ADDENDUM TO THE TOXICOLOGICAL PROFILE FOR JET FUELS (JP-5 and JP-8)

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
Atlanta, Georgia 30333

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CONTENTS

ADDENDUM for JET FUELS (JP 5 AND FP 8)
Supplement to the 1998 Toxicological Profile for Jet Fuels

Background Statement

This addendum to the Toxicological Profile for Jet Fuels (JP-5 and JP-8) supplements the profile that was released in 1998.

Toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). CERCLA mandates that the Administrator of ATSDR prepare toxicological profiles on substances on the CERCLA Priority List of Hazardous Substances and that the profiles be revised "no less often than once every three years." CERCLA further states that the Administrator will "establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" [Title 42, Chapter 103, Subchapter I, § 9604 (i)(1)(B)].

The purpose of this addendum is to provide to the public and to federal, state, and local agencies a non-peer reviewed supplement of the scientific data that were published in the open peer-reviewed literature since the release of the profile in 1998.

Chapter numbers in this addendum coincide with the Toxicological Profile for Jet Fuels JP-5 and JP-8 (ATSDR 1998). This document should be used in conjunction with the profile. It does not replace it.

2. HEALTH EFFECTS

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

2.2.1 Inhalation Exposure

The toxicity of JP-8 aerosols has been examined in a number of studies conducted by the University of Arizona (Baldwin et al. 2001, 2007; Harris et al. 1997a, 1997b, 1997c, 2000a, 2000b, 2000c, 2002, 2007a, 2007c, 2008; Herrin et al. 2006; Hilgaertner et al. 2011; McGuire et al. 2000; Pfaff et al. 1996; Robledo and Witten 1998, 1999; Robledo et al. 2000; Wang et al. 2001; Wong et al. 2004). In most of these studies, JP-8 aerosols were generated using a DeVilbiss Ultra-Neb nebulizer and aerosol concentrations were measured after each exposure using a seven-stage cascade impactor. However, this system was only capable of measuring aerosol concentrations; the JP-8 vapor concentrations were not quantified. Hilgaertner et al. (2011) compared this generation/measurement methodology to one in which a Lovelace jet nebulizer was used to aerosolize the jet fuel and vapor and aerosol concentrations were measured using an in-line, real-time total hydrocarbon analysis system. The study found that a total exposure to 1000 mg/m^3 JP-8 represents an exposure to 125 mg/m^3 aerosolized JP-8 and 875 mg/m^3 JP-8 vapor. Thus, reporting only the aerosol levels likely underestimated the actual exposure to JP-8. Although, Hilgaertner et al. (2011) and Herrin et al. (2006) estimated that the aerosol only concentrations represented only one-eighth of the total JP-8 exposure, ATSDR has not corrected the reported exposure concentration; however, it is noted whether the reported concentrations were for the aerosol component only or aerosol and vapor components.

2.2.1.2 Systemic Effects

Respiratory Effects. Nose-only exposure of male F344 rats to 520 mg/m^3 (aerosol component only) of aerosolized JP-8 1 hour/day for 7 days induced thickening of the epithelium of the terminal bronchioles (Pfaff et al. 1996). Exposure to 814 mg/m^3 induced widespread pulmonary congestion with hemorrhaging in the distal lung. In rats exposed to 495 mg/m^3 or 1,094 mg/m^3 for 28 days, electron microscopy showed degeneration of the alveolar type II cells; there was also evidence of edema. Similar effects, but with increased severity, were seen in rats exposed to 469 mg/mg^3 or 1,263 mg/m^3 for 56 days. Examination of bronchoalveolar lavage fluid (BALF) samples showed that exposure to JP-8 induced a

decrease in substance P (SP) and corresponding increases in neutral endopeptidase (NEP) concentration. NEP is the primary tachykinin degradative enzyme in the lung and its origin is primarily epithelial. SP is thought to play a role in airway reactivity and pulmonary epithelial integrity.

A 1-hour nose-only exposure to aerosolized JP-8 at time-integrated mass concentrations of 0, 5, 12, 28, 50, or 113 mg/m^3 (aerosol component only; MMAD of 0, 3.4, 2.2, 2.0, 2.0, and 2.3, respectively) did not significantly alter pulmonary function in male C57BL/6 mice (Robledo and Witten 1998). At 50 mg/m^3 and higher, increased respiratory permeability, as evidenced by increased pulmonary clearance of instilled ^{99m}Tc-labelled diethylenetriamine pentaacetate, was observed. Bronchoalveolar lavage fluid analysis showed increased total protein levels, total cell counts, and neutrophil levels and decreased macrophage levels at 113 mg/m^3 and increased lactate dehydrogenase and N-acetyl-β-D-glucosaminidase activities at ≥28 mg/m^3. Terminal bronchiole lesions were observed at 50 and 113 mg/m^3; no histopathological alterations were observed at lower concentrations. Increased pulmonary clearance, changes in bronchoalveolar lavage fluid biomarkers (increased total protein, increased lactate dehydrogenase activity, and decreased N-acetyl-β-D-glucosaminidase activity), and histopathological alterations were also observed in male B6.A.D. (*Ahr^d/Nat^s*) mice exposed to aerosolized JP-8 1 hour/day for 7 days at time-integrated mass concentrations of 48 or 118 mg/m^3 (aerosol component only) (Robledo et al. 2000). Minimal morphological alterations were noted in the lungs of mice exposed to 48 or 118 mg/m^3. No alterations were observed at 26 mg/m^3. The results of another study by this group (Robledo and Witten 1999) suggest that neurokinin-receptor activation may protect the lungs from the JP-8-induced damage. At higher concentrations [1023 mg/m^3 (aerosol component only) 1 hour/day for 7 days], the histological alterations included ectasia of respiratory bronchioles and alveoli (Wong et al. 2004).

Herrin et al. (2006) examined the effects of JP-8 in mice by using physiological and morphometric techniques. Male C57BL/6 mice were exposed nose-only to mean concentrations of 0, 45, 267, or 406 mg/m^3 (aerosol and vapor components) JP-8 1 hour/day for 7 days. Pulmonary function and respiratory permeability were measured in anesthetized mice 24-30 hours after the last exposure. The only significant effect on physiological measurements was a significant decrease in inspiratory dynamic lung compliance in mice exposed to 406 mg/m^3 JP-8. Ultrastructural examination of lung tissue showed alterations in cellular morphology of alveolar type II cells (which produce surfactant) and in terminal bronchial epithelium in exposed mice without a clear dose dependency. Quantitative morphometry showed that the low- and high-exposure groups had a 36% increase in lamellar body volume density in type II cells relative to their respective controls, confirming the apparent lack of dose-response relationship described in the general morphology assessment.

Wang et al. (2001) examined the age-related differences in the toxicity JP-8 in C57BL/6 mice aged 3.5 months or 12 months exposed nose-only to aerosolized JP-8 1 hour/day for 7 days. The mice were exposed to a 2:1 aerosol/vapor ratio and the time-integrated mass concentration was 995 mg/m^3 (aerosol component only; MMAD of 1.9 μm with a geometric standard deviation of 2.0). In pulmonary function tests there were significant increases in dynamic compliance in the young and adult exposed mice. Increased pulmonary clearance of instilled ^{99m}Tc-labelled diethylenetriamine pentaacetate, indicative of increased respiratory permeability, was also observed in the young and adult mice. Pulmonary clearance was significantly higher in the adult mice, as compared to the young mice; however, the clearance in the adult control mice was also significantly higher than the young control mice. Analysis of bronchoalveolar lavage fluid (BALF) showed significant increases in total cell numbers and percentage of macrophages in the adult and young mice; values for these endpoints were also significantly higher in the young exposed compared to the adult exposed and in the young controls compared to the adult controls. A higher percentage of neutrophils and lower percentage of lymphocytes were observed in adult exposed mice compared to the adult controls and young exposed mice. The levels of tumor necrosis factor-α (TNF-α) in the BALF were significantly increased in the adult exposed group and significantly decreased in the young exposed groups, as compared to their respective controls. Macrophage inflammatory protein-2 levels in the BALF were significantly increased in the adult and young mice; the levels in the adult exposed group was significantly higher than the young exposed group, but no differences were found in the two control groups. PGE_2 release was significantly lower in both exposed groups, as compared to the respective control groups; the levels in the adults were higher than the young exposed groups, but the adult controls also had higher levels than the young control group. The investigators concluded that the young and adult mice had similar toxicities to JP-8, although the inflammatory mechanisms may be different.

Alveolar capillary distention was observed in male Sprague-Dawley rats exposed to 500 or 1000 mg/m^3 JP-8 vapor 6 hours/day for 91 days (Hanas et al. 2010); no effects were observed at 250 mg/m^3.

In an unpublished study conducted by Whitman and Hinz (2001), RD_{50} (concentration resulting in a 50% decrease in respiratory rate) values of 2876 mg/m^3 (95% confidence interval of 2107-3925 mg/m^3) and 1629 mg/m^3 (95% confidence interval of 1418-1871 mg/m^3) were calculated for aerosolized JP-8 and JP-8+100 (concentrations are for aerosol and vapor components), respectively, following a 30-minute head-only exposure in male Swiss-Webster mice. The investigators noted that there were no signs of narcosis or pulmonary irritation for either substance. In another unpublished study (Whitman and Hinz 2004), an

RD_{50} of 3338 mg/m^3 (95% confidence interval of 1759-6332 mg/m^3) was calculated for aerosolized JP-5 (concentrations are for aerosol and vapor components).

Cardiovascular Effects. Multifocal damage, consisting of myocardial scarring and inflammatory cell infiltration, were observed in male Sprague-Dawley rats exposed to 500 or 1000 mg/m^3 JP-8 vapor 6 hours/day for 91 days (Hanas et al. 2010). The extent of the damage increased with the exposure concentration, and no effects were observed at 250 mg/m^3.

Musculoskeletal Effects. Exposure to JP-8 vapor 6 hours/day for 91 days resulted in a reduction in fat cells/globules and cell proliferation in male Sprague-Dawley rats; the extent of the fat cell reduction was concentration related (Hanas et al. 2010). There was a 10% reduction in fat cells at 250 mg/m^3, a 50% reduction at 500 mg/m^3, and a scarce number remained at 1000 mg/m^3.

Hepatic Effects. Several histological alterations were observed in the livers of male Sprague-Dawley rats exposed to 500 or 1000 mg/m^3 JP-8 vapor 6 hours/day for 91 days (Hanas et al. 2010); no liver effects were observed at 250 mg/m^3. The hepatic effects included dilated sinusoids, cytoplasmic clumping, and fatty hepatocytes.

Renal Effects. Proximal tubule damage, consisting of cytoplasmic dumping in the lumen and loss of nuclei, were observed in male Sprague-Dawley rats exposed to ≥250 mg/m^3 JP-8 vapor 6 hours/day for 91 days (Hanas et al. 2010). A dose-related increase in the levels of α-2-microglobulin was also observed in the kidneys at all tested concentrations.

Ocular Effects. Nose-only exposure of male Swiss Webster mice to 1000 or 2500 mg/m^3 (aerosol component only) aerosolized JP-8 + 100 1 hour/day for 7 days did not result in gliosis or histopathological alterations in the retina (McGuire et al. 2000). However, increased immunoreactivity of anti-GSTM antibodies in the retinal Müller, which may be indicative of oxidative stress, was found at both concentrations.

2.2.1.3 Immunological and Lymphoreticular Effects

A study of active duty military personnel performing fuel system maintenance (Rhodes et al. 2003) found significant increases in white blood cell counts, neutrophil levels, and monocyte levels among the workers

with high exposure to jet fuel, as compared to workers with low or no exposure to jet fuels; no significant alterations in lymphocyte subpopulations were observed.

The effects of JP-8 exposure on immune parameters of mice have been studied by Harris and coworkers (Harris et al. 1997a, 1997b, 1997c, 2000a, 2000b, 2000c, 2007a, 2007c, 2008). The initial study by Harris and associates involved nose-only exposure of male and female C57Bl/6 mice to 100, 250, 500, 1000, or 2500 mg/m^3 (aerosol component only) aerosolized JP-8 1 hour/day for 7 days (Harris et al. 1997a, 1997b, 1997c). The interpretation of the results of this study is difficult due to the lack of information on particle size and an evaluation of general toxicity. Exposure to ≥100 mg/m^3 resulted in a significant decrease in viable immune cells from the thymus (Harris et al. 1997a). Exposure to ≥500 mg/m^3 induced significant reductions in spleen and thymus weight (15–18% at 500 mg/m^3) and in viable immune cells recovered from the spleen (Harris et al. 1997a, 1997b). Exposure to JP-8 also affected the number of viable immune cells in the lymph nodes, bone marrow, and peripheral blood in an apparent multiphasic pattern. In the lymph nodes and peripheral blood, low concentrations of aerosolized JP-8 (100 or 250 mg/m^3) resulted in decreases in the number of cells (as compared to controls), increases in the number of cells at 500 and 1000 mg/m^3, and decreases at 2500 mg/m^3; in the bone marrow, increases in cell number were observed at 100 and 250 mg/m^3 and decreases were observed at ≥500 mg/m^3 (Harris et al. 1997a, 1997b). Although flow cytometric analyses showed losses or gains of specific cells in lymphoreticular organs and tissues from exposed mice, the results are difficult to interpret because the number of mice per group ranged from 3 to 21. Stimulation of splenic immune cells with T cell growth factor interleukin-2 (IL-2) resulted in a significant response only in mice exposed to 2,500 mg/m^3 JP-8 (the highest concentrations tested) (Harris et al. 1997a). However, stimulation with the T cell mitogen, concanavalin A, resulted in significant decreases in immune function in mice exposed to ≥250 mg/m^3 JP-8 (Harris et al. 1997a). Similar exposure to 1000 mg/m^3 JP-8+100 (aerosol component only) also resulted in no alteration in the response to IL-2 and impaired response to concanavalin A (Harris et al. 2000b). Harris et al. (1997c) showed that exposure to ≥1,000 mg/m^3 JP-8 resulted in persistent decreases in immune organs weights and decreased immune function that lasted for up to 4 weeks post-exposure. A further study showed that exposure to 1,000 mg/m^3 JP-8 almost completely inhibited natural killer (NK) cell activity, significantly suppressed the generation of lymphokine-activated killer (LAK) cell activity, suppressed the generation of cytotoxic T lymphocyte cells from precursor T cells, and inhibited helper T cell activity (Harris et al. 2000a). The investigators also showed that substance P (SP), a small peptide thought to be involved in airway reactivity and in maintaining pulmonary epithelial integrity, could protect the immune system from JP-8-induced damage and also reverse the damage if administered at appropriate times before and/or after JP-8 exposure (Harris et al. 1997b, 2000c). A study of the time-

course of JP-8-induced effects showed that exposure of mice to 1,000 mg/m^3 (aerosol component only) for 1 hour caused significant spleen and thymus weight loss and loss on viable cells in the spleen within 2 hours after exposure (Harris et al. 2002). It was also shown that immune function, as assessed by the response to mitogens, was impaired 1 hour after exposure and did not recover within 24 hours. In a more recent paper, Harris and coworkers reported that exposure to JP-8 rapidly increases serum levels of two immunosuppressive agents, interleukin-10 (IL-10) and prostaglandin E2 (PGE2) (Harris et al. 2007a). Since treatment with a PGE2 inhibitor did not completely reverse the effects of JP-8, the increased levels of IL-10 and PGE2 could only partially explain all the effects of JP-8 exposure on immune function. Exposure to 1,000 mg/m^3 (aerosol component only) JP-8 1 hour/day for 7 days increased the severity of a viral infection (mice were exposed to A/Hong Kong/8/68 influenza virus one day post-JP-8 exposure) (Harris et al. 2008). Reduced immunocompetence was evidenced by decreased immune cell viability, a significant decrease in immune proliferative responses to mitogens, and loss of $CD3^+$, $CD4^+$, and $CD8^+$ T cells from the lymph nodes, but not from the spleen. In yet another study, Harris et al. (2007c) reported that exposure of mice to 1,000 mg/m^3 (aerosol component only) JP-8 7 days before intravenous injection of B16 tumor cells induced an increase of approximately 8.7-fold in tumor formation in the lungs, whereas mice exposed to JP-8 at the time of tumor induction showed a 5.6-fold increase in the number of tumors. Although the results were not statistically analyzed, the findings were interpreted as a suppressive effect of JP-8 exposure on the immune system leading to increased tumor formation and metastases.

Hilgaertner et al. (2011) found significant decreases in spleen and thymus weights in C57BL/6 mice exposed to 1000, 4000, or 8000 mg/m^3 (aerosol and vapor components) aerosolized JP-8 1 hour/day for 7 days; there were no changes in spleen weights at 2000 mg/m^3. Exposure monitoring conducted in this study showed that the 1000 mg/m^3 concentration resulted in exposure to 125 mg/m^3 JP-8 aerosols and 875 mg/m^3 jet fuel vapors. Thymus weights were significantly decreased at ≥1000 mg/m^3; slight, but statistically significant, decreases in body weight were also observed at ≥1000 mg/m^3; however, the body weights at all concentrations were within 10% of controls. Viable cell levels were significantly decreased in the bone marrow at 8000 mg/m^3, spleen and peripheral blood at 4000 mg/m^3, and thymus at ≥2000 mg/m^3; significant increases in bone marrow and peripheral blood viable cell levels were observed at 4000 and 1000 mg/m^3, respectively.

2.2.1.4 Neurological Effects

Proctor et al. (2011) examined the potential neurotoxicity of JP-8 in 38 active duty Air Force personnel who performed job tasks that involved regular and routine individual personal exposure to JP-8 (high exposure group) and 36 Air Force personnel with low or no exposure to JP-8. The 8-hour geometric mean time-weighted average total hydrocarbon concentrations were 0.53 mg/m^3 (range of 0.24 to 22.01 mg/m^3) and 2.65 mg/m^3 (range of 0.24-73.93 mg/m^3) in the low and high exposure groups, respectively. Neuropsychological battery testing performed on day 1, 2, 4, and 6 were designed to assess attention, reaction time, psychomotor speed and efficiency, memory, and balance. When compared to normative, reference group data obtained from groups of healthy adults (data obtained from clinical test manuals or published studies), there were no significant alterations in performance on neuropsychological tests in the study participants (all groups combined) with the exception of lower performance scores on the Total Recall, Delayed Recall, and retention task tests among 20-29 year old study participants. Interpretation of the results of this study is limited by the lack of comparison between the two exposure groups.

A study of Air National Guard personnel exposed to JP-8 found alterations in performance on several neurocognitive tests (Tu et al. 2004). JP-8 exposure was significantly correlated with poorer performance on measures of divided attention and information processing speed.

The effects of JP-8 fuel on the Functional Observational Battery (FOB), visual discrimination, or spatial learning and memory were studied in male Fischer Brown Norway rats exposed nose-only to 0 or a mean of 1,237 mg/m^3 (aerosol component only) aerosolized JP-8 1 hour/day, 5 days/week for 28 days (Baldwin et al. 2001). Exposure to JP-8 resulted in a significant increase in central nervous system excitability, as assessed in the FOB; exposed rats showed greater motor behavior and increased arousal levels than controls. Exposure to JP-8 did not affect learning and memory for spatial location or visual discrimination learning. According to the investigators, the effects on arousal levels and locomotor activity are consistent with stimulation of the mesolimbic dopaminergic system; however, exposure to JP-8 did not appear to have an important effect on medial temporal-lobe-dependent cognitive function in rats. In a subsequent study, the investigators examined levels of neurotransmitters and their metabolites (norepinephrine, dopamine, dihydroxyphenylacetic acid [DOPAC], serotonin, homovanillic acid, and 5-hydroxyindoleacetic acid) in seven brain areas (cerebral cortex, cerebellum, striatum hippocampus, hypothalamus, midbrain, and brain stem) in rats exposed intermittently to 1,319–1,774 mg/m^3 (aerosol component) JP-8 1 hour/day for 1 to 4 weeks (Baldwin et al. 2007). The only significant effect was an

increase in DOPAC levels in the hippocampal region in exposed rats relative to controls, which was more pronounced as duration of exposure increased.

Neurobehavioral testing was conducted in groups of male Sprague-Dawley rats exposed to 500 or 1000 mg/m^3 JP-8 vapors 6 hours/day, 5 day/week for 6 weeks; 65 days after exposure termination, the rats underwent simple and difficult operant tasks (Ritchie et al. 2001). No differences were observed in the performance of simple tasks. Although no significant differences in performance on the more difficult tasks between the controls and exposed groups were observed, significant decreases in performance were observed between the low and high exposure groups in the two most difficult tasks. Levels of dopamine in the cerebral cortex and DOPAC in the brain levels were significantly higher in both exposure groups, as compared to controls.

Sprague-Dawley rats were exposed to 1000 mg/m^3 JP-8 vapors 6 hours/day, 5 days/week for 6 weeks; neurotoxicity was evaluated 65 days after exposure using a neurobehavioral toxicity assessment battery (Rossi et al. 2001). A significant alteration in performance on the novel appetitive stimulus test (hypothesized to quantify dopamine system sensitization) was observed. Evaluation of serum neurotransmitter levels showed a significant decrease in 5-hydroxyindoleacetic acid levels, a metabolite of serotonin. Levels of DOPAC levels were significantly decreased in the cerebellum and brainstem.

JP-8 fuel was also shown to promote auditory impairment in rats when combined with exposure to noise (Fechter et al. 2007). Exposure of male Long-Evans rats exposed nose-only to 1,000 mg/m^3 JP-8 (mostly vapor) for 1 hour did not result in auditory impairment as assessed by decreased hair cell function. However, exposure to JP-8 followed by exposure to noise induced a greater depression in hair cell function that did noise alone. Also, exposure to JP-8 alone or noise alone slightly increased auditory threshold as measured by recording compound action potentials from the round window. Combined exposure to JP-8 and noise resulted in a higher threshold than with each exposure alone. Histological examination of the cochleae showed that both rats exposed to noise alone and those receiving combined treatment had a slight increase in the number of missing hair cells relative to controls. Repeated exposure to JP-8 for 5 days induced a decrease in hair cell function followed by a slight recovery 4 weeks after exposure. The possibility that the effect of JP-8 is due to induction of oxidative stress was tested by measuring glutathione (GSH) levels in the liver, brain, lung, and cochleae at various times after JP-8 exposure. The results showed that GSH levels were decreased only in the liver. In a later paper, Fechter et al. (2010) replicated their earlier results and reported that no noticeable impairment in hair cell function was observed when rats were exposed to 500 mg/m^3 JP-8 for 4 hours/day for 5 days plus 100-102 dB_{lin}

noise (1 hour/day for 5 days), thus establishing a NOAEL. The investigators further showed that exposure to a synthetic fuel lacking aromatic hydrocarbons followed by noise did not produce a dose-dependent enhancement of noise-induced hearing loss.

An intermediate-duration exposure of rats to 200, 750, or 1500 mg/m^3 JP-8 6 hours/day, 5 days/week for 4 weeks did not result in significant alterations in the number of outer hair cells or hair cell function (assessed by measuring distortion product otoacoustic emission and compound action potential threshold) (Fechter et al. 2012). However, simultaneous exposure to 1500 mg/m^3 (6 hours/day, 5 days/week for 4 weeks) and 85 dB_{lin} noise resulted in significant impairment in hair cell function when measured 10 days after exposure termination, as compared to untreated controls. Four weeks after exposure termination, significant impairment of hair cell function was observed in rats simultaneously exposed to 500, 750 or 1500 mg/m^3 JP-8 and 85 dB noise; however, there were no significant differences between the groups. Noise-only exposure at 85 dB did not result in significant alterations in hair cell function.

Rossi et al. (2001) exposed groups of Sprague-Dawley rats to 1200 mg/m^3 JP-5 vapors 6 hours/day, 5 days/week for 6 weeks. Neurobehavioral toxicity assessment battery tests were conducted 65 days post-exposure. Significant alterations in performance on battery tests were limited to an increase in forelimb grip strength. The only significant alteration in serum neurotransmitter levels was an increase in 5-hydroxyindoleacetic acid. Significant decreases in DOPAC levels in the cortex, increases in dopamine levels in the hippocampus, and decreases in homovanillic acid in the hippocampus were also observed.

2.2.1.6 Developmental Effects

Nose-only exposure of pregnant C57Bl/6 mice to 1,000 mg/m^3 aerosolized JP-8 1 hour/day on gestation days (Gd) 7–21 or 15–21 resulted in significant decreases in thymus and spleen weight, viable immune cells from these organs, and suppressed immune function at 6–8 weeks old, regardless the duration of maternal exposure (Harris et al. 2007b). It appeared that male pups were more severely affected than female pups. Average litter size was also significantly reduced in the exposed groups.

2.2.1.7 Genotoxic Effects

A study of Turkey Air Force personnel exposed to JP-8 found significant increases in the occurrence of sister chromatid exchanges in peripheral lymphocytes; when the personnel were divided by smoking status, only the occurrence in smokers was statistically significant (Erdem et al. 2012). No significant

alterations in occurrence of high frequency of sister chromatid exchange cells, or micronuclei frequency were observed.

2.2.2 Oral Exposure

2.2.2.1 Death

No deaths were observed in groups of male and female Fischer 344 rats administered a single gavage dose of 5000 mg/kg JP-8 or JP-8+100 (Wolfe et al. 1996; unpublished study).

2.2.2.2 Systemic Effects

Respiratory Effects. Administration of up to 1,500 mg/kg/day neat JP-8 by gavage to female Sprague-Dawley rats for 90 days before mating and continuing through gestation and lactation did not induce significant gross or microscopic alterations in the trachea, lung, or nasal turbinates (Mattie et al. 2000; unpublished study).

Cardiovascular Effects. Administration of up to 1,500 mg/kg/day neat JP-8 by gavage to female Sprague-Dawley rats for 90 days before mating and continuing through gestation and lactation did not induce significant gross or microscopic alterations in the heart (Mattie et al. 2000; unpublished study).

Gastrointestinal Effects. Administration of 750 or 1,500 mg/kg/day neat JP-8 by gavage to female Sprague-Dawley rats for 90 days before mating and continuing through gestation and lactation significantly increased the severity but not the incidence of squamous hyperplasia of the stomach; no significant effect was reported at 325 mg/kg/day (Mattie et al. 2000; unpublished study). No significant alterations were reported at any other level of the gastrointestinal tract.

Hematological Effects. Administration of up to 1,000 mg/kg/day of JP-8 to female $B6C3F_1$ mice by gavage in olive oil for 14 days did not significantly alter erythrocyte or leukocyte number (with differential), hemoglobin or hematocrit (Peden-Adams et al. 2001). Comprehensive hematology evaluation of female Sprague-Dawley rats exposed to up to 1,500 mg/kg/day neat JP-8 by gavage for 90 days before mating and continuing through gestation and lactation did not show treatment-related alterations (Mattie et al. 2000; unpublished study).

Significant decreases in hemoglobin levels, hematocrit levels, and red blood cell counts and increases in mean corpuscular volume were observed in female B6C3F1 mice administered via gavage 2500 mg/kg/day JP-8 for 14 days (Keil et al. 2004); mean corpuscular volume was also increased at 1500 and 2000 mg/kg/day.

Musculo/Skeletal Effects. Administration of up to 1,500 mg/kg/day neat JP-8 by gavage to female Sprague-Dawley rats for 90 days before mating and continuing through gestation and lactation did not induce significant gross or microscopic alterations in skeletal muscle or the sternum (Mattie et al. 2000; unpublished study).

Hepatic Effects. Absolute and relative (to body weight and to brain weight) liver weight of female Sprague-Dawley rats administered ≥750 or 1,500 mg/kg/day neat JP-8 by gavage for 90 days before mating and continuing through gestation and lactation was significantly increased in a dose-related manner; no significant effect was reported at 325 mg/kg/day (Mattie et al. 2000; unpublished study). However, this effect was not accompanied by significant changes in clinical chemistry tests or in microscopic appearance of the liver. Administration of up to 1,000 mg/kg/day of JP-8 to female B6C3F_1 mice by gavage in olive oil for 14 days did not significantly alter relative liver weight (Peden-Adams et al. 2001).

Renal Effects. Relative (to brain weight) kidney weight of female Sprague-Dawley rats administered ≥750 or 1,500 mg/kg/day neat JP-8 by gavage for 90 days before mating and continuing through gestation and lactation was significantly increased in a dose-related manner; no significant effect was reported at 325 mg/kg/day (Mattie et al. 2000; unpublished study). However, urine parameters were not significantly affected by treatment with JP-8 and there were no treatment-related histological alterations in the kidneys. Administration of up to 1,000 mg/kg/day of JP-8 to female B6C3F_1 mice by gavage in olive oil for 14 days did not significantly alter relative kidney weight (Peden-Adams et al. 2001).

Dermal Effects. Administration of 1,500 mg/kg/day neat JP-8 by gavage to female Sprague-Dawley rats for 90 days before mating and continuing through gestation and lactation significantly increased the severity but not the incidence of perianal dermatitis; no significant effect was reported at ≤750 mg/kg/day (Mattie et al. 2000; unpublished study).

Body Weight Effects. Body weight of male and female Sprague-Dawley rats administered ≥1,500 mg/kg/day neat JP-8 by gavage for 90-day before mating was significantly lower (>10%) than controls,

the NOAEL was 750 mg/kg/day (Mattie et al. 2000; unpublished study). Terminal body weights in the females exposed to 1500 mg/kg/day were not significantly different than the controls.

Metabolic Effects. Administration of up to 1,500 mg/kg/day neat JP-8 by gavage to female Sprague-Dawley rats for 90 days before mating and continuing through gestation and lactation did not induce significant alterations in serum levels of glucose or electrolytes (Mattie et al. 2000; unpublished study).

Other Effects. Administration of up to 1,500 mg/kg/day neat JP-8 by gavage to female Sprague-Dawley rats for 90 days before mating and continuing through gestation and lactation did not induce significant gross or microscopic alterations in the pancreas or urinary bladder (Mattie et al. 2000; unpublished study).

2.2.2.3 Immunological and Lymphoreticular Effects

Administration of up to 1,500 mg/kg/day neat JP-8 by gavage to female Sprague-Dawley rats for 90 days before mating and continuing through gestation and lactation did not induce significant gross or microscopic alterations in the spleen or mandibular and mesenteric lymph nodes (Mattie et al. 2000; unpublished study).

Peden-Adams et al. (2001) examined the immunotoxicity of JP-8 in female B6C3F_1 mice. Mice were administered 0, 500, or 1,000 mg/kg/day JP-8 by gavage in olive oil for 14 days before immunosuppression was assessed. End points examined included spleen and thymus weight and organ cellularity, natural killer cell activity, cytotoxic T-cell activity, mitogen-induced lymphocyte proliferation, nitrogen production by peritoneal macrophages, plaque-forming cell response to sheep red blood cells (SRBC), delayed type hypersensitivity, and susceptibility to tumor B16F10 or *Listeria monocytogenes* challenges. Of all the end points measured, only the plaque forming cell response was significantly reduced in the low- and high-dose groups in a dose-related manner. Dudley et al. (2001) tested the hypothesis that JP-8 may exert immunosuppression by acting through the AhR (aryl hydrocarbon receptor). Tests conducted in B6C3F_1 mice and the Ah-non responsive DBA/2 mouse strain showed that both strains were equally sensitive to JP-8's toxicity including end points such as thymus weight and cellularity, liver weight, and specific IgM antibody responses. In addition, JP-8 did not induce CYP1A1 or promote down regulation of the AhR when evaluated by Western blot in either strain of mice. The results suggested that JP-8 may exert immunotoxicity via an AhR-independent mechanism.

Gavage administration of JP-8 in olive oil to female B6C3F1 mice resulted in decreases in thymic cellularity at ≥ 2000 mg/kg/day and decreases in thymic CD8+, CD4+, and CD4+/CD8+ T-cell subpopulations at 2000 mg/kg/day; no changes in the CD4/CD8 ratios or the relative percentages of T-cell subpopulations were observed (Keil et al. 2004). In the spleen, cellularity and absolute values of T-cell phenotypes were not affected; an increase in the percentage of CD4+ cells was observed at 1000 and 2000 mg/kg/day. In the bone marrow, there was a 47% increase in colony-forming units at 2000 mg/kg/day, but no alteration in total bone marrow cellularity. Alterations in immune function were also observed; suppression of the antibody plaque-forming cell response to sheep red blood cells (sRBC) was observed at ≥500 mg/kg/day. However, serum levels of anti-sRBC IgM were not altered when measured by either ELISA or hemagglutination (Keil et al. 2004).

2.2.2.5 Reproductive Effects

Administration of up to 3,000 mg/kg/day neat JP-8 by gavage to male Sprague-Dawley rats for 70 days before mating with untreated females had no significant effect on pregnancy rate or gestation length (Mattie et al. 2000; unpublished study). In addition, sperm parameters measured in epididymal sperm samples (sperm concentration, motile sperm concentration, percent motility, velocity, linearity, maximum amplitude of lateral head displacement [ALH], mean ALH and beat/cross frequency) were not significantly affected by exposure to JP-8.

Administration of up to 1,500 mg/kg/day neat JP-8 by gavage to female for 90-day before mating and continuing throughout gestation did not significantly affect pregnancy rate, gestation length, or litter size (Mattie et al. 2000; unpublished study). Gross and microscopic examination of the ovaries and uterus did not reveal treatment-related alterations.

2.2.2.6 Developmental Effects

Administration of up to 1,500 mg/kg/day neat JP-8 by gavage to female Sprague-Dawley rats for 90-day before mating and continuing throughout gestation and lactation did not significantly affect percent live pups (Mattie et al. 2000; unpublished study). However, on postnatal day (PND) mean body weight from pups born to dams administered 325, 750, and 1,500 mg/kg/day JP-8 were reduced by approximately 5, 8, and 11% relative to controls. By PND 90, body weights of pups from the mid- and high-dose groups were about 2% lower than controls. Neurodevelopmental testing of these pups showed a significant alteration in the total score for the swimming development test at ≥325 mg/kg/day on PND 8 and at ≥750 mg/kg/day on PND 14; however, no significant alterations in total score were observed on PNDs 10, 12,

16, 18, or 20 (Mattie et al. 2001; unpublished study). The alterations in the total scores were primarily due to swimming direction scores; significant decreases in direction scores were observed on PND 6 (≥750 mg/kg/day), PND 8 (≥325 mg/kg/day), and PND 14 (≥750 mg/kg/day); no alterations in angle of head or limb usage scores were observed at any time point. No significant alterations in surface righting (tested on PND 4), negative geotaxis (tested on PND 5), or water maze performance (tested on PNDs 70 and 77) were observed. The investigators suggested that the results in the swimming development test were indicative of a possible developmental delay in motor coordination; however, the delay did not affect motor ability at later ages (Mattie et al. 2001; unpublished study).

Keil et al. (2003) studied immune parameters, host resistance, body and organ weights (spleen, thymus, and liver), hematology parameters, and thyroid hormones in C57BL/6 mice offspring from dams administered 0, 1,000, or 2,000 mg/kg JP-8 fuel by gavage in olive oil on GD 6–15. Evaluations were conducted at 3 and 8 weeks of age. Exposure to JP-8 fuel resulted in a significant decrease in thymic cellularity and increase in spleen weight at 8 weeks of age. Hematological parameters were not significantly affected by gestational exposure to JP-8. There were no dose-related alterations in thymic and splenic lymphocytic subpopulations at weaning or in adult offspring. A significant decrease in B-cell lymphocyte proliferation was reported in high-dose offspring at weaning, T-lymphocyte proliferation was not affected at weaning or in adult offspring. Exposure to JP-8 did not induce compound-related alterations in macrophage parameters. Significant dose-related decreases in the IgM plaque-forming cell response to SRBC occurred in adult offspring from both dose groups (46 and 81% decreases). Exposure to JP-8 did not significantly affect bone marrow cellularity, stem cell proliferation, or splenic NK cell function. Adult offspring exposed to JP-8 showed no significant change in susceptibility to infection with *Listeria monocytogenes*, but susceptibility to B16F10 tumor challenge was decreased in both dose groups. Finally, serum T4 levels were significantly reduced (38%) in high-dose adult offspring.

2.2.2.8 Cancer

No studies were located regarding cancer in humans or animals exposed to JP-5 or JP-8. A single study provided information regarding cancer of kerosene in animals. Male and female Sprague-Dawley (50/sex/group) rats were exposed to 0, 500, or 800 mg/kg kerosene by gavage in olive oil 4 days/week for 104 weeks (Maltoni et al. 1997). The study was terminated after 123 weeks, at which time survivors underwent complete necropsy and all major organs and tissues were prepared for microscopic examination. It should be noted that no statistical analyses of the results were performed. It appeared that the percent of animals bearing malignant tumors may have been increased in the high-dose group; a

Fisher Exact test conducted by ATSDR showed that the increase in malignant tumors in the high-dose group was not statistically significant (p=0.0623). Exposure to kerosene did not seem to increase the percent of females bearing mammary cancers (6, 6, and 10% in the control, low- and high-dose groups, respectively). In addition, kerosene did not seem to increase the percent of animals bearing various head cancers (Zymbal gland, ear duct, nasal cavity, oral cavity, and head). Finally, the percent females bearing malignant tumors of the uterus and vagina appeared elevated in the exposed groups, but there was no dose-response relationship (2, 14, and 10% in the control, low- and high-dose groups, respectively).

2.2.3 Dermal Exposure

2.2.3.2 Death

No deaths were observed in groups of male and female New Zealand White rabbits following a 4-hour application of 2000 mg/kg JP-8 or JP-8+100 under occluded conditions (Wolfe et al. 1996; unpublished study).

2.2.3.2 Systemic Effects

Cardiovascular Effects. Application of 300 µL of JP-8 to a clipped area of the neck of male Long-Evans rats 7 days per week resulted in slight and predominantly perivascular lymphocyte infiltration in the heart (Larabee et al. 2005). Approximately 80% of the myocardial fibers showed fat infiltration. It should be noted that a quantitative assessment was not provided.

Hepatic Effects. Application of 300 µL of JP-8 to a clipped area of the neck of male Long-Evans rats 7 days per week resulted in spotty, isolated hepatic cell death and loss of cytoplasm with shrinking nuclei in a small percentage of hepatic cells (Larabee et al. 2005). It should be noted that only a qualitative description of the results was provided.

Renal Effects. Repeated application of 300 µL of JP-8 to a clipped area of the neck of male Long-Evans rats 7 days per week induced renal tubular cell death in approximately 10% of the proximal tubules (Larabee et al. 2005). This was not observed in control preparations, but quantitative data were not provided.

Dermal Effects. Application of 250 µL of JP-8 fuel to the clipped skin of male Fischer rats for 1 hour resulted in granulocyte infiltration into the skin to epidermal separation from the basement membrane and

vacuolization (Kabbur et al. 2001). These morphological changes were observed as early as 2 hours after exposure started and were most prominent 6 hours after exposure started. The morphological changes were preceded by an increase in biomarkers of inflammation such as interleukin (IL)-1α and inducible nitric oxide synthase protein and nitrite levels in the skin. Similar results were reported by Gallucci et al. (2004) who noted that application of 300 µL JP-8 to the clipped area of the skin of male Long-Evans rats for 7 days induced thickened epidermis and profound inflammatory infiltration. This was associated with changes in the expression of numerous proinflammatory cytokines. Application of 230 µL JP-8 to the skin of hairless rats under occluded conditions for 1 hour significantly increased the cytokine IL-1α in blood and TNFα in the skin 24 hours after dosing (Chaterjee et al. 2006). In New Zealand White rabbits, application of 0.5 mL JP-8 to clipped skin for 4 hours resulted in moderate irritation when tested under occluded conditions and slight irritation when tested under semi-occluded conditions (Hurley et al. 2011; unpublished study). Another study found slight skin irritation in New Zealand White rabbits administered 0.5 mL JP-8 under semi-occluded conditions for 4 hours (Wolfe et al. 1996; unpublished study). Slight skin irritation was also found following administration of 1 of 2 formulations of JP-8+100.

Repeated application of 335 µL of JP-8 fuel to the clipped skin of female weanling Yorkshire pigs by means of a fuel-soaked fabric induced slight erythema at 5 hours and increased erythema at 5 days (Monteiro-Riviere et al. 2001). Light microscopy showed slight intracellular epidermal edema at 5 and 24 hours and at 5 days post-dosing. An increase in transepidermal water loss (TEWL, a measure of stratum corneum barrier function) was observed at the 5-day observation time under occluded conditions (Hill-Top chamber used to occlude the site) following JP-8 exposure and at the 24-hour and 5-day observation times following JP-8+100 exposure. Application sites also had intra-corneal micro-abscesses filled with inflammatory cells and epidermal thickening was evident. Further studies using electron microscopy showed that the primary ultrastructural changes after fuel exposure involve alterations in the lipid bilayers of the skin that would likely affect the epidermal-dermal barrier in a manner that would allow further fuel absorption (Monteiro-Riviere et al. 2004). The results from an additional study from this group of investigators indicated that individual aliphatic hydrocarbons such as tridecane, tetradecane, and pentadecane are the principal source of JP-8-induced irritation (Muhammad et al. 2005b). Kanikkannan et al. (2001) showed that a 24-hour skin treatment with 250 µL JP-8 in male Yucatan minipigs significantly increased TEWL at 2 and 24 hours after exposure and caused moderate erythema and moderate to severe edema 1 hour after exposure. Similar results were reported in Sprague-Dawley hrBi hairless rats following nonocclusive application of 14 µL JP-8 or JP-8+100 4 times/day for 5 days, except that no edema was observed (Kanikkannan et al. 2002). Singh and Singh (2004) reported increase in TEWL in New Zealand male white rabbits after application of 50 µL JP-8 to the shaved back and left

covered for 1 hour; this was due to rupture of the skin barrier and increase in temperature. Chatterjee et al. (2006) also reported an increase in TEWL in hairless rats applied 230 µL JP-8 for 1 hour.

Once daily application of 0.156 mL JP-8 or JP-8+100 to the skin of Fischer rats under non-occluded conditions for 7 to 28 days resulted in erythema and edema characterized as very slight during the first few days of exposure and well-defined by the end of the first week of exposure (Baker et al. 1999; unpublished study). Thereafter, the severity of the erythema did not increase with exposure duration. Histopathological alterations observed in the skin included spongiosis, orthokeratosis, parakeratosis, hyperplasia, hypergranulosis, dyskeratosis, inflammatory infiltrates, edema, and vasodilation. In animals exposed for 28 days and allowed to recover for 7-28 days, the histopathological alterations were limited to hypergranulosis

In a 2-year dermal exposure study in male mice, moderate skin irritation was observed during the first 24 weeks of dermal exposure to 50 µL undiluted straight-run kerosene applied twice per week (the investigators did not note whether the test was done under occluded conditions) (Nessel et al. 1998). Marked irritation was observed from week 64 to the end of the study. Slight irritation was observed when the mice were exposed to 50 µL of a 50% diluted solution (mineral oil was used as the diluent) 4 times per week.

2.2.3.3 Immunological and Lymphoreticular Effects

Application of 25 µL of JP-8 on the back of the ear of female CBA/Ca mice for 3 consecutive days induced local lymph node proliferative activity; a stimulation index of 3.17 was determined, indicating that JP-8 was a weak skin sensitizer (Kanikkannan et al. 2000). Adding butylated hydroxytoluene (BHT, an antioxidant additive) to the JP-8 resulted in a lower stimulation index (2.83), although the difference was not statistically significant. The investigators speculated that BHT may inhibit the formation of oxidative products and free radicals from JP-8. Application of 50 µL JP-8 to the shaved back of adult female C3H/HeN mice for 4–5 days resulted in significant inhibition of contact and delayed-type hypersensitivity, but application for ≤3 days was without significant effect (Ullrich 1999). This occurred regardless of whether the contact allergen was applied directly to the JP-8 treated site or at a distant untreated site. A single exposure to a higher dose (240 µg) resulted in suppressed delayed-type hypersensitivity in female C3H/HeN mice (Ramos et al. 2004, 2007). Exposure to 300 µL significantly depressed the ability of splenic T lymphocytes to proliferate in response to plate-bound monoclonal anti-CD3 (Ullrich 1999). JP-8 (300 µL) also significantly increased serum levels of the cytokine IL-10. A

subsequent study showed that dermal application of JP-8 suppressed immune memory in mice previously exposed to *Candida albicans* (Ramos et al. 2002). Ullrich and Lyons (2000) showed that immune suppressive cytokines, presumable produced by JP-8 treated epidermal cells, are responsible for the immune suppression seen in JP-8-treated mice, and that blocking and/or neutralizing their production *in vivo* overcomes the immunotoxic effects of JP-8. In a more recent study, application of 300 μL of JP-8 to the skin of C57BL/6 mice resulted in significant suppression of contact hypersensitivity (Limón-Flores et al. 2009). However, no immune suppression was observed in treated mice that were mast cell deficient, suggesting that mast cells mediate immune suppression. Additional experiments showed that prostaglandin E_2 (PGE_2) is the critical mast cell product activating immune suppression and suggested that mast cells migrate from the skin to draining lymph nodes, thereby transmitting the immunosuppressive signal from the skin to the immune system. Ramos et al. (2007) suggested that the aromatic hydrocarbons present in JP-8 were the immunosuppressive agents. S-8 synthetic fuel, which is devoid of aromatic hydrocarbons, did not result in suppression of delayed-type hypersensitivity; however, immunosuppression was observed when a mixture of hydrocarbons (benzene, toluene, ethylbenzene, xylene, 1,2,4-trimethylbenzene, cyclohexylbenzene, and dimethylnaphthalene) was added to the S-8.

Negative results were observed in a skin sensitization test of JP-8 and JP-8+100 in male Hartley guinea pigs which exhibited edema (Wolfe et al. 1996; unpublished study).

2.2.3.7 Genotoxic Effects

In a study of DNA damage among Air Force personnel, no significant differences in mean comet assay measurements between different JP-8 exposure categories (high, medium, or low potential exposure) were observed (Krieg et al. 2012). Because the high exposure workers wore respirators, it is presumed that dermal contact was the primary route of exposure. No associations were found for benzene or naphthalene work shift air levels and DNA damage. However, significant associations were found between pre-shift breath benzene levels and mean tail DNA damage and mean tail (Olive) moment; but the number of cells with highly damaged DNA was statistically decreased as pre-shift benzene breath level increased. In contrast, mean tail DNA and mean tail (Olive) moment decreased as post-shift breath benzene levels increased. Pre- and post-shift naphthalene breath levels were not significantly associated with DNA damage. The post-shift number of cells with highly damaged DNA was significantly associated with urinary levels of a metabolite of 2-(2-methoxyethoxy)ethanol [(2-methoxyethoxy)acetic acid (MEAA)] levels; however, the association was no longer statistically significant when MEAA levels were adjusted for creatinine levels.

Significant increases in the frequency of micronuclei were observed in peripheral blood polychromatic erythrocytes following application of 240 mg JP-8 to the shaved backs of female C3H/HeNCr (MTV-) mice (Vijayalaxmi et al. 2004). Although an increase in micronuclei frequency was also observed in bone marrow cells, the difference over controls was not statistically significant. However, when the experiment was repeated, no statistically significant alterations in micronuclei frequency were observed in the peripheral blood or bone marrow (Vijayalaxmi et al. 2006). Additionally, a three-day repeated exposure to 240 mg/day did result in increases in micronuclei formation.

2.2.3.8 Cancer

A significant increase ($p < 0.01$) in the number of animals 12/50) with benign and malignant skin tumors was observed in male mice exposed to 50 µL undiluted (100%) straight-run kerosene applied to the back twice per week for up to 2 years (the investigators did not note whether the test was done under occluded conditions), as compared to controls (0/50) exposed to mineral oil (Nessel et al. 1998). The tumor types included squamous cell carcinoma, papilloma, and fibrosarcoma. Moderate to marked skin irritation was also observed in these animals, and Nessel et al. (1998) noted that the increased tumor frequency was only observed in the presence of significant skin irritation. No tumors were observed in mice administered 50 µL of 50% kerosene solution (diluted with mineral oil) applied 4 times per week or 28.5% diluted solution applied 7 times per week.

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.3 Dermal Exposure

Using a tape stripping method which used naphthalene as a marker of JP-8 exposure, Nylander-French and associates (Chao and Nylander-French 2004; Mattorano et al. 2004) demonstrated the dermal absorption of JP-8 through human skin. The amount of naphthalene removed in the tape strips was inversely related to the post-exposure time. Mattorano et al. (2004) estimated that five minutes after exposure, 70% of the naphthalene remained on the skin of fuel cell maintenance workers; after 10 minutes, only 33% remained on the skin and after 20 minutes, approximately 1% remained. In a subsequent study by this group (Chao et al. 2005), a significant relationship between exposure category (high, moderate, or low exposure based on job titles) and naphthalene levels detected via tape stripping in

various areas of the body was found among Air Force fuel-cell maintenance workers. Multivariate linear regression models also showed that skin irritation and increasing duration of exposure increased JP-8 dermal absorption.

Kim et al. (2006b) estimated the apparent permeability coefficient (K_P) of aromatic and aliphatic components of JP-8 by measuring blood levels of these components in blood after dermal only exposure to JP-8 in 10 healthy adult volunteers. The rank order of the apparent K_p values was naphthalene>1-methyl naphthalene=2-methyl naphthalene>decane>dodecane>undecane.

An *in vitro* percutaneous absorption study showed that the absorption of 4 components of JP-8 (tridecane, nonane, naphthalene, and toluene) through pig skin and human skin was proportional to their composition in JP-8 (Kanikkannan et al. 2001).

Another *in vitro* porcine skin percutaneous absorption study using radiolabelled naphthalene, dodecane, and hexadecane as markers for JP-8 absorption showed that naphthalene (1.17%) had the highest absorption (measured as the percentage of the dose), followed by dodecane (0.63%) and hexadecane (0.18%) (Riviere et al. 1999). However, no significant differences in the amount of the compound that penetrated the skin were found; 1.47%, 1.11%, and 1.21% of the naphthalene, dodecane, and hexadecane dose, respectively, penetrated the skin.

An *in vitro* study examining the absorption of JP-8 components, found increased absorption of aromatic hydrocarbons such as ethyl benzene, p-xylene, and trimethylbenzene in pig skin that was previously exposed to JP-8, as compared to unexposed skin (Muhammad et al. 2005a).

In an *in vitro* of rat skin to JP-8, McDougal et al. (2000) showed that 13 components penetrated the skin after a 3.5 hour exposure; the components included diethylene glycol monomethyl ether, decane, methyl naphthalenes, trimethyl benzenes, undecane, naphthalene, xylene, dimethyl naphthalenes, toluene, dodecane, nonane, ethyl benzene, and tridecane. The aromatic hydrocarbon components penetrated the skin better than the aliphatic components. The permeability coefficients ranged from 8.0×10^{-2} for diethylene glycol monomethyl ether to 1.4×10^{-5} for dodecane. The components with lower octanol/water partition coefficients were found to have the larger permeability coefficients. At the end of the 3.5 hour exposure, only 6 components were detected in the skin, all aliphatic compounds with high octanol/water partition coefficients: nonane, decane, undecane, dodecane, tridecane, and tetradecane.

2.3.5 Physiologically Based Pharmacokinetic (PBPK/Pharmacodynamic (PD) Models

2.3.5.1 Summary of PBPK Models

Kim et al. (2006a) developed a four-compartment dermatotoxicokinetic model which accurately predicted the time-course of absorption and appearance in the blood of 6 components of JP-8 (naphthalene, 1-methyl naphthalene, 2-methyl naphthalene, n-decane, n-undecane, and n-dodecane) in humans following administration of JP-8 to the forearm. The mean apparent permeability coefficients for the 6 components are 5.3×10^{-5}, 3.2×10^{-5}, 2.9×10^{-5}, 6.5×10^{-6}, 1.6×10^{-6}, and 4.5×10^{-7} for naphthalene, 2-methyl naphthalene, 1-methyl naphthalene, decane, dodecane, and undecane, respectively.

With the goal of developing a PBPK model for inhaled JP-8, Campbell and Fisher (2007) examined the metabolic interactions of two JP-8 components, m-xylene and ethylbenzene. At low JP-8 concentrations (<400 mg/m^3), minimal or no metabolic interactions were found. At the highest concentration (2700 mg/m^3), a 40 and 46% increase in the area-under-the-concentration curve values for blood xylene and ethylbenzene, respectively, was found. These data were used for the development of a PBPK model for inhaled synthetic and fossil-derived jet fuel (Martin et al. 2012). The model for jet fuel which examined aerosol and vapor exposure was developed using submodels for six aliphatic and aromatic hydrocarbon markers (n-octane, n-decane, n-tetradecane, toluene, ethylbenzene, and m-xylene).

2.5 RELEVANCE TO PUBLIC HEALTH

Genotoxicity. Significant evidence of DNA damage, as evaluated using the Comet assay, was found in human peripheral lymphocytes following a 4- and 8-hour exposure to JP-8 or JP-5 (Jackman et al. 2002) and in H4IIE rat hepatoma cells (Grant et al. 2001). The amount of damage appeared to be concentration-related.

2.6 BIOMARKERS OF EXPOSURE AND EFFECT

2.6.1 Biomarkers Used to Identify and/or Quantify Exposure to JP-8

A study of Air Force personnel exposed to high (fuel cell maintenance workers), moderate (regular contact with jet fuel via fuel handling, distribution, recovery, and testing), and low (subjects without direct contact) levels of JP-8 found exposure-related increases in benzene and naphthalene levels in expired air (Egeghy et al. 2003). Multivariate analysis found a high correlation between airborne naphthalene and a priori JP-8 exposure categories and was not highly influenced by background sources and cigarette smoking. It contrast, benzene levels in post-exposure breath were significantly related to pre-exposure breath benzene levels and recent smoking; suggesting that breath benzene levels may not be a good biomarker of JP-8 exposure.

Several studies have examined the possible association between exposure to JP-8 in Air Force fuel cell maintenance workers and urinary excretion of several potential biomarkers, particularly 1- and 2-naphthol. Urinary levels of naphthalene, 1-naphthol, and/or 2-naphthol were higher in workers with high levels of JP-8 exposure as compared to workers with low levels of exposure (Serdar et al. 2003; Smith et al. 2012) and the levels of 1- and 2-naphthol in urine were correlated with naphthalene air levels (Serdar et al. 2004; Smith et al. 2012). Other studies of Air Force fuel cell maintenance workers found a statistical association between urinary 2-naphthol levels and dermal exposure to JP-8; however, no association was found for urinary 1-naphthol levels (Chao and Nylander-French 2004; Chao et al. 2006). However, exhaled breath naphthalene and breathing zone naphthalene levels significantly predicted urinary 1-naphthol and 2-naphthol levels (Chao et al. 2006). Regression analysis showed that breathing zone naphthalene levels was a significant predictor of urinary 1-naphthol levels (after controlling for smoking status, pre-shift 1- and 2-naphthol levels, and post-shift creatinine levels), but did not predict urinary 2-naphthol levels; time in the fuel tank was a significant predictor of 1- and 2-naphthol levels (Smith et al. 2012). High levels of urinary benzene were also found in the high exposure workers; however, the levels were similar to levels found in smokers (Serdar et al. 2003).

Urinary level of (2-methoxyethoxy)acetic acid, a metabolite of 2-(2-methoxyethoxy)ethanol (MEAA) which is added to JP-8, was shown to be a suitable biomarker of JP-8 exposure in oral and dermal exposure studies in mice (B'Hymer et al. 2005). In Air Force personnel, MMEA was detected in 94% of the urine samples of personnel in the high exposure group, 34% in the medium exposure group, and 3% in the low exposure group (B'Hymer et al. 2012b). The mean urinary MEAA levels (both unadjusted and adjusted for creatinine) in the high exposure group were significantly higher than the medium and low

exposure groups, and the mean of the medium exposure group was significantly higher than the low exposure group. B'Hymer et al. (2012a) compared two other potential biomarkers of JP-8 exposure in Air Force personnel: *S*-benzylmercapturic acid (BMA), a metabolite of toluene, and *S*-phenylmercapturic acid (PMA), a metabolite of benzene, to the results from the B'Hymer et al. (2012b) study of MEAA. BMA was detected in almost all urine samples from personnel in the high (98%), medium (97%), and low (95%) exposure categories, and the mean levels were significantly higher in the high exposure group, as compared to the low exposure group; however, no difference was found between the high and medium groups. When BMA levels were adjusted for creatinine levels, no significant differences were found between the groups. PMA was detected in 34, 24, and 20% of the personnel in the high, medium, and low exposure groups, respectively. Mean levels of PMA were significantly higher in the high exposure group, as compared to the medium and low exposure groups; however, when the PMA levels were adjusted for creatinine levels, no significant differences were found between the three exposure categories. Based on these results, B'Hymer et al. (2012a) concluded that MEAA is a suitable biomarker of JP-8 exposure because it appears to be relatively specific for JP-8 exposure and is easily detected at levels that allow for distinguishing differences in exposure levels.

Kang-Sickel et al. (2011) examined the potential use of naphthyl-keratin adduct (NKA) levels in the skin as a potential biomarker of dermal exposure to JP-8 among Air Force fuel maintenance workers. NKA levels correlated with urine naphthalene levels, but did not correlate with dermal, breath, or breathing zone naphthalene levels or with urinary 1-naphthol, 2-naphthol, or total naphthol levels. However, regression analyses showed that log-transformed dermal naphthalene levels and age were inversely associated with skin naphthyl-keratin adduct levels, and l levels of total skin NKA increased with exposure duration (on sampling day). The investigators noted that as more naphthalene was absorbed into the stratum corneum and metabolized by keratinocytes to form keratin adducts, less would remain on the surface of the stratum corneum for sampling by tape-stripping which may explain the inverse association between dermal naphthalene levels and adduct levels.

3. CHEMICAL PHYSICAL INFORMATION

No updated data.

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

No updated data.

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5. POTENTIAL FOR HUMAN EXPOSURE

No updated data.

6. ANALYTICAL METHODS

No updated data.

7. REGULATIONS AND ADVISORIES

No updated data.

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