposure. However, the activity of CYP1A1, responsible for the metabolism of BaP to reactive/toxic products, was not altered in lung or liver. The CYP2B1/1A1 ratio, an indirect indicator of the pattern of BaP toxication/detoxication, was then decreased in the lungs by *m*-xylene exposure, suggesting increased toxication, and remained unchanged in the liver.

In mice, effects such as weakness, lethargy, short and shallow breathing, unsteadiness, tremors, and paresis were commonly observed shortly after acute dosing with toluene, but were not commonly evident 15–60 min postexposure (Crookes et al., 1993). Bushnell (1988) indicated that inhalation exposure of rats to *p*-xylene (1600 ppm, 4 h/d, for 1 or 5 d) increased efficiency of autoshaping for an operant task (light lever pressing force), but suppressed response rates in an automaintained reversal learning paradigm without affecting reversal rate.

Hearing loss, predominantly at high frequencies, was observed in rats following subacute inhalation exposure to xylene (composition was 10% *o*-, 80% *m*-, and 10% *p*-xylene). The effect was seen following exposure to 3.5 g/m^3 or above for 14 h/d, 7 d/wk for 6 wk, or to 6.4 g/m^3 for 8 h/d for 3 d (Pryor et al., 1987). Similarly, Crofton et al. (1994), exposing rats to 1800 ppm mixed xylenes 8 h/d for 5 d, reported increased thresholds for the midfrequency tones (e.g., 8 and 16 kHz), with exacerbation (to include 24 kHz) detected following combined exposure to xylenes and toluene.

Andersson et al. (1981, 1983) reported that subacute exposure of rats to a higher concentration (2000 ppm) xylene, *o*-xylene, *m*-xylene, *p*-xylene, and/or ethylbenzene produced discreet and specific increases in dopamine (DA) and noradrenaline (NA) levels and turnover in various parts of the hypothalamus and median eminence, consistent with reductions in secretion of prolactin, corticosterone, and thyroid-stimulating hormone. Interestingly, these authors reported that *o*-xylene, but not the *p*- or *m*-isoforms, resulted in reduced DA turnover in various portions of the forebrain. While these exposures induced significant modulations of neurotransmitter release and turnover 16–18 h postexposure, the changes were not correlated with observable changes in locomotor activity or other behaviors. Zibrowski et al. (1998) reported bursts of rhythmical fast waves (>1 mV, peak frequency approximately 16 Hz; mean

frequency approximately 20 Hz) elicited in the olfactory bulb and pyriform cortex in waking or urethane-anesthetized rats by olfactory stimulation with mixed xylene vapor. Similarly, Gralewicz et al. (1995) showed that rats exposed to *m*-xylene 6 h/d, 5 d/wk, for 3 mo exhibited significantly increased expression of spontaneous neocortical spike-and-wave discharges (SWDs), compared to controls, as long as 84 d postexposure. Such paroxysmal activity may be disruptive to attentional processes, feeding control, or normal sleep, and may reflect accelerated aging of the CNS.

Exposure of pregnant dam rats to xylene vapors 6 h/d, 5 d/wk throughout the gestational period disrupted prenatal and postnatal development (Mirkova et al., 1983). Studies by the National Toxicology Program (NTP/NIH, 1986a), however, reported no evidence of carcinogenicity in mice exposed repeatedly to toluene.

n-Hexane

Hexane is perhaps the most toxic of the alkanes, at least when administered by oral exposure; ingestion of very small quantities induces nausea, vertigo, and severe bronchial and intestinal irritation. It is believed that 50 g is a fatal dose in humans (Bingham et al., 2000). Current standards set maximum vapor exposure at 100 ppm for 8 h (8-h TLV) (O'Donoghue, 1985); however, there is some evidence that humans occupationally exposed to <100 ppm can exhibit cumulative toxicity in the PNS.

Hexane metabolites are cytotoxic to Schwann cells (Kamijima et al., 1996), reducing DNA synthesis in a concentration-dependent manner. Mice exposed to 2000 ppm hexane 24 h/d, 6 d/wk for 1 yr exhibited hind leg muscle degeneration; rats exposed to 10,000 ppm hexane for 6 h/d, 5 d/wk, for 13 wk exhibited decreased locomotor activity, consistent with decreased weight gain and nasal irritation (Dunnick et al., 1989). Additionally, *n*-hexane induces significant lung damage. Rabbits exposed to 3000 ppm 8 h/d, for 8 d, developed emphysema and scattered microhemorrhages (Lungarella et al., 1980); the same exposure 8 h/d, 5 d/wk for 24 wk led to pulmonary fibrosis and papillary tumors (Lungarella et al., 1984). When pregnant female rats were exposed to 1000 ppm, 6 h/d, for 9 d, the pups showed reduced postnatal growth (Bus et al., 1979). Rats given single oral doses of several hexane metabolites displayed thymic atrophy after 7 d; however, thymuses from rats given the metabolites for 7 d did not atrophy (Upreti et al., 1986).

A large cancer study using 800 male and female rats and mice was recently reported for *n*-hexane exposure (Daughtrey et al., 1999). Animals were exposed for 6 h/d, 5 d/wk for 2 yr to hexane concentrations up to 9000 ppm. There were no significant differences in mortality among rats or mice, as compared to controls. Rats displayed no differences in tumor incidence for either sex, at any concentration. Female mice, however, exhibited a decreased incidence of severe cystic endometrial hyperplasia, and an increase in hepatocellular adenomas and carcinomas, compared to males. No known published reports link leukemia or lymphoma to hexane exposure.

HEALTH EFFECTS OF EXPOSURE TO HYDROCARBON FUEL PERFORMANCE ADDITIVES

Electrical Conductivity/Static Dissipater (SDA) Additives

Stadis 450 is added to JP-8, JP-8+100, or Jet A-1 (allowed in Jet A, JP-5) at <3 mg/L fuel. Stadis 450 consists of 35–60% toluene, 5–20% solvent naphtha, <5% naphthalene, 1–10% dodecylbenzenesulfonic acid, <0.06% benzene, <5% isopropyl alcohol, 1–10% dinonylnaphthylsulfonic acid, and 1–10% proprietary chemical (MSDS Stadis 450, 2000a). There are no published animal or human studies of possible Stadis 450 toxicity, although the toxicity of several of the chemical constituents of the additive are discussed in other sections of this article.

Corrosion Inhibitor/Lubricity Additive

The corrosion inhibitor DCI-4A or Corrosion Inhibitor No. 4A (Octel Starreon LLC, Littleton, CO) (consistent with MIL-I-25017 or QPL-25017) is most commonly used (0.85–11 mg/L). DCI-4A consists of 20–30% xylene, 0–5% ethylbenzene, and 70–80% proprietary chemical. DCI-4A or one of 17 acceptable corrosion inhibitors/lubricity improvers are added to JP-8, JP-8+100, JP-5, or JP-4 (optional in Jet A-1). There are no published studies of human or animal toxicity from DCI-4A exposure (MSDS DCI-4A, 2001), although the health effects of xylenes and ethylbenzene are discussed in other sections of this article.

Icing Inhibitors (Fuel System Icing Inhibitors, or FSIIs)

FSIIs (0.08–0.20% volume/volume [v/v]), consistent with MIL-DTL-85470, CAN/CGSB-3.526, and ASTM D4171, most commonly used are diethylene glycol monomethyl ether (DiEGME) or the structural analog ethylene glycol monomethyl ether (EGME). Other icing inhibitor additives, used infrequently, include 100% 2–6-di-*tert*-butyl-4-methylphenol; 100% 2,4-dimethyl 6-*tert*-butyl 2,4-dimethylphenol; 100% 2,6-di-*tert*-butylphenol; and 75% minimum 2,6-di-*tert*-butylphenol: 25% maximum *tert*-butylphenols and tri-*tert*-butylphenols. Due to the possibility of interaction between FSIIs and the water layer in large fuel tanks, anti-icing additives are used minimally in Jet A or Jet A-1 assigned to large commercial aircraft. Generally DiEGME, with less potential for dermal absorption than EGME, is used for anti-icing applications in JP-8, JP-8+100, and JP-5, although EGME or combinations of EGME/DiEGME are still used at some U.S. military bases. It should be noted that, until recently, solutions containing high concentrations of EGME or DiEGME were commonly sprayed on the wings of military and commercial aircraft to remove icing, resulting in possible respiratory exposure of flightline personnel. EGME is a water-soluble solvent used in a variety of products including printing inks, textile dyes, leather finishes, and epoxy resin coatings. Because glycol ethers such as DiEGME or EGME, during deterioration, absorb oxygen content from fuels, they additionally function as biocides for aerobic microorganisms in the fuel.

Being among the most water-soluble constituents of jet fuels, high concentrations of DiEGME or EGME can be found at the interface between the fuel and water typically found in the bottoms of fuel storage tanks. For this reason, higher than specified concentrations of EGME or DiEGME are sometimes added to fuel formulations to counteract transportation-induced loss of anti-icing additives to the water layer. Thus, dermal exposure of fuel workers to the water layer, as may occur during routine maintenance of fuel storage tanks, would be expected to result in possible exposure to abnormally high levels of the anti-icing additives.

Being water soluble, EGME and DiEGME exhibit a highest capacity for systemic absorbance from dermal, oral, or pulmonary exposure. McDougal et al. (2000; McDougal & Robinson, 2002) reported that, of the 13 chemical components of JP-8 to penetrate a rat skin diffusion cell preparation in measurable quantities, DiEGME exhibited the highest rate (51.5 $\mu g/cm^2$ skin/h). Assuming the mean surface area of both hands of a man to be 840 cm^2 and the penetration in human skin to be 1/3 of the penetration of rat skin (McDougal et al., 2000), then the maximum systemic absorbance of DiEGME through the hands of a JP-8–exposed fuel worker would be predicted to be 51.5 $\mu g/cm^2/h \times 840\,cm^2 \times 0.33 = 140\,mg/h$, or 1.12 g/8-h shift. While it would be atypical for a fuel worker wearing chemically resistant gloves to experience long-term wetting of the hands with JP-8, it is not common for such personnel to experience saturation with JP-8 of large areas of their cotton uniforms or jumpsuits (Ritchie, Still et al., 2001).

A number of human studies reported the following observed effects in workers exposed chronically to EGME: reduced testis size, sperm count, and serum testosterone; reduced WBC count, mean corpuscular volume, and hemoglobin; reduced total T and T-helper cell counts (Johanson, 2000).

Yamano et al. (1993) evaluated the toxicity of DiEGME, reporting decreased relative weights of thymus and pituitary gland, WBC and RBC counts, hemoglobin concentrations, and hematocrit levels in rats administered doses up to 4 g/kg/d for 11 d. The authors further reported teratological deficits with lower dose exposure of rat dams. In a study of dermal toxicity, Hobson et al. (1986) exposed male guinea pigs to 1 g/kg/d EGME, 1 g/kg/d DiEGME, 200 mg/kg/d DiEGME, or 40 mg/kg/d DiEGME for 90 d. There was significantly reduced testes, spleen, and mean body weight in the EGME group compared to the DiEGME exposure groups and controls. Additionally, there was a significantly reduced spleen weight in the 1 g/kg/d and 200 mg/kg/d DiEGME exposure groups compared to controls. In all EGME-exposed animals, moderate to severe degeneration of the seminiferous tubules of the testes was noted, with complete loss of spermatogenic cells. There was a significant elevation in serum lactate dehydrogenase (LDH) activity, compared to controls, in the 1 g/kg/d EGME and DiEGME exposure groups. All EGME and DiEGME exposure groups were shown to exhibit significantly increased urinary calcium excretion levels. EGME-exposed animals exhibited significantly decreased RBC counts and increased mean cell volumes, consistent with a significant lymphopenia and neutrophilia relative to controls. Similar effects have been reported in mice, rats, and rabbits

exposed by oral gavage or inhalation to EGME at from 12 mg/kg/d to 1 g/kg/d (Nagano et al., 1979; Miller et al., 1981, 1983).

Antioxidants

Antioxidants interrupt a chain of chemical reactions in fuel, preventing the formation of peroxide, soluble gum, and insoluble particulate deposits on fuel-system components produced by oxidation. Fuels that have been hydrotreated to remove mercaptans often lose naturally occurring antioxidants, requiring addition of antioxidant additives. At least six different additive packages are used (17.2–24 mg/L), including butylated hydroxytoluene (BHT or 2,6-di-*tert*-butyl-4-methylphenol), 6-*tert*-butyl-4-methylphenol, or 2,4-dimethyl-6-*tert*-butylphenol (DTBP), or combinations of these lipid peroxidase inhibitors ([1] 75% BHT:25% 6-*tert*-butyl-4-methylphenol and/or DTBP; [2] 72% DTBP:28% BHT and/or 6-*tert*-butyl-4-methylphenol; [3] 55% DTBP:15% BHT:30% mixed methyl and dimethyl *tert*-butylphenols). One or more of these antioxidant additives, generally BHT, are added to JP-5, JP-8 + 100, or unleaded gasoline (allowed in Jet A, Jet A-1). BHT is additionally used in cosmetic and pharmaceutical prepar- ations, as well as in some foods, to prevent oxidative rancidity of fats and oils (added at 0.02–0.1%). BHT may additionally exhibit limited antiviral activity and anti-microbial properties, and may reduce the dermal oxidizing properties of certain kerosene-based jet fuels.

Metal Deactivators (MDAs)

Metal deactivator additives, or chelating agents, suppress the catalytic effect that some metals in fuels (particularly copper and zinc) induce on the surfaces of fuel systems and tanks. *N,N*-Disalycylidene-1,2-propanediamine (2–5.8 mg/L) is used for most applications. There is no available MSDS for *N,N*-disalycylidene-1,2-propanediamine and no published research on possible human or animal risk.

Detergent/Dispersant

As previously discussed, the Betz-Dearborn SPEC-AID 8Q462 (U.S. distribution) or Shell Oil Aviation (international distribution) Turboline FS10 (Aero-Shell 101) JP-8 + 100 thermal stability (TS) package includes a detergent/dispersant additive designed to minimize carbon or coke deposits, clean engine deposits, and serve as a high temperature fuel stabilizer. The MSDSs for Turboline FS100 or SPEC-AID 8Q462 (MSDS, Turboline FS1000, 2000b; MSDS, SPEC-AID 8Q462, 2000c) indicate that possible hazardous constituents of the product include heavy naphtha solvent (<129 ppm), naphthalene (6–10%), and two proprietary chemicals (unknown %).

Biocides

Biocides may be added, in special applications, to fuels at 100 ppm or directly to the water phase (water layer) to control colonization of bacteria and fungus. Presently, three commercial biocides are available for use in kerosene-based jet fuels, Biobor JF (MIL-S-53021A, Hammonds Fuel, Houston, TX) containing

2-2′-oxybis (4,4,6-trimethyl-1,3,2-dioxaborinane) and 2,2′-(1-methyltrimethylenedioxy)-bis-(4-methyl-1,3,3-dioxaborinane) in a petroleum naphtha solvent; Kathon FP 1.5 (Rohm and Hass, Jarrow, U.K.) containing 5-chloro-2-methyl-4-isolthiazolin-3-one and 2-methyl-4-isothiazolin-3-one in a propylene glycol solvent; and Kerocide D 1.5 (Organo Chimique, France), containing 5-chloro-2-methyl-4-isolthiazolin-3-one and 2-methyl-4-isothiazolin-3-one in a DiEGME solvent (personal communication, Navy Environmental Health Center, VA). There are no published studies on toxicity effects of exposure to the biocide products discussed.

Octane Enhancers

Octane enhancers are used only in unleaded gasoline, and never in kerosene-based jet fuels, to ensure a more complete combustion of fuel mixture and a reduction in hazardous emissions.

Ignition Controllers

Ignition controllers are used only in unleaded gasoline, and never in kerosene-based jet fuels, as an engine cylinder lubricant.

Table 1 summarizes the required and allowed use of performance additives in JP-5, JP-8, JP-8+100, Jet A, and Jet A-1, as well as in kerosene and JP-4 (for comparison purposes).

COMPONENTS OF COMBUSTION EXHAUST

In many cases, occupational exposure to neat, vaporized, or aerosolized kerosene-based jet fuel occurs concurrently with exposure to combustion exhaust from jet fuels, DF, and/or gasoline. Literally all personnel working at military bases with aircraft, on military aircraft carriers, or at commercial airports experience jet fuel exhaust on a daily basis. When working in fuel handling or aircraft maintenance occupations, concurrent exposure to raw fuel and fuel combustion exhaust is nearly unavoidable. Similarly, exposure of personnel living near military or commercial airports includes low levels of both raw fuel (vapor/aerosol) and combustion exhaust. A recent investigation of exhaust from military aircraft ground support equipment using JP-8, DF, or gasoline indicated particulate mass concentrations from 0.09–1.1 g/kg fuel, and emphasized that particle size distribution varied as a function of engine condition and engine load (Kelly et al., 2003). The following chemical components of kerosene-based jet fuel combustion exhaust have been identified:

1. Inorganic gases. CO, CO_2, NO_x, SO_x, formed from the reaction of nitrogen in the air, or carbon or sulfur in jet fuel with atmospheric oxygen during fuel combustion.
2. Volatile organic compounds (VOCs). Alkanes, cycloalkanes, alkenes, and aromatic hydrocarbons (including pentane, butane, 1,3-butadiene, benzene, toluene, ethylbenzenes, xylenes) derived from incomplete combustion of fuels.
3. Raw fuel. Up to 30% aerosolized uncombusted fuel, as a function of engine type, engine mechanical condition, and environmental temperatures.

TABLE 1. Performance Additives in Kerosene-Based Jet Fuels, JP-4, Unleaded Gasoline, and Kerosene

	JP-8	JP-8 + 100	JP-5	Jet A	Jet A-1	JP-4	Unleaded gasoline	Kerosene
Carbon range	C_6–C_{18}	C_6–C_{18}	C_8–C_{17}	C_6–C_{18}	C_6–C_{18}	C_5–C_{14}	C_4–C_{12}	C_6–C_{18+}
Specification	MIL-T-83133		MIL-T-5624	ASTM D 1655		MIL-T-5624	ASTM D4814	
Dates of fuel use	1991–Present	Ongoing transition	1951–Present	1972 + –Present	1972 + –Present	1951–1996	Ongoing	Ongoing
Performance additives:								
1. Electrical conductivity/static dissipater	Required	Required	Allowed	Allowed	Required	Required	Not used	Not used
2. Corrosion inhibitor/ lubricity improver	Required	Required	Required	Not used	Allowed	Required	Required[b]	Not used
3. Icing inhibitor	Required	Required	Required	Allowed[a]	Allowed[a]	Required	Required[b]	Not used
4. Antioxidant	Allowed	Required	Required	Allowed	Allowed	Allowed	Required[b]	Not used
5. Metal deactivator	Allowed	Required	Allowed	Allowed	Allowed	Allowed	Required[b]	Not used
6. Detergent/ dispersant	Not used	Required	Not used	Not used	Not used	Not used	Required[b]	Not used
7. Biocide	Not used	Not used	Not used	Allowed	Allowed	Not used	Not used	Not used

TABLE 1. Performance Additives in Kerosene-Based Jet Fuels, JP-4, Unleaded Gasoline, and Kerosene (*Continued*)

	JP-8	JP-8 + 100	JP-5	Jet A	Jet A-1	JP-4	Unleaded gasoline	Kerosene
8. Octane enhancer	Not used	Not used	Not used	Not used	Not used	Not used	Required[b]	Not used
9. Ignition controller	Not used	Not used	Not used	Not used	Not used	Not used	Required[b]	Not used

Note. Table adapted from the Naval Health Research Center (NHEC) Kerosene-Based Fuels Comparison Chart:

1. Static dissipater = Stadis 450 (50–60% toluene, <1% benzene, 5–10% heavy aromatic naphtha, <5% isopropyl alcohol, 1–10% dodecylbenzenesulfonic acid, 1–20% proprietary chemicals).
2. Corrosion inhibitor/lubricity improver = DCI-4A (20–30% xylenes; 0–5% ethylbenzene; 70–80% proprietary [organic acids] chemicals).
3. Icing inhibitors = diethylene glycol monomethyl ether (DiEGME); or 100% 2-6-di-*tert*-butyl-4-methylphenol; 100% 2,4-dimethyl, 6-*tert*-butyl-2,4-dimethylphenol; 100% 2,6-di-*tert*-butylphenol; 75% minimum 2,6-di-*tert*-butylphenol:25% maximum *tert*-butylphenols and tri-*tert*-butylphenols.
4. Antioxidants = *N,N*-di-*sec*-butyl-*p*-phenylenediamine; 2,6-di-*tert*-butyl-4-methylphenol; 2,6-di-*tert*-butylphenol; 75% minimum 2,6-di-*tert*-butylphenol:25% maximum *tert*-butylphenols and tri-*tert*-butylphenols; 72% minimum 2,4-dimethyl-6-*tert*-butylphenol:28% maximum *tert*-butyl methylphenols and *tert*-butyldimethylphenols; 55% mimimum 2,4-dimethyl-6-*tert*-butylphenol:15% minimum 2-6-di-*tert*-butyl-4-methylphenol:30% maximum mixed methyl and dimethyl-*tert*-butylphenols.
5. Metal deactivator = *N,N*-disalycylidene-1,2-propanediamine.
6. Detergent/dispersant = numerous available formulations.

[a] Generally added to fuel for smaller commercial aircraft.

[b] Unleaded gasoline (MOGAS) for comparison:

Corrosion inhibitor/lubricity improver: one or more of: organic acids; phosphoric acids; sulfonic acids.

Icing inhibitor: isopropyl alcohol.

Antioxidants: one or more of: *N,N*-dialkylphenylenediamines; 2,6-dialykylphenols, 2,4,6-trialkylphenols; butylated methyl phenols; butylated dimethyl phenols; triethylene tetramine di(monononylphenolate).

Metal deactivators: one of more of the following: *N,N*-disalicylidene-1,2-ethanediamine; *N,N*-disalicylidene-propanediamine; *N,N*-disalicylidene-cyclohexanediamine; disalicylidene-*N*-methyl dipropylene triamine.

Octane enhancer: one or more of: methyl *t*-butyl ether (MTBE); *t*-butyl alcohol; ethanol; methanol.

Ignition controller: tri-*o*-cresylphosphate.

Detergent/dispersant: one or more of the following: alkylamine phosphates; poly-isobutene amines; long-chain alkyl phenols; long-chain carboxylic acids; long-chain amines.

4. Oxygenated organics. Carbonyl compounds, including formaldehyde, acetaldehyde, crotonaldehyde, acrolein, and benzaldehyde.
5. Polycyclic aromatic hydrocarbons (PAHs). Including anthracene, phenanthrene, fluoranthene, pyrene, chrysene, benzo[b,k]fluoranthene, cyclopental[c,d]pyrene, benzo[e]pyrene, benzo[a]pyrene, benzo[a]anthracene, indo[1,2,3-c,d]pyrene, benzo[g,h,i]perylene, perylene, coronene, and chrysene.
6. Alcohols. Including methanol and ethanol.
7. Ozone. Formed by the interaction of VOCs, NO_x, and sunlight.
8. Particulate matter. Elemental carbon, sulfate, and nitrate aerosols, both PM10 (particulate matter, diameter 10 μm) and microfine particles, PM2.5. Even exposure to combustion exhaust from common in-home kerosene heaters can emit CO, NO_2, SO_2, formaldehyde, and particulates; PAHs; nitrated PAHs; alkyl benzenes; pentachlorphenol; phthalates; hydronaph-thalenes; aliphatic hydrocarbons, alcohols, and ketones; and other organic compounds, some of which are known mutagens (Traynor et al., 1990; Cheng, 1998).

Exposure to high levels of combustion exhaust is not limited to military or commercial environments. It was shown, for example, that home kerosene heaters can emit CO, NO_2, SO_2, formaldehyde, and particulates; PAHs; nitrated PAHs; alkyl benzenes; pentachlorphenol; phthalates; hydronaphthalenes; aliphatic hydrocarbons, alcohols, and ketones; and other organic compounds with neurotoxic potential (Traynor et al., 1990; Cheng, 1998).

HEALTH EFFECTS FROM EXPOSURE TO SELECTED FUEL COMBUSTION EXHAUST COMPONENTS

Carbon Monoxide

CO is a colorless, odorless gas that is released from the combustion of many materials (NLM, 1996), including JP-8. CO levels present in JP-8 exhaust of J79 jet engines at idle power (at 50 m behind the engines) was found to be 25 ppm in July (summer) and 30 ppm in February (cold start-up) (Kobayashi & Kikukawa, 2000). Reported CO concentration levels in the exhaust of various JP-8–fueled, idling U.S. aircraft engines range from 85–758.2 ppm (AFAPL, 1976; van Schaack, 1994). CO is, of course, toxicologically important because it competes with O_2 for hemoglobin binding, resulting in the formation of carboxyhemoglobin. Hemoglobin CO saturation levels of 50–80% are associated with unconsciousness and death. Signs and symptoms of CO hemoglobin saturation approaching dangerous levels (20–30%) include headache, weakness, nausea, and dimness of vision (MNL, 1996). The effects of CO poisoning are cumulative in individuals with repeat intoxication episodes, such as traffic police and garage workers (Smith, 1986) and are exacerbated by a number of factors including the smoking of tobacco products. As CO dissociates from hemoglobin relatively rapidly (half life: 5–6 h), chronic CO poisoning may not be readily apparent at clinical presentation. Chronic exposure to low levels of CO produces

medical symptoms associated with many other disease states, including chronic fatigue, headache, dizziness, nausea, and mental confusion, and is often mistaken for other illnesses (Knobeloch & Jackson, 1999). CNS neurons are particularly sensitive to the toxic effects of prolonged hypoxia produced by CO exposure (Gordon & Amdur, 1991). Exposure to CO may also damage the vasculature system (Thomsen & Kjeldsen, 1975) and was shown to accelerate arteriosclerosis genesis in animals fed high-fat diets (Hanig & Herman, 1991).

Oxides of Sulfur

SO_x (SO, SO_2, SO_3) is produced during the combustion of JP-8 (Yost & Montalvo, 1995). Both the sulfur content of the fuel lot and the choice of performance additives, as well as a number of environmental conditions, may influence the SO_x content in the combustion exhaust. Exposure to airborne SO_x is associated with respiratory irritation and other respiratory effects (NML, 1998a). Exposure to 5 ppm SO_2 is associated with dryness of the nose and throat and an increase in resistance to bronchial air flow; 6–8 ppm SO_2 produces a decrease in tidal respiratory volume; 10 ppm is associated with sneezing, cough, and irritation; 20 ppm is associated with bronchospasm; 50 ppm causes extreme discomfort, but no injury after exposures of <30 min (Thienes & Haley, 1972; NML, 1998a). Chronic occupational exposure to SO_X was associated with various health conditions including alteration of smell and taste, increased fatigue, neurotic and vegeto-asthenic nervous system disorders, chronic bronchitis, and pulmonary emphysema (ILO, 1983; Duffell, 1985; Stjernberg et al., 1986). Smelter workers occupationally exposed to SO_2 at an average of 1 ppm experienced accelerated loss of pulmonary function; chronic exposure to 2 ppm was associated with pulmonary disease (Ferris et al., 1979). The most recent evaluation of SO_2 by IARC (1992) concluded there is limited evidence for the carcinogenicity of SO_2 in experimental animals, but inadequate evidence for the carcinogenicity of SO_2 in humans (not classifiable as to its carcinogenicity to humans, Group 3).

Oxides of Nitrogen

NO_x (NO and NO_2) are produced from the burning of coal, oil, and petroleum-containing fuels and may be produced during the partial or complete combustion of JP-8 (Miyamoto, 1986; Kobayashi & Kikukawa, 2000). Concentrations of NO_x and NO_2 present in JP-8 exhaust at 50 m behind J79 jet engines at idle power were measured at 0.5–1 ppm (Kobayashi & Kikukawa, 2000) and 0.7 ppm, respectively (Miyamoto, 1986). Exhaust from a J85-5 engine fueled with JP-8 produced between 1.07 and 3.05 ppm NO_x when measured directly behind the exhaust outlet (AFAPL, 1976). NO and NO_2 are primarily respiratory and eye irritants with a reported threshold of 10–20 ppm (Sharp, 1978). Chronic exposure to low concentration of NO was reported to induce chronic irritation of the respiratory tract, cough, headache, loss of appetite, dyspepsia, and corrosion of the teeth (NML, 1998b, 1998c). Chronic inhalation of NO (0.5 ppm) by rabbits was shown to produce an emphysemalike destruction of the alveolar

septa; however, the long-term effects of NO inhalation in humans remains conjectural (Prows & Leikauf, 2001). Inhalation of NO_2 has found to produce effects on host defenses against infectious pulmonary disease, lung metabolism, biochemistry, function, and structure (NML, 1998c), and chronic exposure to NO_2 may be associated with chronic obstructive pulmonary disease (COPD) (Prows & Leikauf, 2001). However, Prows and Leikauf (2001) also note that many of the studies presented as supporting this hypothesis are from populations with simultaneous inhalation exposures to complex mixtures including NO_2. The 8-h TWAs for NO and NO_2 are 25 ppm and 3 ppm, respectively (ACGIH, 1999).

Formaldehyde

Formaldehyde can be formed by the incomplete combustion of kerosene-based jet fuels and was detected in the exhaust of military aircraft at concentrations of 0.86–2.78 ppm (50 m behind the aircraft), as a function of the power setting of the engine, ambient temperature, and relative humidity (Kobayashi & Kikukawa, 2000). Concentrations of formaldehyde from the exhaust of jet engines from F16 aircraft (F110 engines powered with JP-8) were determined to be 0.10–9.42 ppm, depending on the throttle setting of idle, 30% or 60% power, or if afterburners were engaged (van Schaack, 1994). Concentrations of formaldehyde in the exhaust from KC135 aircraft (CFM-56 engines) was found to be 13.3 ppm when at idle (van Schaack, 1994). Formaldehyde is a concentration-dependent irritant of the eyes and mucous membranes at low level exposures (Horvath et al., 1988). Inhalation of formaldehyde is associated with rhinitis, anosmia, laryngospasm, tracheitis, and gastroenteritis (NLM, 1999). Similarly, occupational exposure to JP-8 exhaust was shown to irritate the eyes and respiratory tract (Miyamoto, 1986; Kobayashi & Kikukawa, 2000). Dermal exposure to formaldehyde was found to produce allergic skin reactions; repeat dermal exposure was found to produce eczematoid dermatitis in sensitive individuals (Wyatt et al., 2001). Formaldehyde is classified as being probably carcinogenic to humans (Group 2A) (IARC, 1995) and as a probable human carcinogen (B1) by the U.S. EPA (IRIS, 1989). Both IARC and the U.S. EPA base their carcinogenic assessments for formaldehyde on limited evidence for carcinogenicity in humans and sufficient evidence in animals. Average air concentration levels of formaldehyde corresponding to cancer risks of 10^{-5} or 10^{-6} have been set at 0.08 and 0.8 $\mu g/m^3$, respectively (IRIS, 1989). An oral reference dose (Rfd) for formaldehyde of 0.2 mg/kg/d was set by the U.S. EPA (IRIS, 1989). The U.S. EPA has not, however, set an inhalation reference concentration (Rfc) for formaldehyde (IRIS, 1989). The Occupational Safety and Health Administration (OSHA) has set the 8-h TWA and 15-min STEL for occupational exposure to formaldehyde of 0.75 and 2 ppm, respectively (OSHA, 1998). The ACGIH has set a ceiling limit for formaldehyde of 0.3 ppm in the workplace (ACGIH, 1999).

Elemental Carbon

Complete or partial combustion of kerosene-based jet fuels was shown to generate elemental carbon (carbon black). Pirkle (2000) measured the 8-h

TWA for elemental carbon from C-130 aircraft engines, reporting ranges between <0.001 to $0.014\,mg/m^3$ for ground crews involved in various maintenance and operation activities. Exposure to elemental carbon was found to produce conjunctivitis, epithelial hyperplasia of the cornea, and eczematous inflammation of the eyelids (Sax, 1984). Inhalation of elemental carbon is associated with increased mucociliary transport and airway resistance (Friberg et al., 1979). Perhaps the major human risk for repeated exposure to elemental carbon is the possible development of aerosols, in which respirable carbon particles combine with and transport other fuel constituents with toxicity potential to the lung. The possible critical importance on health consequences of aerosol phase exposure to kerosene-based jet fuels is discussed in subsequent sections of this report.

MICROBIAL CONTAMINATION OF FUEL

Jet fuel may be delivered to military base or commercial airport destinations by truck, train, ship, or underground metal pipeline (up to hundreds of miles) and is generally stored in above- or below-ground metal tanks containing many thousands of gallons. Due to atmospheric water condensation during transportation or storage, and/or seepage of groundwater into below-ground tanks, there is commonly a significant water layer formed at the bottom of fuel storage tanks (Chevron, 1997). In U.S. Navy ships carrying JP-5, jet fuel tanks may additionally be utilized for ballast control, requiring partial filling with, and emptying of, sea water, resulting in abundant interfacing of fuel and saltwater. In each case, there is minimal water solubility of the jet fuel, as well as a direct interface between the tank water layer and fuel. Yang et al. (1992) determined the water solubility of JP-5, for example, to be proportional to the reciprocal of absolute temperature from 0–60 °C, such that water in fuel oil would become increasingly condensed when the temperature was shifted from a high to a low temperature. Typically, water-saturated, kerosene-based jet fuel contains 40–80 ppm water at 70 °F (Chevron, 1999). Additionally, due to surfactant properties of naturally occurring chemical components, contaminants, and specific performance additives (i.e., TS package) of jet fuels, there is the possibility (as a function of fuel temperature) for varying presence of suspended free water droplets (Chevron, 1999).

Edmonds and Cooney (1967) were among the first researchers to identify microbial contamination of hydrocarbon fuels. Bacteria and fungi (yeasts and molds) are known to colonize hydrocarbon fuels such as JP-8 or Jet A/A-1 (Ferrari et al., 1998). Such contaminants can contribute to fuel filter plugging, corrosion of internal tank surfaces, reduction of fuel pH, and development of additional surfactants, increasing the content of suspended water droplets in fuel. Bacterial colonies in enclosed fuel storage tanks, aircraft/vehicle tanks, and contaminated groundwater can be anaerobic or aerobic, as neat fuel may contain as much as 300 ppm oxygen. Long-term storage of fuels may allow conditions to become sufficiently anaerobic for growth of sulfide-generating

anaerobes. Water and trace metals, as commonly occur in metal pipelines, fuel tanks, and as fuel contaminants are required factors for microbial colonization of fuels (Ferrari et al., 1998). Bacteria have been identified in hydrocarbon fuels that (using iron[III], nitrate, or sulfate as electron acceptors) anaerobically degrade fuel constituents including toluene, *m*-xylene, benzene, naphthalene, and ethylbenzene (Spormann & Widdel, 2000). The capacity for anaerobic utilization of alkylbenzenes was observed in members of the alpha, beta, gamma, and delta subclasses of *Proteobacteria*. Furthermore, denitrifying bacteria and sulfate-reducing bacteria with the capacity for anaerobic alkane degradation have been isolated that are members of the beta and delta subclass, respectively. For example, toluene is activated in anaerobic denitrifying bacteria by addition of fumarate to yield benzylsuccinate, which is then further metabolized via benzoyl-CoA. For a further example, ethylbenzene, in anaerobic denitrifying bacteria, is dehydrogenated to 1-phenylethanol and further to acetophenone (Spormann & Widdel, 2000). There has, however, been minimal investigation of possible fuel contamination with metabolic by-products of microbial degradation of fuel components.

Organisms colonizing hydrocarbon fuels congregate at the fuel/water interface of tank bottoms, where they grow as a consortium that may include as many as 55 separate microbial species (Zwolinski et al., 2000). This consortium is usually bound together within a complex biofilm consisting of residual biomass from dead organisms, as well as compounds secreted by viable organisms. Yang et al. (1992) determined that spores of microbes could survive in fuel when water content ranged from 5 to 80 ppm, but that higher water content was not conducive to spore survival. *Cladosporium resinae* was reported to survive as long as 3 yr in sealed jars of "dry" fuel, then to proliferate rapidly with the addition of small amounts of water. Myers (1984) found that three strains of *Staphylococcus aureus* and one strain each *of Pseudomonas aeruginosa, Bacillus subtilis*, and *Clostridium sporogenes* remained viable for over 2 yr in crude oil samples, with the degree of survival being inversely proportional to the aromatics content of the sample.

Hydrocarbon constituents in petroleum-contaminated environments, including groundwater and soil, may similarly support bacterial and fungal colonization. In a study of soil contaminated with oily cuttings from an offshore drilling project, bacteria of the genera *Pseudomonas, Brevundimonas sphingomonas, Acinetobacter, Rhodococcus, Arthrobacter*, and *Corynebacterium* and fungi belonging to *Aspergillus, Penicillium, Beauveria, Acremonium, Cladosporium, Fusarium*, and *Trichoderma* were identified (Chaineau et al., 1999). In an evaluation of 350 samples of commercial Jet A-1, Ferrari et al. (1998) reported that 85% of samples contained fungus ≤ 100 colony-forming units (cfu)/L (range <1–2000 cfu/L). The predominant fungi were *Cladosporium resinae* and *Aspergillus fumigatus*, although *Mucor, Penicillium, Achromonium*, and *Cephalosporium* were also identified. The aerobic heterotrophic microorganisms found in water samples at the bottom of tanks were mostly bacteria, with counts varying from 100 to 8.8×10^7 cfu/ml, with 85% of samples

containing 10^4–10^7 cfu/ml. There was a preponderance of *Pseudomonas*, although bacterial contaminants belonging to the genus *Flavobacterium, Aeromonas, Serratia, Actomomycetes, Vibrio*, and *Bacillus* were also identified. Sulfate-reducing bacteria (i.e., *Desulfovibrio* and *Desulphotomaculum*) were detected in 80% of water samples.

The identity of possible microbial contaminants of jet fuel during storage has not been determined. However, based on the identity of organisms known to colonize fuels, residual biomass in tank bottoms could include bacterial lipopolysaccharide (LPS) or endotoxin from gram-negative bacteria and mycotoxins and $\beta(1\rightarrow 3)$-glucans from fungi. Airborne endotoxin or LPS is a documented inhalation hazard in workplaces, at least where bacteria are known to colonize oil-based metal-machining fluids due to the heat stability of endotoxin (Mattsby-Baltzer et al., 1989). Fungal mycotoxins may induce powerful and heterogeneous biological effects, including carcinogenic, mutagenic, teratogenic, estrogenic, hemorrhagic, immunotoxic, nephrotoxic, hepatotoxic, dermotoxic, and neurotoxic consequences in animals (Steyn, 1995), and specific human disorders including alimentary toxic aleukia, aflatoxicosis, and esophageal cancer (Pohland, 1993).

Residual biomass in jet fuels stored in metal tanks (including aircraft and vehicle fuel tanks) could become airborne through aerosolization from leakage, spillage, or high-altitude fuel jettisoning, or through partial combustion of fuels by aircraft and vehicles. Additionally, exposure to fuel-contaminated groundwater or soil could result in exposure to colonizing bacteria or fungi. While there is no published evidence of human risk from exposure to microbial contamination of kerosene-based jet fuel, there is little or no scientific investigation of this possibility.

At least three biocide additives have been approved for use in Jet A or Jet A-1 and can be added to either the fuel or to the water phase only. Additionally, there is limited evidence that specific performance additives in kerosene-based jet fuels may either reduce fuel contamination through antimicrobial actions or increase possible contamination by increasing the water content of stored fuels. The anti-icing additives DiEGME or EGME, being hydrophilic, sequester in or near the water layer within storage tanks in very high concentrations and, through reduction of free oxygen, may reduce aerobic microbial colonization, but possibly increase colonization of anaerobic species. If DiEGME or EGME are added to storage tanks containing a significant water layer, a reaction with the additive may result in formation of a thick, gelatinous interface layer. Human dermal exposure to this interface layer, as can occur during routine tank cleaning and maintenance operations, could result in exposure to DiEGME and/or EGME in high concentrations, as well as to microbial colonies. The JP-8+100 additive package, on the other hand, may increase the water content of fuel in aircraft tanks, and thus the potential for microbial colonization relative to the JP-8 formulation through surfactantlike actions may reduce the efficiency of water removing filter systems (personal communication, Stonecipher).

KEROSENE-BASED JET-FUEL-INDUCED DEATHS

There are no published reports of human death associated with a single kerosene-based jet-fuel exposure (Selden & Ahlborg, 1986, 1987, 1991; ATSDR, 1998d; McDougal et al., 2000), except as may occur from explosion or fire. The September 2001 World Trade Center and U.S. Pentagon attacks with hijacked commercial aircraft demonstrated the explosive combustion potential of at least the Jet A jet fuel formulation. Air sampling near the World Trade Center indicated significant levels of unburned and partially burned jet fuel, as well as PAHs and other chemical constituents of Jet A in the atmosphere for several days following the attack (Lioy et al., 2002).

Animal deaths following repeated JP-8, JP-5, or kerosene exposure and human or animal deaths from a single oral kerosene exposure have been documented. Parker et al. (1981) reported the deaths of two rats within 48 h following an acute exposure to 47 g/kg JP-5 by oral gavage. Vernot et al. (1990a) reported no deaths in rats exposed by oral gavage to 25 ml/kg neat Jet A.

Mattie et al. (1991), exposing male and female rats and male mice by whole-body inhalation to JP-8 vapor (0, 500, or 1000 mg/m^3) continuously for 90 d, reported a significantly increased mortality in exposed male rats (up to 9 mo postexposure) versus exposed female rats or control males. Mattie et al. (1991) hypothesized that necrotizing dermatitis associated with fighting among males or a "male rodent-specific" renal disorder (Alden, 1986) associated with the exposures may have accounted for the increased mortality observed. Similarly, Ritchie, Rossi et al. (2001) reported the death of 2 of 32 male rats (6.25%) exposed for 6 h/d, 5 d/wk for 10 wk to 500 or 1000 mg/m^3 JP-8 vapor. At necropsy, both subjects exhibited abnormality of the kidneys, while one rat additionally exhibited pulmonary edema and hemorrhage. There was no direct lethality in male F-344 rats exposed to JP-8 in vapor/aerosol form during exposures to 520 mg/m^3 for 1 h/d for 7 d, or to 495 mg/m^3 for 1 h/d for 28 d (Pfaff et al., 1995). Similarly, no rats exposed by whole-body inhalation for 4 h to 3.7 g/m^3 JP-8 or JP-8+100 died (AFAL, 1996). The acute oral LD_{50} for Jet A is >20 g/kg, while for JP-5 the oral LD_{50} is >60 g/kg (Koschier, 1999).

Death in mice occurred after daily dermal administration of 30–40 g/kg JP-5 for 14 d, but not after daily administration of 5–20 g/kg (NTP/NIH, 1986b). Vernot et al. (1990a) reported no deaths in rabbits exposed dermally to 5 ml/kg Jet A. Exposure of mice or rats to 150 or 750 mg/m^3 JP-5 vapor continuously for 90 d resulted in no deaths (Air Force, 1985; Cowan & Jenkins, 1981; Gaworski et al., 1984).

Carpenter et al. (1976), exposing rats to deodorized kerosene vapor (up to 100 mg/m^3 for 6 h/d, 5 d/wk), reported 2 deaths among 10 male rats (20% mortality) exposed for 3, 8, or 13 wk. Both deaths were attributed to bronchopneumonia and severe lung hemorrhage. Vernot et al. (1990b) reported no deaths in rats exposed by whole-body inhalation to 5 g/m^3 kerosene for 4 h. Oral gavage of rats with 5 g/kg kerosene or dermal application of 2 g/kg kerosene to rabbits resulted in no deaths (Vernot et al., 1990b). The oral LD_{50}

in rats for kerosene was estimated at >2 g/kg (Koschier, 1999). Recently, Aslani et al. (2000) orally exposed groups of 6 goats each to 10, 20, or 40 ml/kg kerosene, respectively. While no goats exposed to 10 or 20 ml/kg died, all goats exposed to 40 ml/kg kerosene had severe signs of poisoning and died within 4 h to 11 d after dosing. Clinical signs in these goats included severe bloating, frequent coughing, vomiting, expelling of kerosene from the mouth and nose, star-gazing, depression, recumbence, and dyspnea. Postmortem changes were gangrenous pneumonia, pleuropneumonia, congestion in brain and kidney, perivascular and perineuronal edema in brain tissue, and renal nephrosis.

A number of human deaths have been reported from kerosene exposure (Majeed et al., 1981; Pearn et al., 1984; Gupta et al., 1992; Lucas, 1994; Singh et al., 1995; Dutta et al., 1998; Segev et al., 1999; Thomas et al., 2000). In general, these deaths were reported in countries in which kerosene is commonly used for home heating, cooking, and illumination, and occurred most commonly in children accidentally ingesting the fuel. In the majority of cases, oral ingestion of kerosene resulted in respiratory symptoms, ranging from pulmonary irritancy, to pneumonitis, to neutrophilic alveolitis with the presence of lipid-laden macrophages, or evidence of lipoid pneumonia in severe cases. As a common home remedy to kerosene ingestion is self-induced emesis, the reported effects often resulted from lung aspiration with kerosene occurring during the emetic response (Lucas, 1994).

BODY WEIGHT EFFECTS

There are no published human studies of changes in body weight as a function of occupational exposure to kerosene-based jet fuels. A number of animal studies have, however, indicated at least transient changes in body weight parameters as a function of kerosene-based fuel exposures. The AFIERA study (2001) of JP-8 exposed military personnel indicated a difference in body weight between "high-dose" and "low-dose" occupational exposure for males (but not females), with a mean body weight of 178 lb recorded for the high-dose group versus 186.7 lb for the low-dose group. It must be remembered that comparison with preexposure body weights was not conducted.

Rossi et al. (2001) and Ritchie, Rossi et al. (2001) reported numerically reduced, but not significantly different, mean body weights during exposure (6 h/d, 5 d/wk, for 6 wk) to 500 or 1000 mg/m^3 JP-8 vapor or 1200 mg/m^3 JP-5 vapor, as compared to room air control. In each case, mean body weights for fuel-exposed and control were nearly identical 7–14 d postexposure. Similarly, there was no significant change in body weight gain in male or female mice or female rats following 90-d continuous exposure to 750 mg/m^3 JP-5 vapor (Gaworski et al., 1984; Air Force, 1985). Male rats exposed continuously for 90 d to JP-8 vapor (500 or 1000 mg/m^3) showed reduced mean body weights during the exposure and throughout the postexposure period (Mattie et al., 1991). It should be noted that a number of the male rats in this study exhibited "male-rat-only" nephropathy, possibly contributing to the effect observed.

Similarly, the growth rate of male rats exposed to 150 or 750 mg/m^3 JP-5 vapor/aerosol was significantly retarded, while no effects were observed in similarly exposed beagle dogs (Air Force, 1978). Female rats in the same study exhibited normal mean body weights and rates of body weight increase. Similarly, male rats dosed with neat JP-8 (0, 750, 1500, or 3 g/kg) daily by gavage for 90 d exhibited a significant and dose-related weight loss relative to vehicle controls (Mattie et al., 1995). It should be considered that some of the subjects in this study exhibited gastrointestinal and perianal irritancy, possibly contributing to the body weight effects observed. Finally, no change in mean body weights was observed in rats exposed (6 h/d, 5 d/wk, for 13 wk) to 100 mg/m^3 deodorized kerosene vapor (Carpenter et al., 1976).

In summary, effects on mean body weight and rate of weight gain in laboratory animals exposed to kerosene-based jet fuels appear to be related to animal species, gender, fuel type, route of delivery, and induction of deficits in specific organic systems influencing food ingestion or metabolic processes.

Zibrowski et al. (1998) has advanced an interesting theory to explain temporary weight loss during some hydrocarbon fuel exposure. The authors recorded the induction of 20-Hz fast waves in the rhinencephalon, pyriform cortex, or hippocampal dentate gyrus of rats during exposure to *n*-heptane, toluene, or kerosene. These waves, similar to those observed in prey animals in the presence of predator odors, were consistent with suppressed feeding.

EFFECTS OF SINGLE-DOSE, ACUTE EXPOSURE

The major occupational safety concerns with acute kerosene-based jet fuel exposure involve possible sensory or respiratory system irritancy, motor system incapacitation, or cognitive deficits sufficient to impair occupational performance. Acute exposures to high concentrations of kerosene-based jet fuels may occur infrequently during fuel spills or equipment failures, or more routinely during certain aircraft maintenance operations (i.e., removal of foam from military aircraft fuel tanks). Possible acute performance consequences of concern from such exposures might include, for example, disequilibrium and falling from aircraft wings or disorientation of avionics personnel. Possible chronic health effects of concern might include, for example, ocular, pulmonary, or dermal consequences more severe than acute irritation.

There is only one published study of acute effects in humans from exposure to any kerosene-based jet fuel formulation. The following symptoms are summarized from a study (Porter, 1990) in which two Navy aviators exposed for <1 h to an unknown "high level" of jet fuel vapor/aerosol due to in-flight leakage into the aircraft cabin: burning eyes (hyperemic conjunctiva); nausea/vomiting; incoordination/impairment of eye-hand coordination; anorexia; euphoria and laughing; fatigue; mild hypertension; apparent intoxication; and memory impairment (i.e., recalling emergency procedures, flight plan information, and personal information). While several of these effects persisted for up

to 96 h postexposure, none was present after that time point. A similar report of high concentration JP-4 (unleaded gasoline:kerosene) exposure of military aircraft personnel indicated similar acute symptomology (Davies, 1964). Acute ingestion of kerosene in humans, as was previously described, commonly results in severe pulmonary system health consequences, from irritancy to lipoid pneumonia and can include CNS consequences.

To date, there have been only a small number of published studies exploring possible health effects in animals from single-dose, acute exposure to JP-8, excepting those previously discussed specifically exploring lethal dose (LD_{50}) parameters. Kinkead et al. (1992a) reported JP-8 ocular exposure (0.1 ml/eye) of female rabbits for 2 min to be nonirritating. Similarly, dermal exposure of female rabbits to 0.5 ml JP-8 for 24 h was found to be only mildly irritating (mild erythma). Finally, dermal sensitization testing of male guinea pigs indicated a sensitization response in 10% of animals (weak sensitizing potential). AFAL (1996) exposed male or female rats orally to 5 mg/kg JP-8 or JP-8+100 (Mobil or Betz-Dearborn additive packages), male rabbits dermally to 0.5 ml/kg JP-8 or JP-8+100, male guinea pigs to 0.1 ml (sensitization) JP-8 or JP-8+100 for 10 d, and male and female rats by whole body inhalation to 3.7 g/m^3 JP-8 or JP-8+100 vapor for 4 h. With oral exposures, there were no deaths or persisting signs of toxicity observed, although postexposure lethargy, shallow breathing, and minor weight loss were commonly observed. In rabbits, 4-h dermal exposure with JP-8 resulted in slight erythema, although animals exposed to JP-8+100 were generally normal. Guinea pigs exposed to 0.1 ml JP-8 or JP-8+100 for 10 d exhibited no significant dermal sensitization response when challenged with the same dose 14 d postexposure. Rats exposed by whole-body inhalation for 4 h to 3.7 g/m^3 JP-8 or JP-8+100 (Mobil additive package) vapor exhibited eye and upper respiratory irritation. All exposed animals survived for 14 d postexposure with no obvious lesions. Rats exposed to JP-8+100 (Betz-Dearborn) vapor exhibited significantly greater mean body weight, from 10–14 d postexposure than animals exposed to JP-8+100 (Mobil). Finally, Vernot et al. (1990a) reported minimal mild skin irritation potential in rabbits exposed dermally to 5 ml/kg neat Jet A. Casaco et al. (1982) reported that inhalation exposure of rabbits to 32.3 g/m^3 kerosene aerosol for 4–9 min resulted in reduced tidal volume and dynamic lung compliance, bronchoconstriction, and increase in pulmonary resistance. Bronchoconstriction was also seen in guinea pigs exposed to 20.4 g/m^3 kerosene aerosol for 5 min (Garcia Mesa et al., 1988).

There are a number of published studies of JP-8 in vitro acute toxicity, in which cell cultures or other tissues are exposed acutely to kerosene-based jet fuels. Each of these studies is summarized in the section appropriate for the body organ associated with the cell or tissue culture.

Additionally, preliminary results of the AFIERA study (2001) reported "acute" exposure effects of JP-8 in military personnel. Because all subjects in this study experienced repeated occupational exposure to JP-8 for at least 4 mo before the acute exposure, these results are considered in subsequent sections of this article.

SELF-REPORTED AND MEDICALLY DIAGNOSED SYMPTOMS

Since the 1991–1996 conversion from predominant use of JP-4 jet fuel (40–50% kerosene:50–60% unleaded gasoline) to kerosene-based JP-8 by the USAF and U.S. Army, there have been increased self-reported and/or medically diagnosed complaints from exposed personnel. In a comparison between military workers occupationally exposed to high levels of JP-8 versus those exposed to low levels or unexposed to JP-8, there were significant differences in incidence of the following self-reported symptoms: dizziness, imbalance, walking difficulties, general weakness/fatigue, difficulty gripping objects, numbness/tingling of limbs; itching skin, blisters/skin rashes on hands/arms, chemical allergy, difficulty breathing, chest tightness, excessive sweating, trouble concentrating, forgetfulness, and perception that "life's work is impacting health," perception that "current job is impacting health." Additionally there were numerically greater incidences in self-reporting by the high exposure group of the following symptoms: headache, blurry vision, tremors, tearing eyes, chronic pain/use of pain medication, heart palpitations, scaly skin, and weeping skin (Olsen et al., 1998; AFIERA, 2001). An extensive medical records review for the same subjects, however, indicated that there were no significant differences between either male or female JP-8–exposed subjects versus controls (low exposure groups) for the mean number of healthcare provider visits for: skin disease, gastrointestinal concerns, sports-related injuries, workplace injuries, other injuries, respiratory conditions, neurological conditions, musculoskeletal conditions, cardiovascular conditions, or urogenital complaints. Total healthcare provider visits were nearly identical for exposure groups, including 220 males and 45 females. There was no published comparison, however, of U.S. military health complaints with those expressed by European fuel workers who may have been exposed to JP-8 since 1972, or with those expressed by commercial airport workers who may have been exposed to Jet A or Jet A-1 throughout their occupational careers.

A series of at least six journal articles published in Europe from 1976 to 1983 (Knave et al., 1976a, 1976b, 1978, 1979; Mindus et al., 1978; Struwe et al., 1983) documented self-reported and medically diagnosed symptoms in jet engine manufacturing/repair workers exposed to jet fuels and hydrocarbon solvents for as long as 41 yr. A listing of these symptoms (Ritchie, Still et al., 2001) reflects remarkable congruency to those recently reported for JP-8 exposure (AFIERA, 2001), although it was believed that much of the occupational exposure of these Scandinavian workers occurred to MC77, a "JP-4–like" jet fuel containing a high percentage of unleaded gasoline.

Although JP-4 typically contains significantly higher concentrations of certain C_6–C_8 toxicants (i.e., benzene), there are at least two factors that must be considered in comparing relative toxicity potentials among these fuels. While JP-8 and JP-5 exhibit higher flash points, lower vapor pressures, and increased handling safety as compared to JP-4, both JP-8 and JP-5 necessarily vaporize more slowly from skin, clothing, environmental surfaces, soil, and

groundwater and are more likely to be found in aerosolized versus vapor phase compared to JP-4 (Allen et al., 2000). These characteristics of kerosene-based jet fuels may then actually provide increased human dermal exposure to raw fuel as well as increased respiratory exposure to fuel in aerosol phase. Indeed, Baker et al. (1999) demonstrated that JP-8 is more irritating to rats than JP-4 when equal volumes are applied dermally. Further, workers commonly complain of JP-8 odor persisting on the skin and in the saliva for more than 12 h postexposure, and "sweating out" of jet fuel during unassigned weekend hours (Ullrich & Lyons, 2000; Ritchie, Still et al., 2001). Similar complaints for previous JP-4 exposure were not documented in the literature.

Finally, human exposure to JP-8 combustion byproducts may actually induce increased irritation of the mucous membranes of the respiratory tract, compared to exhaust from JP-4 combustion, as JP-8 exhaust may contain higher concentrations of the respiratory irritant formaldehyde (Kobayashi & Kikukawa, 2000). To date, no published research has compared relative irritancy from JP-8 versus JP-4 exhaust exposures.

CARCINOGENIC EFFECTS (NONDERMAL)

There have been no published epidemiological studies of carcinogenesis where hydrocarbon exposures were limited to kerosene-based jet fuels. As JP-8 was used extensively by the USAF and U.S. Army only since 1991–1996, the follow-up period for cancer induction in the United States is probably only sufficient for evaluating JP-5, used by the U.S. Navy since 1951. Although JP-8 was used since 1972 by the militaries of some European countries, and Jet A and Jet A-1 have been used domestically and internationally, respectively, for over 20 yr, there are no published epidemiological studies of cancer induction.

The most widely quoted studies of carcinogenic effects were conducted by Selden and Ahlborg (1986, 1987) from a cohort of 2182 Swedish military personnel (86%) and others (14%) exposed to MC77 ("JP-4 like") jet fuel, MC75 (Jet A-1 equivalent), isopropyl nitrate, leaded aviation gas (AVGAS), and/or hydrocarbon solvents. Air monitoring in the work environments of these individuals indicated mean jet fuel vapor concentrations often exceeding 350 mg/m^3. Unfortunately, the cohort was followed up for only 6 yr (1974–1982). These studies indicated no unexpected incidence of neoplasms, cancers in specific tissues, or death during the follow-up period.

Selden and Ahlborg (1991) conducted a further epidemiological study of a cohort of 2176 workers at a military base in Sweden with substantial exposure to MC77, MC25 (a leaded synthetic jet fuel), MC55 (containing 0.08% tetraethyl lead v/v), and/or hydrocarbon solvents. Although a cluster of malignant tumors (10 incidences among 2176 personnel) was suspected at this base, a 9- to 10-yr follow-up by the authors identified no unexpected cancer morbidity or death risk. During the follow-up period, 3 new cases of malignant lymphoma were detected versus 3.21 expected tumors of the lymph system. In fact, the overall standardized mortality rate (SMR) for all malignant tumors in the cohort were

unexpectedly low, possibly due to a "healthy worker" effect. It should be noted that in most military studies summarized in this review, control groups consist of non-exposed or "low"-exposure military personnel, whose mean levels of physical fitness and general medical health may significantly exceed that expected from an age-equated sample of the general public.

In a recent review article, Duarte-Davidson et al. (2001) summarized a series of experiments conducted in the United Kingdom evaluating human cancer risk from occupational exposure to petroleum products (and benzene) at various oil refineries. It was concluded that petroleum industry (manufacturing and distribution) workers exhibited a higher incidence of malignant neoplasms in the lungs, larynx, esophagus, stomach, intestine, rectum, kidneys, and prostate as compared to the general population (Rushton, 1993a, 1993b, 1993c). It should be noted that these health effects occurred in workers exposed to numerous different hydrocarbon fuels and combustion products. Siemiatycki et al. (1987) examined a cohort of 3726 cancer patients in Montreal, Canada, of whom 43 reported occupational exposure to jet fuel and/or AVGAS, and 234 reported occupational exposure to kerosene for up to 20+ yr. There was a significantly elevated rate of kidney cancer (7 of 43 cancer patients) among workers with occupational jet fuel/AVGAS exposure), compared to the predicted risk.

Bunin et al. (1994) reported a significant association between repeated use of kerosene fuel during pregnancy and subsequent development of astrocytic glioma (astrocytoma) and primitive neuroectodermal tumors (PNET) in children exposed during gestation.

It has long been recognized that benzene, a component of all kerosene-based jet fuels, is a human carcinogen with the capacity to induce at least acute non-lymphocytic leukemia (i.e., acute myelogenous leukemia) (Duarte-Davidson et al., 2001). Indeed, there are over 100 published studies indicating a possible relationship between repeated exposure to benzene or compounds containing benzene (i.e., gasoline, solvent products, and tobacco products) and the development of AML or other nonlymphoblastic leukemias (Rushton & Romaniuk, 1997; Duarte-Davidson et al., 2001). It was concluded in a recent review article that the lowest mean occupational exposure concentration of benzene that was reliably shown to increase the probability of incidence of leukemia is approximately 32–80 mg/m^3, and that the risk of leukemia induction in the general public from average atmospheric exposure concentrations (estimated at 3.7–42 $\mu g/m^3$) is minimal (Duarte-Davidson et al., 2001). As all existing kerosene-based jet fuels contain a small percentage of benzene (0.08–0.8% v/v) (MSDS, JP-8, 1995), there is opportunity for repeated exposure of occupational fuel workers through both dermal and inhalation routes. All published atmospheric measurements of benzene concentrations on military and commercial flight lines are, however, substantially below 32 mg/m^3 (Pleil et al., 2000). While there are no published data relating kerosene-based jet fuel exposure to development of either acute myeloid leukemia (AML) or acute lymphocytic leukemia (ALL) (Lewis et al., 1997; Rushton and Romaniuk, 1997), it must be considered that exposure to JP-8, in at least some rodent

strains, can result in severe immunosuppression (Harris et al., 1997a, 1997b, 1997c, 2000; Ullrich, 1999; Ullrich & Lyons, 2000). Immune suppression may reduce protection against specific viral infections, a possible causative factor in development of ALL, AML, or other cancers (zur Hausen, 1991; Dorak, 1996). Coexposure to JP-8, gasoline, DF, some hydrocarbon solvents, and/or tobacco smoke, as can occur in some occupational settings, may provide a body burden of benzene that is significantly greater than would be expected from occupational or environmental exposure to JP-8 alone (Pleil et al., 2000).

Additionally, it was shown for in vitro human T-cell (HPB-ALL and Jurcat line) models that exposure to various PAHs found in kerosene-based fuel (e.g., benzo[a]pyrene, anthracene, and benz[a]anthracene) can, through cell binding, result in modulation of Ca^{2+} mobilization, and in significant suppression of lymphocytic immune cell function (Krieger et al., 1994). These authors additionally reference a number of previously published studies indicating similar outcomes for in vivo exposures to PAHs (Blanton et al., 1986).

Smith (1996) developed a hypothesis for the mechanism underlying development of other nonlymphoblastic leukemias from benzene exposure. This theory contains the following key components: (1) inhalation, oral ingestion, or dermal penetration of benzene; (2) activation of blood-transported benzene in the liver to phenolic metabolites (phenol, hydroquinone, catechol, and 1,2,4-benzenetriol); (3) blood transport of these metabolites to the bone marrow; (4) metabolic conversion of these metabolites in the bone marrow (via peroxidase enzymes) to semiquinone radicals and quinones; (5) generation of reactive oxygen species (ROS) via redox cycling; (6) damage to tubulin histone proteins, topoisomerase II, and other DNA-associated proteins; and (7) consequent genetic damage, including DNA strand breakage, mitotic recombination, chromosome relocations, and aneuploidy, resulting in possible development of a leukemic clone. Smith (1996) further hypothesized that maternal exposure to benzene and other environmental toxicants may provide the most likely mechanism for induction of nonlymphoblastic leukemias.

There is substantial evidence that repeated dermal exposure to any of a number of hydrocarbon fuels may induce skin tumors in at least animals. Studies investigating kerosene-based, jet-fuel-induced tumors are discussed in the following section.

DERMAL TOXICITY, INCLUDING TUMORIGENESIS

Because military or commercial fuel workers and aircraft maintenance personnel are typically unprotected against dermal exposure to kerosene-based jet fuels, except by chemically resistant gloves and boots, there is extensive opportunity for repeated exposure of the unprotected body surface. As workers often experience partial soaking of clothing with fuel during lengthy maintenance operations, there may be prolonged dermal exposure (2–6 h) as often as 2–3 d/wk for many years. Of all health complaints from fuel-exposed workers, among the most common are itching or burning skin, skin redness or rash, skin dryness or dermatitis, skin lesions or weeping, or skin sensitization (Koschier,

1999; Riviere et al., 1999; Pleil et al., 2000; McDougal et al., 2000; Kanikkannan et al., 2000; Allen et al., 2000; Kabbur et al., 2001; Ritchie, Rossi et al., 2001; AFIERA, 2001). Perhaps more importantly, reduction in the integrity in the dermal barrier by repeated exposure to kerosene-based fuels may increase systemic exposure to other occupational toxicants and environmental microbials, as well as to toxic components of the fuel itself during subsequent exposures.

From a military perspective, the recent (1991–1996) USAF and U.S. Army transition from predominant use of JP-4 to nearly exclusive use of JP-8 (and/or JP-8+100) provides a new dermal toxicity issue. Because JP-4 was more volatile than JP-8, and evaporated from skin and clothing more rapidly, the use of JP-8 necessarily increases the expected duration of dermal exposure of equally protected personnel (Baker et al., 1999). The planned transition (by 2008) by the U.S. Navy from shipboard use of JP-5 (less volatile than JP-8) to use of JP-8, by the same logic, should slightly reduce dermal exposure duration.

There have been no published laboratory studies of human dermatoses from exposure to kerosene-based jet fuels. However, Jee et al. (1986) investigated development of dermatoses among females employed in a ball bearing manufacturing plant in which there was common exposure to kerosene (5 h/d, 5 d/wk) during handling of kerosene-soaked parts. Among 79 workers tested, 51 workers (65%) had erythema with or without desquamation over the interdigital spaces, 12 individuals (15%) had eczematous lesions, 3 individuals (4%) had defatting dermatitis, and only 13 subjects (16%) were asymptomatic. These incidences were significantly greater than observed in a matched control population. Five subjects exhibited blisters, skin reddening, flaccid bullae, pustules, soreness, burning, edema, and denudation of the skin following acute exposures to unspecified concentrations of kerosene (Tagami & Ogino, 1973). In the same studies, human subjects exposed dermally to 1.5 ml of 55–85% solutions of kerosene reported dose-dependent dermatitis. Topical administration of a single 1-ml kerosene dose to human subjects was reported to result in (1) impaired protein synthesis, but with normal DNA replication and collagen synthesis; (2) cellular damage of the epidermis and mild edema; and (3) limited cytolysis and enlarged intercellular spaces in the stratum corneum and spinous cells of the epidermis (Lupulescu et al., 1973; Lupulescu & Birmingham, 1975, 1976).

There have been a large number of in vivo and in vitro animal studies investigating both the dermal penetration and dermal toxicity of kerosene-based jet fuels or kerosene. Skin irritation was not detected in male rabbits following a single dermal application (0.5 ml) of neat JP-5 or JP-8 (Schultz et al., 1981). Kinkead et al. (1992a), however, reported mild skin irritation in rabbits receiving a single dermal application of JP-8, but not JP-5 (Kinkead et al., 1992b).

Kanikkannen et al. (Kanikkannen, Burton et al., 2001; Kanikkannen, Patel et al., 2001) examined percutaneous absorption of JP-8 and several of its component chemicals (1000 µl/exposure) across both pig ear skin and human cadaver skin. A sample of JP-8 was placed on a porcine or human skin sample mounted on a Frantz diffusion cell for 24 h, with perfusion samples collected at

0.5, 1, 2, 4, 8, 12, and 24 h. In general, the representative chemical constituents of JP-8 tested (aliphatics = ^{14}C-tridecane [C_{13}, molecular weight = 185.4], and ^{14}C-nonane [C_9, molecular weight = 128.3]; aromatics = ^{14}C-naphthalene [C_{10}, molecular weight = 128.2], and ^{14}C-toluene [C_7, molecular weight = 92.1]) permeated through both human and porcine skin at concentrations approximately proportional to their composition in JP-8 (tridecane > nonane > naphthalene > toluene). It was hypothesized that permeation in a closed (nonevaporative) system is relatively independent of the molecular weights or water partition coefficients of the JP-8 component chemicals. However, when the percent dose absorbed was plotted against time, the absorption of naphthalene exceeded tridecane (only compounds compared). Additionally, in vivo studies were conducted with Yucan minipigs, evaluating dermal toxicity of neat JP-8, 100% nonane, or 100% toluene exposure (250 µl/subject). In these experiments, transepidermal water loss (TEWL), skin capacitance (moisture content), and skin irritation (erythema and edema) were evaluated before treatment and at 1, 2, and 24 h after a 24-h exposure. All chemical applications elevated the TEWL (neat JP-8 > nonane > toluene), with JP-8 increasing the TEWL by 300% at 24 h compared to baseline levels. JP-8 produced a moderate erythema and severe edema that was greater than with exposure to toluene or nonane alone. Though the JP-8–induced edema decreased after 24 h, the degree of erythema remained the same for >24 h. The disruption of barrier function of skin, as indicated by increased TEWL after exposure to JP-8, was hypothesized to increase permeation of its own components and/or other chemicals or infectious agents exposed to skin (Kanikkannen et al., 2001a, 2001b).

Similarly, Riviere et al. (1999) assessed the percutaneous absorption and cutaneous deposition of topically applied (25 µl fuel/5 cm^2 skin) neat Jet A, neat JP-8, aged (evaporated) JP-8, or JP-8 + 100 by monitoring the absorptive flux of these marker components [^{14}C-naphthalene (C_{10}, molecular weight = 128), ^{3}H-dodecane (C_{12}, molecular weight = 170), and ^{14}C-hexadecane (C_{16}, molecular weight = 226)], simultaneously applied to isolated perfused porcine skin flaps. In all studies, skin surface, stratum corneum, skin and fat, and perfusate concentrations were measured over 5 h. Naphthalene absorption into the perfusate displayed a clear peak absorptive flux at approximately 30 min (0.013% of dose), while dodecane (0.003% of dose) and hexadecane (0.001% of dose) showed more prolonged (approximately 1.5 h) and lower absorption flux profiles. While dodecane constituted 4.7% of the Jet A sample, its absorption (from JP-8 exposure) was only 67% of naphthalene absorption (that constituted only 1.1% of the Jet A sample volume). Additionally, naphthalene, being more volatile than dodecane, would be expected to evaporate from the skin in an open system at a more rapid rate. This result may challenge the previously discussed findings of Kanikkannen et al. (2001), predicting dermal absorption of jet fuel constituents as a function of their volume (v/v) percentage of the total mixture. The result is, however, consistent with findings reported by McDougal et al. (1999, 2000). It should be noted that dermal penetration for the three JP-8 components measured by Riviere et al.

(1999) was only about 1.5% of the applied dose within 5 h. For JP-8, the rank order of (5 h) absorption into the perfusate for all marker components was naphthalene > dodecane > hexadecane, although deposition within the stratum corneum was hexadecane (9.84% of dose) > dodecane > naphthalene (2.12% of dose). Naphthalene absorption into the perfusate was similar across all fuel types; however, total penetration of naphthalene into and through skin was JP-8+100 > Jet A > JP-8 > aged JP-8, while perfusate absorption for dodecane was JP-8 > JP-8+100 > Jet A > aged JP-8. While the authors hypothesized that the JP-8+100 additive may have increased dermal absorption of naphthalene, it must be considered that the JP-8+100 additive package itself adds 126 mg/L naphtha solvent to the fuel formulation. Relative dodecane absorption and total penetration was greatest from aged JP-8, explained logically by the increased evaporation of lighter fractions with aging. These studies appear to indicate that while dermal absorption from kerosene-based jet fuels may be relatively consistent across fuels, the relative absorption of different fuel constituents cannot be predicted by a mere knowledge of the v/v concentration of those constituents within the fuel. Rather, the chemical characteristics of individual constituents (i.e., volatility, molecular weight, hydrophilicity, lipid solubility, etc.) and interactive effects of the performance additive package may be more important in predicting deposition in skin, fat, and blood.

McDougal et al. (1999, 2000) used diffusion cells to measure both the flux of JP-8 and components across rodent skin (2–3 times more permeable than human skin) and the kinetics of absorption into the skin. Total summed flux of the hydrocarbon components was 20.3 $\mu g/cm^2/h$ (excluding the additive DiEGME). Thirteen individual components of JP-8 penetrated into the receptor solution (DiEGME > decane > methyl naphthalenes > trimethylbenzene > undecane > naphthalene > xylenes > dimethyl naphthalenes > toluene > dodecane > nonane > ethyl benzene > tridecane) ranging from a high flux of 51.5 $\mu g/cm^2/h$ for the additive DiEGME (only 0.08% weight/weight [w/w] of JP-8) to a low of 0.334 $\mu g/cm^2/h$ for tridecane (2.7% w/w of JP-8). There was a substantial difference in peak penetration times, ranging from 30 min with DiEGME, to 120 min for tridecane. Aromatic components penetrated most rapidly. Six aliphatic components (decane > dodecane > decane > tridecane > tetradecane > nonane) were identified in the skin. These authors suggested that the rate of dermal penetration of aromatics, etc., might be too low to induce acute systemic toxicity with typical real-world exposures, although the absorption of aliphatic components into the skin may be sufficient to induce dermal irritation and edema.

Upreti et al. (1989) exposed mice to kerosene 15–60 min/d for 7 d by wrapping the hind feet with a muslin cloth wetted with kerosene (0.1 ml). Repeated exposure to kerosene produced histologic changes in the foot pad skin and popliteal lymph nodes, as well as changes in hematologic profile, significant decreases in relative weight of thymus, spleen, and abdominal lymph nodes, and altered histology. These systemic consequences of relatively brief dermal exposures to kerosene are mentioned in this section only to emphasize the possible importance of this exposure route in human risk assessment of jet fuels.

Kanikkannan et al. (2000) evaluated JP-8, JP-8+100, and Jet A as possible skin sensitizers in female mice, using the murine local lymph node assay (LLNA). It was reported that JP-8 (stimulation index [SI]=3.17), but not Jet A (SI=2.44) or JP-8+100 (SI=2.38), was a mild skin sensitizer. As mentioned previously, JP-8+100 contains the antioxidant butylated hydroxytoluene (BHT), a metal deactivator (MDA), a dispersant/detergent, and a naphtha solvent not found in JP-8 or Jet A. It was shown that BHT in JP-8+100 appeared to reduce its dermal toxicity > JP-8 > Jet A, although the other components of the JP-8+100 additive package were not tested independently. It was hypothesized that the antioxidant BHT may function to reduce the free radical content of JP-8+100 applied dermally, as compared to applications of neat JP-8 or neat Jet A, and thus reduce at least the acute irritancy and skin sensitization potential. Additionally, the surfactantlike action of the TS additive package in JP-8+100 (personal communication, Stonecipher) may influence dermal (or pulmonary) absorption, although this possibility has not been studied.

Baynes et al. (2001) investigated the influence of military additives DiEGME, 8Q21 (a TS package detergent/dispersant), and Stadis 450 on the dermal deposition of marker aliphatic (dodecane) and aromatic (naphthalene) constituents in Jet A. It should be remembered, however, that Jet A normally does not contain the additives evaluated in this study. Porcine skin sections were used to identify diffusion of jet fuel components in an in vitro system, and isolated perfused porcine skin flaps (IPPSFs) were used to evaluate diffusion in a viable skin model with an intact microvasculature. In these 5-h studies, Jet A, Jet A+DiEGME, Jet A+8Q21, Jet A+Stadis 450, Jet A+DiEGME+8Q21, Jet A+DiEGME+Stadis 450, Jet A+8Q21+Stadis 450, and neat JP-8 were tested. In general, naphthalene absorption (0.76–2.39% of dose) was greater than dodecane absorption (0.10–0.84% of dose), while the IPPSFs alone demonstrated that dodecane absorption was significantly greater in JP-8, containing at least three performance additives, than in Jet A. Synergistic interactions with 8Q21+Stadis 450 enhanced systemic absorption of either naphthalene or dodecane, while DiEGME+Stadis 450 increased naphthalene (1.88% dose) and dodecane (2.02% dose) penetration into both the skin and fat tissues of IPPSFs. These findings were supported by the fact that 8Q21+Stadis 450 significantly increased dodecane flux and permeability in porcine skin sections, but 8Q21 alone reduced marker diffusion in both membrane systems. Furthermore, dodecane is more likely than naphthalene to remain in the stratum corneum and skin surface at 5 h, and DiEGME mixtures played a significant role in skin and surface retention of both markers. In summary, the data suggest that various combinations of these three performance additives in at least Jet A can potentially alter the dermal disposition of aromatic and aliphatic fuel components in skin. More importantly, products of two-factor interactions were not predictable from single-factor exposures and, by extension, cannot be extrapolated to three-factor interactions.

Allen et al. (2000) examined the capacity of acute JP-8, JP-8+100, or Jet A exposure to induce or suppress cytokine release for in vitro preparations. Primary

human keratinocytes were exposed to 0.1% JP-8, JP-8+100, or Jet A for 24 h, and evaluated for release of the proinflammatory cytokines tumor necrosis factor-alpha (TNF-alpha) and interleukin-8 (IL-8). IL-8 release was noted for all three fuels within 8 h and continued to rise through 24 h, compared to controls. Additionally, mRNA for IL-8 was elevated by 4 h postexposure for all fuel exposures. Maximal levels of TNF-alpha release were seen at 4 h and decreased in a time-dependent manner through 24 h, although these levels remained above control at all time points assayed. In a subsequent publication, similar experiments were conducted using primary porcine keratinocytes (PKC) or immortalized porcine keratinocyte cell lines (MSK3877). In PKC, JP-8, Jet A, or JP-8+100 induced results similar to those seen with primary human keratinocytes, although exposure of MSK3877 resulted in only a slight upregulation of TNF-alpha with a significant decrease in the proinflammatory cytokine interleukin-8 (IL-8) after 8 h of exposure (Allen et al., 2001). The authors concluded that JP-8, JP-8+100, and Jet A induce the proinflammatory cytokine IL-8 for in vitro human keratinocyte preparations, providing a basis for possible in vitro dermal inflammation, and cautioned that use of porcine models for human risk assessment of jet fuel dermal exposures must be carefully examined. Chou et al. (2002) reported three–tenfold increases in release of IL-8 from human epidermal keratinocyte (HEK) cultures following brief exposure to mid-length hydrocarbon chain lengths (C9-C13), as compared to similar exposure to hydrocarbon fractions with lower or higher chain lengths. Exposure to hydrocarbon chain lengths $<$C9 was, however, more likely to induce cell apoptosis than was exposure to C9-C13.

Recently, Rosenthal et al. (2001) reported that JP-8 exposure of skin fibroblast or human keratinocyte cell cultures or grafted human keratinocytes, in a concentration-related manner, resulted in necrosis, but not apoptotic responses. Exposure to levels of JP-8 (80 μg/ml) sufficient to induce apoptosis in lung or immune system cultures (Stoica et al., 2001) induced neither apoptosis nor necrosis in skin cell cultures. Exposure to higher levels of JP-8 ($>$200 μg/ml), however, resulted in morphological and metabolic changes typical of necrotic changes, although certain proapoptotic proteins were still upregulated and antiapoptoic proteins were downregulated in affected cells. It was hypothesized that although different cell types exhibit differing sensitivity to JP-8, interference with mitochondrial function may be common to both necrotic and apoptotic outcomes.

Similarly, Kabbur et al. (2001) exposed F-344 rats dermally to JP-8 for 1 h, then evaluated several measures of dermal toxicity at 0, 1, 2, 4, and 6 h postexposure. At 1–2 h postexposure, there were significant increases (11–34%) in levels of the proinflammatory cytokine interleukin (IL)-1 alpha, as compared to baseline, and in levels of inducible nitric oxide synthase (iNOS) at 4–6 h postexposure. Additionally, pathological changes in exposed skin were detected including local inflammation and increased numbers of granulocytes in skin samples collected 2–6 h postexposure. Rogers et al. (2002), applying JP-8 to rat skin for 1 h, reported formation of oxidative species (1–4 h postexposure) and low-molecular-weight DNA (4–6 h postexposure) as potential indicators of JP-8–induced skin injury.

A number of studies (Bingham et al., 1965, 1979; Easley et al., 1982; Witschi et al., 1987; Biles et al., 1988; Clark et al., 1988; McKee et al., 1989; Freeman et al., 1993; Broddle et al., 1996; Nessel et al., 1999; Nessel, 1999) have documented tumorigenic potential of dermally applied petroleum derived middle distillate fuels (i.e., jet fuel, kerosene, diesel fuels, home heating oils). More specifically, it was reported that middle distillate petroleum (MDP) streams, similar to JP-8 without performance additives, increased the incidence of skin cancer in mice treated dermally for ≤ 24 mo. No dermal cancer was found in B6C3F mice following dermal exposure to 250 or 500 mg/kg/d JP-5 for up to 103 wk, although malignant lymphomas were noted in 39% of females treated with 250 mg/kg/d JP-5 (compared to 15% of controls and 11% of females dosed at 500 mg/kg/d) (NTP/NIH, 1986b). However, unspecified skin tumors were identified in C3HF/Bd mice following dermal exposure to 22.9 (but not 42.2 mg) mg/animal/d for 40 wk, or to 5.7–42.2 mg/animal/d for 60 wk (Schultz et al., 1981). Clark et al. (1988, 1989), exposing male and female C3H/HeN mice dermally to Jet A 3 times/wk for up to 103 wk, reported significant increases in incidence of both squamous cell carcinoma (+26%) and fibrosarcoma (+28%) as compared to mineral oil and 0.15% benzo[a]pyrene control exposures. It should be noted that many animals were studied for < 105 wk due to severe dermal inflammatory and degenerative effects. A major finding of these studies was that severe hydrotreating of fuels studied (petroleum- and shale-derived naphtha, JP-4, Jet A, crude oils) eliminated dermal carcinogenicity.

Walborg et al. (1998) exposed groups of CD-1 mice 2 times/wk for 2 wk dermally to a number of a petroleum middle distillates (PMD), including hydrodesulfurized (HDS) kerosene. The authors measured induction of sustained, potentiated epidermal hyperplasia as predictive of skin tumor promotion. Four quantitative biomarkers of epidermal hyperplasia were evaluated: (1) epidermal thickness; (2) number of nucleated epidermal cells per unit length of basement membrane; (3) labeling index of epidermal cells; and (4) induction of epidermal ornithine decarboxylase (ODC) activity. Fuel-induced skin irritation was evaluated visually and/or histopathologically. HDS kerosene produced dose-dependent skin irritation and epidermal hyperplasia that was significantly greater than in control. Of the four short-term markers of tumor promotion assessed, labeling index and epidermal ODC activity were predictive of the relative promoting activities of the fuel tested. An interesting finding of this study was that formulations with high toluene content, while generally non-tumorigenic, induced such severe epidermal toxicity that meaningful identification of markers became impossible.

Ingram et al. (1993) applied a number of light hydrocarbon oils, including 3 kerosenes, dermally to mice 3 times/wk for up to 6 wk. It was found that relative penetration through the skin surface or via hair follicles was directly related to the degree of epidermal necrosis observed, and that penetration within and around the hair follicles occurred predominantly as long as the epidermis was relatively intact. Kerosene exposures generally induced epidermal necrosis within 1 wk, with repeated cycles of necrosis and healing responses

evident throughout the 6-wk regimen. It was hypothesized that when the epidermal barrier layer was damaged, follicular entry became less important, and that severe kerosene-induced epidermal damage was probably sufficient for skin tumors to arise by a nongenotoxic mechanism.

In general, the numerous animal studies reporting dermal tumorigenesis following repeated exposure to hydrocarbon fuel formulations appear consistent with human data showing high incidence of dermatoses in ball bearing workers exposed repeatedly to kerosene (Jee et al., 1986). Whether a similar result will occur in humans exposed repeatedly to kerosene-based jet fuels remains unknown. There appears to be increasing evidence that severe, long-term fuel-induced dermal irritation, necrosis, and regeneration may be integrally related to possible tumorigenesis (Biles et al., 1988; Clark et al., 1988; Ingram and Grasso, 1991; Freeman et al., 1993; McKee et al., 1994; Walborg et al., 1998). Freeman et al. (1993), in a 2-yr skin painting study in mice, reported skin tumors in 44% of mice painted with jet fuel 2 times/wk throughout the study, but in only 2% of mice in which dosing was suspended for 2–3 wk whenever severe skin irritation was identified in 20% of the group. Additionally, Freeman et al. (1993) provide limited evidence that dermal carcinogenicity from hydrocarbon fuel exposures may not be significantly related to either PAH content, or to the aromatic hydrocarbon and sulfur content of at least the fuels tested.

Ingram and Grasso (1991), in a review article, cite two possible mechanisms by which repeated dermal exposure to kerosene-based jet fuels might induce skin tumors by nongenotoxic mechanisms. The first mechanism requires that potent promoting agents, as may occur in kerosene-based jet fuels, bind to and activate protein kinase C, possibly stimulating sustained epidermal hyperplasia without severe skin damage. The more likely mechanism involves fuel-induced production of severe skin damage by cumulative irritancy, giving rise to marked epidermal hyperplasia with repeated episodes of damage and regeneration. The possible tumor induction by either mechanism may result from oncogene activation, as possibly stimulated by release of oxidative enzymes from inflammatory cells.

PULMONARY SYSTEM EFFECTS

Because kerosene-based jet fuel vapor/aerosol and fuel combustion exhaust products enter the atmosphere from a wide range of sources (i.e., military bases, commercial airports, fuel manufacturing/storage facilities, aircraft, aircraft fuel jettisoning, vehicles, equipment), there is extensive opportunity for repeated pulmonary system exposure of the general public to at least vapor phase (Tunnicliffe et al., 1999). Among personnel working near these sources, there is ample opportunity for repeated inhalation exposure to both aerosol and vapor phase. The AFIERA study (2001) of occupational JP-8 exposure indicated a significantly increased self-reporting of difficulty breathing and chest tightness among personnel exposed repeatedly to high-dose as compared to low-dose concentrations. While definitive research has not been published, there

would appear to be a major difference in health impact, at least in laboratory animals, from aerosol versus vapor-phase exposure.

A number of animal studies have been published examining pulmonary toxicity from JP-8 exposures. Mattie et al. (1995) reported no significant histopathological changes in the lungs or nasal turbinates of male rats administered up to 3 g/kg/d JP-8 by oral gavage once daily for 90 d. This finding indicates that the reported pulmonary toxicity from kerosene-based jet fuel exposure occurs from a direct interaction between the vapor or aerosol and the pulmonary system, as opposed to effects from systemic exposure. Mattie et al. (1991) exposed male F-344 rats and C57Bl/6 mice of both sexes to JP-8 vapor at 0, 500, or 1000 mg/m^3 on a continuous basis for 90 d followed by recovery until approximately 24 mo of age. In this study, no pulmonary lesions or other significant histopathology was reported. Robledo et al. (1999) hypothesized that even noncytotoxic exposures to JP-8 aerosol, which may preclude pathological lung injury, may exert a detrimental effect on bronchial epithelial barrier function. Such effects may, then, modulate the protective barrier provided by the lung against absorption of potential toxicants (including hydrocarbon fuel components), resulting possibly in both increased systemic toxicity and cytotoxic lung injury.

Significant pulmonary toxicity in mice was demonstrated in rodents exposed to JP-8 vapor/aerosol concentrations as low as 50 mg/m^3 for as little as 1 h/d for 7 d (Witten, 1992, 1993; Robledo & Witten, 1998, 1999). This response targeted the bronchiolar epithelium, leading to significantly increased respiratory permeability to 99*m*-technetium–labeled diethylenetriamine pentaacetic acid, peribronchiolar edema, and mild cellular necrosis. However, mice administered the neurokinin-1 (NK1) receptor agonist substance P (SP) after each JP-8 exposure exhibited the appearance of normal pulmonary values and tissue morphology (Robledo et al., 1995). In contrast, endogenous NK1 receptor antagonism by CP-96345 administration exacerbated JP-8–enhanced permeability, alveolar macrophage toxicity, and bronchiolar epithelial injury (Robledo et al., 1995). These data indicate that NK1-receptor activation, at least by the neuropeptide SP, may have a protective role in preventing the development of hydrocarbon-induced lung injury. There is similar evidence that administration of surface surfactants to the lung before hydrocarbon fuel exposures may greatly reduce histopathology in sheep (Widner et al., 1996).

Loss of alveolar barrier protection and at least some histopathology associated with JP-8 vapor/aerosol exposure was hypothesized to be consistent with depletion or suppression of SP (Pfaff et al., 1996). SP is a neuropeptide of the tachykinin group, located primarily in the capsaicin-sensitive, unmyelinated nerves of the pulmonary airways. Depletion of SP by capsaicin injection in rats was shown to significantly increase the susceptibility of the lungs to JP-8 vapor/aerosol-induced histopathology (Pfaff et al., 1993). Further, capsaicin pretreatment before JP-8 aerosol exposure was shown to increase airway sensitivity to histamine (Witten et al., 1992). SP induces pulmonary effects including bronchoconstriction, maintenance of bronchoepithelial integrity, stimulation of

lung secretions, and modulation of inflammatory cells (Pfaff et al., 1996). The enzyme most responsible for metabolism of tachykinins, including SP, in the lungs is neutral endopeptidase (NEP), or enkephalinase. As NEP is primarily an epithelial cell–derived enzyme, it is hypothesized that JP-8 vapor/aerosol exposure of the lung, as a function of dose, induces epithelial cell injury that releases NEP into the BALF, resulting in the increased metabolism and inactivation of SP. SP depletion, in turn, results in increased alveolar–capillary membrane barrier permeability and possibly more severe histopathological damage to the lung (Pfaff et al., 1996). Thus, the addition of SP to the lungs might be expected to reduce or eliminate JP-8 induced histopathology.

In additional studies, exposure of mice to 48 or 118 mg/m^3 JP-8 aerosol for 1 h/d for 7 d resulted in (1) increased lung permeability; (2) perivascular edema; (3) Clara-cell vacuolization; (4) intra-alveolar hemorrhage; (5) alterations in type II epithelial cells, including cell death; (6) BALF increases in total protein and lactic dehydrogenase (LDH); (7) reduced *N*-acetyl-beta-D-glucosaminidase (NAG) levels; and (8) reduced alveolar macrophage counts (Robledo et al., 2000).

F-344 rats exposed to 497 or 520 mg/m^3 JP-8 in vapor/aerosol phase for 1 h/d for 7 or 28 d exhibited significantly increased pulmonary resistance, and increased alveolar clearance of a radiolabeled compound (99*m*-technetium–labeled diethylenetriamine pentaacetic acid), consistent with possible disruption of the alveolar–capillary membrane barrier (Chen et al., 1992; Air Force, 1994). No appreciable increase in these effects, however, occurred from 7 to 28 d of vapor/aerosol exposure (Witten et al., 1992; Chen et al., 1992; Air Force, 1994). This finding might imply that repeated exposure to moderate dose levels of JP-8 would initially induce pulmonary health effects that would not become more severe with increasing duration of exposure to the same or lower concentrations.

Hays et al. (1995) exposed male rats for 1 h/d for 7, 28, or 56 d to 500 (low dose) or 813–1094 mg/m^3 (high dose) JP-8 vapor/aerosol. Rats in all groups experienced perivascular and interstitial edema as well as thickening of the alveolar septa, accompanied by leukocytic infiltration. Morphological changes induced by JP-8 at these dose levels peaked at 28 d of exposure. Alveolar permeability generally increased with increasing JP-8 exposure in a dose-related manner. Similarly, Pfaff et al. (1995) reported significant changes in terminal bronchiolar airways accompanied by subendothelial edema in rats exposed for 28 d to 500–1000 mg/m^3 JP-8 vapor/aerosol.

Wang et al. (2002) investigated inflammatory mechanisms in the lung in response to JP-8 exposure using alveolar type II epithelial (AIIE) and pulmonary alveolar macrophage (PAM) cell cultures and co-cultures. It was shown that AIIE cultures, alone, secreted increased levels of interleukin (IL)-1beta and IL-6 in response to JP-8, while PAM cultures, alone, secreted IL-1beta, IL-10 and TNF-alpha. When co-cultured, AIIE/PAM responses to JP-8 for IL-1beta, IL-6 and TNF-alpha secretion were not different from control levels, although IL-10 levels were increased up to 1058% of control in response to 0.8 µg/mL JP-8 (100% ETOH vehicle). This data indicates, first, that PAM may regulate cytokine

release from AIIE cells in response to jet fuel exposure. Secondly, it is suggested that the increased expression of IL-10 in the co-culture may partially explain previously reported JP-8–induced pulmonary immunosuppression through: (1) reducing total secretion of the proinflammatory cytokin IL-1beta; (2) reducing total secretion of the IL-6, a cytokine responsible for B-cell differentiation into antibody forming cells; (3) reducing total secretion of the cytotoxic TNF-alpha; and (4) possibly through inhibiting in vitro production of the anti-viral interferon-gamma.

Pfaff et al. (1996) exposed F-344 rats by nose-only exposure to an aerosol/vapor mix of JP-8 (7, 28, or 56 d at 469–520 $mg/m^3/h$ or 814–1263 $mg/m^3/h$). As was shown previously (Robledo et al., 1995; Pfaff et al., 1995), JP-8–exposed animals exhibited a dose-dependent as well as duration-determined reduction in BALF substance P concentration, consistent with the significant histopathological changes in lower pulmonary structures.

Recently, Boulares et al. (2002) demonstrated in rat lung epithelial cells (RLE-6TN) that brief exposure to JP-8 both induced the generation of reactive oxygen species (RAS) and depleted the endogenous antioxidant glutathione (GSH), related to apoptotic cell death. JP-8–induced cell death was inhibited by exogenous glutathione (GSH) or the thiol-containing antioxidant *N*-acetylcysteine. This protective effect was associated with marked inhibition of both the activation of caspase-3 and the loss of the mitochondrial membrane potential induced by JP-8.

Wang et al. (2002) reported recently that age of animal subjects must be considered in evaluation of jet fuel induced deficits on the pulmonary system. These authors compared effects of exposure of C57BL/6 mice to $1 g/m^3$ JP-8 for 1h/d for 7 d at 3.5 months versus 12 months of age. It was shown that while animals in both age groups exhibited increased lung dynamic compliance, lung permeability, and BALF cell counts, and decreased PGE2, there were significant differences, as a function of age of exposure, on parameters including BALF cell differential, TNF-alpha, and 8-iso-PGF2 (prostoglandin-F2 receptor) levels.

Witzmann et al. (1999) examined protein expression in whole lung tissue from male mice exposed for 1 h/d for 7 d to 1 or 2.5 g/m^3 JP-8 aerosol. Of 42 proteins upregulated (up to +94%) or downregulated (to –30%), 13 were identified as most impacted by JP-8 aerosol exposure. These proteins are involved in four functional areas: (1) protein synthesis; (2) toxic/metabolic stress and detoxification; (3) lung ultrastucture; or (4) functional responses to CO_2 handling, acid-base homeostasis, and fluid secretion. Research in progress indicates that exposure of rats to JP-8 vapor (250, 500, or 1000 mg/m^3), 6 h/d for 91 d, may, in a concentration-related manner, result in upregulation, then downregulation of antiapoptotic proteins in the lung (personal communication, Witzmann).

Recently, Stoica et al. (2001) reported that JP-8 (80 µg/ml, solubilized in 0.5% ethanol) induced apoptosis, but not necrosis, in a rat lung alveolar type II epithelial cell line (RLE-6TN). It was shown that soon after JP-8 exposure, RLE-6TN cells exhibited markers of apoptotic cell death: caspase-3 activation, poly (ADP-ribose) polymerase (PARP) cleavage, chromatin condensation, cytochrome *c* release from the mitochondria, and genomic DNA cleavage into both oligonucleosomal (DNA ladder) and high-molecular-weight fragments. It was hypothesized that JP-8 exposure, at least at low levels, damaged the mitochon-

drial mechanism sufficiently to induce release of cytochrome *c* and initiate the caspase cascade, but not sufficiently to completely compromise mitochondrial ATP function, resulting in cell necrosis. It was shown further that modulations resulting in overexpression of antiapoptotic proteins (i.e., Bcl-x_L or Bcl-2) in the culture reduced apoptosis in response to JP-8 exposure, while modulations resulting in overexpression of proapoptotic proteins (i.e., Bax or Bad) enhanced the apoptotic response to JP-8 exposure. Higher concentrations of JP-8, perhaps sufficient to induce necrosis, were not evaluated in this study.

Finally, research being prepared for publication indicates statistically significant upregulation or downregulation of the expression of 216–277 different proteins in the lungs of male Sprague-Dawley rats exposed to JP-8 vapor (250, 500, or 1000 mg/m^3) 6 h/d, continuously for 91 d. Expression of a number of these proteins, as a function of dose, have been identified as either antiapoptotic or proapoptotic in function (personal communication, Witzmann).

As was previously described, a wealth of human data exists on the indirect pulmonary toxicity of orally ingested kerosene, as this is a common form of poisoning in countries using this fuel to power home and commercial heating, cooking, and illuminating systems (Goodwin et al., 1988). Oral ingestion of kerosene (typically by children) involving aspiration of the lungs (i.e., through kerosene-induced or self-induced emesis) results commonly in chemical pneumonitis, pulmonary effusion, and pulmonary edema, with possible formation of pneumatoceles. The mechanism for this common outcome of kerosene ingestion is largely unknown, although similar health effects do not occur from oral ingestion without lung aspiration (Dice et al., 1982).

Repeated human exposure to kerosene vapor was shown to induce or aggravate human bronchoconstriction, asthma, chronic bronchitis, or other airway hyperreactivity conditions (Rodriquez de la Varga et al., 1990). There was, however, no throat irritation in 6 human laboratory subjects exposed for 15 min to approximately 140 mg/m^3 kerosene vapor (Carpenter et al., 1976).

As was previously described, Casaco et al. (1982) reported that inhalation exposure of rabbits to 32.3 g/m^3 kerosene aerosol for 4–9 min resulted in reduced tidal volume and dynamic lung compliance, bronchoconstriction, and increased pulmonary resistance. Bronchoconstriction was also seen in guinea pigs exposed to 20.4 g/m^3 kerosene aerosol for 5 min (Garcia Mesa et al., 1988). Sanabria et al. (1984) administered neat kerosene aerosol to male guinea pigs 15 min/d for 30 d. Subsequent necropsy indicated erosion of the tracheal epithelium, thickening of the interalveolar septa, and alveolar infiltration. The eosinophilic infiltration was hypothesized to represent an immunological response, possibly to sulfur contaminants of the fuel, resembling reactions of immediate hypersensitivity. It was hypothesized (Casaco, Garcia et al., 1985; Casaco, Gonzalez et al., 1985; Garcia Mesa et al., 1988) that kerosene-induced airway hyperreactivity is related to inhibition of the acetylcholinesterase (AChE) activity in airways, decreased the efficiency of the calcium uptake by the sarcoplasmic reticulum, and increased activity of airway lysosomal enzymes. No histopathological changes in the lungs of dogs or rats were identified, however, following exposure to 100 mg/m^3 kerosene vapor for up to 13 wk (Carpenter et al., 1976).

Finally, Aslani et al. (2000) exposed goats by intratracheal administration of 10, 20, or 40 ml/kg kerosene. Animals in the highest dose group had severe signs of poisoning and died within 4 h to 11 d after dosing. Postmortem examination of these goats indicated gangrenous pneumonia and pleuropneumonia, in addition to significant histopathology in a number of other organ systems.

IMMUNE, LYMPHORETICULAR, HEMATOPOIETIC, AND OTHER HEMATOLOGICAL EFFECTS

There are few published studies investigating human immune, lymphoreticular, hematopoietic, or other hematological effects of kerosene-based jet fuel exposure. Inhalation exposure for <1 h to an unknown concentration of JP-5 vapor/aerosol did not induce any short-term or persisting hematological effects in two military pilots (Porter, 1990). Children exposed accidentally to kerosene through oral ingestion exhibited increased leukocyte counts in 37–80% of reported cases (Nouri & Al-Rahim, 1970; Majeed et al., 1981; Dudin et al., 1991). A recent study compared blood samples from 45 USAF aircraft maintenance personnel exhibiting higher blood and breath (benzene, naphthalene) levels of JP-8 with those from 78 occupational controls exhibiting low blood and breath levels of JP-8. Workers exposed to higher levels of JP-8 presented significantly elevated WBC, neutrophil, and monocyte counts, although there were no significant differences between groups for total lymphocytes, T-cells, T-helper cells, T-suppressor cells, natural killer cells, or B-cells (Rhodes et al., 2003).

In the relative absence of human health effects studies, there are a large number of animal studies demonstrating significant immune, lymphoreticular, hematopoietic, or hematological modulations during and following exposure to kerosene-based jet fuels or kerosene. The changes are especially important to human health issues, as it is well known that such effects may directly or indirectly (1) increase susceptibility to infectious agents; (2) increase the probability of development of certain cancers (Freeman et al., 1993; Broddle et al., 1996); (3) increase the probability of development of autoimmune diseases; (4) increase the toxicity potential of exposure to other chemicals and stressors; or (5) negatively impact a wide diversity of neurobehavioral functions (i.e., reduced endurance, cognitive capacity, etc.) (Ritchie, Still et al., 2001).

MacEwen and Vernot (1983, 1984, 1985) exposed male and female rats continuously to JP-8 vapor for 90 d (550 or 1000 mg/m^3), then examined blood parameters 0 d, 2 wk, 2 mo, 9 mo, and 21 mo postexposure. Although there was a significant variance among blood parameters for the controls, the authors reported significant reductions in RBC and hemoglobin volume consistent with significant decreases in WBC counts. Mattie et al. (1995) reported a significantly increased spleen/body weight ratio (without spleen histopathology) in male Sprague-Dawley rats administered 3 g/kg/d (but not 750 or 1500 mg/kg/d) neat JP-8 by oral gavage for 90 d. There were no histopathological changes detected in the lymph nodes. In the same study, rats sacrificed immediately

postexposure were assayed for RBC count, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, RBC distribution width, mean corpuscular hemoglobin concentration, hematocrit, platelet count, and differential leukocyte count. Although results were not necessarily dose related, the following significant differences were found, compared to controls, in at least one of the three exposed groups: (1) percent neutrophils, increased; (2) percent eosinophils, reduced; (3) percent basophils, decreased; (4) percent lymphocytes, decreased; and (5) number of platelets, increased.

Dudley et al. (2001) reported that oral gavage exposure of mice to 2 g/kg/d JP-8 for 7 d resulted in significant decreases in thymus weight and cellularity (mean = −37 to −40%). Similarly, exposure to 1–2 g/kg/d JP-8 resulted in a significantly reduced plaque-forming cell (PFC) response to sheep RBC suspension injection, a sensitive measure of immunological disruption. Further, Dudley et al. (2001) tested the hypothesis that JP-8–induced immunosuppression in mice may occur through a mechanism related to the aryl (aromatic) hydrocarbon receptor (AhR). To test this hypothesis, an Ah-responsive mouse strain (B6C3F1) and a classically nonresponsive mouse strain (DBA/2) bearing a lower affinity AhR were gavaged with JP-8 for 7 d. The results suggest that both mouse strains were equally sensitive to JP-8 toxicity at several endpoints, including thymus weight and cellularity, liver weight, and specific immunoglobulin M (IgM) antibody responses. These results suggested that JP-8 may exert its toxicity via an AhR-independent mechanism.

Several recent studies (Harris et al., 1997a, 1997b, 1997c, 2000; Ullrich, 1999; Ullrich & Lyons, 2000) indicated severe immunosuppression in rodents exposed dermally to neat JP-8 or by inhalation to JP-8 in aerosol phase. Harris et al. (2000) exposed female C57Bl/6 mice by nose-only exposure to 1 g/m^3 JP-8 aerosol phase for 1 h/d for 7 d. Mice were sacrificed 1 h following the final exposure and were assayed for spleen natural killer (NK) and lymphokine activated killer (LAK) cell activity. NK cells are known to be involved in immune surveillance against newly developed malignancies, in defense against viral infections, and in control of immune B cell function. It was shown that JP-8–exposed mice were significantly deficient in both NK and LAK activity (during incubation with IL-2) in response to challenge with prototypical tumor cell lines (i.e., YAC-1). Additionally, JP-8 aerosol exposure significantly reduced cytotoxic T-lymphocyte precursor (CTLp) activity and significantly impacted helper T-cell function, as measured by proliferation in response to a variety of stimuli (in the absence of exogenous cytokines). Previously, Harris et al. (1997a, 1997b) reported that brief exposure of mice to JP-8 aerosol (as low as 100 mg/m^3) for 1 h/d for 7 d resulted, as soon as 2–4 d postexposure, in reduced immune system organ weights, loss of viable immune cell numbers (T cells, B cells, monocytes/macrophages), and suppression of a number of immune functions (i.e., T-cell mitogenesis) for up to 28 d following the brief exposures.

Harris et al. (1997c) found that administration of aerosolized substance P (SP) (15 min after each JP-8 exposure, at 1 μm or 1 nm concentration) protected

JP-8 exposed animals from losses of viable immune cell numbers, but not losses in immune organ weights. Further, exposure of animals to SP inhibitors generally increased the immunotoxicity from JP-8 exposure. SP appeared to act on all immune cell populations equally (as analyzed by flow cytometry), as no one immune cell population appeared to be preferentially protected by SP. Also, SP administration was also capable of protecting JP-8–exposed animals from loss of immune function at all aerosol concentrations of JP-8 utilized (up to 2.5 g/m^3).

Ullrich (1999) found that dermal exposure of female mice to JP-8, via either multiple small exposures (50 µl/d for 5 d) or a single large dose (250–300 µl), resulted in immune suppression. The induction of contact hypersensitivity was impaired in a dose-dependent manner regardless of whether the contact allergen was applied directly to the JP-8–treated skin or at a distant, previously untreated dermal site. In addition, the generation of a classic delayed type hypersensitivity reaction to a bacterial antigen (*Borellia burgdorferi*) injected into the subcutaneous space was suppressed by dermal application of JP-8 at a distant site. The ability of splenic T lymphocytes from JP-8–treated mice to proliferate in response to plate-bound monoclonal anti-CD3 was also significantly suppressed. Interleukin-10 (IL-10), a cytokine with potent immunosuppressive activity, was found to be upregulated in the serum of JP-8–treated mice, suggesting that the mechanism of systemic immune suppression may involve the upregulation of cytokine release by JP-8. JP-8–induced immunosuppressive effects were found to occur 24–48 h postexposure.

In one of very few studies of the potential toxicity of Jet A (the fuel used to power virtually all domestic commercial aircraft), Ramos et al. (2002) identified immunosuppressive effects similar to those reported for JP-8 dermal exposure. Mice were immunized with the fungal pathogen *Candida albicans* and, at different times after immunization (10 to 30 d), various doses of JP-8 or Jet A were applied dermally. Both the elicitation of delayed-type hypersensitivity (DTH) (mice challenged 10 d after immunization) and immunological memory (mice challenged 30 d after immunization) were significantly suppressed in a dose-dependent manner. Dermal exposure to either multiple small fuel doses across 4 d or a single large dose suppressed DTH to *Candida albicans*. Blocking the production of prostaglandin E(2) by a selective cyclooxygenase-2 inhibitor (SC 236) significantly reversed jet fuel-induced suppression of immunologic memory.

Finally, Ullrich and Lyons (2000) conducted follow-up studies in an effort to elucidate the mechanisms underlying JP-8–induced immunosuppression in mice. Again, it was shown that JP-8 exposure induced a highly selective effect on immune function. T-helper-1 cell-driven, cell-mediated immune reactions (i.e., delayed type hypersensitivity and immunity to intracellular microorganisms) and (CD3-driven) T-cell proliferation were (up to 100% suppression) modulated by JP-8, while antibody formation was not influenced. It is noteworthy to recognize that nearly identical suppression of T-helper-1 cell function occurs following exposure to ultraviolet radiation (i.e., sunlight) (Brown et al., 1995),

a possible cofactor during typical military JP-8 exposures. Further, it was shown that administration of interleukin-12 (IL-12), monoclonal anti-IL-10, and the selective cyclooxygenase-2 (COX-2) inhibitor SC 236 (all known to suppress release of IL-10) blocked JP-8–induced immunosuppression. It was hypothesized that JP-8 exposure (at least dermal or respiratory exposure) may induce release of prostaglandin E(2) (PGE2), initiating a cascade of events involving IL-4 and IL-10 that ultimately results in the specific immunosuppression previously described. Again, administration of IL-12, monoclonal anti-IL-10, or COX-2 blocked JP-8–induced immunosuppression.

Parker et al. (1981) exposed rats to a single dose of 18.9 g/kg JP-5 by oral gavage and reported increased RBC count, decreased WBC counts, and increased erythrocyte counts. NTP/NIH (1986b) reported extramedullary hematopoiesis by the spleen in mice receiving 500–8 g/d JP-5 by dermal administration, 5 d/wk for 13 wk. Additionally, granulocytic hyperplasia in the bone marrow and hyperplasia in the lymph nodes of some dermally exposed mice were reported. Male and female beagle dogs exposed continuously for 90 d to JP-5 (750 mg/m^3) exhibited a statistically significant decrease in hemoglobin volume and RBC count, a decrease in serum albumin levels, and sporadic modulation of blood urea nitrogen concentrations (Air Force, 1978). Female dogs exposed to 750 mg/m^3 and male dogs exposed to 150 or 750 mg/m^3 JP-5 vapor showed a significant increase in RBC fragility. Female rats exposed to 150 or 750 mg/m^3 JP-5 and male rats exposed to 750 mg/m^3 had significantly increased levels of creatine and blood urea nitrogen (Air Force, 1978).

Keil et al. (2002) exposed female mice by oral (2 g/kg/d) or dermal exposure (50 µl/subject/d) for 7 d to JP-8. Decreases in thymus weight and cellularity were observed in mice exposed orally, but not dermally. While no differences in JP-8–exposed mice (versus controls) were reported for NK cell activity, mitogen-induced lymphocytic proliferation, or splenic T-cell subpopulations, significant suppression of the plaque-cell-forming (PFC) response was observed following either dermal or oral routes of exposure.

No hematological effects were recorded in rats or dogs exposed to 100 mg/m^3 deodorized kerosene for 6 h/d, 5 d/wk, for 13 wk (Carpenter et al., 1976). Similarly, no microscopic or histopathological changes were identified in the spleens of kerosene-exposed rats or dogs. Beagle dogs exposed to 750 mg/m^3 JP-5 vapor/aerosol continuously for 90 d exhibited statistically reduced hemoglobin, RBC count, and RBC fragility, consistent with significantly decreased serum albumin levels (Air Force, 1978). In the same study, female rats exposed to 150 or 750 mg/m^3 or male rats exposed to 750 mg/m^3 for 90 d exhibited increased levels of creatine and blood urea nitrogen. In rats (20 mg/m^3) and dogs (10 mg/m^3), however, a slight increase was detected in the ratio of polymorphonuclear neutrophilic leukocytes at 13 wk. Rats exposed by oral gavage to a single kerosene dose (12 g/kg) exhibited no significant weight or histopathological change in the spleens (Muralidhara et al., 1982). Upreti et al. (1989) reported a decrease in splenic weights (without histopathological changes) and an organ/body weight decrease in the lymph nodes and thymus

(with reduced thymic lobule cellularity and thymic cortical lymphocytes) of male mice following daily dermal exposure to 0.1 ml kerosene for 7 d. Additionally, kerosene-exposed mice exhibited increased cellular populations of the popliteal and axial lymph nodes, as well as decreased bone marrow nucleated cell counts. In the same animals, reduced hemoglobin concentration, increased erythrocyte and WBC counts, and increased incidence of polymorphonuclear leukocytes were identified.

Rao and Pandya (1980) reported that kerosene, 3 or 20 h following a single ip injection in female rats, may inhibit hepatic delta-aminolevulinic acid (ALA) synthetase and delta-ALA dehydratase activities in the heme biosynthesis pathway, possibly accounting for some reported hematological changes in exposed animals. Interestingly, ip administration of benzene alone increased delta-ALA synthetase activity by up to 200% (Rao & Pandya, 1980), while administration of *n*-hexane or *n*-heptane alone significantly increased alkaline phosphatase activity (Goel et al., 1988), and administration of naphthalene alone (oral for 10 d) increased liver weight, lipid peroxidation, and aniline hydroxylase activity (Rao & Pandya, 1981). In further study, Rao et al. (1984) found that subcutaneous exposure of male Wistar rats to kerosene (0.5 ml/kg, 6 d/wk, for 35 d) resulted in increases in the weights of the spleen and peripheral lymph nodes, an increase in DNA, RNA, protein, and lipid contents of the spleen, and treatment-related lesions in the spleen, thymus, and lymph nodes. Biochemical assays identified significantly reduced serum acetylcholinesterase, carboxylesterase, and albumin, but increased levels of serum alkaline phosphatase activity.

Finally, it was shown that exposure to the anti-icing performance additives in some kerosene-based jet fuels may, alone, induce significant health effects. DiEGME is the predominant anti-icing additive used in jet fuels and has generally replaced EGME in JP-5 and JP-8. Male guinea pigs were dermally exposed to 1, 0.2, 0.04, or 0 g/kg/d DiEGME for 5 d/wk, 6 h/d, for 13 wk. Another group of animals was similarly exposed to 1 g/kg/d EGME. Splenic weights were reduced as a result of exposure to EGME (1 g/kg/d) or DiEGME (1 or 0.20 g/kg). Hematologic changes in EGME-exposed guinea pigs included mild anemia with increased erythrocytic mean corpuscular volumes and a lymphopenia with increased neutrophils. Similar hematological changes were not observed in animals exposed to DiEGME. Serum creatine kinase activity was increased in animals exposed to EGME, and serum lactate dehydrogenase activity was increased in EGME and 1 g/kg/d DiEGME-exposed animals (Hobson et al., 1986).

CENTRAL NERVOUS SYSTEM EFFECTS

There are only a small number of published studies reporting effects of repeated kerosene-based jet fuel exposure on human CNS or PNS function. In the AFIERA (2001) study of military workers occupationally exposed to JP-8, the high-dose exposure group, as compared to the low-dose exposure group

self-reported significantly more incidence of neurologically related symptoms, including dizziness, imbalance, walking difficulties, general weakness/fatigue, difficulty gripping objects, numbness/tingling of limbs, trouble concentrating, and forgetfulness, and numerically greater incidence of headache, blurry vision, tremors, and chronic pain.

Smith et al. (1997) reported the effects on postural balance of 0.8–30 yr (mean = 4.56 yr) of exposure to JP-8 (although some subjects also reported an exposure history to JP-4). Exposed subjects and matched controls were tested before the work shift (12–24 h rest from exposure) and again after 4–6 h of occupational exposure to JP-8. Subjects were evaluated for the capacity to maintain postural equilibrium on a standard postural balance platform during each of four testing conditions: (1) eyes open, stable platform; (2) eyes closed, stable platform; (3) eyes open, standing on 4 in foam; (4) eyes closed, standing on 4 in foam. Workers exposed for ≥9 mo to JP-4/JP-8 exhibited significantly increased postural sway patterns, relative to controls, but only during the most difficult testing condition, in which eyes were closed and the subject stood on a 4-in-thick section of packing foam. Performance deficits were correlated with breathing space and breath levels of benzene (5.03 ± 1.4 ppm), toluene (6.11 ± 1.5 ppm), and xylenes (6.04 ± 1.4 ppm), but not naphtha (491.6 ± 108.9 ppm). The reported deficits were subchronic/chronic and were not significantly modulated by the acute 4- to 6-h JP-8 occupational exposures. Further, in the AFIERA study (2001) of JP-8 occupational exposure, the high-exposure group, as compared to low-exposure controls, exhibited a significant deficit on testing for postural equilibrium during forward bending of the torso. This testing condition is generally considered to be more difficult than the "eyes closed, standing on foam" testing condition. It should be noted that workers in the AFIERA (2001) study were generally younger and reported less duration of exposure to JP-8 and no exposure history to JP-4, as compared to subjects tested in the previous study (Smith et al., 1997). Similar to the 1997 study result, deficits in postural equilibrium exhibited by workers with subchronic or chronic exposure to JP-8 were generally not exacerbated by acute exposure to JP-8. Persisting postural equilibrium deficits are known to reflect deficits in brainstem vestibular or proprioceptive control systems, but may additionally reflect deficits in peripheral proprioceptive mechanisms (Smith et al., 1997).

McInturf et al. (2001) measured learning of an eyeblink classically conditioned (Pavlovian) response (EBCC) in JP-8–exposed USAF personnel (JP-8; $n = 28$) and matched controls ($n = 46$). Subjects learned a classically conditioned association between an 85-dB, 1000-Hz tone (conditioned stimulus, or CS) and a 3–5-psi (pounds/in^2) corneal airpuff (unconditioned stimulus, or US), such that the CS eventually elicited an eyeblink response (conditioned response, or CR). Subjects were trained following a 14–72-h rest from occupational exposure, then relearned the task 30–90 min following a 4–6-h return to work. It was reported that JP-8–exposed personnel were significantly deficient, relative to controls, in both the acquisition (percentage of trials in which CR

was elicited by the CS) of the habit and the mean time from onset of the CS to the peak eyeblink response (CR). Deficits in EBCC acquisition are known to identify deficits in brainstem (e.g., cochlear, pontine, red nuclei) and cerebellar (e.g., nucleus interpositus) function (McInturf et al., 2001). Deficits in EBCC acquisition and performance appeared to reflect subchronic and chronic, but not acute, JP-8 exposure.

Odkvist et al. (1983, 1987) examined the effects of chronic exposure to jet fuel on audiological and vestibulo-oculomotor function in 8 jet mechanics exposed for 15–41 yr (mean = 25 yr). Although it is thought that much of the exposure of these workers occurred to jet fuels (i.e., MC77) containing a high percentage of unleaded gasoline, this study is reviewed for its similarity in CNS effects to those reviewed in the preceding paragraphs. Although there was no indication of any abnormal deficit in peripheral auditory mechanisms or thresholds, exposed workers exhibited significant deficit rates on Interrupted Speech Discrimination (38%) and Cortical Response to Frequency Glides (50%) tests. The former test, sensitive to lesions of the central auditory pathways and auditory cortex, evaluated capacity of subjects to discriminate human speech interrupted at 4, 7, or 10 times/s. The latter test, highly sensitive to lesions of the cerebello-pontine and other auditory pathways, required the subject to identify frequency glides, in a 1000-Hz tone, of 50 Hz or 200 Hz within 167 ms or 140 ms, respectively. The outcome of vestibulo-oculomotor tests indicated significant results on Broad-Frequency Visual Suppression and Broad Frequency Smooth Pursuit tests, but reflected no deficit in the sensory organs. For the former test, subjects were required to suppress the vestibulo-oculomotor reflex in order to fixate a dot on a full visual field screen moving with a rotating chair. Unlike during the testing of solvent-exposed workers, jet-fuel-exposed workers did not exhibit a significant deficit on the Visual Suppression test until it was made more difficult by use of broad frequency pseudo-random swings. In the latter test, subjects were asked to follow a small target moving at a velocity of 10 or 25°/s across a monitor, with the dependent measure being the eye speed between saccades. Values below 8 and 18°/s, respectively, were considered significantly abnormal. This research appears to indicate the workers exposed chronically to jet fuel (mean = 25 yr) may exhibit subtle deficits in the higher level inhibition (cerebellar, cortical, etc.) of brainstem functions, which may remain undetected without use of complex testing batteries. It was hypothesized that deficits in the oculomotor system commonly observed in animals and humans following hydrocarbon solvent exposures may reflect a decreased inhibition of the vestibulo-oculomotor reflex, presumably exerted by the cerebellum (Odkvist et al., 1983).

Olsen et al. (1998), evaluating a small number of military fuel workers during occupational exposure to JP-4, then again following USAF conversion to JP-8, reported several significant decreases in neurobehavioral function in workers following the JP-8 conversion, as compared to unexposed controls. Using the MicroCog neurocognitive functioning battery (tests of attention/mental control, memory, reasoning/calculation, spatial processing, and reaction

time), it was generally shown that unexposed workers scored numerically higher on all tests as compared to workers exposed occupationally to JP-4, then JP-8. On the Reaction Time index, a test of motor response speed, unexposed controls exhibited significantly faster reaction time scores than did JP-8 workers 6 months following the transition from JP-4 to JP-8.

Finally, the neurobehavioral capacity of USAF workers with high-dose occupational exposure to JP-8 was compared to that of workers with low-dose exposure (AFIERA, 2001). These military workers were evaluated 14–72 h following the last occupational exposure to JP-8, and again following a 4–6-h return to occupational responsibility. High-dose workers exhibited a number of significant deficits on the BARS/GASH (Behavioral Assessment and Research System/Global Assessment System for Humans) battery, as compared to the low-dose exposure group. Subjects classified as high JP-8 exposure exhibited significantly reduced performance (subchronic/chronic effect), relative to low exposure controls, on the following tests administered after a 14–72-h rest from occupational exposure:

1. Digit Span—Forward/Backward. A series of numbers was presented sequentially on a computer screen, and the subject was asked to reproduce the sequence on a numbered keyboard in the same order or in reverse order. The length of the sequence increased until a criterion was met, or the subject consistently failed.
2. Symbol Digit: A coding test in which digits were paired with symbols in a 2×9 matrix of squares on a computer screen. A similar matrix occurring at the bottom of the screen contained the symbols, but not the digits. The subject was required to type in the digit that was previously paired with each of up to nine symbols.
3. Tapping, Preferred Hand: The subject was instructed to press (tap) a designated console button as rapidly as possible, first with the index finger of the preferred hand, then of the nonpreferred hand (single tapping), then alternating between the index fingers of the preferred and nonpreferred hands (dual tapping).

The same subject group exhibited significantly reduced performance (acute effect), as compared to the initial testing session, when retested after a 4–6-h return to occupational responsibility (JP-8 exposure) on the following tests:

1. Tapping, Preferred Hand: As described earlier.
2. Dual Tapping: As described earlier.
3. Delayed Matching-to-Sample: DMTS is a test requiring the subject to view a complex visual pattern, then choose the pattern observed initially from three choices, presented following a short, variable delay.

Deficits in the high exposure JP-8 group appeared to reflect significant, acute, or subchronic/chronic reduction in higher cognitive capacity (Digit Span,

Symbol Digit, Matching-to-Sample tests), emphasizing impaired short-term memory, and in simple motor skills (Tapping tests).

A number of animal studies of kerosene-based jet fuel neurotoxicity have been published. Mattie et al. (1995) reported no clinical signs of neurotoxicity (functional observational battery, FOB) in female rats treated orally with 0–2 g/kg/d JP-8 from gestational d 6–15. Also this study indicated no histopathological changes in the brains or sciatic nerves of male rats administered 750, 1500, or 3000 mg/kg JP-8 by gavage once daily for 90 d.

Several studies reported the effects of repeated exposure (6 h/d, 5 d/wk, for 6 wk) of adult rats to JP-8 vapor (500 or 1000 mg/m^3) or JP-5 vapor (1200 mg/m^3). In these studies, it was shown that repeated JP-8 exposure modulated neurobehavioral capacity in several brain areas, and that this modulation persisted for up to 200+ d postexposure. Repeated JP-8 exposure to 1 g/m^3 reduced the capacity of rats to learn highly difficult (but not simple) operant tasks, compared to lower dose (500 mg/m^3) JP-8 or control exposures. In the most difficult task (Incremental Repeated Acquisition [IRA] test), rats were required, on a daily basis, to learn operant lever pressing sequence chains including from one (i.e., press the left lever) to four successive responses (i.e., press the left, then center, then left, then right lever) for food reinforcement. These results would appear to indicate that higher cortical systems in the rat may be modulated by repeated high-dose JP-8 exposure but not by repeated lower dose exposures, while systems responsible for simple learning tasks may be unimpaired (Ritchie, Rossi et al., 2001). Unexpectedly, in this study, rats repeatedly exposed to 500 mg/m^3 JP-8 vapor exhibited slightly improved performance on the most complex operant tasks, as compared to controls. The authors hypothesized that lower dose JP-8 exposures may have activated portions of the CNS (up to 200 d postexposure), an effect previously reported for operant responding following acute exposures to toluene (Glowa 1981; Wada et al., 1988; Wada, 1997, 1999).

Further, repeated exposure to 1 g/m^3 JP-8 was shown to significantly increase approach of the exposed rats to a novel appetitive stimulus, as compared to controls (Rossi et al., 2001). This result was interpreted as possibly indicating sensitization of the forebrain dopaminergic system. Examination of neurotransmitter levels in the brains and blood of JP-8–exposed rats indicated (1) a significantly increased level of dopamine (DA) in the cortex; (2) a significantly increased level of DOPAC (3,4-dihydroxyphenylacetic acid), the major metabolite of DA, in the brainstem; and (3) a decreased level of the serotonin (5-HT) metabolite 5-HIAA (5-hydroxyindole acetic acid) in the serum as long as 200+ d postexposure.

Baldwin et al. (2001) exposed rats to JP-8 vapor/aerosol (with or without substance P) for 1 h/d for 28 d (1059 mg/m^3 for 25 d, then to 2491 mg/m^3 for 3 d), then tested the animals using the functional observation battery (FOB), as well as the Morris water maze, a test of spatial discrimination and learning. While exposed rats (with or without substance P) exhibited no deficits on the Morris water maze, relative to controls, these rats exhibited significant postexposure

weight loss, increased rearing, reduced grooming, increased open-field spontaneous locomotor activity, and increased swimming speed relative to controls.

Repeated exposure to JP-5 vapor (1.2 g/m^3) induced a significant increase in forelimb grip strength, relative to controls (Rossi et al., 2001). The authors hypothesized that this fuel-induced change in neurobehavioral capacity may reflect long-term modulation of brainstem inhibitory systems. Additionally, the fuel-exposed rats exhibited a large numerical increase in approach to a novel appetitive stimulus, similar to the approach tendency of JP-8 vapor–exposed rats (Rossi et al., 2001). In the brains of JP-5–exposed rats, as measured up to 85 d postexposure, there was a significant increase in DA in the hippocampus relative to controls, a significant increase in DOPAC in the cerebral cortex, and a significant reduction in the serotonin metabolite homovanillic acid (HVA) in the hippocampus. Bogo et al. (1984) compared the relative neurobehavioral toxicity, for U.S. Navy applications, of petroleum-derived (P-JP-5) versus shale-derived (S-JP-5) JP-5 jet fuel. S-JP-5 contained higher percentages of alkanes, partially hydrogenated polynuclear aromatics, and other nitrogen-containing compounds than did P-JP-5. S-JP-5 was included in this study because the U.S. Navy (as part of the Navy Project Independence) utilized limited amounts of shale oil in the refining of JP-5, although this is an uncommon source in the refining of other jet fuels (Bogo et al., 1984). Adult Sprague-Dawley rats were either orally (3–8 ml/kg or 24 ml/kg) dosed one time, or were exposed by inhalation for 30 d (1100 mg/m^3) to JP-5 vapor/aerosol. Among the orally gavaged groups, subjects lost up to 30% of body weight within 4 d postexposure. This change, however, was reversed to normal levels by 7 d postexposure. Water volume intake, among both S-JP-5 and P-JP-5 groups, was reduced by up to 30% during the first 2 d postexposure, but increased by 4 to significantly above control levels. However, S-JP-5–exposed rats exhibited water volume intakes of nearly 200% of baseline on d 4 postexposure, and continued to show increased water consumption throughout the remainder of the 36-d study. Additionally, P-JP-5–exposed rats exhibited significantly increased home cage activity at 2.5–6 h postexposure, but a subsequent significant reduction in home cage activity, relative to controls, during the remainder of the study. Additional studies of rotarod performance, somatosensory evoked potential (SEP), and shock-induced aggression produced no differences between fuel-exposed and control animals. From the inhalation studies, a significant polydipsia was recorded, relative to controls, on exposure d 8 for P-JP-5–exposed rats, and on d 9 for S-JP-5–exposed animals. From d 13–36, both exposure groups consumed significantly more water than did controls. While the increased water volume may have reflected fuel-induced renal toxicity, it remains unknown if this observation may have reflected a behavioral sensitization of the CNS. This apparent polydipsia may be consistent with the fuel induced changes in appetive approach reported by Ritchie, Rossi et al. (2001) and Rossi et al. (2001).

In combination, these studies of subchronic or chronic exposure of humans or animals to JP-5 or JP-8 would appear to indicate persisting changes

in at least cortical, brainstem, and cerebellar systems, as manifested by changes in neurobehavioral capacity and/or neurotransmitter levels. Baldwin et al. (2001) concluded that repeated exposure of rats to JP-8 aerosol results in increased arousal levels and locomotor activity akin to repeated psychostimulant administration that is mediated by the mesolimbic dopaminergic system.

Although repeated respiratory inhalation of kerosene vapor or combustion exhaust is very common in countries using this fuel for illumination, cooking, and heating, and accidental oral ingestion of the fuel may be a major source of childhood poisoning, there is a minimal scientific literature detailing possible kerosene-induced neurotoxic health consequences. Acute exposure to kerosene in humans, as a function of increasing dose, was reported to result in irritability, restlessness, ataxia, drowsiness, convulsions, semiconsciousness, unconsciousness, or death (Aldy et al., 1978; Akamaguna and Odita, 1983; Mahdi, 1988; Majeed et al., 1981, 1988; Dudin et al., 1991; Lucas, 1994). Similarly, long-term exposure to low kerosene vapor concentrations was reported to produce non-specific CNS symptoms, such as nervousness, loss of appetite, and nausea (WHO Working Group, 1985), that may not be related to possible hypoxia effects. Carpenter et al. (1976) indicated that human exposure to 140 mg/m^3 vapor for 15 min resulted only in olfactory fatigue and an unusual taste sensation.

Edelfors and Ravn-Jonsen (1992), using rat CNS synaptasomal membranes, reported that exposure to the in vitro preparation to kerosene resulted in reduced activity of the enzyme (Ca^{2+}/Mg^{2+})-ATPase and subsequently increased levels of intracellular Ca^{2+}, resulting in increased neurotransmitter release. This result may provide an alternative to the hypoxia mechanism for kerosene-induced neurobehavioral effects.

There is one published study of the in vitro effects of acute exposure to JP-8 on nervous system tissue. Grant et al. (2000) investigated the in vitro cytotoxicity and electrophysiological effects of JP-8 on neuroblastoma x glioma (NG108-15) cell cultures, as well as on embryonic hippocampal neurons. Acute JP-8 (in 0.5% ethanol) exposure of the hippocampal neurons proved to be highly toxic (IC_{50} of $<2\,\mu$g/ml), while, in contrast, the NG108-15 cells were much less sensitive. Electrophysiological examination of NG108-15 cells showed that incubation with JP-8 at 1 μg/ml did not alter significantly any of the electrophysiological properties. However, exposure to JP-8 at 10 μg/ml during a current stimulus of +46 pA decreased the amplitude of the action potential to 83 ± 7%, the rate of rise (dV/dt_{MAX}) to 50 ± 8%, and the spiking rate to 25 ± 11% of the corresponding control levels. These results demonstrate JP-8–induced cytotoxicity varies among cell types, and for the first time that CNS neurons may alter electrophysiological function without cell death in response to JP-8 exposure.

Additionally, there is one published study of the effects of hydrocarbon fuels exhaust on the rat brain. Microinjection of exhaust emissions containing PAHs and nitro-PAHs into the hippocampus or striatum induced significant lesions, with tissue loss and disappearance of immunoreactivity for glial fibrillary acidic protein (GFAP), tyrosine hydroxylase activity, and AChE activity

(Andersson et al., 1998). A comprehensive review of the neurotoxicity of acute and repeated exposure to various hydrocarbon fuels and solvents was recently published (Ritchie, Still et al., 2001).

OCULAR AND AUDITORY SYSTEMS

As previously indicated, self-reported health effects from occupational fuel workers may include tearing of the eyes and blurred vision (Ritchie, Still et al., 2001; AFIERA, 2001). Two aviators exposed to a high level of JP-5 reported a burning sensation in the eyes, while one experienced itching, watering eyes for 24 h postexposure. One of the aviators was diagnosed with hyperemic conjunctiva that persisted for 4 d postexposure (Porter, 1990). Eye irritation, however, was not reported by 6 volunteers exposed for 15 min to 140 mg/m^3 deodorized kerosene vapor (Carpenter et al., 1976). There are no reports of more serious human eye injury from repeated exposure to kerosene-based jet fuel vapor or aerosol.

There are few animal studies examining ocular irritancy in response to laboratory exposure to kerosene-based jet fuels. Kinkead et al. (1992a, 1992b), after applying 0.1 ml neat JP-5 or JP-8 to the conjunctiva of rabbits, reported no ocular irritancy 20–30 s postexposure. Vernot et al. (1990a) reported minimal eye irritation (Draize scoring technique) in rabbits following corneal surface exposure to 0.1 ml neat Jet A for 20–30 s.

McGuire et al. (2000) evaluated whether brief (1 h/d for 7 d) inhalation exposure of mice 1 or 2.5 g/m^3 JP-8+100 (containing 2,6-di-*tert*-butyl-4-methylphenol, as the antioxidant) would result in possible toxicity of the retina. It was shown that JP-8+100 exposure resulted in significant increases in reactivity to anti-glutathione-*S*-transferase *mu*-1 (GSTM1) antibodies in the radial glial Muller cell perikarya and fibers, as compared to controls. It was concluded that increased expression of GST detoxification isoenzymes in the retinas of JP-8+100–exposed mice indicated possible toxicity in this sensory organ, with the possibility of resultant increased passage of xenobiotics across the retinal-brain barrier.

There are no human or animal studies indicating peripheral auditory system deficits following acute or repeated exposure to kerosene-based jet fuels, although there is a significant literature detailing such deficits in animals or humans exposed repeatedly to doses of toluene higher than those found in jet fuels (Morata et al., 1997; Campo et al., 1999; Hougaard et al., 1999; McWilliams et al., 2000).

RENAL SYSTEM EFFECTS

There are no published studies indicating kerosene-based jet fuel–induced deficits in the renal systems of humans. In the AFIERA (2001) study of JP-8 occupational exposure, there were no significant health effects involving the renal system, or increased incidence of related, self-reported health complaints.

Acute human inhalation exposure to JP-5 vapor/aerosol resulted in no detectable renal system effects (Porter, 1990). However, children and adults accidentally poisoned with kerosene by oral ingestion, while typically exhibiting normal urinalysis tests, may reflect albuminuria in a few cases (Nouri & Al-Rahim, 1970; Mahdi, 1988; Dudin et al., 1991).

There are a number of studies indicating significant, and sometimes fatal renal complications in male rats exposed repeatedly to JP-8, JP-5, or kerosene. Alden (1986) concluded that the majority of male rats that may die during or following repeated exposure to kerosene-based jet fuels typically exhibit renal complications.

Acute oral exposure of rats to as much as 12 g/kg kerosene or 12.15 g/kg deodorized kerosene resulted in no change in kidney/body weight ratio, and only slight cellular infiltration and vacuolization (Muralidhara et al., 1982). Hyaline droplets were found in the kidneys of 2 male rats that died 48 h following an acute exposure to 47.2 g/kg by oral gavage (Parker et al., 1981), although the effect was not seen in rats that died in less than 48 h, or in rats that survived more than 14 d following oral gavage exposure to 18.9–37.8 g/kg. In the majority of rats that died in less than 14 d of receiving an oral gavage dose of 19–48 g/kg JP-5, eosinophilic hyaline droplets were found in the cytoplasm of epithelial cells in the kidney proximal tubules (Bogo et al., 1983).

Lymphocytic inflammation was induced in the urinary bladder of mice during chronic dermal application of JP-5 (NTP/NIH, 1986b), although shorter duration dermal exposures to kerosene or JP-5 did not induce renal toxicity (NTP/NIH, 1986b; Upreti et al., 1989). In another repeated exposure study, male and female rats and female mice were exposed to petroleum-derived or shale-derived JP-5 vapor (150 or 750 mg/m^3) for 90 days (MacEwen & Vernot, 1985). Immediately postexposure, approximately 75% of male rats sacrificed exhibited nephrosis and renal tubular necrosis. Mattie et al. (1991) exposed Fischer-344 rats and C57Bl/6 mice of both sexes to JP-8 vapor by whole-body inhalation at 0, 500, and 1000 mg/m^3 on a continuous basis for 90 d, and then allowed recovery until approximately 24 mos of age. In a number of male rats, the kidneys developed a reversible ultrastructural increase in size and propensity for crystalloid changes of phagolysosomal proteinic reabsorption droplets in the proximal convoluted tubular epithelium. A specific triad of persisting light microscopic renal lesions occurred, but functional change was limited to a decrease in urine concentration compared to controls that persisted throughout the recovery period. Specifically, hyaline droplets were formed in the cytoplasm of the proximal tubule cells of the renal cortex. The hyaline droplets contained high concentrations of the protein alpha 2μ-globulin. It is hypothesized that the protein accumulates in the cytoplasm of the tubules, as binding slows the normal degradation of the protein with chemical constituents of JP-8 or their metabolites. The tubules near the corticomedullary junction become dilated and filled with coarsely granular casts and necrotic debris, resulting in nephron obstruction and chronic necrosis (Bruner, 1984; Alden, 1986; Mattie et al., 1991). While initially there was substantial concern for a similar fuel-induced renal toxicity in exposed humans, all available evidence indicates that the alpha 2μ-globulin

protein is synthesized exclusively by adult male rats (but not by male mice). While other species, including humans, synthesize proteins that share significant homology with alpha 2μ-globulin, none of these proteins have been shown to induce a similar renal toxicity (Flamm & Lehman-McKeeman, 1991). This type of hydrocarbon exposure (i.e., jet fuels, gasoline, etc.) toxicity was shown to progress in some cases to kidney cancer in the male rat (Bruner, 1984) but, again, is not considered relevant to humans (Flamm & Lehman-McKeeman, 1991).

In a follow-up study, Mattie et al. (1995) exposed male Sprague-Dawley rats by oral gavage for 90 d to 750, 1500, or 3000 mg/kg/d JP-8. As with inhalation exposures (Mattie et al., 1991), significant quantities of hyaline droplets were detected in the kidneys of male rats in all exposure groups. Urine samples were collected within 24 h postexposure and analyzed for protein, creatine, total volume, and metabolite content. Although observed results were not necessarily dose related, the following significant differences, compared to controls, were reported for at least one of the three exposure groups: (1) sodium, increased; (2) chloride, increased; (3) glucose, decreased; (4) total bilirubin, increased; (5) creatine, increased; (6) total triglycerides, decreased; (7) aspartate aminotransferase activity, increased; and (8) alanine aminotransferase (ALT) activity, increased. Additionally, four metabolites (retention times, 11.84, 12.82, 13.68, 16.05 min) were identified in the urine of one or more fuel-exposed groups that were not present in the urine of controls.

Recently, Witzmann, Carpenter et al. (2000) found that repeated exposure of male Sprague-Dawley rats to 1 g/m^3 JP-8 vapor (6 h/d, 5 d/wk for 6 wk) resulted in a significant modulation of expression (from −36% to +315% of control) of several renal proteins, as measured 82 d postexposure. These proteins were generally involved in kidney ultrastructure or in the detoxification of systemic xenobiotics. Exposure of male mice to aerosolized JP-8 (1 g/m^3 for 1 h/d, for 5 d) resulted in a significant modulation of expression (from −22% to +178% of control) of several renal proteins related to ultrastructural abnormalities, altered protein processing, metabolic effects, and paradoxical stress protein/detoxification system responses (Witzmann, Bauer et al., 2000). Research indicates statistically significant upregulation or downregulation of the expression of 77–96 different proteins in the renal cortex of male Sprague-Dawley rats exposed to JP-8 vapor (250, 500, or 1000 mg/m^3) 6 h/d, continuously for 91 d (personal communication, Witzmann).

HEPATIC SYSTEM EFFECTS

There are no published studies on hepatic function in humans exposed to kerosene-based jet fuels. Dossing et al. (1985), however, reported persisting (2–4 wk postexposure) increased liver metabolism (i.e., antipyrine clearance) in 91 jet fueling personnel exposed repeatedly to European jet fuels that may have contained a high gasoline content. In these subjects, serum aspartate aminotransferase (AST) and alkaline phosphatase activities were unchanged

from controls. A similar result, including increased liver metabolism of both antipyrine and metronidazole, was found in 18 gasoline filling station attendants (Dossing et al., 1988).

A large number of animal studies have been conducted with multiple routes of exposure (acute or repeated) to kerosene-based jet fuels or kerosene that indicate at least short-term hepatotoxicity. Parker et al. (1981) exposed male Sprague-Dawley rats orally to a single dose of shale-derived or petroleum-derived JP-5 at 24–60 ml/kg (18.9–47.2 g/kg). Establishing an LD_{50} of >60 mg/kg for petroleum-based JP-5, it was noticed that deceased animals had swollen and mottled livers with accentuated lobular patterns and hepatocytic necrosis, while surviving rats showed hepatic periportal fatty changes, and significantly increased activities of serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), and lactate dehydrogenase (LDH). In continuing studies (Parker et al., 1981; Bogo et al., 1983, 1984), rats administered a single oral gavage dose of 24 ml/kg (18.9 g/kg) JP-5 and sacrificed 1–3 d later exhibited swollen and mottled livers, with degeneration of periportal hepatocytes. LDH, SGOT, and SGPT activity levels were increased in most animals from 6 h to 5 d postexposure. Liver sections indicated mitotic figures and increased numbers of binucleated cells. However, when male Sprague-Dawley rats were exposed to 1.1–1.6 g/m^3 JP-5 vapor, 6 h/d, 5 d/wk for 6 wk, there was no significant liver pathology or changes in serum liver enzyme activity levels.

In a series of subchronic inhalation studies, male and female beagle dogs, male and female F-344 rats, and female C56Bl/6 mice were exposed to JP-5 (150 or 750 mg/m^3) vapor continuously for 90 d (MacEwen & Vernot, 1978, 1980, 1981, 1982, 1983, 1985; Gaworski et al., 1984, 1985). In 100% of dogs exposed to 750 mg/m^3 JP-5 vapor and in 33% of those exposed to 150 mg/m^3, liver swelling and clouding of hepatocytes was observed; in some dogs with high exposure, increased liver weights and liver/body weight ratios and decreased SGPT activity levels were also seen (MacEwen & Vernot, 1978). In rats exposed to 750 mg/m^3 shale-derived JP-5 vapor continuously for 90 d, both males and females exhibited liver vacuolization that was also present in females exposed to 150 mg/m^3. In a study of lesser duration exposure to JP-5 vapor (no aerosol phase), there were no adverse liver or serum enzyme effects in rats exposed for 6 h/d, 5 d/wk for 6 wk (Bogo et al., 1984). In mice exposed to 150 mg/m^3 or 750 mg/m^3 petroleum-derived JP-5 vapor for 90 d, females (no males tested) exhibited focal fatty changes and diffuse cytoplasmic vacuolation in the liver postexposure that was not present at the end of a 19- or 21-mo follow-up. Interestingly, in a preliminary study, female C56Bl/6 mice were exposed continuously to 1.5 g/m^3 JP-5 respirable aerosol for 6 d, resulting in the death of over 50% of the mice.

Mattie et al. (1995) dosed male rats by oral gavage with JP-8 (750, 1500, 3000 mg/kg) daily for 90 d. Although there were no histopathological or weight changes in the livers of exposed rats, there was an increase in the activities of liver enzymes AST and alanine aminotransferase (ALT). There was a significant liver/body weight increase in JP-8-exposed rats, in a dose–related manner, as

well as an increase in total bilirubin and a decrease in triglycerides in exposed groups. Dudley et al. (2001) reported that oral gavage exposure of mice to 1 or 2 g/d JP-8 for 7 d resulted in significant increases in liver weight and liver/body weight ratio, compared to controls.

Muralidhara et al. (1982) exposed mice to single doses of 12 g/kg kerosene or 12.15 mg/kg deodorized kerosene with no significant hepatic effects, although mild cellular infiltration and liver vacuolization was noted in some subjects. Starek and Vojtisek (1986) reported in vitro inhibition of respiration of liver tissues in rats acutely administered high doses of kerosene by oral gavage, and impairment of the biotransformation of hexobarbital and phenacetin using in vivo preparations. Additionally, acutely dosed rats exhibited an increase in concentration of lactate and pyruvate in the blood and liver, a decrease in glucose concentration in the blood, and reduction of glycogen content in the liver and skeletal muscle, with an increase of LDH activity in the liver.

Rao et al. (1984), exposing male Wistar rats to kerosene (subcutaneous, 0.5 ml/kg, 6 d/wk, for 35 d), reported increases in the liver weight, with an increase in DNA, RNA, protein, and lipid contents of liver, lesions of the liver, and an increase in liver alkaline phosphatase activity and a decrease in benzo[a]pyrene hydroxylase levels.

Using electrophoretic techniques (proteomic assay), Witzmann et al. (2000a) determined that exposure of male rats to 1 g/m^3 JP-8 vapor for 6 h/d, 5 d/wk, for 6 wk resulted in a persisting numerical, but not significantly different, increase in total abundance of lamin A (NCBI Accession No. 1346413) in the liver. Lamin A is hypothesized to be important in nuclear membrane integrity. Research indicates statistically significant upregulation or downregulation of the expression of 107–117 different hepatic proteins in the livers of male Sprague-Dawley rats exposed to JP-8 vapor (250, 500, or 1000 mg/m^3) 6 h/d, continuously for 91 d (personal communication, Witzmann, Bobb et al., 2002).

Grant et al. (2000), exposing H4IIE liver cells to JP-8 in 0.5% ethanol, demonstrated a mean inhibitory concentration (IC_{50}) of 12.6±0.4 μg/ml. Comparison of JP-8 toxicity for exposure of hepatic (H4IIE) cells with similar exposure of several CNS cell lines indicated significantly less sensitivity in liver cells.

Finally, it was demonstrated that the PAHs in hydrocarbon fuels or combustion exhaust will, in the presence of an active AhR induce expression of a number of phase 1 enzymes (e.g., cytochrome P-4501A1) and phase 2 enzymes (e.g., glutathione *S*-transferase) in the liver. This effect was demonstrated both through in vitro investigations (Franzen et al., 1988; Kress and Greenlee, 1997; Lewtas et al., 1997) and through detection of increased oxidative metabolism of antipyrine, aminopyrine, ethlymorphine, aniline, and benzo[a]pyrene in rats or humans (fuel filling attendants) (Dossing et al., 1985, 1988).

CARDIOVASCULAR SYSTEM

Mild hypertension was reported for 4 d postexposure in one of two aviators exposed for <1 h to a high concentration of JP-5 (Porter, 1990). In the AFIERA

study (2001) of occupational JP-8 exposure, there was significantly more self-reporting of chest tightness and numerically increased self-reporting of heart palpation in high-dose versus low-dose exposure groups, although there were no differences between these groups in medical visits for these symptoms. Tachycardia was reported in children accidentally poisoned with kerosene (Coruh & Inal, 1966; Akamaguna & Odita, 1983).

In animals, Mattie et al. (1995) reported no histopathological changes in the hearts of male rats administered 750, 1500, or 3000 mg/kg JP-8 by oral gavage once daily for 90 d. In studies to determine the LD_{50} by oral gavage for JP-5, Parker et al. (1981, 1986) reported cardiovascular collapse that was unrelated to myocardial necrosis in male Sprague-Dawley rats that died. However, rats dosed with approximately 20 g/kg JP-5 exhibited no increase in enzymes indicative of myocardial insult (serum creatine phosphokinase) when necropsied 3 d postexposure.

Carpenter et al. (1976) reported no treatment-related histopathological changes in the heart tissues of rats or beagle dogs with low-dose kerosene exposures (100 mg/m^3, 6 h/d, 5 d/wk, for 13 wk). There were no significant changes in heart weight or histopathology in rats following a single oral gavage exposure to 12–12.15 g/kg kerosene (Muralidhara et al., 1982). Noa and Illnait (1987a, 1987b), exposing guinea pigs to an extremely high vapor/aerosol concentration of kerosene (20.4–43 g/m^3) 15 min/d for 21 d, reported induction of aortic plaques that resembled those seen in arteriosclerosis in that species. Additionally, these authors measured significantly increased serum cholesterol and decreases in high density lipoprotein (HDL) in the exposed guinea pigs.

There is no published evidence of cardiac epinephrine sensitivity responses to kerosene-based jet fuels in either humans or animals, although it was shown that several components of kerosene-based jet fuels (i.e., benzene) are potent inducers of cardiac arrhythmia at ≥155 g/m^3 in the presence of epinephrine (Chenoweth, 1946).

MUSCULOSKELETAL EFFECTS

There are no human studies indicating musculoskeletal system effects from kerosene-based jet fuel exposure in humans. However, the AFIERA study (2001) of JP-8 occupationally exposed workers indicated that high-dose exposure, as compared to low-dose exposure, resulted in significantly more self-reported complaints of general weakness/fatigue, difficulty gripping objects, and numbness/tingling of limbs, as well as a numerically greater incidence of self-reported generalized pain.

Mattie et al. (1995) reported no histopathological changes in the sternum or skeletal muscle of male rats administered 750, 1500, or 3000 mg/kg JP-8 by gavage once daily for 90 d. In beagle dogs and rats, exposure to up to 100 mg/m^3 deodorized kerosene for 6 h/d, 5 d/wk, for 13 wk resulted in no histopathological changes in the musculoskeletal system (Carpenter et al., 1976). Mice treated dermally with JP-5 (up to 500 mg/kg, 5 d/wk, for 90 or 103 wk) did not develop adverse musculoskeletal effects (NTP/NIH, 1986b).

ENDOCRINE SYSTEM

There are no published studies of JP-8–induced deficits on the endocrine systems of humans, although results of the AFIERA (2001) study of JP-8 occupational exposure effects for the endocrine system were not complete at the time of publication of this report.

Mattie et al. (1995) reported no histopathological changes in the adrenal glands or pancreas of male rats administered 750, 1500, or 3000 mg/kg JP-8 by gavage once daily for 90 d. There were no histopathological changes in the adrenal glands or in relative adrenal gland weights in rats following single-dose administrations by oral gavage of up to 12 g/kg kerosene or 12.15 g/kg deodorized kerosene (Muralidhara et al., 1982). Similarly, Upreti et al. (1989) reported no adrenal gland effects with repeated dermal exposure of mice to kerosene. Rao et al. (1984), however, reported adrenal lesions in male rats exposed subcutaneously to kerosene (0.5 ml/kg, 6 d/wk for 35 d).

METABOLIC EFFECTS

There are no published studies of metabolic function in humans following kerosene-based jet fuel exposure, and very few animal studies specifically examining fuel-induced changes in metabolism. There are, however, a very large number of studies reviewed in other sections of this report that indicate fuel-induced changes in gene or protein expression in specific organ or cellular systems that are known to influence metabolic processes.

In rodents, there are a large number of studies indicating transient reduced weight or rate of weight gain, as compared to controls, during inhalation, dermal, or oral exposure to kerosene-based jet fuels. These studies are discussed in a previous section of this article. There were no significant metabolic changes indicated in blood chemistry assays of rats exposed continuously to JP-8 vapor (500 or 1000 mg/m^3) for 90 d (Mattie et al., 1991). Starek and Vojtisek (1986) reported decreased blood glucose levels in rats after repeated inhalation exposure to kerosene vapor averaging 58 mg/m^3 and increases in blood lactate and pyruvate levels at a mean concentration of 231 mg/m^3.

REPRODUCTIVE AND DEVELOPMENTAL EFFECTS

There are only two published studies of possible kerosene-based jet fuel exposure effects on the human reproductive system, and one published human study of developmental effects from kerosene exposure. In the first reproductive study, LeMasters et al. (1999) examined a number of sperm parameters (sperm concentration, sperm motion, viability, morphology, morphometrics, and stability of sperm chromatin) in USAF personnel exposed repeatedly to JP-8/JP-4 and/or hydrocarbon solvents. A comparison of sperm parameters preexposure versus after 15–30 wk of occupational responsibility indicated no significant differences for any measure. In a developmental study of kerosene effects, Bunin

et al. (1994) reported a significant association between repeated use of kerosene fuel during pregnancy and subsequent development of astrocytic glioma (astrocytoma) and primitive neuroectodermal tumor (PNET) in intrauterinally exposed children.

No histological changes were noted in the reproductive systems of male or female mice dermally exposed to 2–8 g/kg JP-5, 5 times/wk for 13 wk, or in mice exposed to 250 or 500 mg/kg JP-5 5 times/wk for 103 wk (NTP/NIH, 1986). Two recent animal studies similarly examined the effects of 91 d of exposure (6 h/d, 7 d/wk) to JP-8 vapor (0, 250, 500, or 1000 mg/m^3) or exposure for 6 h/d, 5 d/wk for 6 wk to 1 g/m^3 JP-8 vapor on the reproductive systems of adult male Sprague-Dawley rats (Briggs et al., 1999, 2001). No significant effects on sperm morphology, quality, or concentration were reported for any exposure concentration. Sperm motility measures, however, indicated a dose-related decrease in motility that was significantly different from controls (1000 mg/kg vs. 0 mg/kg groups). Proteomic analysis of testis samples from control and JP-8–vapor-exposed rats identified seventy-six different testis proteins were significantly increased (83%) or decreased (17%) in abundance in vapor-exposed groups as compared to controls, although dose-response profiles were often non-linear. For example, significantly over-expressed proteins included: mitochondrial aldehyde dehydrogenase (ALDH1), androgen receptor-associated protein 24, calreticulin, HSP 86, integrin beta-7 subunit, IL-18, lactate dehydrogenase, lamin B, osmotic stress protein 94, protein kinase C-binding protein Zeta-1, serum albumin, sperm-associated Tat-binding protein, and T-complex polypeptide 1 (Witzmann et al., 2003). The downregulation of several proteins expressed during spermatogenesis may suggest reduced spermatogenesis with longer duration exposures to JP-8.

Because approximately 12% of active-duty USAF, Navy, and Army personnel are women of childbearing age, there is increasing interest in possible reproductive or developmental effects of jet fuel exposure. Cooper and Mattie (1996) reported that JP-8 did not produce fetal malformation after oral exposure (0, 500, 1000, 1500, or 2000 mg/kg/d) exposure of pregnant rat dams during gestation d 6–15. Dams in the 1-, 1.5-, and 2-g/kg/day groups gained significantly less body weight during pregnancy than did controls. Embryo toxicity was, however, indicated by a significant reduction in fetal body weight (13–15%) in the 1.5- and 2-g/kg/day dose groups. In continuing research, Mattie et al. (2001) exposed female rats by oral gavage to 0, 325, 750, or 1500 mg/kg/day JP-8 for 21 wk, including 90 d prior to gestation and lactation. Body weights from the high-dose group were significantly decreased, relative to controls, on postnatal d 4–21. Developmental testing indicated no marked differences among exposure groups and controls for surface righting and negative geotaxis. For swimming ability, however, there was a significant dose-related reduction in exposed versus control animals, leading the authors to hypothesize a fuel-related delay in development of coordinated motor movements related to the swimming task.

Schreiner et al. (1997) evaluated the reproductive and developmental toxicity of HDS kerosene applied dermally in Sprague-Dawley rats. Although the kerosene was diluted with mineral oils to minimize dermal irritation, dermal

absorption similar to neat kerosene exposure was reported. Kerosene was administered at 494 (60% kerosene), 330 (40%), or 165 (20%) mg/kg/d for 7 wk (premating, mating to d 19 of gestation) to females, and for 8 wk to males. Dams and litters were sacrificed on postpartum d 4 and males were sacrificed within the following week. Kerosene exposure produced slight to moderate skin irritation at the highest dose (494 mg/kg/d) in both sexes but no apparent maternal, reproductive, or developmental toxicity. Additionally, no clinical signs of toxicity and no effects on body weight, food consumption, or absolute organ weights were observed. Relative kidney weights were heavier than controls in male rats at the high dose. There were no marked differences in mean number of corpora lutea, implantation sites, and live pups per litter, and no gross or microscopic deficits were observed in the male or female reproductive organs. Pups born from treated dams showed body weights and weight gains comparable to controls. Finally, Harris et al. (2000) reported reduced natural killer (NK) cell function in mice following brief, repeated exposure to JP-8 aerosol. Lanier (1999) hypothesized that reduced NK cell function in female rodents may result in reduced placentation during gestation and, thus, impaired reproductive ability.

Finally, Hobson et al. (1986) reported that male rats exposed dermally for 13 wk to 1 g/kg/d of EGME, an anti-icing additive in some kerosene-based jet fuels, resulted in significantly reduced testicular weights. Similarly, inhalation exposure of male rats to EGME for 4 h at 1.9 or 3.1 g/m^3 resulted, respectively, in spermatid damage or testicular atrophy (Johanson, 2000).

GASTROINTESTINAL SYSTEM

One of two pilots exposed to an undetermined concentration of JP-5 for $<$1 h reported feelings of nausea for $<$24 h (Porter, 1990). In the AFIERA study (2001) of JP-8 occupational exposures, there were no differences between high-dose exposure and low-dose exposure groups in either self-reporting of, or medical visits for, gastrointestinal system symptoms. Long-term human exposure to low kerosene vapor concentrations has, however, been reported to produce nonspecific CNS symptoms related to the GI tract, such as loss of appetite and nausea (WHO Working Group, 1985).

In animals, Mattie et al. (1995) reported gastritis and hyperplasia (stratum corneum of squamous portion) of the stomach, as well as anal dermatitis and hyperplasia in male rats administered 750, 1500, or 3000 mg/kg JP-8 by gavage once daily for 90 d. No histopathological changes were reported in the gastrointestinal systems of dogs or rats exposed to up to 100 mg/m^3 kerosene vapor for 6 h/d, 5 d/wk for up to 13 wk (Carpenter et al., 1976).

GENOTOXIC EFFECTS

There is minimal published human research concerning possible genotoxicity arising from repeated kerosene-based jet fuel exposure. Results of the AFIERA

(2001) occupational JP-8 study for several measures of human genotoxicity were not available at the time of publication of this manuscript. Pitarque et al. (1999) measured SCE, MN, and the Comet (single-cell gel electrophoresis) assay to evaluate genetic damage in peripheral blood lymphocytes from 34 male workers at Barcelona, Spain, airport exposed to low levels of jet fuel (Jet A-1) and hydrocarbon solvents. SCE and MN analyses failed to detect any statistically significant change in the airport workers when compared with controls. The frequency of binucleated cells with MN in the exposed group was, in fact, significantly lower than for controls. However, significant differences in the mean comet length and genetic damage index were observed between the exposed and control groups.

In an extensive in vitro study, JP-8 was evaluated for genotoxicity using the following assays: Ames, mouse lymphoma, unscheduled DNA synthesis, and dominant lethal. JP-8 was not mutagenic in the Ames assay and did not induce mutation in mouse lymphoma cells. In the unscheduled DNA synthesis tests, it was shown that JP-8 exposure induced significant incorporation of radiolabeled thymidine, indicating unscheduled DNA synthesis. In the dominant lethal assay in both mice (0.13–1.3 ml/kg) and rats (0.1–1 ml/kg), JP-8 exposure did not induce genetic damage in germ cells. In all assays, JP-8 was cytotoxic at concentrations of ≤5 µl/ml (Brusick & Matheson, 1978).

Recently, Grant et al. (2001) investigated the in vitro genotoxicity of JP-8 on H4IIE rat hepatoma cells. DNA damage was evaluated using the Comet assay. Cells were exposed for 4 h to JP-8 (solubilized in ethanol at 0.1% [v/v]) to concentrations ranging from 1 to 20 µg/ml. Exposure to JP-8 resulted in an overall increase in mean comet tail moments. Addition of DNA repair inhibitors hydroxyurea (HU) and cytosine arabinoside (Ara-C) to cell culture with JP-8 resulted in accumulation of DNA damage strand breaks and an increase in comet tail length. JP-8, in the concentrations used in this study, did not result in cytotoxicity or significant apoptosis, as measured using the terminal deoxynucleotidyl transferase (TDT)-mediated dUTP-X nick end labeling (TUNEL) assay. These results demonstrated that concentration-relevant exposures to JP-8 result in DNA damage to H4IIE cells and suggested that DNA repair is involved in mitigating these effects. JP-5 was reported to induce no mutagenicity in the Ames assay when activated with S9 (Aroclor-induced rat liver enzymes) (Schultz et al., 1981), or in *Salmonella typhimurium* preincubation assays (NTP/NIH, 1986b).

Genomics research evaluating the effects of repeated exposure (6 h/d for 91 d) to JP-8 in vapor phase (1 g/m^3) on whole brain tissue indicates that 5 identified genes were significantly upregulated, while 2 others were downregulated (Lin et al., 2001). The induced genes, according to their presumed functions, included: (1) glutathione *S*-transferase Yb subunit 4 mu (GSTM2); metabolism of cofactors, vitamins and related substances; possible prostaglandin E2 modulator; (2) cytochrome P-4503A1 (CYP3A1); P450-PCN1P; complex lipid and xenobiotic metabolism; (3) gastric inhibitory polypeptide precursor (GIP); glucose-dependent insulinotrophic polypeptide; (4) alpha-1-antiproteinase precursor; alpha-1-proteinase inhibitor; alpha-1-antitrypsin; protease inhibitor;

and (5) polyubiquitin; stress response protein. The results also identified two genes that were downregulated by JP-8 vapor exposure: (1) beta-alanine–sensitive neuronal gamma-aminobutyric acid (GABA) transporter, Na^+- and Cl^--dependent GABA transporter-3 (GAT-3); and (2) ATP2B2 (PMCA2); calcium transporting ATPase plasma membrane calcium pump (ATPase isoform 2). These JP-8 vapor-induced changes in gene expression in the brain suggest both a general response to xenobiotic-induced stress (i.e., increase in GST, P-450 and ubiquitin), and a more specific possible effect on GABAergic modulation of cerebellar and brainstem function (i.e., decrease in GAT-3 and PMCA2). Particularly in the case of the two downregulated genes, there would appear to be consistency with deficits in both postural equilibrium (Smith et al., 1997) and learning of the eyeblink classically conditioned (EBCC) response (McInturf et al., 2001) observed in military personnel exposed repeatedly to jet fuel, as both habits are known to depend upon cerebellar and/or brainstem circuitry.

Kerosene administered ip (0.02–0.18 ml/day for 5 d or 0.04–0.4 ml for 1 d) did not alter the frequency of chromosomal aberration in bone marrow cells of mice (Conaway et al., 1984). Kerosene was also negative in the *Salmonella*/mammalian microsome mutagenicity assay (preincubation assay = 0.001–5 µl/plate ± S9 [plate test] and 6.25–50 µl ± S9).

SUMMARY

1. There is little evidence that acute or long-term exposure to kerosene-based jet fuels or kerosene results directly in cancer, serious organic disease, or death in humans. There is, however, an abundance of scientific evidence that repeated dermal exposure to specific hydrocarbon fractions of jet fuels can, possibly as a consequence of severe and repeated dermal irritancy, result in skin cancer in at least laboratory animals.
2. Health effects of kerosene-based jet fuel or kerosene exposure may be subtle but persisting and may occur during prolonged periods of low-dose exposure.
3. Health consequences from repeated exposure to kerosene-based jet fuels or kerosene may not reflect linear dose relationships (i.e., U or inverted-U dose relationships may occur), such that results from studies reporting nonlinearity cannot be ignored. It is very possible that low-dose exposure to kerosene-based jet fuels may induce hormesis (i.e., neurobehavioral hormesis).
4. Individual (and interspecies) differences in organ-specific chemical detoxification systems may account for significant differences in observed health effects from kerosene-based jet fuel or kerosene exposures. Endogenous and exogenous factors that modulate organ-specific metabolic, detoxification, and/or elimination systems (i.e., dermal, pulmonary, hepatic, ocular, and renal) may greatly increase or decrease the toxicity of fuel exposures.
5. Kerosene-based jet fuel or kerosene-induced health effects may require complex neurobehavioral, proteomic, genomic, and metabol tests for early identification.

6. There are major differences in kerosene-based jet fuel or kerosene-induced health effects as a function of the fuel type (including performance additive package), exposure duration (acute vs. long-term), route of administration (dermal vs. respiratory vs. oral), and exposure phase (vapor vs. aerosol vs. raw fuel).
7. Seemingly minor changes in fuel formulations, particularly involving low carbon-number fractions or fuel performance additives, can significantly modulate exposure health consequences and must be carefully researched before widespread implementation.
8. From animal studies it appears that brief exposure to at least JP-8, in at least aerosol or raw fuel phase, can result in immunosuppression.
9. There is consistent evidence from animal studies, as well as limited human data, that repeated exposure to kerosene-based jet fuels or kerosene results reliably in significant hematological changes, including altered RBC and WBC counts, as well corpuscular and hemoglobin volumes.
10. Results of human, animal, and in vitro studies indicate that prolonged occupational level exposure to kerosene-based jet fuels or kerosene can result in persisting changes in at least brainstem/cerebellar systems, as well as in complex neurobehavioral performance capacity.
11. Animal and in vitro studies indicate that acute or long-term exposure to at least JP-8, in at least aerosol phase, can result in persisting (i.e., apoptotic) damage to the pulmonary system.
12. Animal, in vitro, and limited human studies indicate, minimally, significant changes in hepatic metabolism of xenobiotics and, maximally, significant and persisting histopathology in the liver following repeated exposure to kerosene-based jet fuels or kerosene.
13. Human, animal, and in vitro studies indicate that acute or long-term dermal exposure to at least JP-8 can result in recurring damage to the dermal barrier (i.e., necrotic).
14. There is limited evidence from animal studies that exposure of females to at least JP-8 can result in developmental deficits in offspring.
15. While there is little evidence that exposure to kerosene-based jet fuels or kerosene induces significant mutagenicity, there is substantial evidence in humans, animals, and in vitro preparations that dose-relevant exposures can result in DNA damage, including strand breaks.
16. It remains possible that exposure to microbial contaminants (including microtoxins) in kerosene-based jet fuels containing small quantities of water can account for health effects in exposed personnel.

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