



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
OFFICE OF RESEARCH AND DEVELOPMENT  
ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE  
CINCINNATI, OHIO 45268

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SUBJECT: 3QTR FY92 Master List Response Table Request

FROM: Joan S. Dollarhide *Joan S. Dollarhide* (513) 569-7300  
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Superfund Health Risk Technical Support Center  
Chemical Mixtures Assessment Branch

TO: Gerald Hiatt  
U.S. EPA  
Region IX

Attached please find the following responses requested from the 3QTR 1992 Master List of Chemical Specific Risk Assessment Issue Papers:

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- Fuel (Diesel) - Provisional RfD; Oral Slope Factor Summary and Provisional Weight-of-Evidence Group D *marine diesel only, RfD = 0.0008 mg/kg/d* = 56 ppb
  - Fuel (Gasoline) - Provisional RfD; Provisional Oral Slope Factor Group C, RfD = 0.2 mg/kg/d = 140 ppb
  - Fuel (JP-4) - Provisional RfD; Oral Slope Factor Summary and Provisional Weight-of-Evidence Group D *RfD = 0.0008 mg/kg/d* = 56 ppb
  - Fuel (JP-5) - Provisional RfD; Oral Slope Factor Summary and Provisional Weight-of-Evidence Group D *RfD = 0.0008 mg/kg/d* = 14 ppb

Please feel free to contact Superfund Technical Support Center at (513) 569-7300 if you need further assistance.

Attachment

*low confidence*

cc: R. Barnett (Region IX)  
J. Dinan (OS-230)  
B. Means (OS-230)

K. Poirier (ECAO-Cin) - chair RSD/RfC group



## Attachment

### Risk Assessment Issue Paper for: Oral Systemic and Carcinogenic Toxicity for Multiple Fuels

#### INTRODUCTION

The requestor requested oral toxicity values for the insoluble and non-volatile components of hydrocarbon fuels found in the soil and groundwater. Sources of contamination were reported to be aviation gasoline (AVGAS), diesel fuel, and the jet fuels JP-4 and JP-5. According to the requestor, the chemical analyses at the sites usually report concentrations of gasoline, diesel, and kerosene.

All of these fuels are complex hydrocarbon mixtures produced by distillation of crude oil. They may contain hundreds of hydrocarbon components, as well as additives. The actual composition for any given fuel will vary depending on source of the crude oil, refinery processes used, and product specifications. Aviation gasoline is similar to automotive gasoline. It is a mixture of relatively volatile hydrocarbons [primarily C<sub>4</sub>-C<sub>12</sub> paraffins (66-69%), olefins (6-8%), and aromatics (24-27%), including benzene (0.5-5%)] that are distilled at temperatures of 25-170°C, to which additives such as dye, tetraethyllead, and antioxidant may be added (IARC, 1989a). Jet and diesel fuels are middle distillates that are composed of less volatile hydrocarbons, generally coming off the distillation column at temperatures of 150-360°C. JP-5 is essentially a specially-refined type of kerosene consisting of C<sub>9</sub>-C<sub>16</sub> paraffins (53%), cycloparaffins (31%), aromatics (16%), and olefins (0.5%). The benzene content of JP-5 is typically < 0.02% (IARC, 1989b; NTP, 1986). A small amount of polycyclic aromatic hydrocarbons (PAHs) may be present as well. JP-4, a "wide-cut" jet fuel, is a blend of kerosene with lower-boiling naphtha streams, such as those used to produce gasoline (IARC, 1989b). Consequently, it comprises hydrocarbons in the C<sub>4</sub>-C<sub>16</sub> range and contains a higher percentage of benzene (0.5%) than JP-5. There are three types of diesel fuel: diesel fuel #1 (a straight-run distillate that is basically the same as kerosene), diesel fuel #2 (a blend of diesel fuel #1 with higher-boiling streams), and diesel fuel #4 or marine diesel fuel (a blend of diesel fuel #2 with high-boiling residual oils) (IARC, 1989c). Diesel fuels consist primarily of C<sub>9</sub>-C<sub>20</sub> hydrocarbons. For marine diesel fuel these are roughly 13% paraffins, 44% aromatics, and 44% naphthalenes (NTP, 1986). Marine diesel fuel may also contain >10% PAHs, and even the lower-boiling diesel fuel #2 may contain as much as 5-10% PAHs (IARC, 1989c).

As provided by the requestor, chemical analysis of soil and groundwater samples showed high concentrations of gasoline, diesel, and kerosene present in the samples, along with smaller amounts of soluble, volatile components of these fuel mixtures such as benzene, toluene, xylenes, and ethylbenzene.

We have confirmed that oral toxicity values for these fuels are not available from the usual Agency sources (U.S. EPA, 1992a,b,c; 1991a,b). These fuels are not the subjects of ATSDR toxicological profiles. The only published U.S. EPA document available for any of these fuels is a carcinogenicity assessment for gasoline (U.S. EPA, 1987a), which also gives some information on JP-4 and JP-5. IARC has reviewed the carcinogenicity and toxicity data for gasoline (IARC, 1989a), jet fuels (IARC, 1989b), and diesel fuels (IARC, 1989c). These documents were examined for information pertinent to derivation of quantitative oral toxicity values. In addition, computer searches of TOXLINE (1981-1991), RTECS, HSDB, and TSCATS were performed for AVGAS, gasoline, JP-4, JP-5, diesel, and kerosene and inspected for relevant information. Defense Technical Information Center Searches of Technical Report Summaries were checked for any additional pertinent studies.

### HEALTH EFFECTS SUMMARY

#### Gasoline

The health effects resulting from exposure to gasoline have been summarized in some detail in previous reviews (U.S. EPA, 1987a; IARC, 1989a; Anonymous, 1989). Only a brief review of this literature is presented here. Acute ingestion of gasoline may result in burning of the mouth and throat, gastrointestinal irritation, nausea, vomiting, and diarrhea (Anonymous, 1989). Very large doses can produce unconsciousness, coma, and death. The fatal dose for humans has been estimated to be 10 g for children and 350 g for adults (Anonymous, 1989). The central nervous system effects of acute gasoline exposure have been studied in more detail following inhalation exposure; effects such as headache, dizziness, nausea, and drowsiness may occur at around 500 ppm, more severe effects such as anesthesia, loss of reflexes, convulsions, and delirium may occur at 1000-5000 ppm (after 15-60 minutes), and unconsciousness, coma, and death may occur at >5000 ppm (Anonymous, 1989). CNS

Studies in animals of health effects resulting from repeated exposure to gasoline have identified other target organs, in addition to the central nervous system. Gavage administration of 500 or 2000 mg/kg/d of unleaded gasoline for 4 weeks (5 d/wk) produced hyaline droplet nephropathy in the kidneys of male rats kidneys

(Halder et al., 1985). Hyaline droplet nephropathy is a renal lesion characterized by the presence of cytoplasmic hyaline droplets in the proximal tubular epithelium, necrosis and exfoliation of tubular cells, and blockage and dilation of tubular segments near the corticomedullary junction with casts of necrotic cell debris. In a subsequent study, it was shown that repeated gavage doses of unleaded gasoline as low as 30 mg/kg/day (9-day exposure) can produce this lesion (Olson et al., 1987).

Hyaline droplet nephropathy was also the most prominent effect observed in studies of subchronic gasoline inhalation. Among male and female rats and monkeys exposed to wholly-vaporized unleaded (384 or 1552 ppm) or leaded (103 or 374 ppm) gasoline intermittently (6 hr/d, 5 d/wk) for 90 days and monitored for clinical signs, organ and body weight changes, shifts in hematological and urinary parameters, gross and microscopic lesions, pulmonary function, and central nervous system response, the only effect reported was increased incidence and severity of regenerative epithelium and dilated tubules in the kidneys of male rats exposed to 1552 ppm (Kuna and Ulrich, 1984; MacFarland, 1984). A study that was designed specifically to investigate the renal effects of unleaded gasoline vapor detected hyaline droplet nephropathy in male rats exposed to wholly-vaporized unleaded gasoline at concentrations as low as 40 ppm (exposure was 6 hr/d, 5 d/wk for 90 days); the incidence and severity of these lesions increased with concentration (Halder et al., 1984).

The lungs have been reported to be a target of inhalation exposure to leaded gasoline vapor. Rats of both sexes exposed to 100 ppm of leaded gasoline (containing 0.45 g/l tetraethyllead) vapor intermittently (8 hr/d, 5 d/wk) for 12 weeks developed lesions in the lung parenchyma ranging from scattered foci of interstitial fibrosis to widespread sclerosis; these lesions were often accompanied by alveolar collapse (Lykke and Stewart, 1978; Lykke et al., 1979).

The neurological effects of prolonged exposure to unleaded gasoline vapor have also been studied. Fischer 344 rats of both sexes were exposed to 1500 ppm of unleaded gasoline vapor intermittently (6 hr/d, 5 d/wk) for 18 months, with interim sacrifices at 6 and 12 months (Spencer, 1983). Although no unique clinical or pathological changes were observed in exposed rats, age-related changes such as axonal dystrophy and degeneration in the distal gracile tract of the spinal cord were found to be more extensive in exposed rats than in controls.

Reliable data concerning the reproductive effects of gasoline were not located. The single developmental toxicity study located (Litton Bionetics, 1978) was inconclusive. In this study, mated female Charles River rats [CRL: COBS CD(SD)BR] were exposed to 0, 400, or 1600 ppm of unleaded gasoline on days 6-15

of gestation (6 hr/d). There was an apparent increase in the incidence of skeletal abnormalities in the high-dose group (significant when using the fetus as the unit of comparison). However, this increase was not significant when using the litter as the unit of comparison (the approach recommended by U.S. EPA, 1991c). The variations observed were primarily related to delayed bone ossification. The biological significance of these variations is uncertain (Khera, 1981), but U.S. EPA (1991c) considers them to be a possible indication of developmental toxicity. Another result of this study was that all the fetuses in one litter from the high-dose group were extremely small. It is not clear if this effect was related to exposure, however.

One study of chronic gasoline exposure was located. Groups of Fischer 344 rats (100/sex/group) and B6C3F1 mice (100/sex/group) were exposed to whole vapors of unleaded gasoline at 0, 67, 292, or 2056 ppm intermittently (6 hr/d, 5 d/wk) for 103-113 weeks (MacFarland et al., 1984). Body weight gain was significantly reduced in male rats (after 13 weeks), female rats (after 26 weeks), and male mice (after 66 weeks) exposed to 2056 ppm. Interim sacrifices at 3 and 6 months revealed dose-related hyaline droplet nephropathy in all exposed groups of male rats. In addition, both absolute and relative kidney weight were increased in high-dose male rats. At later sacrifices, hyaline droplet nephropathy was obscured by the onset of progressive glomerulonephrosis, which is characteristic of aging rats. Mineralization of the renal pelvis occurred with a dose-related incidence in male rats from 6 months through the end of the study. In addition, several preneoplastic changes were noted in exposed male rats during the second year of the study, including karyomegaly, hyperplasia, and one early benign renal cortical adenoma in a high-dose male rat. At final sacrifice there was a seemingly dose-related increase in the incidence of primary renal tumors in exposed male rats. Incidence rates were 0 in controls, 1 (carcinoma) in low-dose male rats, 5 (2 adenoma, 2 carcinoma, 1 sarcoma) in intermediate-dose male rats, and 7 (1 adenoma, 6 carcinoma) in high-dose male rats. In addition, there was a renal sarcoma in one intermediate-dose female rat. The authors attributed these tumors to gasoline exposure, noting that spontaneous incidence of renal tumors in Fischer 344 rats is extremely low. In mice, there was an increased incidence of hepatocellular tumors (adenomas and carcinomas) in high-dose females. Incidence rates for the various treatment groups were 14% (controls), 19% (low-dose), 21% (intermediate-dose), and 48% (high-dose). Two renal tumors (adenoma and adenocarcinoma) were observed in high-dose female mice. kidney tumors

Epidemiological studies in humans have not positively demonstrated an association between gasoline exposure (usually assumed based on occupation) and cancer (IARC, 1989a; U.S. EPA, 1987a). However, some studies have reported results suggestive of such an association. For example, Siemiatycki et al. (1987)

reported an increased risk of kidney cancer in men exposed to aviation gasoline, Stemhagen et al. (1983) provided some evidence for an association between gasoline service station employment and risk of primary liver cancer, and Howe et al. (1980) provided limited evidence of an association between petroleum industry employment and risk of bladder cancer.

IARC (1989a) concluded there was inadequate evidence for carcinogenicity of gasoline in humans and limited evidence for carcinogenicity of unleaded automotive gasoline in experimental animals. Based on these conclusions and supporting data showing (1) that gasoline induces unscheduled DNA synthesis in mice in vivo and in mouse, rat, and human hepatocytes in vitro, (2) that the light straight-run naphtha and light catalytically cracked naphtha streams used to blend gasoline produce skin tumors in dermally-exposed mice, and (3) that gasoline components such as benzene (Group 1) and 1,3-butadiene (Group 2B) are known or suspected carcinogens, IARC concluded that gasoline is possibly carcinogenic to humans (Group 2B).

#### Diesel and Jet Fuels (Kerosene)

Toxicity data for diesel and jet fuels have been summarized by IARC (1989b, 1989c). Because of the fundamental similarities among these fuels (all are middle distillates) they are discussed together below. As noted in the introduction, JP-5 is a refined type of kerosene, and JP-4 is a blend of kerosene with lower-boiling naphtha streams (such as used to produce gasoline).

Acute inhalation of jet fuel vapors has been reported to produce dizziness, headache, nausea, and fatigue in exposed workers (IARC, 1989b). In addition, there is evidence that chronic inhalation of jet fuel vapors (time-weighted average of 300 mg/m<sup>3</sup> for 17 years) may induce neurasthenic symptoms (e.g., fatigue, anxiety, mood changes, and memory difficulties) in exposed workers (Knave et al., 1978, 1979). Other systemic effects associated with exposure of humans to jet fuels were not identified. However, two people dermally exposed to diesel fuel both experienced renal failure (IARC, 1989c). In a monitoring study intended to explore the association between cancer and exposure to various petroleum-derived fuels, Siemiatycki et al. (1987) found increased risk of kidney cancer among workers exposed to jet fuel and increased risk of squamous-cell lung cancer and prostate cancer among workers exposed to diesel fuel. No conclusive evidence of carcinogenicity in humans was located, however, for either fuel.

Acute toxicity studies in animals determined oral LD50 values of >60 ml/kg for jet fuel JP-5, >5.0 g/kg for jet fuel JP-4, and 7.5 g/kg for diesel fuel in rats (Beck et al., 1984; Clark

et al., 1989; Parker et al., 1981). Single oral doses of JP-5 as low as 1 ml/kg produced behavioral effects in rats (Bogo et al., 1984), and a dose of 24 ml/kg of JP-5 produced hyaline droplet nephropathy and hepatic fatty change in male rats (Parker et al., 1981). Oral studies in animals were available only for acute exposure durations; studies of the subchronic/chronic toxicity of diesel and jet fuels were conducted only by the inhalation and dermal routes.

Continuous 90-day inhalation exposure of Fischer-344 rats (75/sex/group), C57BL/6 mice (150 females/group) and pure-bred beagle dogs (3/sex/group) to 0, 150 or 750 mg/m<sup>3</sup> of petroleum or shale-derived JP-5 produced effects on the kidney, liver, blood, and nasal mucosa of the JP-5 exposed groups (Gaworski et al., 1984; Bruner, 1984; MacEwen and Vernot, 1985). The most obvious changes were seen in the kidneys of exposed male rats, which developed hyaline droplet nephropathy, as described above for gasoline. The incidence of hyaline droplet nephropathy was close to 100% in both low- and high-concentration groups, but a clear dose response was noted in severity, with only minimal renal changes occurring at 150 mg/m<sup>3</sup> and moderate lesions at 750 mg/m<sup>3</sup>. Other indications of renal toxicity in male rats exposed to 750 mg/m<sup>3</sup> were significantly elevated BUN and plasma creatinine, and significantly increased absolute and relative kidney weights. Treatment-related renal lesions observed in male rats held for life following 90-day exposure to JP-5 were abundant deposits of mineralized material in medullary tubules and renal papillary hyperplasia. The liver was also a target of JP-5 in this study; mild hepatocellular fatty change and vacuolization were reported in rats and mice exposed to 150 or 750 mg/m<sup>3</sup>, and mild, diffuse hepatocellular swelling (determined to be due to excessive glycogen accumulation) was observed in dogs exposed to 750 mg/m<sup>3</sup>. There were some discrepancies between the liver effects of petroleum- and shale-derived JP-5, but the researchers questioned the significance of these differences. Other effects of JP-5 exposure were slightly reduced red blood cell count, hematocrit, and hemoglobin in rats and dogs (statistically significant only in male rats exposed to 750 mg/m<sup>3</sup>), mild nasal inflammatory changes in rats (all groups exposed to shale JP-5), and moderately decreased body weight gain in rats (males at both concentrations, females at 750 mg/m<sup>3</sup>).

Continuous 90-day inhalation exposure to 500 or 1000 mg/m<sup>3</sup> of JP-4 produced results similar to those for JP-5 (MacEwen and Vernot, 1984, 1985; MacNaughton and Uddin, 1984). The most obvious effect was hyaline droplet nephropathy in male rats, which was noted in both dose groups and accompanied by increased kidney weight, increased plasma creatinine, and decreased urine osmolality. The most prominent effect in exposed female mice was centrilobular hepatocellular fatty change, which occurred with an incidence of 88% in the low dose group, 89% in the high dose

group, and 6% in controls. In dogs, there was a dose-related increase in BUN and elevated serum globulin and total protein at both dose levels. An earlier study of intermittent 8-month exposure to 2500 or 5000 mg/m<sup>3</sup> reported only organ weight changes in male rats exposed to the high dose level and a transient increase in red blood cell fragility in female dogs (MacNaughton and Uddin, 1984). Decreased body weight was reported for male rats exposed to 500 or 1000 mg/m<sup>3</sup> intermittently for 1 year (MacEwen and Vernot, 1981; MacNaughton and Uddin, 1984).

Continuous 90-day exposure to 50 or 300 mg/m<sup>3</sup> of marine diesel fuel derived from petroleum or shale produced results similar to the other middle distillates (MacEwen and Vernot, 1985; Bruner, 1984). The primary effects in rats were hyaline droplet nephropathy and reduced body weight gain in males at both doses. The incidence of fatty change in the liver of female mice was elevated in both exposure groups (85-94%) compared to controls (35%) for shale-derived fuel. Fatty change was not increased by exposure to petroleum-derived marine diesel fuel. Increased lung and liver inflammation were also reported to be results of marine diesel fuel exposure in female mice. The only changes noted in dogs, all of which were mild in degree, were increased osmotic fragility of red blood cells, increased frequency of cytoplasmic vacuolization of hepatocytes (due to accumulation of excess glycogen), and elevated BUN.

Both JP-5 and marine diesel fuel produced lesions in the kidneys of C3Hf/Bd mice treated dermally with undiluted fuel 3 times/wk for 60 weeks (Easley et al., 1982). The lesion was distinct from the hyaline droplet nephropathy seen in male rats following oral or inhalation exposure and characteristically consisted of atrophied and degenerating nephrons supported by an intact reticulum, with a high incidence of papillary necrosis. Although both male and female mice were affected, the incidence of renal lesions was much higher in females. Kidney lesions were not observed in a second dermal study in which B6C3F1 mice were treated with up to 500 mg/kg of JP-5 or marine diesel fuel diluted in acetone 5 times/wk for 103 weeks (NTP, 1986). JP-5 also failed to produce skin tumors or other neoplasms in this study. Marine diesel fuel produced a slight, but significant dose-related increase in the incidence of squamous cell neoplasms of the skin (primarily carcinomas) that was considered by NTP to be equivocal evidence of carcinogenicity in male and female mice. Jet fuel JP-4 has also been reported to produce skin tumors following chronic dermal treatment of mice (Clark et al., 1988). Although diesel fuel #2 did not produce tumors by itself, it did promote the development of skin tumors initiated by other chemicals (Slaga et al., 1986). The evidence suggests that both tumor promotion and complete carcinogenesis of middle distillates, including jet and diesel fuels, is probably due to chronic irritation and hyperplasia produced by these chemicals

promoter



(McKee et al., 1989; Skisak, 1991).

The reproductive and developmental toxicity of diesel and jet fuels has not been well studied. Inhalation of up to 400 ppm of jet fuel A, which is similar to JP-5, on days 6-15 of gestation produced no embryotoxic, fetotoxic, or teratogenic effect in rats (IARC, 1989b). The occurrence of maternal toxicity was not reported. A similar lack of developmental toxicity was reported for an unspecified diesel fuel (IARC, 1989c).

IARC (1989b, 1989c) concluded that marine diesel fuel is possibly carcinogenic to humans (Group 2B), but that light diesel fuels and jet fuels are not classifiable as to their carcinogenicity in humans (Group 3).

#### QUANTITATIVE RISK ASSESSMENT

Existing oral data are inadequate for use in quantitative risk assessment. Alternative approaches for derivation of oral toxicity values are (1) route-to-route extrapolation from the inhalation data or (2) basing estimates of toxicity for these complex mixtures on the toxicity of important components and assuming the effects are additive. There are several problems associated with using the inhalation data to produce oral toxicity values. One is that pharmacokinetic data are not available to indicate whether absorption is similar by the different routes, making it necessary to proceed with the unverified assumption of equal absorption. Another problem is that for hydrocarbon fuels composition of the water soluble fraction differs markedly from that of the original mixture (Coleman et al., 1984). The more soluble components such as benzene and naphthalene and their derivatives occur in much higher proportions in the water soluble fractions of the fuels than in the original mixtures. This difference in composition is likely to have some effect on toxicity, although the type and magnitude of the probable change is uncertain (one might guess toxicity of the water soluble fraction would be greater, and that of the remaining insoluble fraction would be less, but no data are available to address this point). An additional concern about basing the toxicity estimate on the original fuel, and this would apply even if the data were obtained by studies using drinking water exposure, is that differential volatilization and biodegradation will further alter the composition of the fuel mixtures in the environment. The relative contribution of various compounds to both the water soluble fraction and the remaining insoluble fraction will change continuously with the passage of time due to differential occurrence of these fate processes.

Available evidence suggests that humans are not likely to experience these effects (U.S. EPA, 1991d). Therefore, hyaline droplet nephropathy and related endpoints (including renal carcinogenicity) were not considered in the development of quantitative oral toxicity values.

The oral toxicity values derived in the following sections were derived by route-to-route extrapolation from inhalation data on the fuels that are the source of contamination at the Superfund sites in question. When using these values it should be noted that in addition to the usual uncertainties associated with route-to-route extrapolation and derivation of toxicity values, there is an additional element of uncertainty due to the difference in composition between the original fuel mixtures and their nonvolatile or less-soluble fractions which are of concern to the requestor.

### Gasoline:

#### Derivation of oral RfD:

A provisional oral RfD for unleaded gasoline can be derived by using the results of the chronic inhalation study (MacFarland et al., 1984) and performing route-to-route extrapolation. In this study, Fischer 344 rats (100/sex/group) and B6C3F1 mice (100/sex/group) were exposed to 0, 67, 292, or 2056 ppm of whole vapors of unleaded gasoline 6 hours per day, 5 days per week for 103-113 weeks. Body weight gain was reported to be significantly reduced (although the actual body weight data were not presented) in male rats (after 13 weeks), female rats (after 26 weeks), and male mice (after 66 weeks) exposed to 2056 ppm. The NOAEL for this effect was 292 ppm. Adjusting for intermittent exposure and converting to mg/m<sup>3</sup> produces an adjusted NOAEL of 230 mg/m<sup>3</sup>:

$$\begin{aligned}\text{NOAEL}_{\text{ADJ}} &= 292 \text{ ppm} \times (6 \text{ hr}/24 \text{ hr}) \times (5 \text{ days}/7 \text{ days}) \times \\ &\quad (108/24.45) \\ &= 230 \text{ mg/m}^3,\end{aligned}$$

where 108 is the mean molecular weight of unleaded gasoline (Anonymous, 1989) and 24.45 is a constant. Male rats were not considered as the basis for the RfD because weight loss in these animals may have been related to hyaline droplet nephropathy, which is not a relevant endpoint for humans (see discussion above). Conversion to an equivalent oral dose (EOD) was performed for female rats and male mice by assuming equal absorption by inhalation and oral routes and using standard reference values for body weight and inhalation rate (U.S. EPA, 1987b):

$$\begin{aligned}\text{EOD (female rat)} &= 230 \text{ mg/m}^3 \times (1/0.229 \text{ kg}) \times (0.24 \text{ m}^3/\text{day}) \\ &= 241 \text{ mg/kg/day} \\ \text{EOD (male mouse)} &= 230 \text{ mg/m}^3 \times (1/0.0373 \text{ kg}) \times (0.063 \text{ m}^3/\text{day}) \\ &= 388 \text{ mg/kg/day}\end{aligned}$$

The female rat was chosen as the basis of the RfD because these animals received a lower equivalent oral dose than male mice and displayed greater susceptibility by becoming significantly underweight 40 weeks earlier. The RfD is calculated from the equivalent oral dose in female rats by applying an uncertainty factor of 1000 (10 for intraspecies variation, 10 for interspecies variation, and 10 for deficiencies in the database):

$$\text{RfD} = 241 \text{ mg/kg/day} \times (1/1000) = 2 \times 10^{-1} \text{ mg/kg/day}.$$

In this way, a provisional RfD of  $2 \times 10^{-1}$  mg/kg/day was calculated for unleaded gasoline.

Confidence in the critical study (MacFarland et al., 1984) is medium because even though hematology, clinical chemistry, and histopathology endpoints were monitored throughout the study, the focus was on results related to carcinogenicity; results relating to systemic toxicity were not well reported. For example, effects on body weight are discussed, but the actual data are not presented. Confidence in the data base is (low) because oral studies were not available and it was necessary to derive the provisional oral RfD based on route-to-route extrapolation from an inhalation study. In addition, supporting data were not available via any route of exposure. Also, the reproductive and developmental effects of gasoline have not been adequately studied. Therefore, overall confidence in the provisional RfD is low.

#### Cancer weight-of-evidence classification:

The available epidemiological studies found no substantial evidence of carcinogenicity of gasoline to humans. Chronic inhalation of unleaded gasoline produced renal tumors in male rats and liver tumors in female mice (MacFarland et al., 1984). However, the development of kidney tumors in male rats as a sequela of hyaline droplet ( $\alpha_1$ -globulin) nephropathy, as occurred with gasoline inhalation exposure, is not considered to be predictive for tumor development in humans (U.S. EPA, 1991d). The elevated incidence of liver tumors in female mice constitutes limited evidence of the carcinogenicity of unleaded gasoline in animals [see U.S. EPA (1986) for discussion of this issue]. Other data suggesting that unleaded gasoline has carcinogenic potential include positive results in both in vivo and in vitro assays for unscheduled DNA synthesis, the production of skin tumors in dermal carcinogenicity assays by distillation streams used to blend gasoline, and the presence of carcinogenic components such as benzene (Group A) and 1,3-butadiene (Group B2). Based on the available evidence, unleaded gasoline can be assigned to U.S. EPA (1986) weight-of-evidence Group C: possible human carcinogen. An earlier U.S. EPA document assigned unleaded gasoline to Group B2 as a probable human carcinogen (U.S. EPA, 1987a), but that document predates the U.S. EPA (1991d) conclusion that the male rat kidney tumors produced by gasoline

are not predictive for humans, and therefore should not contribute to the weight-of-evidence or dose-response assessment of carcinogenicity.

#### Derivation of oral slope factor:

An inhalation unit risk of  $2.1 \times 10^{-3} \text{ ppm}^{-1}$  was calculated by U.S. EPA (1987a) based on the incidence of hepatocellular adenomas/carcinomas in female mice exposed to unleaded gasoline. Although this value has been published by U.S. EPA, it is not verified and/or available on IRIS (U.S. EPA, 1992a,c) and so should be considered an interim value. This inhalation unit risk can be converted to an oral slope factor in humans by first converting to  $(\text{mg}/\text{m}^3)^{-1}$ ,

$2.1 \times 10^{-3} \text{ ppm}^{-1} \times (24.45/108) = 4.75 \times 10^{-4} (\text{mg}/\text{m}^3)^{-1}$ ,  
where 24.45 is a constant and 108 is the mean molecular weight of unleaded gasoline (Anonymous, 1989), and then dividing by the adult human reference inhalation rate of  $20 \text{ m}^3/\text{day}$  and multiplying by the reference body weight of 70 kg:

$$4.75 \times 10^{-4} (\text{mg}/\text{m}^3)^{-1} \times (1/20 \text{ m}^3/\text{day}) \times (70 \text{ kg}) = \\ 1.7 \times 10^{-3} (\text{mg}/\text{kg}/\text{day})^{-1}.$$

In the absence of any data to the contrary, absorption by the oral and inhalation routes is assumed to be equal. Therefore, a provisional oral slope factor of  $1.7 \times 10^{-3} (\text{mg}/\text{kg}/\text{day})^{-1}$  can be calculated for unleaded gasoline.

Group C

#### Diesel and Jet Fuels (Kerosene)

##### Derivation of oral RfDs:

The data are sufficient to derive provisional oral RfDs for the jet fuels JP-4 and JP-5 and marine diesel fuel based on subchronic inhalation studies with these chemicals. For JP-5, pure-bred beagle dogs (3/sex/group), Fischer-344 rats (75/sex/group), and C57BL/6 mice (150 females/group) were exposed continuously to 150 or 750  $\text{mg}/\text{m}^3$  of petroleum or shale-derived JP-5 for 90 days (Gaworski et al., 1984; MacEwen and Vernot, 1985). A LOAEL of 150  $\text{mg}/\text{m}^3$  was identified based on hepatocellular fatty change and vacuolization in female mice. Although response rates were similar in both low- and high-dose groups, this is a mild, reversible lesion and use of this LOAEL for risk assessment appears to be reasonable. Conversion to an equivalent oral dose (EOD) is effected by assuming equal absorption by the inhalation and oral routes and by using standard reference values (U.S. EPA, 1987b) for female C57BL/6 mouse body weight (0.0246 kg) and inhalation rate ( $0.040 \text{ m}^3/\text{day}$ ):

$$\text{EOD} = 150 \text{ mg}/\text{m}^3 \times (0.040 \text{ m}^3/\text{day}) \times (1/0.0246 \text{ kg}) \\ = 244 \text{ mg}/\text{kg}/\text{day}.$$

Applying the maximum uncertainty factor of 10,000 (reflecting five areas of uncertainty: variation within and between species,

use of a LOAEL, extrapolation to chronic duration, and deficiencies in the database) produces a provisional oral RfD of  $2 \times 10^{-2}$  mg/kg/day for JP-5. If a toxicity value is needed for kerosene (because of the manner in which chemical analyses for the site are reported), the provisional oral RfD for JP-5, which is a refined kerosene, would be the most appropriate.

Studies on JP-4 and marine diesel fuel were conducted in a manner similar to the study on JP-5. Exposure concentrations were 500 and 1000 mg/m<sup>3</sup> for JP-4 and 50 and 300 mg/m<sup>3</sup> for marine diesel fuel. LOAELs of 500 and 50 mg/m<sup>3</sup> were identified for JP-4 and marine diesel fuel, respectively, based (as was the case for JP-5) on fatty change in the livers of female C57BL/6 mice (MacEwen and Vernot, 1985; MacNaughton and Uddin, 1984). Equivalent oral doses and provisional RfDs were calculated in the same manner as for JP-5. For JP-4, the equivalent oral dose of the LOAEL was 813 mg/kg/day and the provisional RfD was  $8 \times 10^{-2}$  mg/kg/day. For marine diesel fuel, the equivalent oral dose of the 50 mg/m<sup>3</sup> LOAEL was 81 mg/kg/day, and the provisional RfD was  $8 \times 10^{-3}$  mg/kg/day.

Confidence in the critical studies (Gaworski et al., 1984; MacEwen and Vernot, 1985; MacNaughton and Uddin, 1984) is medium. These studies used adequate numbers of test animals from several species and included examination of a variety of endpoints, including hematology, blood chemistry, and histopathology, but they included only two dose levels, failed to identify NOAEL values, and were not generally well reported. Confidence in the data base is low because it was necessary to use inhalation studies and route-to-route extrapolation to calculate provisional RfDs for oral exposure, the inhalation studies used were of subchronic rather than chronic duration, and no studies of developmental or reproductive toxicity were available. Therefore, overall confidence in these provisional RfDs is low.

#### Cancer weight-of-evidence classifications:

Epidemiological studies provided no conclusive evidence for carcinogenicity of diesel or jet fuels to humans. Skin painting assays in animals have reported positive results for some of these fuels, but this response is apparently due to epigenetic processes related to skin irritation (McKee et al., 1989), and therefore, not necessarily relevant to exposure by other routes. Oral or inhalation cancer bioassays were not located. Based on the available data, diesel fuel and the jet fuels JP-4 and JP-5 can be assigned to U.S. EPA (1986) weight-of-evidence Group D: not classifiable as to human carcinogenicity.

## Derivation of oral slope factors:

Classification of a chemical in weight-of-evidence Group D precludes quantitative risk assessment (U.S. EPA, 1986).

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