2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO JP-5, JP-8, AND JET A FUELS IN THE UNITED STATES

JP-5, JP-8, and Jet A are kerosene-based jet fuels. They are refined by a straight distillation of crude or shale oil, or a distillation of crude or shale oil in the presence of a catalyst. The jet fuels are, however, refined under more stringent conditions and contain various additives not found in kerosene; Jet A serves as the base fuel for JP-8. The performance-enhancing additives found in JP-5, JP-8, and Jet A include antioxidants (including phenolic antioxidants), static inhibitors, corrosion inhibitors, fuel system icing inhibitors, lubrication improvers, biocides, and thermal stability improvers. These additives are used in specified amounts as governed by commercial and military specifications. Jet fuels are composed of more than 200 aliphatic and aromatic hydrocarbons (C_6-C_{17+}); the exact composition of a jet fuel is also dependent upon the crude oil from which it is refined. Because of this inherent variability, little information exists on the exact chemical and physical properties of jet fuels.

Many of the constituents of JP-5, JP-8, and Jet A fuels are volatile and will evaporate into the air when jet fuels are spilled accidentally onto soils or surface waters. Other components of these jet fuels are more likely to dissolve in water following spills to surface waters or leaks from underground storage tanks. Some of the chemicals in jet fuels may slowly move down through the soil to the groundwater. The chemicals that evaporate will undergo photodegradation by atmospheric oxidants such as hydroxyl radicals. The photooxidation half-life range for a group of representative chemicals of kerosene, JP-5, JP-8, and Jet A was reported as 0.2–1.1 days. In soil and water, the constituents of JP-5, JP-8, and Jet A fuels are biodegraded at varying rates. Exposure to JP-5, JP-8, and Jet A fuels by the general population is expected to be low and could occur through atmospheric, soil, or groundwater contamination. Military or civilian personnel who are employed in jet fuel storage or re-fueling activities are generally at higher exposure dose risk via inhalation and dermal routes to these substances than the general population. Occupational exposure could involve exposure to raw fuel, vapor phase, aerosol phase, a mixture of vapors and aerosols, or fuel combustion exhaust. General population exposure is most likely to occur in populations living near military installations using JP-5 or JP-8 or commercial airports using Jet A. Airborne exposure to jet fuel vapors and/or aerosols can result from fuel spillage, engine cold starts, and high-altitude fuel jettisoning. Jet fuel spills can also result in exposure via contaminated groundwater or soil.

Because JP-5, JP-8, and Jet A fuels are complex mixtures of both aliphatic and aromatic hydrocarbons, exposure is typically measured by monitoring the total hydrocarbon concentration (THC) and the levels of certain aromatic substances, such as benzene, toluene, ethylbenzene, xylene, and naphthalene, that are present in jet fuels. Since there are multiple sources of these components in the environment, exposure studies usually include a control population that has had little or no exposure to jet fuels in order to establish a baseline level of these substances that would exist in the absence of jet fuel exposure. In a study of Air Force personnel exposed to JP-8 during regular work shifts, the geometric mean concentration of THC in the breathing zone of a high exposure group was 4.4 mg/m^3, while that of a low exposure group was 0.9 mg/m^3. The geometric mean concentrations of naphthalene were reported as 4.8 and 0.7 $\mu g/m^3$ for the high and low exposure groups, respectively. See Chapter 6 for more information on levels of exposure and environmental fate of JP-5 and JP-8.

2.2 SUMMARY OF HEALTH EFFECTS

Although JP-5 and Jet A fuels have been used for over 60 years and JP-8 was identified by the Department of Defense as its single military fuel over 30 years ago, there are very little data on the toxicity of kerosene-based jet fuels in humans. Most of the studies focused on the potential neurotoxicity of JP-8 fuel. Single studies in humans exposed to JP-8 fuel reported increases in white blood cell neutrophil and monocyte levels with no change in lymphocyte subpopulations and an inverse association between aliphatic hydrocarbons in exhaled breath and serum levels of luteinizing hormone (LH). However, exposure to JP-8 was not associated with higher odds of menstrual disorders. Limited information is available on the carcinogenic potential of jet fuels in humans. Studies in laboratory animals have examined the toxicity of JP-5, JP-8, and Jet A fuels following inhalation, oral, or dermal exposure and have reported a number of targets of toxicity, including the lungs, liver, skin, immunological system, nervous system, and developing organism. Although renal effects have also been observed in male rats exposed to JP-5 or JP-8, the lesions are considered to be characteristic of $alpha_{2u}$-globulin nephropathy, which is only observed in male rats and is not considered to be toxicologically relevant to humans. JP-5 was not carcinogenic in mice in a 2-year dermal bioassay. Increases in skin tumors were observed in mice dermally exposed to Jet A for 52–62 weeks; however, tumors were only observed at concentrations resulting in significant skin damage (inflammation and necrosis). Similarly, increased numbers of skin tumors were observed in mice that received applications of undiluted kerosene on the skin for 2 years, but this occurred only in the presence of moderate-to-marked skin damage. No inhalation or oral studies evaluated the carcinogenicity of JP-5, JP-8, or Jet A in laboratory animals; no increases in tumor incidences were observed in rats administered kerosene by gavage for 2 years.

Neurological Effects. Studies in subjects occupationally exposed to JP-8 have reported alterations in balance associated with cumulative exposure to benzene, a component of JP-8, and alterations in neuropsychological test results in workers with daily exposures to <10 mg/m^3 JP-8. Another study of workers did not find an association between daily exposures to JP-8 and balance. A study of veterans found alterations in reaction time on divided attention tests following 3 weekly 7-minute exposures to 0.00057 ppm JP-8 vapor. Kerosene induces neurological effects in humans, as evidenced in many reports of acute accidental ingestion of this fuel. Neurological effects noted most frequently in these reported cases included unconsciousness or semiconsciousness, drowsiness, restlessness, and irritability. There are limited data that suggest that the central nervous system effects following ingestion of kerosene are due to hypoxia from kerosene-induced respiratory impairment. In laboratory animals, JP-5 and JP-8 caused alterations in performance in a battery of tests in rats exposed to 1,200 mg/m^3 JP-5 vapor or 1,000 mg/m^3 JP-8 vapor in intermediate-duration inhalation studies. Exposure to 1,000 mg/m^3 JP-8 vapor also resulted in impaired performance on higher cognitive tests, but not on simple memory tests. Another study found hyperlocomotive activity and increased arousal levels in rats exposed to aerosolized JP-8 for 4 weeks. In contrast, lethargy was observed in mice administered Jet A gavage doses of 100 mg/kg/day and was observed once in most rats exposed to 500 mg/kg/day. In addition to the central nervous system effects, exposure to JP-8 can result in auditory effects. Acute- and intermediate-duration exposure to JP-8 followed by exposure to noise resulted in alterations in the peripheral auditory system and the central auditory processing area.

Respiratory Effects. No human studies have examined the potential of JP-5, JP-8, or Jet A to induce respiratory effects. Respiratory effects are a common finding in humans ingesting kerosene; the observed effects include bronchopneumonia, bronchitis, pneumonitis, lung infiltrates and effusions, cough, dyspnea, and tachypnea. However, these effects are likely attributable to aspiration of the kerosene. The results of studies in laboratory animals suggest that the respiratory tract is a target for airborne JP-8. Most of this information comes from a series of studies conducted at the University of Arizona in which rats and mice were exposed to aerosolized JP-8 1 hour/day for 1 or 7 days. There are several limitations to these studies: the primary limitation being that only the aerosol component of the test atmosphere was measured, resulting in a large underestimation of the JP-8 exposure (the studies' limitations are discussed in greater detail in Section 3.2.1). These studies reported an increase in respiratory permeability, increased lung resistance, and terminal bronchiole lesions. These effects were usually accompanied by increased biomarkers of inflammation in bronchoalveolar lavage fluid (BALF). In contrast, an acute-duration study in which rats were exposed to Jet A aerosols and vapors and most intermediate-duration

inhalation studies involving exposure to JP-5 or JP-8 vapor did not report respiratory effects. The exception is the finding of enlarged alveolar capillaries in rats exposed to 500 mg/m^3 JP-8 vapor 6 hours/day for 90 days; the no-observed-adverse-effect level (NOAEL) was 250 mg/m^3. No histological alterations were observed in the respiratory tracts of rats exposed to ≤1,980 mg/m^3 Jet A aerosols and vapors 4 hours/day, 5 days/week for 14 days, in rats continuously exposed to ≤1,000 mg/m^3 JP-8 vapor for 90 days, or in rats, mice, and dogs continuously exposed to ≤750 mg/m^3 JP-5 vapor for 90 days. One possible explanation for the conflicting results between studies is the differences in the composition of the test atmosphere. For example, a vapor test atmosphere could contain a higher percentage of low molecular weight, more volatile compounds than the raw fuel, and aerosolizing the jet fuel could generate liquid droplets enriched in higher molecular weight n-alkanes.

Hepatic Effects. Several studies in laboratory animals provide evidence that the liver is a sensitive target of jet fuel toxicity; however, the findings are not consistent across studies, which may be due to species or strain differences or differences in the physical properties of the fuel (e.g., aerosols versus vapor). Continuous exposure to ≥150 mg/m^3 JP-5 vapor resulted in hepatocellular fatty changes and vacuolization in mice. In similarly exposed rats and dogs, exposure to 750 mg/m^3 JP-5 vapor resulted in no effects in rats and mild diffuse hepatocellular swelling in dogs. Dilated sinusoids and fatty hepatocytes were observed in rats exposed to ≥500 mg/m^3 JP-8 vapor for 91 days; another 90-day study found no histological alterations in rats exposed to 1,000 mg/m^3 JP-8 vapor. A 14-day exposure to 1,980 mg/m^3 Jet A vapor and aerosol also did not result in histological alterations or changes in alanine aminotransferase (ALT) levels. In acute-duration gavage studies, increases in ALT and aspartate aminotransferase (AST) levels were observed in rats administered a single gavage dose of 19 mg/kg JP-5 or single or repeated gavage doses of >18,000 mg/kg JP-5. Intermediate-duration gavage administration of ≥750 mg/kg/day JP-8 for 90 days in rats resulted in non-dose-related increases in ALT and AST; this study also found an increase in total bilirubin levels at ≥750 mg/kg/day, but no histological alterations. A 90-day gavage exposure to 500 mg/kg/day Jet A also did not result in histological alterations in the livers of rats or mice; the exposure did result in an increase liver weight and enlarged livers in rats. Chronic dermal exposure to 500 mg/kg/day JP-5 resulted in liver amyloidosis in mice.

Dermal Effects. Studies in rats, mice, rabbits, and pigs demonstrate the dermal toxicity of topically applied JP-5, JP-8, and Jet A. Similar effects have been observed for all three fuel types, although the results of one study suggests that Jet A may be slightly more irritating than JP-8 in pigs exposed for 5 hours. Single 1-hour exposures to low concentrations did not result in visible damage to the skin; however, evidence of inflammation (increased granulocyte infiltration and increased levels of

inflammatory biomarkers) was observed. Additionally, ultrastructural changes suggest that jet fuel exposure alters the epidermal-dermal barrier, which could result in increased absorption. Overt signs of dermal toxicity have been observed following repeated exposures; effects ranged from erythema and edema to dermatitis to ulceration. The severity of the lesions increased with duration and concentration. Other factors that can affect the dermal toxicity include the test vehicle and whether the application site is occluded. At a given dose, undiluted jet fuel resulted in more severe erythema and desquamation, as compared to jet fuel diluted in mineral oil or acetone:olive oil. Occluding the application site resulted in moderate-to-severe erythema and moderate edema as compared to slight erythema when the application site was not occluded.

Immunological Effects. Inhalation, oral, and dermal studies in animals have shown that exposure to JP-8 and Jet A can affect immune parameters; immunotoxicity has not be adequately evaluated in JP-5 studies. A number of alterations in immune parameters were reported in a series of acute-duration studies in which mice were exposed to JP-8 vapors and aerosols 1 hour/day. However, most of the studies only measured the aerosol component of the test atmosphere, which underestimated the JP-8 exposure, and the animals were likely exposed to plasticizers (see Section 3.2.1 for discussion of the limitations of this series of studies conducted by the University of Arizona). Effects included decreased viable immune cells in the thymus, lymph nodes, and peripheral blood; impaired response to stimulation with the T cell mitogen concanavalin A; increased severity in the response to influenza virus infection; and suppressed immune response to injected tumor cells. A later study by this group in which the vapor and aerosol components of the test atmosphere were measured found decreased thymus weight and the proliferative response to stimulation with antigens at ≥1,000 mg/m^3 JP-8 vapor and aerosol (1 hour/day for 7 days); at higher concentrations, decreases in viable immune cells were observed in the thymus, spleen, peripheral blood, and bone marrow. Decreases in spleen and thymus weights and an impaired response to concanavalin A were observed in mice exposed to aerosolized Jet A in another University of Arizona study. A study of Jet A by another investigator did not find alterations in spleen weights or splenocyte phenotypes in rats exposed to Jet A aerosols and vapors for 14 days. The results of the two Jet A studies cannot be directly compared because the first study did not measure the vapor component of the test atmosphere. In acute-duration (14-day) oral studies that assessed multiple immune parameters in mice, JP-8 suppressed humoral immunity, as evidenced by an altered response to sheep red blood cells (SRBCs) at the lowest dose tested, 500 mg/kg/day. Dermal exposure to ≥50 µL JP-8 inhibited contact and delayed hypersensitivity in mice and ≥25 µL suppressed immune memory in mice previously exposed to *Candida albican*s. Dermal exposure to Jet A also resulted in suppression of delayed type hypersensitivity in mice. Production of prostaglandin E_2 by mast cells and of suppressive cytokines, presumably by epidermal

cells, were proposed as possible mechanisms involved in the immunotoxicity of dermally applied JP-8. JP-8 was also shown to be a weak skin sensitizer; however, neither JP-8+100 nor Jet A were skin sensitizers. Intermediate-duration dermal exposure to Jet A did not result in alterations in spleen or thymus weights, spleen lymphocyte phenotypes, or response to SRBCs.

The issue of which component or components in JP-8 are responsible for the immune effects of this fuel has been explored in a few studies. Acute inhalation exposure of mice to a synthetic fuel (S8) with no polycyclic aromatic hydrocarbons (PAHs) induced immune effects similar to JP-8, suggesting that the PAHs in JP-8 are not responsible for the immune effects. Exposure of mice to vapors of jet fuel kerosene (Jet A free of performance additives) and in the same range of concentrations as in the studies mentioned above did not suppress innate, humoral, or cell-mediated immunity, suggesting that the additives, at least in part, are responsible for the effects of JP-8 on immune parameters. In yet a third study, dermal exposure of mice to S8 did not induce immune suppression, as measured by the delayed-type hypersensitivity reaction (DTH). However, when a cocktail of seven of the most prevalent aromatic hydrocarbons in JP-8 were added to S8, exposure to the latter resulted in suppression of DTH.

Developmental Toxicity. Assessment of standard developmental end points showed that JP-8 was not embryotoxic or teratogenic in rats exposed orally during gestation, although fetal weight was decreased with doses (≥1,000 mg/kg/day; administered via gavage) that significantly reduced (≥31%) maternal body weight gain during gestation and pup body weights were decreased on postnatal days (PNDs) 4 and 11 at maternal gavage dose of 1,500 mg/kg/day. Inhalation (University of Arizona study, which only measured the aerosol component) or oral (1,000 mg/kg/day) exposure of pregnant mice to JP-8 resulted in suppressed immune function in the offspring when assessed before 8 weeks of age. JP-8 also induced a transient delay in motor coordination in offspring from rats exposed to ≥325 mg/kg/day before and during gestation and during lactation. The developmental toxicity of JP-5 and Jet A has not been evaluated.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for JP-5, JP-8, and Jet A fuels. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based

on noncancerous health effects only and do not consider carcinogenic effects. MRLs may be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs may be revised.

Inhalation MRLs

Acute-Duration Inhalation MRL

JP-5. Information on the acute toxicity of airborne JP-5 is limited to a study in mice that estimated a concentration resulting in a 50% reduction in respiratory rate (RD_{50}) following a 30-minute exposure to JP-5 vapor and aerosol (Whitman and Hinz 2001); the RD_{50} was 3,338 mg/m^3. This study is not considered a suitable basis for an acute-duration inhalation MRL because a limited number of end points were examined and because of the short exposure duration.

JP-8. Although a number of studies have examined the acute toxicity of airborne JP-8, the studies focused on a small number of potential targets of toxicity. The studies reported signs of respiratory and ocular irritation, immunotoxicity, and altered auditory function. Signs of upper respiratory irritation and ocular irritation have been observed in rats following a 4-hour exposure to 3,430 mg/m^3 JP-8 vapor or 3,570 mg/m^3 JP-8+100 vapor (Wolfe et al. 1996). However, no signs of respiratory or ocular irritation were observed in rats following a 4-hour exposure to 4,440 mg/m^3 JP-8 vapor and aerosol or 4,540 mg/m^3 JP-8+100 vapor and aerosol (Wolfe et al. 1996). RD_{50} values of 2,876 and 1,629 mg/m^3 were calculated for a 30-minute exposure to JP-8 or JP-8+100 vapor, respectively (Whitman and Hinz 2001). Wong et al. (2008) reported significant increases in inspiratory and expiratory lung resistance in mice exposed to 53 mg/m^3 JP-8 vapor and aerosol 1 hour/day for 7 days (Wong et al. 2008). However, Herrin et al. (2006) did not find significant alterations in lung function in mice exposed to 45 or 267 mg/m^3 JP-8 vapor and aerosol 1 hour/day for 7 days, but did find a decrease in inspiratory dynamic lung compliance at

406 mg/m^3. It is unclear why the studies had conflicting results for lung function. Both studies found ultrastructural changes in the morphology of alveolar type II cells, particularly increases in lamellar body volume density at all tested concentrations. Suppression of the immune response to mitogens was observed in mice exposed to 1,000 mg/m^3 JP-8 vapor and aerosol 1 hour/day for 7 days (Hilgaertner et al. 2011). At higher concentrations, decreases in the number of viable immune cells were observed in the thymus (2,000 mg/m^3), spleen and peripheral blood (4,000 mg/m^3), and bone marrow (8,000 mg/m^3). Exposure of rats to 1,000 mg/m^3 JP-8 mostly vapors for 4 hours/day for 1 or 5 days did not result in auditory impairment or damage to cochlear hair cells (Fechter et al. 2007); however, a loss of cochlear hair cell function was observed in rats exposed to 2,000 mg/m^3 JP-8 vapor 4 hours/day for 5 days (Fechter et al. 2010). Exposure to 1,000 mg/m^3 for 1 or 5 days followed by a 1- or 4-hour exposure to noise with an intensity of 97–105 dB resulted in impaired hair cell function, as compared to rats exposed only to noise or only to JP-8 (Fechter et al. 2007, 2010); no alterations were observed in rats exposed to 500 mg/m^3 JP-8 followed by 4 hours of noise with 97–99 dB intensity (Fechter et al. 2010).

In addition to these acute-duration inhalation studies, investigators at the University of Arizona conducted a number of respiratory toxicity and immunotoxicity studies. However, the interpretation of these studies is limited by an inaccurate measurement of the concentration of JP-8 in the test atmosphere and the possible exposure to plasticizers (see Section 3.2.1 for a more complete discussion of these studies). The studies involved nose-only exposure for 1 hour/day for 1 or 7 days, and only reported exposure levels for the aerosol component of the test atmosphere. These studies found lung tissue damage and impaired lung function (Hays et al. 1995; Pfaff et al. 1995, 1996; Robledo and Witten 1998; Robledo et al. 2000; Wong et al. 2004) and immunosuppression (Harris et al. 1997a, 1997b, 1997c; 2007b, 2007c, 2008). The observed effects in rats and mice included increases in inspiratory resistance and inspiratory dynamic pulmonary compliance (Pfaff et al. 1995), an increase in lung permeability (Hays et al. 1995; Pfaff et al. 1995; Robledo and Witten 1998), congestion with hemorrhaging in the distal lung (Hays et al. 1995; Pfaff et al. 1996; Robledo and Witten 1998), and ectasia of respiratory bronchioles and alveoli (Wong et al. 2004). Electron microscopic examination also revealed breaks in the alveolar capillary membrane, congestion of small blood vessels and capillaries, and changes in type II cells, which included swollen mitochondria, fused lamellar bodies, and short irregular microvilli (Hays et al. 1995). The immunological effects included decreases in the number of viable immune cells in the thymus and spleen (Harris et al. 1997a, 1997b), alterations in the number of viable immune cells in the lymph nodes, peripheral blood, and bone marrow (Harris et al. 1997a, 1997b), an impaired immune response to concanavalin A (Harris et al. 1997a, 1997c), an increased severity of influenza virus infection (Harris et al. 2008), and suppression of the immune response to injected tumor cells (Harris et al. 2007c). This group also found a decrease in the

number of viable immune cells in the thymus and spleen, as well as suppressed immune function in the at 6–8-week-old offspring of rats exposed to JP-8 on gestation days (GDs) 7–21 or 15–21 (Harris et al. 2007b).

Although the available database on the acute toxicity of JP-8 consists of a number of studies providing evidence that the lungs and immune system are targets of toxicity, there is some uncertainty as to whether these are the most sensitive targets of toxicity for JP-8. No acute studies were identified that examined all regions of the respiratory tract, other systemic targets such as the liver, or neurological end points (outside of the potential auditory effects); findings from longer-term JP-8 inhalation or oral studies suggest that these may be potential targets of toxicity. Additionally, the Herrin et al. (2006), Hilgaertner et al. (2011), and Wong et al. (2008) studies, which identified the lowest adverse effect levels, all involved a 1 hour/day exposure to JP-8 for 7 days. There is considerable uncertainty in extrapolating from a 1-hour exposure to a continuous exposure as the resulting MRL might be overly conservative. Thus, the database was considered inadequate for derivation of an acute-duration inhalation MRL for JP-8.

Jet A. Information on the acute toxicity of Jet A is limited to two studies conducted by Sweeney et al. (2013) in which rats were exposed to Jet A aerosol and vapor 4 hours/day, 5 days/week for 14 days. Although these studies found some subclinical alterations, such as alterations in bronchoalveolar lavage fluid parameters that could be indicative of lung inflammation, the findings were not consistent across studies or concentration-related. The study did not find any histological alterations at exposure levels as high as 1,980 mg/m^3. Additionally, no alterations in spleen organ weights or immune cell population were found. The Sweeney et al. (2013) studies are well-designed studies that examined a number of potential targets of Jet A toxicity. However, they are not suitable as the basis of an acute-duration inhalation MRL because the highest tested concentration is a NOAEL and it is ATSDR's practice to not derive MRLs based on free-standing NOAEL values.

Intermediate-Duration Inhalation MRL

JP-5

- An MRL of 2 mg/m^3 has been derived for intermediate-duration inhalation exposure (15–365 days) to JP-5 vapor.

Information on the toxicity of JP-5 following intermediate-duration inhalation exposure comes from a study in which rats, mice, and dogs were continuously exposed to JP-5 vapors for 90 days (Gaworski et al. 1984). In mice and dogs, the liver was the most sensitive target of toxicity. Hepatocellular fatty

changes and vacuolization were observed in female mice exposed to ≥150 mg/m^3 JP-5 vapor (Gaworski et al. 1984) and diffuse hepatocellular swelling was observed in male and female dogs exposed to 750 mg/m^3 JP-5 vapor (Gaworski et al. 1984). Gaworski et al. (1984) also reported a significant increase in the occurrence of hyaline droplets in the proximal renal tubules of male rats exposed to ≥150 mg/m^3 JP-5 vapor; no renal lesions were observed in female rats, female mice, or male and female dogs (Gaworski et al. 1984). The renal effects observed in the male rats is likely due to an accumulation of alpha$_{2u}$-globulin in hyaline droplets, which can lead to cell necrosis, regeneration of tubule cells, and tubular hyperplasia (EPA 1991a; Hard et al. 1993). The production of alpha$_{2u}$-globulin appears to be unique to male rats and the accumulation of alpha$_{2u}$-globulin in hyaline droplets and subsequent renal damage is not considered to be relevant to humans (EPA 1991a; Flamm and Lehman-McKeeman 1991; Hard et al. 1993; Swenberg 1993). A neurobehavioral study found an increase in forelimb grip strength in rats exposed to 1,200 mg/m^3 JP-5 vapor 6 hours/day, 5 days/week for 6 weeks (Rossi et al. 2001); no other alterations in performance on the neurobehavioral battery tests were observed.

The available data on the intermediate-duration toxicity of JP-5 vapors have identified two targets: the liver in mice and dogs and the nervous system in rats. These end points are consistent with the results of intermediate-duration vapor exposure studies with JP-8 (Hanas et al. 2010; Ritchie et al. 2001; Rossi et al. 2001). Immunotoxicity has also been identified as a sensitive end point following acute inhalation exposure to JP-8 and is likely a target for JP-5 toxicity. The lowest reliable LOAEL for immunotoxicity following inhalation exposure to JP-8 was 1,000 mg/m^3 in rats exposed 1 hour/day for 7 days (Hilgaertner et al. 2011). This LOAEL is much higher than the LOAEL for liver effects, suggesting that an MRL based on liver effects would be protective for potential immune effects.

The 150 mg/m^3 concentration that resulted in hepatocellular fatty changes and vacuolization in mice continuously exposed to JP-5 vapor for 90 days (Gaworski et al. 1984) was selected as the point of departure for the MRL; the effects were considered minimally adverse and the concentration was identified as a minimal LOAEL. A human equivalent concentration of the LOAEL (LOAEL$_{HEC}$) was calculated by multiplying the LOAEL by the ratio of the human to mouse blood:gas partition coefficient ratio. Because human and mouse blood:gas partition coefficients are not measurable for a complex mixture such as JP-5, a default value of 1 was used for the human-animal blood:gas partition coefficient ratio; thus, the LOAEL$_{HEC}$ was 150 mg/m^3. The minimal LOAEL$_{HEC}$ of 150 mg/m^3 was divided by an uncertainty factor of 90 (3 for the use of a minimal LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustment, and 10 for human variability), resulting in an intermediate-duration inhalation MRL of 2 mg/m^3 for vapor exposure.

JP-8

- An MRL of 3 mg/m^3 has been derived for intermediate-duration inhalation exposure (15–365 days) to JP-8 vapor.

In a well-designed intermediate-duration inhalation study, no systemic effects were observed in rats continuously exposed to concentrations of JP-8 vapor as high as 1,000 mg/m^3 for 90 days (Mattie et al. 1991). However, another study involving a 91-day intermittent exposure to JP-8 vapors (6 hours/day, 7 days/week) reported a number of systemic effects in two of the three rats exposed to 500 mg/m^3 including enlarged alveolar capillaries, myocardial scarring, 50% reduction in fat cells in the bone marrow, and dilated hepatic sinusoids with fatty hepatocytes (Hanas et al. 2010). It is unclear why these studies had conflicting results. Both studies also reported kidney effects in the male rats. Mattie et al. (1991) reported hyaline nephropathy in males exposed to ≥500 mg/m^3 JP-8 vapor and Hanas et al. (2010) reported proximal tubule damage in males exposed to ≥250 mg/m^3 JP-8 vapor; no renal lesions were observed in the female rats in the Mattie et al. (1991) study. As noted in the discussion of the intermediate-duration JP-5 data, the renal effects were likely due to an accumulation of alpha$_{2u}$-globulin in hyaline droplets and the effect is not considered relevant to humans. A number of studies have reported neurobehavioral alterations and auditory effects in rats following exposure to JP-8 vapor. Impaired learning of moderately difficult tasks was observed in rats exposed to1,000 mg/m^3 JP-8 vapor 6 hours/day, 5 days/week for 6 weeks (Ritchie et al. 2001); this effect was not observed at 500 mg/m^3. A similar exposure to 1,000 mg/m^3 JP-8 vapor also resulted in an alteration in a novel appetitive stimulus test, which was hypothesized to quantify dopamine system sensitization in rats (Rossi et al. 2001); no other alterations in performance on the neurobehavioral battery tests were found. Intermediate-duration exposure to JP-8 vapor also results in damage to the auditory system. Exposure to 1,000 mg/m^3 JP-8 vapor also resulted in central auditory processing dysfunction, but no damage to cochlear hair cells, in rats exposed 6 hours/day, 5 days/week for 4 weeks (Guthrie et al. 2014, 2015). Another study found significant alterations in auditory function in rats exposed to 1,500 mg/m^3 JP-8 vapor 6 hours/day, 5 days/week for 4 weeks (Fechter et al. 2012). However, simultaneous exposure to JP-8 and non-damaging noise (85 dB) resulted in impaired auditory function, as compared to the control group; exposure to 85 dB noise alone did not significantly impair auditory function. In addition to these studies, three University of Arizona studies have reported edema and inflammation of the terminal bronchioles in rats exposed 1 hour/day for 28 or 56 days to JP-8 aerosols and vapors (Hays et al. 1995; Pfaff et al. 1995, 1996). Hays et al. (1995) also found increased lung epithelial permeability and alveolar permeability.

The Hanas et al. (2010) study identified the lowest LOAEL (500 mg/m^3) for JP-8 vapors; however, the alveolar capillary, cardiac, and bone marrow effects have not been observed in other JP-8 studies or in studies with JP-5 or Jet A. The liver effects are similar to those observed in mice exposed to JP-5 vapors (Gaworksi et al. 1984); however, no liver effects have been observed in rats exposed to JP-8 vapor (Mattie et al. 1991), JP-5 vapor (Gaworski et al. 1984), or administered JP-8 via gavage (Mattie et al. 1995). Given the small number of animals tested (3/group) and the conflicting results with more robust studies, the Hanas et al. (2010) study was not selected as the basis of an MRL. Rather, the NOAEL of 500 mg/m^3 for neurotoxicity identified in the Ritchie et al. (2001) study was selected as the point of departure. The NOAEL was adjusted for intermittent exposure (6 hours/day, 5 days/week) resulting in a $NOAEL_{ADJ}$ of 89 mg/m^3. The $NOAEL_{HEC}$ of 89 mg/m^3 was calculated by multiplying the $NOAEL_{ADJ}$ by the default human to rat blood:gas partition coefficient ratio of 1 (blood:gas partition coefficients are not measurable for a complex mixture such as JP-8). Dividing the $NOAEL_{HEC}$ by an uncertainty factor of 30 (3 for animal to human extrapolation with dosimetric adjustment and 10 for human variability) results in a JP-8 intermediate-duration inhalation MRL of 3 mg/m^3 for vapor exposure.

Jet A. No intermediate-duration studies evaluated the inhalation toxicity of Jet A precluding derivation of an MRL.

Chronic-Duration Inhalation MRL

Chronic-duration inhalation MRLs for JP-5, JP-8, and Jet A fuels were not derived due to the lack of reliable chronic-duration studies.

Oral MRLs

Acute-Duration Oral MRL

JP-5. Data on the acute oral toxicity of JP-5 are limited to two single exposure studies in rats. A single gavage dose of 18,912 mg/kg/day JP-5 resulted in an increase in white blood cell levels, hepatocyte vacuolization, and weight loss (Parker et al. 1981). Another study by Parker et al. (1981) reported hepatocellular vacuolization and hyaline droplet in renal tubular epithelial cells in male rats administered via gavage 47,280 mg/kg/day. An acute-duration oral MRL was not derived for JP-5 due to the lack of repeated exposure studies.

JP-8

- An MRL of 3 mg/kg/day has been derived for acute-duration oral exposure (≤14 days days) to JP-8.

Acute-duration studies evaluating the oral toxicity of JP-8 (administered via gavage) have primarily focused on immunological and developmental toxicity. Suppressed humoral immunity, specifically an impaired response to SRBCs, has been observed in mice administered 1,000 mg/kg/day JP-8 for 7 days (Dudley et al. 2001) or 500 mg/kg/day JP-8 for 14 days (Keil et al. 2004; Peden-Adams et al. 2001); the NOAEL identified in the 14-day study was 250 mg/kg/day. At 2,000 mg/kg/day, decreases in thymus weight and cellularity were observed (Dudley et al. 2001); no other immune effects were found. The three immunotoxicity studies also reported significant increases in liver weight at 1,000 mg/kg/day (Dudley et al. 2001; Keil et al. 2004; Peden-Adams et al. 2001); the studies did not include a histological examination of the liver. A developmental study also conducted by this group found decreases in the plaque-forming response to SRBCs in the offspring of mice administered 1,000 mg/kg/day on GDs 6–15 (Keil et al. 2003). A small decrease (4–6%) in fetal weights was observed in a study in which rat dams were administered 1,000 mg/kg/day JP-8 on GDs 6–15 (Cooper and Mattie 1996); decreases in maternal weight gain and maternal deaths were also observed at this dose level.

The lowest-adverse-effect level identified in the acute-duration JP-8 oral database is 500 mg/kg/day for altered immune function in mice (Keil et al. 2004). The immunotoxicity NOAEL of 250 mg/kg/day was selected as the point of departure for the MRL. Although the systemic toxicity of JP-8 has not been adequately addressed in the available acute-duration oral studies, intermediate-duration oral studies (Mattie et al. 1995, 2000) suggest that liver or other systemic effects are not likely to occur at doses lower than the lowest LOAEL for immunotoxicity (500 mg/kg/day). An additional end point that has not been adequately addressed in the acute oral studies is the potential for neurodevelopmental effects; this was the most sensitive end point following intermediate oral exposure. However, the LOAEL (350 mg/kg/day) from the intermediate study (Mattie et al. 2001) is similar to the lowest acute-duration LOAEL (500 mg/kg/day) and it is likely that the MRL using 250 mg/kg/day point of departure would be protective of neurodevelopmental effects.

The acute-duration oral MRL for JP-8 of 3 mg/kg/day was derived by dividing the NOAEL for immunological effects (Keil et al. 2004) by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Jet A. No acute-duration oral studies were identified for Jet A precluding derivation of an MRL.

Intermediate-Duration Oral MRL

JP-5. No studies examined the toxicity of JP-5 following intermediate oral exposure precluding derivation of an MRL.

JP-8

- An MRL of 0.3 mg/kg/day has been derived for intermediate-duration oral exposure (15–365 days) to JP-8.

Three studies have examined the toxicity of JP-8 following intermediate-duration oral exposure (administered via gavage). Administration of 750 mg/kg/day JP-8 to male rats for 90 days resulted in stomach hyperplasia, increases in serum ALT and AST activities, perianal dermatitis, hypoglycemia, and hyaline droplet formation in the kidneys (Mattie et al. 1995). In a 90-day study in female rats, stomach hyperplasia was observed at 750 mg/kg/day and perianal dermatitis was observed at 1,500 mg/kg/day; no alterations in blood glucose levels were observed (Mattie et al. 2000). The Mattie et al. (2000) study also found no effects on male or female fertility. Maternal exposure to JP-8 for 90 days prior to mating and during gestation resulted in an 11% decrease in pup body weight on postnatal day (PND) 4 (Mattie et al. 2000) and a dose-related decrease in coordinated motor movements on a swimming test at ≥325 mg/kg/day (Mattie et al. 2001). This effect was only observed at ≥325 mg/kg/day on PND 8 and at ≥750 mg/kg/day on PND 14; no alterations were observed on PND 10, 12, 16, or 18. The investigators suggested that the effect was due to a delay in motor coordination related to delayed neurodevelopment of the cerebellum and noted that PND 8 corresponds with maturation of the basket cells in the cerebellum and PND 14 corresponds with eye opening time and the final days of cellular organization and development of functional integrity in the cerebellum (Mattie et al. 2001). No other alterations in performance on neurobehavioral tests were observed in the offspring.

The intermediate-duration toxicity of ingested JP-8 has been investigated in systemic toxicity, reproductive toxicity, and developmental toxicity studies. The most sensitive effect appears to neurodevelopmental. The intermediate-duration database is lacking immunotoxicity studies; however, a comparison of the NOAEL (250 mg/kg/day) and LOAEL (500 mg/kg/day) values from an acute-duration oral study (Keil et al. 2004) with the LOAEL (325 mg/kg/day) from the Mattie et al. (2001) neurodevelopmental study suggests that an MRL based on this LOAEL should be protective for immunological effects. An intermediate-duration oral MRL of JP-8 was calculated by dividing the LOAEL of 325mg/kg/day by an uncertainty factor of 1,000 (10 for the use of a LOAEL, 10 for

extrapolation from animals to humans, and 10 for human variability) resulting in an MRL of 0.3 mg/kg/day.

Jet A. Information on the intermediate-duration oral toxicity of Jet A comes from a 90-day gavage study in rats and mice. Significant increases in absolute and relative liver weights and enlarged liver were observed in female rats administered 500 mg/kg/day Jet A for 90 days (Smith et al. 1999); no histological alterations were observed. Increases in salivation and a shoveling behavior were also observed in rats exposed to 100 or 500 mg/kg/day; the investigators suggested that these effects were likely due to mouth irritation. No other biologically-relevant effects were observed in rats. No systemic effects were observed in similarly exposed male mice; the highest tested concentration was 500 mg/kg/day (Smith et al. 1999). However, lethargy and hunched posture were observed in mice administered 100 or 500 mg/kg/day; lethargy was also observed in mice administered 20 mg/kg/day, but was only observed once in 5 of the 15 exposed mice. Similarly, lethargy was observed in rats administered 500 mg/kg/day, but in most rats it was only observed once in the 90-day exposure period (Smith et al. 1999).

There are limited data evaluating the toxicity of Jet A following intermediate-duration oral exposure. The most sensitive effects were signs of mouth irritation in rats and lethargy and hunched posture in mice administered ≥100 mg/kg/day Jet A (Smith et al. 1999). These clinical observations have not been observed in Jet A inhalation studies (Sweeney et al. 2013) and it is not known whether the effects were seen because the animals received the Jet A as a bolus dose and would not occur if the Jet A fuel was administered in drinking water or food, which are relevant routes of human exposure. In the absence of additional information on the mechanisms involved in the induction of lethargy or mouth irritation, the database was not considered adequate for derivation of a Jet A intermediate-duration oral MRL.

Chronic-Duration Oral MRL

Chronic-duration oral MRLs for JP-5, JP-8, and Jet A were not derived due to the lack of reliable chronic-duration studies.