# HUMAN HEALTH RISK ASSESSMENT OF STOCKPILED SOILS AT THE MARINA VILLAGE DEVELOPMENT

ALAMEDA, CALIFORNIA

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# 1.0 INTRODUCTION

## 1.1 Objective and Scope

The objective of this report is to analyze the potential human health risks to workers posed by exposure to diesel fuel present in soil at the Marina Village Development in Alameda, California. This risk assessment analyzes site conditions and defines the types and extent of human health hazards, if any, posed by exposure to diesel fuel in soil in the absence of remedial (corrective) action.

At present, risk assessment techniques have not been developed by the EPA or other regulatory agencies to assess the human health effects of exposure to complex petroleum hydrocarbon mixtures such as diesel fuel, gasoline, and crude oil. Due to the lack of adequate animal testing and uncertainties regarding the effects of "weathering" (i.e., the loss of components of a complex petroleum hydrocarbon mixture due to volatilization, biodegradation, biotransformation, and dissolution of mixture components) on the physical, chemical, and toxicological properties of petroleum hydrocarbon mixtures, methodologies for assessing the risks associated with contact with these mixtures in soil have been slow to develop.

In order to address many of the uncertainties surrounding the potential toxicity and carcinogenicity of diesel fuel, we have performed a thorough review of available animal and human literature concerning the toxicological and carcinogenic effects of diesel fuel. In order to provide the reader with necessary background information concerning the risks associated with contact with diesel fuel affected soils, we have also reviewed the physical and chemical characteristics of several types of virgin diesel fuels. The physical, chemical, toxicological, and carcinogenic characterstics of diesel fuels (and related hydrocarbon mixtures) are evaluated in Appendix A. Appendix A also presents the rationale for the risk assessment methods used to develop lifetime cancer risk estimates from exposure to diesel fuel affected soils.

Section 2 of this report contains a brief description of analytical results obtained to date for stockpiled soil. Methods and assumptions used to assess human exposure to diesel fuel affected soils are presented in Section 3. Section 4 provides a brief synopsis of methods developed in Appendix A for assessing the human health

risks assoociated with exposure to diesel fuel affected soils. Section 5 characterizes the risks associated with exposure to diesel fuel affected soils under exposure conditions defined in Section 3 of the report.

The principal guidance documents used to prepare this report are the "Human Health Evaluation Manual (Volume I)," and the "Exposure Factors Handbook" (USEPA, 1989a; 1989b). These documents provide federal guidance for evaluating exposures and risks.

For information on site background, history, a description of the sampling and analyses performed to date, we refer the reader to reports previously submitted by Geomatrix.

## 2.0 REVIEW OF ANALYTICAL RESULTS FOR THE STOCKPILED SOIL

### 2.1 Sampling Results of the Soil Stockpile

Approximately 5,000 cubic yards of soil containing petroleum hydrocarbons (primarily containing highly weathered diesel fuel) were stockpiled at the 2 acre site in 1988 during excavation and cleanup of a nearby area. A brief history of the site and analysis of soils from the stockpile is provided below. These soils (at varying depths) were sampled to determine total petroleum hydrocarbon (TPH) concentrations. Possible sources of the petroleum hydrocarbons were also identified. From the April 1988 analyses, sources of petroleum hydrocarbons were attributed primarily to diesel fuel #6 and to a much lesser extent, motor oil. Twelve soil borings were analyzed for TPH in April 1988. Sample analysis performed in June 1988 characterized TPH concentrations as "diesel" for 14 samples. Likewise, 4 additional stockpile soil samples were subjected to TPH analyses and reported as "diesel" with no further characterization in October 1990.

Combining the results of the three analytical reports, a total of 30 soil samples were collected from the stockpile and analyzed for TPH (as diesel). TPH was not detected in 3 samples at a detection limit of 50 mg/kg. The arithmetic mean of the detected TPH concentrations was 622 mg/kg. The maximum detected TPH value was 13,000 mg/kg. The 95% upper confidence limit for the 30 samples (including 4 undetected samples represented at one-half the detection limit) was 696 mg/kg when calculated according to EPA methods specified in Risk Assessment Guidance for Superfund (EPA, 1989).

Several soil samples from the stockpile were also analyzed for volatile organic compounds or benzene, toluene, ethylbenzene, and xylene (BETX). Of eleven samples subjected to BTEX analysis, benzene and ethylbenzene were detected in a single samples at concentrations of 0.005 mg/kg and 0.010 mg/kg, respectively. Toluene was detected in a 9 of 11 samples at a maximum detected concentration of 0.066 mg/kg. Xylene was detected in two samples at concentrations of 0.056 mg/kg and 0.004 mg/kg. 1,2-Dichlorobenzene, 1,3-dichlorobenzene, and 1,4-dichlorobenzene were not detected at detection limits of 0.005 mg/kg.

## 2.2 Chemicals/Petroleum Hydrocarbon Mixtures of Interest

This risk assessment primarily focuses on exposure and health risks which may be associated with contact with diesel fuel in soil. However, because benzene, toluene, ethylbenzene, and xylene were also detected in soil, these chemicals are also conservatively selected as chemicals of interest on their occurrence in one or more of 11 samples analyzed for volatile organic compounds. Exposures to diesel fuel will be calculated using the 95% upper confidence limit for diesel fuel in stockpile soils. Conservatively, human exposure to benzene, toluene, ethylbenzene, and xylene will be calculated using the maximum detected concentrations in soil. The calculation of exposure estimates for diesel fuel, benzene, toluene, ethylbenzene, and xylene from contact with stockpiled soil is discussed in Section 3.0.

# 3.0 EXPOSURE ASSESSMENT

The objectives of the exposure assessment are to evaluate potential pathways of human exposure to the chemicals of interest in the stockpiled soils. Typically, once complete exposure pathways are identified, chemical intakes associated with each pathway and each potentially exposed population are calculated. This section analyzes exposure conditions possibly associated with the hypothetical future use of the stockpiled soils as fill material for a commercial business.

Human exposure to the chemicals present in soil may occur via three routes; these are ingestion, inhalation, and skin contact. This exposure assessment calculates chemical intakes based on assumptions which are representative of "reasonable maximum exposure" (RME). For RME estimates, exposure assumptions and parameters were selected to represent the 90th or 95th percentile for various assumptions including duration of exposure, years exposed, exposure point concentrations, and others. The intent of the RME case is to calculate chemical intakes which would not underestimate exposure under conservative exposure conditions.

## 3.1 Characterization of Exposure Conditions

Although hypothetical, we have conservatively assumed that the stockpiled soil will be used as fill material for a commercial area. Further, we assume that the material will be present at the surface and available for human contact. Although it is reasonable to expect that the stockpiled material would not comprise all the fill material used at the site (for example, in many cases, soil is brought in for landscaping or gardening) and that areas where fill is typically used are often covered with surface soil or sod, we have assumed that there is no impediment to direct contact with the chemicals of interest in soil.

## 3.2 Quantification of Exposure

### 3.2.1 Estimation of Exposure Concentrations

Th 95% UCL exposure point concentration for TPH in stockpiled soils (assumed to be used as fill for the future scenario) was calculated according to methods recommended in EPA (1989a). Undetected data were represented by including a

value equal to 1/2 the detection limit (25 mg/kg) for each undetected chemical (EPA, 1989a).

95% Upper confidence limits (95% UCL) were calculated according to the formula:

$$95\%\ UCL = e^{\left(\bar{y} + 0.5\, s^2 + \frac{sH_{1-\alpha}}{\sqrt{n-1}}\right)}$$

where:

e = the exponential function

$\bar{y}$ = arithmetic mean of n log-transformed data measurements

$s^2$ = variance of n log transformed data measurements

$H_{1-\alpha}$ = value looked up in a table (Gilbert, 1987)

n = the number of samples

As stated in Section 2, exposure point concentrations for benzene, toluene, ethylbenzene, and xylene were set equal to the maximum detected concentration.

### 3.2.2 Estimation of Chemical Intakes

Chemical intakes from soil may be calculated once is known and the factors associated with an office worker's exposure to the chemicals of interest in soil may be assessed. Equations used to calculate chemical intakes from soil and surface water are taken from the EPA's Human Health Evaluation Manual (EPA, 1989a) and are presented in Table 3-1. Exposure variables used to calculate chemical intakes from soil via inhalation, ingestion, and dermal contact are presented in Table 3-2.

For the purpose of calculating intake of the chemicals of interest from soil, the following dermal uptake fractions were assumed: benzene, 0.01; toluene, 0.10, ethylbenzene, 0.10, and xylene, 0.10. The selection of these variables is discussed in the uncertainties section of this document. To account for the matrix effect of soil on the dermal absorption of diesel fuel, diesel fuel in soil was assumed to be 20% as available for absorption as diesel fuel directly applied to the skin. This modification is used to account for the extrapolation from the results of animal studies where

## Table 3-1
## Calculation of Intakes of the Chemicals of Interest in Stockpiled Soil

| Exposure Pathway | Exposure Equation | Exposure variables |
|---|---|---|
| **Air** | | |
| Inhalation of particulate phase chemicals in soil | $\frac{C \times PC \times IR \times RF \times ET \times EF \times ED \times CF}{BW \times AT}$ | C = Concentration of chemical in particulate (mg/kg)<br>PC = Particulate Concentration in Air ($mg/m^3$)<br>IR = Inhalation Rate ($m^3$/hour)<br>RF = Respirable Fraction (unitless)<br>ET= Exposure Time (hours/day)<br>EF = Exposure Frequency (days/year)<br>ED = Exposure Duration (years)<br>CF = Conversion Factor ($10^{-6}$ kg/mg)<br>BW = Body Weight (kg)<br>AT =Averaging Time (period over which exposure is averaged (for non-carcinogens: ED x 365 days/year; for carcinogens: 70 years x 365 days/year) |
| **Soil** | | |
| Ingestion of soil | $\frac{CS \times IR \times FI \times EF \times ED \times CF}{BW \times AT}$ | CS = Chemical concentration in soil (mg/kg)<br>IR = Ingestion rate (mg soil/day)<br>FI = Fraction ingested from contaminated source<br>EF = Exposure frequency (days/year)<br>ED = Exposure duration (years)<br>CF= Conversion factor ($1 \times 10^{-6}$ kg/mg)<br>BW = Body weight (kg)<br>AT =Averaging time (period over which exposure is averaged (for non-carcinogens: ED x 365 days/year; for carcinogens: 70 years x 365 days/year) |

Table 3-2
(contd)

| Exposure Pathway | Exposure Equation | Exposure variables |
|---|---|---|
| Dermal absorption of chemicals in soil | $\frac{CS \times SA \times AF \times ABS \times EF \times ED \times CF}{BW \times AT}$ | CS = Chemical concentration in soil (mg/kg)<br>SA = Skin surface area available for contact ($cm^2$)<br>AF = Adherence of soil to skin ($mg/cm^2$)<br>ABS = Fraction of chemical absorbed through the skin (unitless)<br>EF = Exposure frequency (days/year)<br>ED = Exposure Duration (years)<br>CF= Conversion factor ($1 \times 10^{-6}$ kg/mg)<br>BW = Body Weight (kg)<br>AT =Averaging Time (period over which exposure is averaged (for non-carcinogens: ED x 365 days/year; for carcinogens: 70 years x 365 days/year) |

## Table 3-2
## Summary of Exposure Assumptions for a Hypothetical Site Worker: Ingestion, Dermal Absorption, and Inhalation of Chemicals Present in Stockpiled Soils

| Exposure Parameter | Value | Reference |
|---|---|---|
| Body weight | 70 kg | EPA, 1991a |
| Ventilation rate | 20 $m^3$ of air per work shift | EPA, 1991a |
| Soil particulate concentration in air | 0.10 $mg/m^3$ | |
| Fraction of particulate respirable | 0.5 | |
| Exposure frequency | 250 days per year | EPA, 1991a |
| Exposure duration | 25 years | EPA, 1991a |
| Soil Ingestion rate | 50 mg per day | EPA, 1991a |
| Fraction of soil from fill (stockpiled soil) | 1 | - |
| Amount of soil adhering to skin | 1 $mg/cm^2$ | EPA, 1991b |
| Skin surface area exposed | 2000 $cm^2$ (hands and one-half of the arms) | EPA, 1989b |

diesel fuel was directly applied to the skin versus the exposure likely to result from diesel fuel affected soils. Soil has been shown to decrease percutaneous absorption of organic chemicals by 80% over that applied in organic solvents by 80% (Wester et al., 1990). In addition, Watkin and Hull (1991) have indicated that for soil-sorbed contaminants, mass transfer of chemicals in soil can take hours longer than the expected duration of exposure due to the kinetic behavior of the chemical-soil complex. Desorption of hydrophobic chemicals (such as those likely to remain in weathered diesel fuel) from soil is not an energetically favored reaction, indicating that mass transfer of hydrophobic chemicals from the soil particle to the skin may take far longer than the typical period in which skin is in contact with soil (4 to 8 hours).

### 3.2.3 Exposure Estimates for the Worker Exposed to the Chemicals of Interest in Fill (Stockpiled Soil)

Estimated intakes of diesel fuel, benzene, toluene, and xylene are presented in Table 3-3. Chronic daily intakes (CDIs) are calculated for assessing both noncarcinogenic and carcinogenic risk. When assessing noncarcinogenic risk, CDIs are calculated by averaging exposure over a lifetime (70 years). In contrast, noncarcinogenic risks are assessed using exposure estimates calculated over the perido of exposure.

For benzene, toluene, ethylbenzene, and xylene, CDIs for ingested and inhaled chemicals of interest are expressed as exposures rather than absorbed doses. Dermal CDIs are expressed as absorbed doses rather than exposures.

Ingestion, dermal, and inhalation CDIs calculated for diesel fuel are expressed as exposures rather than dermal doses.

In keeping with its relatively higher concentration in soil (696 ppm), diesel fuel exposures were considerably higher than intakes of benzene, toluene, ethylbenzene, and xylene, all of which were present at soil concentrations less than 0.1 mg/kg.

## Table 3-3
## Hypothetical Adult Worker
## Ingestion, Dermal, and Inhalation Intakes of the Chemicals of Interest in Stockpiled Soil

| Chemical | Noncancer Ingestion CDI (mg/kg/day) | Noncancer Dermal CDI (mg/kg/day) | Noncancer Inhalation CDI (mg/kg/day) | Cancer Ingestion CDI (mg/kg/day) | Cancer Dermal CDI (mg/kg/day) | Cancer Inhalation CDI (mg/kg/day) |
|---|---|---|---|---|---|---|
| Diesel Fuel | 3.41E-04 | 3.41E-03 | 6.78E-06 | 1.22E-04 | 1.22E-03 | 2.42E-06 |
| Benzene | 2.45E-09 | 9.78E-10 | 4.87E-11 | 8.74E-10 | 3.49E-10 | 1.74E-11 |
| Ethylbenzene | 3.91E-07 | 1.57E-06 | 7.80E-09 | na | na | na |
| Toluene | 4.40E-07 | 1.76E-06 | 8.77E-09 | na | na | na |
| Xylene | 1.47E-06 | 5.87E-06 | 2.92E-08 | na | na | na |

CDI = chronic daily intake
na = not applicable

# 4.0 TOXICITY ASSESSMENT

For many chemicals, the EPA has derived factors for calculating quantitative estimates of cancer risk and for the evaluation of whether or not a chemical may pose a noncarcinogenic health risk. In this report, EPA-derived factors are used to derive risk estimates for benzene, toluene, ethylbenzene, and xylene. Because the EPA has not derived a basis for assessing the toxicity of diesel fuel, we have prepared a hazard evaluation of diesel fuel (Appendix A) to address address possible risks associated with exposure to diesel fuel in affected soils. The methods used to assess both the potential noncarcinogenic and carcinogenic health effects are discussed in the following section. Final estimates of noncarcinogenic and carcinogenic risk associated with exposure to diesel fuel, benzene, ethylbenzene, toluene, and xylene in stockpiled soils are presented in Section 5 of this report.

## 4.1 Noncarcinogenic Risks

The noncarcinogenic effects of ethylbenzene, toluene, and xylene were assessed by comparing intakes calculated in Section 3.2 with EPA reference doses (RfDs). The EPA definition of the RfD is presented below.

> "The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a portion of the lifetime, in the case of a subchronic RfD, or during a lifetime, in the case of a chronic RfD." (EPA, 1989c)

The EPA derives RfDs for inhalation and oral exposure for subchronic exposures (exposures of 2 weeks to 7 years) and chronic exposures (7 years and longer) for many chemicals. Inhalation and oral reference doses for the chemicals of interest are presented in Tables 4-1 and 4-2. Dermal RfDs and slope factors were assumed to be equal to the oral RfD and slope factor. There is no EPA-derived reference dose for benzene. However, the primary toxicity of concern for benzene is its carcinogenic effects. This toxicity is addressed by calculating cancer risks which may be associated with possible exposure to benzene in soil.

## Table 4-1

## Reference Doses and Slope Factors for the Chemicals of Interest

| Chemical | Inhalation Reference Doses | | | | | Inhalation Slope Factors | | |
|---|---|---|---|---|---|---|---|---|
| | RfD Subchronic (mg/kg/day) | Safety Factor | RfD Chronic (mg/kg/day) | Safety Factor | Non-carcinogenic effects | Slope Factor $(mg/kg/day)^{-1}$ | EPA Group | Carcinogenic Effects |
| Diesel Fuel | - | - | - | - | - | †1.09E-03 | - | Skin tumors |
| Benzene | - | - | - | - | - | 2.90E-02 | A | Leukemia |
| Ethyl benzene | 2.9E-01[a] | 300 | 2.9E-01[a] | 300 | Developmental toxicity | - | - | - |
| Toluene | 5.7E-01[a] | 100 | 1.7E-01[a] | 300 | CNS effects. eye and nose irritation | - | - | - |
| Xylenes | - | - | - | 100 | - | - | - | - |

| Chemical | Oral Reference Doses | | | | | Oral Slope Factors | | |
|---|---|---|---|---|---|---|---|---|
| | RfD Subchronic (mg/kg/day) | Safety Factor | RfD Chronic (mg/kg/day) | Safety Factor | Non-carcinogenic effects | Slope Factor $(mg/kg/day)^{-1}$ | EPA Group | Carcinogenic Effects |
| Diesel Fuel | - | - | - | - | - | 1.09 E-03 | - | Skin tumors in mice |
| Benzene | - | - | - | - | - | 2.90E-02 | A | Leukemia |
| Ethyl benzene | 1.00E+01 | 100 | 1.00E-01 | 1000 | Hepatotoxicity and nephrotoxicity | - | - | - |
| Toluene | 2.00E+00 | 100 | 2.00E-01 | 1000 | Changes in liver and kidney weight | - | - | - |
| Xylenes | 4.00E+00 | 100 | 2.00E+00 | 100 | Hyperactivity, decreased body weight and increased mortality at higher doses | - | - | - |

Adapted from IRIS and US EPA Health Effects Assessment Summary Tables (EPA, 1992a)

†derived in the hazard evaluation for diesel fuel presented in Appendix A

[a]Converted to mg/kg/day from RfC ($mg/m^3$) using the formula: $RfC \times \frac{20\ m^3/day}{70\ kg} = RfD$

RfDs used in this assessment are generally derived from animal studies. Results from these studies are extrapolated to humans using appropriate factors to adjust for uncertainties resulting from:

- Extrapolation from the results of animal studies to humans,
- Variation within individuals of the same species,
- Extrapolation from the results of short-term animal studies and,
- Extrapolation from exposure levels in animal studies which demonstrate an effect rather than a no-effect level.

For any particular chemical, an intake which exceeds the RfD for that chemical indicates that an adverse health effect may be observed. The $\frac{\text{intake}}{\text{RfD}}$ is defined by the EPA to be the hazard quotient (HQ) for a chemical. As a general rule, when the HQ $< 1$, it is unlikely that an adverse health effect will occur. The chance of observing an effect increases as the HQ increasingly exceeds unity. The EPA directs that the HQ for each chemical and each route of exposure be summed to calculate a hazard index (HI). This process conservatively assumes that simultaneous exposure to multiple chemicals at intakes below the RfD may produce an adverse health effect if the HI exceeds one. When calculated according to EPA methods, the HI assumes that the effects of each chemical are additive. The HI is used as a screen to determine whether or not the effects of intake of multiple chemicals may be of concern. If the HI is less than one, there is little reason to expect that any adverse effect will result from concurrent exposure to all of the chemicals of interest.

The EPA does not derive dermal RfDs for chemicals. However, since dermal exposure may add to overall intake of a chemical and possibly cause an adverse effect, the oral RfD is used to calculate a dermal RfD (when an oral RfD is available). The EPA requires that when gastrointestinal absorption of a chemical is low, the oral RfD must be corrected for absorption before it is used to assess health effects possibly associated with dermal absorption of that chemical. However, because gastrointestinal absorption of benzene and alkyl benzenes is relatively complete, unadjusted oral RfDs and slope factors were used to assess the

noncarcinogenic and carcinogenic risks associated with dermal absorption of these chemicals.

No reference dose has been developed to assess the noncarcinogenic effects of exposure to virgin diesel fuel, much less the highly weathered diesel fuel detected in stockpiled soil at the site. The noncarcinogenic effects of exposure to diesel fuel (and weathered diesel fuel) are reviewed in the following discussion.

### 4.1.1 Noncarcinogenic Effects Associated with Diesel Fuel

Acute toxicity studies in animals indicate a relatively low order of toxicity for ingested diesel fuel. The oral $LD_{50}$ in the rat was determined to be 7.5 g/kg (Beck et al., 1982). Due to the relatively low concentrations of diesel fuel detected in stockpiled soils (95% upper confidence limit - 696 mg/kg), it would be impossible to ingest sufficient soil to produce an acute toxic effect.

Pure diesel fuel may also irritate and damage the skin. Middle distillate petroleum products such as diesel fuel may defat the skin after a single contact, leading to irritation, infection, and dermatitis. Massive skin contact with pure diesel fuel has also produced renal toxicity. One adult who used diesel fuel as a shampoo developed oliguria and acute renal failure requiring hemodialysis. Another person who cleaned his hands and arms with diesel fuel for several weeks developed acute tubular necrosis (Gosselin, 1984).

Due to its defatting effect on the skin, pure diesel fuel may enhance its own dermal absorption and thereby increase its own toxicity. However, such a defatting effect is unlikely to occur at concentrations of weathered diesel fuel present in soil. For example, at 696 mg/kg weathered diesel fuel in soil, the concentration is only 0.07% that of pure diesel fuel. In addition, unlike exposure to liquid diesel fuel, the affinity of soil for the more hydrophobic constituents of weathered diesel fuel would lessen partitioning of these chemicals from the soil to the skin. Thus, in addition to the concentration differences between pure diesel and TPH (as diesel fuel) in soil, it is also noteworthy that the dermal absorption of diesel fuel in soil will be lessened due to the high affinity of the soil matrix for the more hydrophobic chemicals that comprise TPH-diesel.

Animal studies indicate that pure diesel fuel is highly irritating to the skin. In a study addressing the primary dermal irritation of diesel fuel (Beck et al., 1982), sores and blisters were produced by the application of 0.5 ml of diesel fuel to shaved areas of the skin in rabbits. These skin damaged areas healed 7 days after removal after the diesel fuel tratment was stopped. When considered as a function of surface area, the dose of diesel fuel applied to the skin of rabbits was 16 mg/cm$^2$.

The same study addressed dermal toxicity of diesel fuel under acute (5 ml/kg on abraded skin of rabbits for 24 hours) and subacute (4 and 8 ml/kg on shaved skin repeated daily for 10 days) exposure conditions. The acute exposure produced mild to moderate skin irritation but no signs of toxicity. The subacute dermal exposure produced mortality at 8 ml/kg. Toxic signs included weight loss with anorexia and signs of acute dermal irritation. Liver and kidney damage were noted at necropsy.

At the concentrations detected in stockpiled soils, contact with TPH (as diesel fuel) in soil is unlikely to be associated with the dermatotoxicity and renal toxicity associated with massive skin exposure to pure diesel fuel. For example, assuming a 696 mg/kg concentration of diesel fuel in soil and a soil loading value of 1 mg/cm$^2$ for the skin, the concentration of TPH on the skin of an exposed individual would be only 0.000696 mg/cm$^2$, an exposure 23,000 times less than the exposure causing skin irritation in the rabbit. Assuming a skin surface area of 2,000 cm$^2$ exposed to soil (the approximate surface area of the arms and hands for an adult), exposure to diesel fuel in soil would be 1.4 mg (2,000 cm$^2$ x 0.000696 mg/cm$^2$ TPH/1 mg soil x 1 mg soil/cm$^2$ of skin). If a body weight of 70 kg is assumed, dermal exposure to TPH would be 0.02 mg/kg at a concentration of 696 mg/kg TPH in soil. Such an exposure is almost 160,000 times lower than the lowest subacute diesel fuel exposure tested by Beck et al. (1982) (4 ml/kg or approximately 3.2 g/kg) in rabbits. Thus, it is highly unlikely that exposure to TPH in soil would produce the dermatotoxic, nephrotoxic, and hepatotoxic responses which may be associated with dermal exposure to pure diesel fuel.

There are no human epidemiological studies of diesel fuel alone. Studies conducted to date have addressed exposure to many petroleum refinery streams or diesel fuel and its combustion products. These human epidemiological studies of combined exposures to numerous petroleum products or diesel fuel combustion products are

not germane to an evaluation of the effects of exposure to weathered diesel fuel in soil.

## 4.2 Carcinogenic Risks

Of the four volatile compounds considered in this assessment, only benzene is considered to be a potential carcinogen. Benzene is listed by the EPA as known human carcinogen and is classified as a Group A chemical based on human epidemiological data.

Although several factors mitigate against considering diesel fuel as a potential carcinogen in humans, we have conservatively evaluated diesel fuel as a potential human carcinogen based on our review of mouse dermal carcinogenicity studies of diesel fuel and other middle distillate petroleum fractions. The slope factor derived for diesel fuel is the geometric mean of the 95% upper confidence limit ($q1^*$) of 21 mouse skin carcinogenicity studies. The derivation of the slope factor for diesel fuel is discussed in considerable detail in the hazard evaluation for diesel fuel (Appendix A).

Slope factors for the potentially carcinogenic chemicals of interest were determined by the EPA by applying the linearized multistage model to data from animal carcinogenicity studies or human epidemiological studies. In the absence of data concerning the carcinogenic potential of very low doses of a chemical, linearized multistage modeling is used to generate estimates of carcinogenic potency. Inherent in the linearized multistage model is the provision that there is no dose, no matter how small, which is not associated with some carcinogenic risk. The EPA defaults to this conservative position in the absence of firm scientific data to support the application of the linearized multistage model. The uncertainties associated with weight of evidence classifications and use of the linearized multistage model are addressed in a later section of this report. Multiplication of the chronic daily intake for carcinogenic effects by the slope factor [in $(mg/kg/day)^{-1}$] produces a unitless estimate of lifetime cancer risk. Increases in lifetime cancer risks calculated by this method are often expressed in terms of 1 in ten thousand (1E-04), 1 in one hundred thousand (1E-05), or 1 in one million (1E-06).

# 5.0 RISK CHARACTERIZATION

The exposure estimates derived in Section 3 and the reference doses and slope factors presented in Section 4 are used to assess the potential for noncarcinogenic risk and quantitative estimates of cancer risk for the hypothetical worker exposed to stockpiled soils. These estimates are presented in Table 5-1 and discussed below.

## 5.1 Noncarcinogenic Risk Characterization

Hazard quotients for ethylbenzene, toluene, and xylene were all well below 1 (the level of initial concern). Even when the hazard quotients were summed for all chemicals and the ingestion, dermal, and inhalation exposure pathways, the hazard index was 28,000 times lower than 1, indicating that the chance of observing any noncarcinogenic adverse health from intake of these chemicals in soil is extremely remote.

As reviewed in Section 4.1.1, weathered diesel fuel concentrations as high as 696 mg/kg (the 95% upper confidence limit for the TPH-diesel concentrations in stockpiled soil) are unlikely to be associated with noncarcinogenic adverse health effects.

## 5.2 Lifetime Cancer Risks

As presented in Table 5-1, ingestion, dermal contact, and inhalation of benzene in soil at 0.005 mg/kg poses no significant risk for the hypothetically exposed worker given that lifetime cancer risks ranging from 1 E-04 to 1E-06 are considered acceptable. The level of lifetime cancer risk is millions of times lower than the 1 in a million lifetime cancer risk level.

Lifetime cancer risks posed by diesel fuel in soil (at the 95% upper confidence limit of 696 mg/kg) were 1E-06 for the ingestion, dermal, and inhalation exposure pathways. Risks from the dermal pathway of exposure were higher than the ingestion pathway due to the conservative assumption that 20% of all weathered diesel fuel components were available for absorption from soil and because the

Table 5-1
Hypothetical Adult Worker
Noncancer and Lifetime Cancer Risk Associated with Ingestion, Dermal Contact, and Inhalation of the Chemicals of Interest in Stockpiled Soil

| Chemical | Chronic Hazard Quotient | | | Lifetime Cancer Risk | | |
|---|---|---|---|---|---|---|
| | Ingestion | Dermal | Inhalation | Ingestion | Dermal | Inhalation |
| Diesel Fuel | - | - | - | 1E-07 | 1E-06 | 3E-09 |
| Benzene | - | - | - | 3E-11 | 1E-11 | 5E-13 |
| Ethylbenzene | 3.91E-06 | 1.57E-05 | 2.69E-08 | - | - | - |
| Toluene | 2.20E-06 | 8.81E-06 | 5.16E-08 | - | - | - |
| Xylene | 7.34E-07 | 3.26E-06 | - | - | - | - |
| **Hazard Index for Exposure Pathway** | 6.8E-06 | 2.8E-05 | 7.9E-08 | | | |
| **Summed Hazard Indices for All Exposure Pathways** | | 3.5E-05 | | | | |
| **Summed Lifetime Cancer Risk for Exposure Pathway** | | | | 1E-07 | 1E-06 | 3E-09 |
| **Summed Lifetime Cancer Risk for All Exposure Pathways** | | | | | 1E-06 | |

amount of soil exposure from dermal exposure (2000 mg of soil; 2000 $cm^2$ of skin surface available for contact with soil x 1 mg of soil per $cm^2$ of skin) is considerably higher than the amount of soil assumed to be ingested per day (50 mg).

Thus, for the worker exposed to diesel fuel and benzene in soil for 250 days per year for 25 years, lifetime cancer risks are estimated to be 1 E-06 (one excess individual with cancer out of one million persons), a value within the range (1 E-06 to 1E-04) considered acceptable by the USEPA.

Uncertainties associated with the risk characterization are discussed below.

### 5.3 Risk Uncertainties

Generally, uncertainties which affect the characterization of risk may be broadly divided into one of two categories. These categories of uncertainties are those uncertainties which may be associated with estimating chemical exposures (i.e., the selection of exposure assumptions and the determination of representative concentrations of the chemicals of interest in soil) and the uncertainties in determining the toxicity or carcinogenicity of a chemical to humans in an environmental setting. Often, toxicological data used to assess human risks are extrapolated from animal studies. Specifically, uncertainties associated with the characterization of risks from exposure to diesel fuel, benzene, ethylbenzene, toluene, and xylene for the hypothetically exposed adult worker are discussed below.

Determining the frequency of human contact with soil is clearly dependent on site-specific factors. In this assessment, we have assumed that adult workers will be exposed to stockpiled soil which is used as fill material. This exposure assessment was conducted using default exposure parameters developed by the EPA (EPA, 1991a). The EPA generally establishes default parameters to represent the 95% upper confidence limit for a particular exposure assumption. Thus, it is very likely that actual exposures to the chemicals of interest in soil would be less than the 250 day per year for 25 years as recommended for use by the EPA as default parameters.

In addition, it was assumed that the worker was exposed only to the stockpiled soils and not other soils. Further, it was assumed that the stockpiled soil was not covered by pavement or other cover. In fact, it is much more likely that any exposure to stockpiled soil used as fill material would be limited by pavement or soil brought in for landscaping or other purposes.

The magnitude of uncertainty associated with the characterization of risk is chemical specific. For example, because the cancer slope factor for benzene is derived from studies in humans, the uncertainty is somewhat less than that for slope factors which are based on studies in animals

A common uncertainty associated with the derivation of cancer slope factors for both diesel fuel (as considered in Appendix A) and benzene is the use of the linearized multistage model. The fundamental principles underlying risk assessment for carcinogenic chemicals remain arguable, including the tenet that every potential carcinogen is associated with some degree of carcinogenic risk, no matter how small the dose. The belief that chemically induced cancer is a non-threshold process is a conservative default policy which the EPA assumes to ensure the protection of human health. However, there is little biological basis to support the widespread application of this policy to all potential carcinogens.

The EPA default policy for potential chemical carcinogens mandates that results from high-dose animal studies be extrapolated to exposures in humans which are thousands of times lower. The EPA uses a mathematical model known as the linearized multistage model to extrapolate from high doses to very low doses. As applied by the EPA (and as used to estimate the cancer slope factor for diesel fuel), the linearized multistage model leads to quantitative estimates of cancer risk which are conservative, upper bound approximations of lifetime cancer risk. The EPA expressed the following uncertainty in using the linearized multistage model to determine carcinogenic risks in humans:

> *"It should be emphasized that the linearized multistage procedure leads to a plausible upper limit to the risk that is consistent with some proposed mechanisms of carcinogenesis. Such an estimate, however, does not necessarily give a realistic prediction of the risk. The true value of risk is unknown, and may be as low as zero. The range of risks, defined by the*

*upper limit given by the chosen model and the lower limit which may be stated as low as zero, should be explicitly stated." (51 Federal Register 33998)*

Thus, according to the EPA commentary cited above, carcinogenic risks estimated using the linearized multistage procedure lead to conservative but not necessarily realistic estimates of risk. The National Research Council has also commented concerning use of the linearized multistage model, stating:

> *"The linearized multistage model is widely used to estimate cancer risks associated with environmental exposures (EPA, 1987) and is said to provide an upper-limit estimate of low-dose response. To some degree, the model's wide use reflects its mathematical flexibility.* ***However, biologic support for the assumption of linearity at low doses remains largely inferential and probably wrong in a high proportion of cases*** *(emphasis added) (Bailar et al., 1988). (NRC, 1989)*

For these reasons, it is likely that the risks calculated in this report will substantially overestimate the actual risks which may be associated with exposure to the benzene and diesel fuel in stockpiled soil.

Additional uncertainties associated with the characterization of the toxicity of diesel fuel relate to the process of weathering. Weathered diesel fuels have not been subjected to animal testing and the extent to which tests of pure diesel fuel may represent weathered diesel fuel is not completely known. However, toxicity testing using pure diesel fuel represents the most reasonable approximation of the toxicity and carcinogenicity of weathered diesel fuel.

## 6.0 SUMMARY

In order to address the potential risks associated with chemicals present in stockpiled soils, this report conservatively considers hypothetical exposure to soil which may result from the use of the stockpiled soil as fill material for a commercial business. In this hypothetical scenario, an adult worker is assumed to be exposed to weathered diesel fuel, benzene, ethylbenzene, toluene, and xylene in soil for 250 days per year for 25 years via incidental soil ingestion, skin contact with soil, and inhalation of airborne soil particles containing these chemicals. The 95% upper confidence limit for diesel fuel (as TPH-diesel) was conservatively used to represent the soil concentration of diesel fuel in order to diesel fuel exposures. Maximum detected concentrations of benzene, ethylbenzene, toluene, and xylene were used to assess the exposures to these chemicals of interest in stockpiled soils.

The noncarcinogenic and carcinogenic risks of benzene, ethylbenzene, toluene, and xylene were assessed using EPA-derived reference doses (RfDs) and cancer slope factors. There is currently no EPA-derived reference dose or cancer slope factor to quantitatively assess the risks associated with exposure to diesel fuel. For this reason, an extensive review of the hazards associated with diesel fuel were undertaken to qualitatively and quantitatively evaluate the risks that may be associated with exposure to weathered diesel fuel in the stockpiled material.

Using the EPA derived reference doses for ethylbenzene, toluene, and xylene and a qualitative evaluation of diesel fuel toxicity in man and animals, it was determined that the hypothetical worker's exposure to stockpiled soil is unlikley to be associated with any adverse noncarcinogenic health risk. The hazard index (an indicator of whether or not noncarcinogenic effects are likely to result from chemical exposure) was thousands of times lower than the level of concern, indicating that exposure to stockpiled soils would not be associated with any noncarcinogenic health risk.

Using the cancer slope factor derived for diesel fuel in Appendix A, the EPA-derived cancer slope factor for benzene, and the conservative estimates of diesel fuel and benzene intake, a combined lifetime cancer risk of one additional individual with cancer in one million persons ($1 \times 10^{-6}$ or 1 E-06) was calculated to

be associated with hypothetical exposure to the stockpiled soil for 250 days per year for 25 years. This level of risk is near the low end of acceptable lifetime cancer risks considered acceptable by the EPA ($1 \times 10^{-6}$ to $1 \times 10^{-4}$), indicating that even under conservatively evaluated exposure conditions, exposure to stockpiled soil would not be associated with unacceptable lifetime cancer risk.

## 7.0 REFERENCES


Beck, L.S., Hepler, D.I., and Hansen, K.L. 1982. The Acute Toxicity of Selected Petroleum Hydrocarbons. In: The Toxicology of Petroleum Hydrocarbons. Ed: H.N. MacFarland, C.E. Holdworth, J.A. MacGregor, R.W. Call, M.L. Kane. Published by the American Petroleum Institute. Washington, D.C.

EPA. 1989a. Risk Assessment Guidance for Superfund. Volume I. Human Health Evaluation Manual (Part A). EPA/540/1-89/002.

EPA. 1989b. Exposure Factors Handbook. Final Report. Office of Health and Environmental Assessment.

EPA. 1989c. Health Effects Assessment Summary Tables. Fourth Quarter. October 1989.

EPA. 1991a. Risk Assessment Guidance for Superfund. Volume 1 Human Health Evaluation Manual. Supplemental Guidance 'Standard Default Exposure Factors'. PB91-921314. March 25, 1991.

EPA. 1991b. Interim Guidance for Dermal Exposure Assessment. 1991. Office of Research and Development. USEPA. EPA/600/8-91/011A.

EPA. 1991c. Health Effects Assessment Summary Tables. Annual FY-1991. PB-91-921199.

EPA. 1992a. Health Effects Assessment Summary Tables. Annual FY-1992. PB-92-921199

Gosselin, R.E., R.P. Smith, H.C. Hodge. 1984. In: Clinical Toxicology of Commercial Products Fifth Edition. Williams and Wilkins. Baltimore. pp. 220-226.

Maibach, Howard I. and Dennis Mark Anjo. 1981. Percutaneous penetration of benzene and benzene contained in solvents used in the rubber industry. Arch. of Environ. Health 256.

NRC (National Research Council). 1989. Drinking Water and Health. Volume 9: Selected Issues in Risk Assessment. National Academy Press: Washington, D.C.

Watkin, G.E. and R.W. Hull. 1991. Factors affecting the dermal bioavailability of hydrocarbons in soil: applicability to human health risk assessment. In: Hydrocarbon Contaminated Soils. Volume I. Editors: E.J. Calabrese and P.T. Kostecki. Lewis Publishers. Chelsea, Michigan. pp 541-554.

# APPENDIX A

# HAZARD EVALUATION OF DIESEL FUELS

## 1.0 INTRODUCTION

This hazard evaluation reviews the chemistry of diesel fuels to give the reader an adequate understanding of the chemical composition of diesel fuels and review the potential carcinogenicity of diesel fuel and related petroleum hydrocarbons in man and animals. This hazard evaluation provides a scientifically based method for assessing the critical health risks which may be associated exposure to diesel fuel in soil using current EPA methods for assessing the risks associated with potential human carcinogens. A glossary is also provided at the end of this Appendix to aid the reader in understanding petroleum refining terms and petroleum products.

## 2.0 CHEMISTRY OF DIESEL FUELS

### 2.1 Description of Diesel Fuels

Diesel fuels are classed as middle distillates and are more dense than gasoline. The product definition in the U.S. Chemical Substances Inventory under the Toxic Substances Control Act is the following:

> Diesel Oil (CAS No. 68334-30-5)
> A complex combination of hydrocarbons produced by the distillation of crude oil. It consists of hydrocarbons having carbon numbers predominantly in the range of $C_9$-$C_{20}$ and boiling in the range of approximately 163-357° C.

The U.S. definition encompasses both diesel fuel No. 1 and diesel fuel No. 2. Diesel fuel No. 1 can be characterized as a straight-run petroleum distillate with a boiling range of 150-400° C (consistent with that of kerosene) and consisting predominantly of hydrocarbons with carbon numbers in the range of $C_9$-$C_{16}$. Diesel fuel No. 2 or automotive and railroad diesel fuel is generally a blend of straight-run and catalytically cracked streams, including straight-run kerosene, straight-run middle distillate, hydrodesulfurized middle distillate, and light catalytically and thermally cracked distillates. The boiling range is generally between 160-360° C. The major component streams of diesel fuels No. 2 and 4 are given in Table 2-1.

Diesel fuel No. 4 for low- and medium-speed engines (also known as a marine diesel fuel) is similar to fuel oil No. 4. It is more viscous than diesel fuel No. 2 and is generally classed as a residual fuel. Diesel fuel No. 4 normally contains up to 15% residual oil components.

Figure 1 summarizes the major fuel manufacturing processes commonly used in petroleum refining to make diesel fuels (middle distillates). Figure 1 also shows the interrelationships that exist between process units in a petroleum refining process. Not all the possible feed and product streams are shown but those of major importance to the blending of the final fuel product. The main purpose for including this figure is to provide a visual aid for understanding the many refinery process stream terms discussed later in this report, specifically, those that comprise diesel.

**Table 2-1**

**Major Component Streams of European Automotive Diesel Oil (Diesel Fuel No. 2) and Distillate Marine Diesel Fuel (Diesel Fuel No. 4)**

| TSCA Inventory Name and ID # | Refinery Process Stream | Automotive Diesel Oil (Vol. %) | Distillate Marine Diesel Fuel (Vol. %) |
|---|---|---|---|
| | Straight run gas oil (atmospheric) | | |
| Straight-run middle distillate [6] | - light | 40-100 | 40-100 |
| Straight run gas oil [7] | - heavy | 0-3 | 0-50 |
| Light vacuum distillate [19] | Vacuum gas oil - | 0-10 | 0-20 |
| Light thermally cracked distillate [30] | Thermally cracked gas oil | 0-20 | 0-30 |
| Light catalytically cracked distillate [24] | Light catalytically cracked gas oil (cycle oil) | 0-25 | 0-40 |

## 2.2 Chemical Composition of Diesel Fuels

Diesel fuel No. 1 is essentially kerosene. It contains normal and branched chain alkanes (paraffins), cycloalkanes (napthenes), and aromatic and mixed aromatic cycloalkanes. Usually, normal alkanes predominate in the mixture resulting in a clean-burning diesel fuel. The boiling range of diesel fuel No. 1 largely excludes the presence of benzene and polycyclic aromatic hydrocarbons. For example, kerosene (essentially equivalent to diesel fuel No. 1) normally contains less than 0.02% benzene and very low levels of 3 to 7-ring PAHs (IARC, 1989).

Diesel fuel No. 2 is essentially equivalent to fuel oil No. 2. Like diesel fuel No. 1, it also contains normal and branched chain alkanes (paraffins) cycloalkanes (napthenes), and aromatic and mixed aromatic cycloalkanes. However, because it is likely to contain cracked stocks as one or more of the blend streams, it also contains olefins and mixed aromatic olefin types such as styrenes. Diesel fuel No. 2 is a more complex mixture than diesel fuel No. 1 and has a lower percentage of straight-run fractions. Diesel fuel No. 2 spans a carbon number range of $C_{11}$-$C_{20}$. The major components of fuel oil No. 2 are presented in Table 2-2. There are discernable differences between fuels due to differences in crude oil types. The most evident differences between types are in the distribution of saturated hydrocarbon types. Nonetheless, the gross compositions are remarkably similar. The presence of catalytically cracked stocks does not result in the introduction of large quantities of olefins. For example, even when the blended product contains 50% catalytic stock, the olefin content is below 10%. While the chemical classes presented in Table 2-2 generally characterizes the molecular structures that predominate fuel oil No. 2, the proportions of the major classes can differ from one crude oil to another. Consequently, there may be appreciable variation in the hydrocarbon composition of distillate fuels. However, the differences are ordinarily not as large as might be anticipated because the specifications that must be met restrict the levels of several physical properties related to the composition.

The levels of some individual polynuclear aromatic hydrocarbons (PAHs) in a sample of commercial grade No. 2 oil are presented in Table 2-3.

## Table 2-2

### Detailed Analyses of Grade 2 Distillate Fuel Oils

| Hydrocarbon Type | Straight-Run No. 2 Furnace Oil | No. 2 Furnace Oil 10% Catalytic Stock | No. 2 Furnace Oil 50% Catalytic Stock |
|---|---|---|---|
| | Volume % | | |
| Paraffins (n- and iso-) | 41.3 | 61.2 | 57.2 |
| Monocycloparaffins | 22.1 | 8.5 | 6.0 |
| Bicycloparaffins | 9.6 | 8.3 | 5.0 |
| Tricycloparaffins | 2.3 | 1.4 | 0.7 |
| Total saturated hydrocarbons | 75.3 | 79.4 | 68.9 |
| Olefins | — | 2.0 | 7.5 |
| Alkyl benzenes | 5.9 | 5.3 | 8.0 |
| Indans/tetralins | 4.1 | 4.3 | 5.4 |
| Dinaphthenobenzenes/indenes | 1.8 | 1.3 | 1.0 |
| Naphthalenes | 8.2 | 5.8 | 6.8 |
| Biphenyls/acenaphthenes | 2.6 | 1.1 | 1.6 |
| Fluorenes/acenaphthylenes | 1.4 | 0.6 | 0.3 |
| Phenanthrenes | 0.7 | 0.2 | 0.5 |
| Total aromatic hydrocarbons | 24.7 | 18.6 | 23.6 |

Source: IARC (1989)

Table 2-3

**Concentration of Polynuclear Aromatic Hydrocarbons In No. 2 Fuel Oil**

| Chemical | Concentration (ppm) |
|---|---|
| Phenanthrene | 429.0 |
| 2-Methylphenanthrene | 7,677.0 |
| 1-Methylphenanthrene | 173.0 |
| Fluoranthene | 37.0 |
| Pyrene | 41.0 |
| Benz[a]anthracene | 1.2 |
| Chrysene | 2.2 |
| Triphenylene | 1.4 |
| Benzo[a]pyrene | 0.6 |
| Benzo[e]pyrene | 0.1 |

Source: IARC (1989)

The total concentration of parent hydrocarbons containing 4 or more rings is just over 80 ppm; the concentration of benzo[a]pyrene is 0.6 ppm. Diesel fuel may also contain minor amounts of n-hexane (>0.1%), benzene (>0.02%), toluene, xylenes, and ethyl benzene (0.25-0.5%).

Diesel oil No. 4 or marine diesel fuels are also complex mixtures whose composition varies widely between sources and even between lots, depending on their refining history and boiling range. The chemical composition of the marine diesel fuel used in the NTP carcinogenesis study consisted of 12.7% paraffins, 43.7% naphthalenes, and 43.6% aromatic compounds or roughly 13% aliphatics and 87% aromatics.

Probably the most complete review of the chemistry of diesel fuels is the study by Griest et al. (1985). This study characterized the chemistry of 11 diesel fuels representing industrial reference, military referee, military-purchased petroleum-derived diesel fuels, 2 fuels from different shale oil retorting and refining operations, and a fuel from tar sands/petroleum co-processing. The results of these studies are given in Tables 2-4 to 2-7. The data in Table 2-4 indicates that all the fuels share the same set of major components consisting of $C_9$ through $C_{21}$ n-paraffins at levels of 1 to 29 mg/g each. Also, branched hydrocarbons, di- and triaromatic hydrocarbons are present. Analyses of the aromatic content of diesel fuels reveal the presence of benzene, (<0.01-0.08 mg/g), and $C_1$-$C_4$ alkyl benzenes (generally 0.3-1 mg/g) such as toluene, ethyl benzene, styrene, and xylene (Table 2-5). The concentrations of these aromatics among diesel fuels are remarkably similar. The average benzo[a]pyrene (B[a]P) concentration among diesel fuels was 0.205 µg/g with values ranging between a low of <0.001 µg/g to a high of 0.84 µg/g (Table 2-6). The inhalable vapors from the fuels consist mainly of $C_2$-$C_{10}$ hydrocarbons (Table 2-7). A comparison of the diesel fuel refined from petroleum crude oils and shale oils indicates that there are similar concentrations of aliphatic hydrocarbons, monoaromatic hydrocarbons, and benzo[a]pyrene, but lower concentrations of di- and triaromatic hydrocarbons in the diesel fuel refined from shale oil.

## Table 2-4 Comparison of Major Organic Compounds (in mg/g) in Diesel Fuels Derived from Petroleum

| | Petroleum-Derived DF-2 or DFM | | | | | | |
|---|---|---|---|---|---|---|---|
| **Sample** | **1910** | **9101** | **1914** | **DF-2-1** | **DF-2-2** | **DF-2-3** | **4616** |
| **Compound** | **Phillips Lot C745** | **Phillips Lot C345** | **DOD Referee** | **Ft. Carson DIO** | **Ft. Carson AMP** | **Ft. Carson EMP** | **WPAFB DFM** |
| $C_8$ | - | - | - | - | 1.0 | 1.3 | - |
| $C_9$ | 4.9 | 3.6 | 2.1 | 4.8 | 4.3 | 4.0 | 3.6 |
| $C_{10}$ | 10.5 | 10.1 | 2.8 | 12.2 | 7.7 | 5.9 | 5.7 |
| $C_{11}$ | 16.9 | 17.1 | 5.7 | 22.6 | 13.4 | 10.4 | 11.2 |
| 3Me-$C_{11}$ | 1.7 | 1.8 | 0.9 | 1.8 | 1.4 | - | 2.8 |
| Napthalene | 1.3 | 1.6 | 2.5 | 2.0 | 1.9 | 1.2 | 2.2 |
| $C_{12}$ | 18.5 | 17.7 | 10.3 | 20.5 | 13.9 | 11.1 | 24.5 |
| 2Me-$C_{12}$ | 2.8 | 2.7 | 2.5 | 2.7 | 2.2 | 1.5 | 5.2 |
| 2Me-Nap | 14.9 | 8.4 | 13.5 | 6.4 | 9.6 | 7.1 | 10.9 |
| $C_{13}$ | 22.6 | 20.4 | 20.2 | 21.7 | 16.7 | 14.8 | 28.2 |
| 1Me Nap | 8.1 | 4.6 | 8.1 | 3.4 | 4.7 | 3.8 | 5.9 |
| 3Me-$C_{13}$ | 2.0 | 2.0 | 2.2 | 1.5 | 1.5 | 1.3 | 3.0 |
| Biphenyl | - | - | 1.2 | - | - | - | - |
| $C_{14}$ | 24.8 | 20.8 | 25.4 | 19.3 | 19.1 | 18.8 | 27.0 |
| 1,3-DiMe Nap | 12.8 | 8.6 | 12.3 | 5.5 | 9.4 | 8.5 | 10.5 |
| 1,5-DiMe Nap | 3.6 | 2.7 | 3.6 | 1.6 | 2.8 | 2.6 | 3.1 |
| 1,4-DiMe Nap | 2.2 | 1.8 | 2.3 | 1.1 | 1.6 | 1.6 | 2.1 |
| 2-Me $C_{14}$ | 5.5 | 5.0 | 5.8 | 3.4 | 3.8 | 3.9 | 6.3 |
| $C_{15}$ | 30.9 | 26.2 | 25.2 | 19.0 | 24.0 | 26.3 | 29.4 |
| Fluorene | 1.3 | 1.4 | 1.2 | 0.6 | 0.9 | 1.3 | 1.5 |
| $C_{16}$ | 28.5 | 24.8 | 19.6 | 14.9 | 21.9 | 25.7 | 26.2 |
| $C_{17}$ | 25.1 | 23.6 | 28.6 | 14.4 | 19.7 | 24.7 | 20.4 |
| Pristane | 8.1 | 7.4 | 6.0 | 3.5 | 4.7 | 5.8 | 6.7 |
| Phen | 2.4 | 3.0 | 1.9 | - | 1.9 | 1.7 | 1.8 |
| $C_{18}$ | 19.7 | 17.0 | 12.3 | 11.8 | 16.0 | 19.3 | 14.6 |
| Phytane | 5.9 | 5.5 | 5.3 | 3.5 | 4.9 | 5.7 | 4.1 |
| $C_{19}$ | 11.9 | 9.2 | 7.3 | 9.2 | 11.7 | 14.7 | 8.2 |
| $C_{20}$ | 5.4 | 3.7 | 4.0 | 6.4 | 8.4 | 10.1 | 5.1 |
| $C_{21}$ | 2.3 | 1.6 | 2.4 | 5.5 | 7.0 | 8.3 | 3.7 |
| 2Me Phen | 1.4 | 1.6 | 1.7 | - | 1.8 | 1.6 | 1.6 |
| $C_{22}$ | - | - | - | 2.9 | 3.8 | 4.4 | 1.4 |
| $C_{23}$ | - | - | - | 1.9 | 2.4 | 2.8 | - |
| $C_{24}$ | - | - | - | - | - | - | - |
| $C_{25}$ | - | - | - | - | - | - | - |
| **Total ID** | **296** | **255** | **237** | **224** | **245** | **249** | **277** |

Source: Adapted from Griest et al., 1985

Table 2-4

## Comparison of Major Organic Compounds (in mg/g) in Diesel Fuels Derived from Shale Oil and Tar Sands - Petroleum Coprocessing

(continued)

| | Shale-Derived DF2 or DFM | | | Petroleum Tar Sands Co-Processed |
|---|---|---|---|---|
| Sample | 4801 | 4802 | 4610 | 9523 |
| Compound | GeoKinetics Suntech w/o Add. | GeoKinetics Suntech w/ Add. | Paraho/SOHIO DFM | Petrol. Tar Sands 1990 DF |
| $C_8$ | 5.8 | 6.5 | 0.3 | - |
| $C_9$ | 5.1 | 5.4 | 2.4 | 9.0 |
| $C_{10}$ | 9.3 | 9.6 | 4.6 | 9.9 |
| $C_{11}$ | 17.3 | 17.7 | 9.6 | 10.1 |
| 3Me-$C_{11}$ | 1.2 | 1.1 | - | 1.6 |
| Napthalene | 1.7 | 1.8 | 0.9 | 5.7 |
| $C_{12}$ | 22.3 | 22.7 | 15.6 | 9.6 |
| 2Me-$C_{12}$ | 2.5 | 2.5 | 2.0 | 2.1 |
| 2Me-Nap | 1.9 | 1.9 | 1.9 | 12.7 |
| $C_{13}$ | 24.2 | 24.8 | 25.4 | 8.1 |
| 1Me Nap | 1.1 | 1.3 | 1.6 | 5.8 |
| 3Me-$C_{13}$ | 1.3 | 1.5 | 2.2 | 0.9 |
| Biphenyl | - | - | - | - |
| $C_{14}$ | 21.4 | 21.5 | 28.8 | 7.6 |
| 1,3-DiMe Nap | 1.0 | 1.0 | 1.3 | 8.0 |
| 1,5-DiMe Nap | - | - | - | 2.4 |
| 1,4-DiMe Nap | 1.8 | 1.8 | 2.7 | 1.2 |
| 2-Me $C_{14}$ | 11.3 | 11.4 | 14.9 | 0.9 |
| $C_{15}$ | 20.6 | 20.6 | 28.9 | 7.0 |
| Fluorene | 0.5 | 0.4 | 1.1 | 0.7 |
| $C_{16}$ | 19.2 | 19.2 | 27.8 | 6.0 |
| $C_{17}$ | 15.8 | 15.9 | 25.5 | 10.5 |
| Pristane | 9.7 | 9.8 | 17.1 | 1.9 |
| Phen | - | - | - | 1.6 |
| $C_{18}$ | 12.2 | 12.4 | 21.5 | 5.2 |
| Phytane | 7.1 | 7.1 | 13.8 | 2.3 |
| $C_{19}$ | 8.8 | 8.7 | 9.0 | 4.5 |
| $C_{20}$ | 5.8 | 5.7 | - | 4.3 |
| $C_{21}$ | 5.1 | 5.1 | - | 4.7 |
| 2Me Phen | - | - | - | 2.1 |
| $C_{22}$ | 2.5 | 2.4 | - | 3.4 |
| $C_{23}$ | 2.0 | 1.8 | - | 2.8 |
| $C_{24}$ | - | - | - | 1.9 |
| $C_{25}$ | - | - | - | 2.0 |
| Total ID | 239 | 241 | 253 | 156 |

Source: Adapted from Griest et al., 1985

Table 2-5

## Comparison of Benzene and Alkyl Benzene Content of Diesel Fuels Derived from Petroleum and Shale Oil

| Compound | Concentration in Fuel, mg/g [a] | | | | |
|---|---|---|---|---|---|
| | Petroleum | | | Shale | |
| | 1910 Phillips | 1914 DOD Reference | DF-2-1 DIO | 4801 Geokinetics Suntech DF-2 | 4610 Paraho SHIO DFM |
| Benzene | 0.026 | 0.082 | 0.048 | 0.01 | 0.027 |
| Toluene | 0.27 | 0.83 | 0.69 | 4.7 | 0.25 |
| Ethyl Benzene | 0.17 | 0.43 | 0.39 | 0.26 | 0.20 |
| m+p Xylenes | 1.3 | 2.0 | 2.5 | 1.0 | 0.66 |
| Styrene | <0.04 | <0.02 | <0.05 | <0.06 | <0.02 |
| o-Xylene | 0.42 | 0.78 | 0.85 | 0.32 | 0.24 |
| i-Propyl Benzene | <0.1 | <0.2 | IR | - | IR |
| n-Propyl Benzene | 0.30 | 0.40 | 0.48 | 0.15 | 0.12 |
| 1,3,5-Trimethyl benzene | 2.0 | 0.90 | 2.4 | 0.87 | 0.43 |
| 4-i-Propyl Toluene | 0.26 | 0.03 | IR | IR | IR |
| n-Butyl Benzene | 0.31 | 0.46 | IR | IR | IR |

Source: Adapted from Griest et al., 1985

[a] IR = incomplete resolution prevented measurement

Table 2-6

## Comparison of Benzo(a)pyrene Content of Diesel Fuels Derived from Petroleum and Shale Oil

| Sample Number | Description | Concentration, µg/g |
|---|---|---|
| | •••Shale Oil-Derived••• | |
| 4610 | Paraho/SOHIO DFM | 0.03 ± 0.005 |
| 4810 | Geokinetics/Suntech DF-2 | 0.09 ± 0.013 |
| | •••Petroleum Derived••• | |
| 9101 | Phillips Reference DF-2, Lot C-345 | 0.08 ± 0.04 |
| 1910 | Phillips Reference DF-2, Lot C-747 | 0.05 |
| 1914 | DOD Referee DF-2 | 0.19 ± 0.01 |
| DF-2-1 | Ft. Carson DIO DF-2 | 0.84 ± 0.10 |
| - | Petroleum DF[a] | 0.07 |
| - | Petroleum DF[b] | <0.001 - 0.42 |

Source: Adapted from Griest et al., 1985
[a]Norris and Hill, 1974
[b]Spindt, 1974

## Table 2-7

## Comparison of Inhalable Organic Compounds in Headspace Vapors of Diesel Fuels Refined from Petroleum and Shale Oil

| Compound | Concentration in Headspace Vapors[a], µg/L | | | | | |
|---|---|---|---|---|---|---|
| | Petroleum | | | | Shale Oil | |
| | No. 1910 Phillips Reference DF-2 | No. 1914 DOD Referee DF-2 | DF-2-1 Ft. Carson DIO DF-2 | No. 4616 WPAFB DFM | No. 4801 Geokinetics-Suntech DF-2 | No. 4610 Paraho-SOHIO DFM |
| i-Pentane | 260 | 520 | 440 | 920 | ND | 150 |
| n-Pentane | 61 | 190 | 260 | 450 | ND | 76 |
| 2,2-Dimethyl Butane | ND | 8 | 5 | 13 | ND | 6 |
| 3-Methyl Pentane | 53 | 79 | 89 | 110 | ND | 41 |
| n-Hexane | 53 | 99 | 190 | 160 | ND | 95 |
| Benzene | 16 | 62 | 33 | 50 | 17 | 29 |
| 3-Methyl Hexane | 34 | 59 | 85 | 66 | 11 | 92 |
| n-Heptane | 42 | 87 | 170 | 80 | 22 | 148 |
| Toluene | 35 | 140 | 110 | 45 | 970 | 30 |
| n-Octane | 35 | 69 | 140 | 53 | 70 | 74 |
| m+p Xylenes | 31 | 61 | 80 | 30 | 26 | 6 |
| n-Noane | 74 | 45 | 140 | 45 | 93 | 38 |
| 1,3,5-Trimethyl Benzene | 23 | ND | 33 | ND | 22 | 8 |
| n-Decane | 53 | 12 | 120 | 25 | 57 | 19 |

Source: Adapted from Griest et al., 1985
[a]ND = Not Detected

In summary, automotive and railroad diesel fuel (diesel fuel No. 2) contains straight-run middle distillate [6] (number in brackets indicates the refinery stream in Figure 1), often blended with straight-run kerosene [5], straight run gas oil [7], light vacuum distillate [19] and light thermally cracked [30] or light catalytically cracked distillates [24]. Some blended marine diesel fuels also contain heavy residues from distillation [98, 21] and thermal cracking [31] operations. In diesel fuel consisting mainly of atmospheric distillates, the content of 3 to 7-ring PAHs is generally less than 5%, but in diesel fuel that contains high proportions of heavy atmospheric, vacuum and light cracked distillates, the PAH content may be as high as 10% (IARC, 1986). Marine diesel fuels may contain even higher levels of PAHs.

# 3.0 HAZARD IDENTIFICATION AND EVALUATION

## 3.1 Introduction and General Considerations

It is fundamental to observe that all chemicals have the potential to cause toxicity and harm under the appropriate set of circumstances. Toxicants are defined as chemical agents which, under certain conditions, may produce adverse effects on biological systems, ranging from minor alterations of normal function to death. The main goal of any risk assessment is to determine those conditions likely to produce harm.

In general terms, risk (R) represents a relationship between the toxicity (T) of the compound and factors related to the exposure (E) to the compound $R = Tf(E)$. Regardless of how risks are expressed, they remain dependent on the toxicity of a compound and the exposure circumstances.

The four basic steps of the risk assessment process are the following:

1. **HAZARD IDENTIFICATION** - The hazard identification summarizes the toxicological data base for the chemical of interest and identifies the potential adverse health effects observed in animal and human studies. Examples of hazard identifications are the USEPA Water Quality Criteria and Health Effects Documents.

2. **HAZARD EVALUATION** - The hazard evaluation is an analysis of the dose-response relationships, potency, and toxicological mechanisms of a chemical. The following points should be analyzed in the hazard evaluation step:

   - The types of toxic responses and sensitive organs and tissues.
   - Species variation in toxic effects.
   - Mechanism(s) of toxicity.
   - The validity of the tests performed in animals and their relevance for extrapolation to man.
   - Animal test doses compared with the expected level of human exposure.

- Available data from long-term occupational exposures and human poisonings. Such an evaluation may provide information regarding expected human effects and act as a test for extrapolations made from animal data.

3. **EXPOSURE EVALUATION** - The exposure evaluation provides estimates of likely human exposure which may result from human contact with the affected environmental medium. The exposure evaluation takes into consideration site-specific characteristics which may affect the potential for human exposure to the chemical.

4. **RISK ASSESSMENT** - The risk assessment integrates the outputs of the exposure evaluation against the risk estimates for the chemical. This provides some determination as to the relative safety or hazard associated with the anticipated exposure.

As mentioned above, the hazard evaluation step involves the quantitative extrapolation from data gathered in animal studies to humans. Generally, there are two situations encountered in making this calculation. The first situation involves the use of a model to extrapolate an acceptable human dose from that dose which produces no effects (the threshold dose) in the animal species tested. The second situation, typically much more complex and uncertain, involves calculating an acceptable exposure for carcinogenic chemicals in which it is assumed that no threshold exists. The USEPA typically assesses non-carcinogenic risks by comparing the estimated exposure level to a reference dose (RfD), and carcinogenic risks using a non-threshold model such as the linearized multistage model.

### 3.1.2 Assessment of Carcinogenic Risks of Diesel Fuel

This assessment uses cancer slope factors to quantitatively assess carcinogenic risks. IC derived the slope factors using the linearized multistage model. This model is the preferred model of the USEPA Carcinogen Assessment Group for risk extrapolation from animals to humans. The multistage model will often be linear in the low-dose region. Cancer risk estimates derived using this model are typically regarded as being relatively conservative. The model assumes that cancer is a multistage process for which a series of mutations are necessary to transform a normal cell into a malignant one. As it is used by the USEPA, the multistage model estimates the upper limit of

carcinogenic potency of a substance by mathematical extrapolation of tumor incidence observed at doses generally much higher than human exposures to predict the upper-limit tumor incidence at the low levels of exposure usually experienced by people.

Quantitative cancer risk estimates are calculated after cancer slope factors are determined using the linearized multistage model. These slope factors are termed "$q_1$" and "$q_1^*$." The term "$q_1$" designates the slope of the dose response curve or the maximum likelihood estimate; whereas "$q_1^*$" is the upper bound (at low doses) of the potency of the chemical in inducing cancer. Thus, the risk estimates using the upper 95% confidence limit from the linearized multi-stage model is conservative, representing the most plausible upper-limit of of the actual risk.

### 3.2 Critical Health Effects Associated With Exposure to Diesel Fuel

We have reviewed the animal and human studies cited in the reference section of this report for the purpose of identifying the critical human health effects associated with short-term (acute) and long-term (chronic) exposure to diesel fuel. In selecting the critical toxicological end-points from which to extrapolate safe human dosages, it is usually prudent to choose the most sensitive species exposed over an appropriate exposure period. At present, lifelong exposure in rats and mice provide the best data for determining toxicity of diesel fuel to chronically exposed humans. As a result of these considerations, lifetime (and partial lifetime) dermal cancer studies were selected as the basis for deriving a cancer slope factor. These studies are reviewed below. We have also included the mutagenicity data for diesel fuel and evaluated the potential toxicological mechanism(s) for diesel fuel carcinogenesis.

#### 3.2.1 Genotoxic Effects of Diesel Fuel

Diesel fuel has been studied in a number of *in vitro* and *in vivo* mutagenicity tests (API, 1978; 1980; Henderson et al., 1981; Conaway et al., 1984; Cragg et al., 1985; NTP, 1986; Lee et al., 1989). A review of the available literature

regarding the genotoxic potential of diesel fuel and middle distillates is presented below.

API (1978) evaluated the mutagenic potential of diesel fuel No. 2 in a battery of tests consisting of a test for mitotic gene conversion in yeast, gene mutation tests in bacteria, gene mutation tests in cultured mammalian cells, and *in vivo* chromosome analysis in rat bone marrow cells.

Diesel fuel was evaluated in plate assays and suspension assays using Ames *Salmonella* tester strains TA-1535, TA 1537, TA-1538, TA-98, and TA-100 and in the yeast strain *Saccharomyces cerevisiae*, D4 both in the presence and absence of mammalian metabolic activation preparations. The plate test results indicated diesel fuel was not mutagenic at doses up to 5 µL per plate. While the authors did not summarize the results for the suspension assays, a review of the raw data indicated that diesel fuel was also not mutagenic. Similarly, diesel fuel was not mutagenic in the mouse lymphoma assay which measures forward mutations at the thymidine kinase locus. In contrast, diesel fuel was clastogenic in the rat bone marrow cytogenetic analysis. Both the intermediate dose level (2.0 mL/kg) and the high dose level (6.0 mL/kg) were clearly outside the normal spontaneous range. A large proportion of aberrations were chromosome fragments.

API (1980) evaluated the ability of diesel fuel to induce dominant lethal mutations in sperm of CD-1 mice. The fuel was administered at two exposure levels of 100 and 400 ppm by inhalation exposure for 6 hours per day, 5 days per week for 8 weeks. The results indicated that diesel fuel did not cause significant increases in either pre- or post-implantation loss of embryos when statistically compared to negative controls. Thus, diesel fuel did not induce dominant lethal mutations in mice at the 2 doses tested.

Henderson et al., (1981) reported that neither the aliphatic or aromatic fractions separated from diesel fuel No. 7911 (not further specified) was mutagenic in the *Salmonella* assay using tester strain TA-100.

Conaway et al., (1984) evaluated the mutagenic potential of a number of petroleum hydrocarbons in a test battery consisting of the Ames *Salmonella*

assay, the L5178Y mouse lymphoma assay, and the rat bone marrow cytogenetics. A summary of the results of this study are presented below:

| Sample | Ames Salmonella Assay[a] | Mouse Lymphoma Assay[a] | Rat Bone Marrow Cytogenetics |
|---|---|---|---|
| Unleaded gasoline | -/- | -/- | - (i.p.)[b] |
| **Kerosene** | **-/-** | **-/-** | **- (i.p.)** |
| Stoddard solvent | -/- | -/- | - (i.p.) |
| **Diesel fuel** | **-/-** | **-/-** | **+ (i.p.)** |
| Jet fuel A | -/- | -/+ | + (v.) |
| **No. 2 fuel oil** | **±/±** | **+/+** | **+ (g.)** |
| Composite motor oil | -/- | -/± | - (g.) |

[a]without/with metabolic activation (+ = positive - = negative ± = equivocal)
[b]route of administration; i.p. = intraperitoneal; g. = gavage; v. = inhalation

Note that the results presented for kerosene, diesel fuel, and No. 2 fuel oil are the only relevant materials for evaluating the mutagenic potential of diesel fuel No. 2 (noted in bold in the preceding table). Kerosene was not mutagenic in the test battery. Diesel fuel was not mutagenic in the Ames *Salmonella* assay using tester strains TA-98, TA-100, TA-1535, TA-1537, and TA-1538 (with and without metabolic activation), or in the mouse lymphoma assay but was judged positive in the rat bone marrow cytogenetics assay. Diesel fuel significantly increased the frequency of chromosomal aberrations in the bone marrow of Sprague-Dawley rats 6-48 hours after a single i.p. injection of 2 or 6 mL/kg bw or after 5 daily i.p. injection of 6 mL/kg bw/day. The No. 2 fuel oil was judged equivocal rather than negative in the Ames *Salmonella* assay because there was relatively high mutant frequencies in tester strain TA-98 at 4 dose concentrations. However, when suspension assays were performed, no increase was observed in the mutant frequency. The No. 2 fuel oil was mutagenic in the mouse lymphoma assay both with and without metabolic activation at the test concentration of 1200 µg/mL (the mutation frequency was 17.1 times the solvent control without metabolic activation). The No. 2 fuel oil administered by gavage for 5 days at doses of 0.125, 0.417, and 1.25 g/kg/day caused a significant increase in the frequency of chromosomal aberrations in the bone marrow of Sprague-Dawley rats only at the low and high doses and not at the intermediate dose.

In evaluating the concordance of the *Salmonella* microsomal assay with the mouse dermal carcinogenesis bioassay for complex petroleum hydrocarbon mixtures, Cragg and co-workers (1985) tested the mutagenic activity of 13 petroleum fractions using tester strains TA-1535, TA-1537, TA-1538, TA-98, and TA-100 both with and without rat S-9 supernatant containing liver microsomes. Of these 13 petroleum fractions, the only fraction that was similar to diesel fuel No. 2 was the straight-run kerosene fraction (350-550° F). The results indicated that none of the 13 samples were mutagenic in the Ames *Salmonella* assay using both plate and suspension techniques at doses up to 10,000 µg/plate.

The NTP (1986) reported that marine diesel fuel was not mutagenic to *Salmonella typhimurium* strains TA-98, TA-100, TA-1535, or TA-1537 at doses up to 3,333 µg/plate. The Ames *Salmonella* assays were performed both in the presence and absence of Aroclor 1254-induced-Sprague-Dawley rat and Syrian hamster S-9 using the preincubation protocol.

Lee et al., (1989) studied the mutagenic responses of 5 petroleum fractions (including diesel fuel) that may be used by the military as obscurants. Each of the 5 samples were tested in the 4 standard *Salmonella* tester strains (i.e., TA-97, TA-98, TA-100, and TA-102) both in the presence and absence of Aroclor 1254-induced rat liver S9 at doses up to 15 µL/plate. None of the 5 petroleum fractions, including 2 types of diesel fuel, were mutagenic.

The interpretation of the results of the genotoxicity studies for diesel fuel and their significance for human hazard assessment is difficult to assess because of conflicting results. The large number of *in vitro* studies summarized below are clearly negative, but the 2 *in vivo* cytogenicity tests indicated that diesel fuel is clastogenic. However, these studies were conducted at near lethal doses (e.g., 2 and 6 mL/kg - note the $LD_{50}$ is 7.5 mL/kg) with no clear dose-response. For example, in the study by Conaway et al. (1984) diesel fuel was clastogenic at the low and high dose, but not at the intermediate dose. Doses of 0.6 mL/kg were not clastogenic in either study. Thus, diesel fuel is not mutagenic in Ames *Salmonella*, yeast, and mouse lymphoma, does not induce dominant lethality, and is not clastogentic at doses of ≤0.6 mL/kg.

| Genotoxicity Test | Response | Type of Diesel Fuel | Reference |
|---|---|---|---|
| Ames *Salmonella* | - | Diesel fuel No 2 | API, 1978 |
| | - | Diesel fuel No 7911 (aromatic and aliphatic fractions) | Henderson et al. 1981 |
| | - | Diesel fuel | Conaway et al., 1984 |
| | - | Kerosene | |
| | ± | No. 2 fuel oil | |
| | - | straight-run kerosene | Cragg et al., 1985 |
| | - | Marine diesel fuel | NTP, 1986 |
| | - | diesel fuel | Lee et al., 1989 |
| Yeast (*Saccharomyces cerevisiae*, D4) | - | Diesel fuel No 2 | API, 1978 |
| Mouse lymphoma | - | Diesel fuel No 2 | API, 1978 |
| | - | Diesel fuel | Conaway et al., 1984 |
| | - | Kerosene | |
| | + | No. 2 fuel oil | |
| Dominant Lethality | - | Diesel fuel | API, 1980 |
| Rat bone marrow cytogenetics | + | Diesel fuel | API, 1978 |
| | + | Diesel fuel | Conaway et al., 1984 |
| | - | Kerosene | |
| | + | No. 2 fuel oil | |

(+ = positive - = negative ± = equivocal)

### 3.2.2 Cancer Studies in Humans

We have reviewed the available epidemiologic data and case reports of the carcinogenicity of petroleum hydrocarbons in humans (Hendricks et al., 1959; Hanis et al., 1982 and 1985; Thomas et al., 1980, 1982, and 1984; Divine et al., 1985; Divine & Barron, 1986; Wen et al., 1982, 1983, 1984 and 1985; Wong & Raabe, 1989; McCraw et al., 1985; Wong et al., 1986; Nelson et al. 1987; Decoufle et al., 1983; Kaplan, 1986, Schottenfeld et al., 1981; Theriault & Provencher, 1987; Hanis et al., 1979; Rushton & Alderson, 1980 and 1981; Alderson & Rushton, 1981 and 1982; Alderson & Rattan, 1980; Malker et al., 1986; and Norell et al., 1986). While several of the epidemiological studies reported involved subjects or occupational groups with mixed exposures, particularly to gasoline and diesel fuel, there are no studies on diesel fuel itself. While the study by Siemiatycki et al., (1987) did separate exposure to diesel fuel from other petroleum hydrocarbons, any conclusions from this study must be viewed with caution because no attempt was made to separate the effects of

exposure to combustion products from those of exposure to the liquid itself. Consequently, it is difficult to make any conclusions concerning the carcinogenicity of diesel fuel in humans especially in light of the known carcinogenic potential of the combustion products. Note that we have nonetheless reviewed this study below for sake of completeness. Since there are no adequate human data regarding the carcinogenic potential of diesel fuel alone, we decided to simply provide the conclusions of IARC concerning the carcinogenicity of petroleum refining in general. These conclusions provide at least some perspective for the potential for diesel fuel to be carcinogenic in man. IARC's conclusions are as follows:

- There is *limited evidence* that working in petroleum refineries entails a carcinogenic risk. This limited evidence applies to skin cancer and leukemia. For all other cancer sites on which information was available, the evidence was inadequate.

IARC's overall evaluation is that occupational exposures in petroleum refining are *probably carcinogenic to humans* (Groups 2A).

In a case control study by Siemiatycki et al., (1987), an increased risk for cancer of the prostate, with an adjusted odds ratio of 1.9 (90% Confidence Interval 1.2-3.0) was observed among men exposed to diesel fuel and its combustion products. However, there was no evidence of a positive dose-response relationship. There was also an increased risk for squamous cell carcinoma of the lung in men (adjusted odds ratio including smoking 1.6 [1.0-2.6 C.I.]). For men with estimated nonsubstantial exposure it was 2.5 (1.3-4.7 C.I.). Mechanics and repairmen who constituted the largest group exposed to diesel fuel and its combustion products had an adjusted odds ratio of 2.0 (0.9-4.2 C.I.).

### 3.2.3 Animal Bioassays

There are numerous studies describing the carcinogenic potential of petroleum hydrocarbons including diesel fuel (Smith et al., 1951; Hueper and Ruchhoft, 1954; Shubik and Saffiotti, 1955; Shapiro and Getmanets, 1962; Saffiotti and Shubi, 1963; Getmanets, 1967; Weil and Condra, 1977; Bingham and Barkley, 1979; Grimmer et al., 1982; Nesnow et al., 1982; Doak et al., 1983; Gradiski et al., 1983; Lewis, 1983; Blackburn et al., 1984; Coomes and Hazer,

1984; Halder et al., 1984; Kane et al., 1984; Karimov et al., 1984; Lewis et al., 1984; Cragg et al., 1985; Blackburn et al., 1986; Dutcher et al., 1986; Karimov et al., 1986; NTP, 1986; Witschi et al., 1987; Biles et al., 1988; Gerhart et al., 1988; API, 1989; McKee et al., 1989a; 1989b). We have reviewed these studies and selected those that provide relevant data concerning the potential carcinogenicity of diesel fuel and middle distillates. These studies are described below.

**Dermal Studies in Mice**

Blackburn et al., (1984, 1986) evaluated the dermal carcinogenicity of undiluted samples derived from crude oil refining using C3H/HeJ mice. In this study, groups of 50 male mice were given twice weekly applications of 50 mg of the samples on shaven interscapular skin for 80 weeks or until a papilloma larger than 1 $mm^3$ developed. The incidence of skin tumors was evaluated in mice surviving at the time in which 1/2 of the tumor bearing animals had developed their tumor or at 60 weeks, whichever came first. Controls consisted of seven groups of 50 mice treated similarly with toluene and four groups of 50 mice that were only shaven. Three skin tumors were observed in toluene treated controls, but none in the controls that were only shaven. The results of this study are summarized in Table 3-1. Note that the results presented for straight-run kerosene, light paraffinic distillate, and hydrotreated kerosene are the only relevant studies for evaluating the dermal carcinogenicity of diesel fuel. The other samples are used in the manufacture of other petroleum products such as gasoline or lubricating oils. The tumor incidence in male mice treated with distillates are as follows: light paraffinic distillate 27/42, straight-run kerosene 9/30 and 4/27, and hydrotreated kerosene 24/38.

**Table 3-1**

**Results of Dermal Studies of the Carcinogenicity of Undiluted Uncracked Distillates and Residues of Crude Oils**

| No. of groups | Sample | No. of survivors | No. with skin tumors | Average latent period (weeks) |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| one | **Light paraffinic distillate (CAS No. 64741-50-0)** | 42 | 27 | 35 |
| one | Heavy paraffinic distillate (CAS No. 64741-51-1) | 34 | 31 | 34 |
| four | Heavy naphthenic distillate (CAS No. 64741-53-3 | 38 | 31 | 50 |
| | | 34 | 25 | 48 |
| | | 27 | 16 | 38 |
| | | 29 | 21 | 42 |
| two | **Straight-run kerosene (CAS No. 8008-20-6)** | 30 | 9 | 70 |
| | | 27 | 4 | 62 |
| one | **Hydrotreated kerosene (CAS No. 64741-46-4)** | 38 | 24 | 79 |
| one | Light straight-run naphtha (CAS No. 64741-46-4) | 44 | 11 | 85 |
| one | Vacuum residue (CAS No. 64741-56-6) | 43 | 1 | 70 |
| two | Hydrotreated heavy naphthenic distillate (CAS No. 64742-52-5) | 41 | 36 | 51 |
| | | 25 | 21 | 57 |
| one | Chemically neutralized/ hydrotreated heavy naphthenic distillate (CAS No. 64742-34-3/64742-52-5) | 20 | 12 | 52 |

Source: IARC, 1989; Blackburn et al., 1984, 1986

Note - the data presented in bold text represents data used to evaluate the carcinogenicity of diesel fuel No. 2.

Lewis et al., (1984) conducted skin cancer bioassays to determine the carcinogenicity of crude oils and major distillate and chemical class subfractions which were applied to the skin. In this study, 2 crude oils which represent extremes in hydrocarbon composition and boiling range distribution were selected for bioassay. The 2 crudes were designated crude C and D. Crude C oil is low in sulfur and is typically used for the manufacture of industrial lubricants and specialty oil. Crude D oil is high in sulfur and is generally used for the production of fuels, solvent-refined lubricants, and waxes. The 2 crudes were separated to produce fractions that correspond to naphtha, kerosene, gas oil, heavy vacuum gas oil, and asphalt. The kerosene, gas oil, and vacuum gas oil fractions were further separated to isolate predominantly aromatic from aliphatic components.

All materials were applied undiluted to groups of 50 male C3H/HeJ mice, 50 mg per application, 2 times per week for a minimum of 18 months or until grossly-observable tumors were found. Materials were applied dermally to the interscapular region. The authors made no distinction between histologically benign and malignant lesions.

The results of the dermal carcinogenesis bioassays are given in Table 3-2. Tumor incidence is expressed as the percent of animals in the effected group[2] and arithmetic average elapsed time in weeks to the appearance of the first tumor in each tumor-bearing animal (latency). The results for the two whole natural crude oils indicated about twice as many tumors in mice treated with crude D, as compared to mice treated with crude C. The authors attributed the differences in tumor incidence to the increased amount of sulfur and polycyclic aromatic hydrocarbon content in Crude D. The material fraction in this study most like diesel fuel No. 2 is the straight run kerosene (350-550° F). The tumor incidence in the kerosene subfraction from crude oils C and D was 30% and 15%, respectively. The data from dermal carcinogenesis studies of the predominantly aromatic and aliphatic components of crude oils C and D are given in Table 3-3. For the aromatic subfractions, there was a

[2] Effective group is defined as the number of animals surviving (a) at the calculated arithmetic mean tumor latency (based on gross examination *in vivo* (b) as of the 60th week of the test, whichever is shorter, plus all animals which died with tumors prior to that time.

## Table 3-2 Tumor Incidence In Mice Receiving Crude Oils and Major Distillate and Chemical Class Subfractions

| % Tumors[1] | Latency[2] | Material | % Tumors[1] | Latency[2] |
|---|---|---|---|---|
| Crude C | | | Crude D | |
| 33 | 76 | Whole Crude | 56 | 64 |
| None Available | | AMB-120° F | 0 | — |
| 21 | 85 | 120-350° F | 25 | 85 |
| **30** | **73** | **350-550° F** | **15** | **62** |
| 17* | 59 | 550-700° F | 3 | 40 |
| 82 | 50 | 700-1070° F | 87 | 34 |
| 0 | — | 1070+ °F | 2 | 70 |
| 0 | — | controls** | 0 | — |
| 2 | 97 | toluene** | 2 | 97 |

Source - Adapted from Lewis et al. (1984)
*apparently this tumor incidence represents a half dose (25 mg/2x/week) due to toxicity at the full dose. The adjusted tumor incidence becomes 34% (Cragg et al., 1985).
**control and toluene tumor incidence reported in (Cragg et al., 1985).
Note - the data presented in bold text represents data used to evaluate the carcinogenicity of diesel fuel No. 2.
[1]based on final effective number. [2]In weeks

## Table 3-3 Tumor Incidence In Mice Receiving Aromatic and Aliphatic Components of Different Subfractions of Crude Oils

| % Tumors[1] | Latency[2] | Material | % Tumors[1] | Latency[2] |
|---|---|---|---|---|
| Crude C | | | Crude D | |
| **Aromatics** | | | | |
| **34** | **64** | **350-550° F** | **30** | **91** |
| 45 | 59 | 550-700° F | 86 | 45 |
| 98 | 44 | 700-1070° F | 38 | 34 |
| **Aliphatics** | | | | |
| **71** | **74** | **350-550° F** | **59** | **78** |
| 32 | 98 | 550-700° F | 22 | 91 |
| 0 | — | 700-1070° F. | 0 | — |

Source - Adapted from Lewis et al. (1984)
Note - the data presented in bold text represents data used to evaluate the carcinogenicity of diesel fuel No. 2. [1]based on final effective number. [2]In weeks

general trend toward higher tumor yields and a strong trend to shorter latencies as the boiling range of the parent fraction increased. This increase was attributed to the PAH content of the higher boiling subfractions. The authors attributed the lower tumor incidence in the group receiving 700-1070 °F Crude D aromatic subfractions to mortality. For the aliphatic subfraction from kerosene, the tumor incidence in the group was 71%. The authors speculated that this subfraction which consists of alkanes, alkylated cycloparaffins and alkylated single-ring aromatics could act as promotors or co-carcinogens.

The NTP (1986) conducted a 2 year dermal carcinogenesis study of marine diesel fuel using B6C3F1 mice. Groups of 50 male and female mice received 250 or 500 mg/kg body weight (bw) marine diesel fuel in 0.1 mL acetone by application to clipped interscapular dorsal skin on 5 days per week for 103 weeks or 84 weeks (high-dose group terminated due to severe ulceration of the skin), respectively. Controls received the vehicle alone. Survival among vehicle control males and females was 30/50 and 40/50, respectively. The results of this study are given in Table 3-4. In low dose males and females, survival at 104 weeks was 20/49 and 12/50, respectively. In high dose males and females, survival at 84 weeks was 26/50 and 29/50, respectively. Survival rates at the end of the studies were reduced ($P<0.01$) in low dose female mice when compared with vehicle controls. Body weight gain was decreased below that of the vehicle controls after week 30 in all groups of mice receiving marine diesel fuels.

There was a marked increase in the incidence of chronic dermatitis in mice receiving marine diesel fuel. Chronic dermatitis was defined as a composite lesion of epidermal histopathologic changes consisting of acanthosis[2], hyperkeratosis[3], and in some instances necrosis and ulceration of the overlying epidermis. Dermal changes usually included fibrosis, increased amounts of melanin, and the presence of acute and chronic inflammatory cell infiltrates.

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[2] a thickening of the germinative layer of the epidermis (caused by hyperplasia).
[3] hypertrophy of the horny layer of the skin.

Table 3-4

**Incidence of Skin Tumors In Mice In A Two-Year Dermal Study of Marine Diesel Fuel**

| Species/ Tumor Type | Vehicle Control | Amount of Marine Diesel Fuel Applied | |
|---|---|---|---|
| | | 250 mg/kg | 500 mg/kg |
| **Male** | | | |
| Tumors at site of application | | | |
| Squamous cell papilloma | 0/49(a) | 0/49 | 1/49 |
| Squamous cell carcinoma | 0/49 | 0/49 | 2/49 |
| Tumors observed at inguinal site (b) | | | |
| Squamous cell papilloma | 1/50 | 0/49 | 0/50 |
| Squamous cell carcinoma | 0/50 | 2/49 | 0/50 |
| Total papillomas and carcinomas, site of application and inguinal skin | 1 | 2 | 3 |
| **Female** | | | |
| Tumors at site of application | | | |
| Squamous cell papilloma | 0/50 | 0/45 | 0/48 |
| Squamous cell carcinoma | 0/50 | 1/45 | 2/48 |
| Tumors observed at inguinal site (b) | | | |
| Squamous cell papilloma | 0/50 | 0/45 | 0/50 |
| Squamous cell carcinoma | 0/50 | 0/45 | 0/50 |
| Total papillomas and carcinomas, site of application and inguinal skin | 0 | 1 | 2 |
| **Male and Female** Total papillomas and carcinomas site of application and inguinal skin | 1 | 3 | 5 |

Source: Adapted from NTP, (1986)

A statistically significant ($p<0.05$) positive trend toward skin tumors (papillomas and carcinomas combined) was observed at the site of application in male mice (vehicle control 0/49; 250 mg/kg 0/49; 500 mg/kg 3/49). The incidence of combined papillomas and carcinomas both at the site of application and the adjacent inguinal skin were 1/50, 2/49, and 3/50 for the vehicle control, 250 mg/kg, and 500 mg/kg dose groups of male mice and 0/50, 1/45, and 2/48 for female mice. While no data were available concerning historical control tumor incidence among acetone-treated animals of this strain, the background incidence of squamous cell papillomas or carcinomas (combined) in untreated male and female B6C3F1 mice was 0.3%-0.4% in over 3,500 observations. The results of the 2 year dermal study indicated that there was a dose-related increased incidences of squamous cell neoplasms of the skin (primarily carcinomas). This data was considered by the National Toxicology Program (NTP) to provide *equivocal evidence of carcinogenicity*[4] for male and female B6C3F1 mice.

Witschi and co-workers evaluated the skin tumorigenicity of crude and refined coal liquids and analogous petroleum products (Witschi et al., 1987). The purpose of the study was to compare the tumorigenicity of crude and upgraded coal liquids and of finished coal-derived and analogous petroleum products. Seven complex hydrocarbon mixtures were tested: a coal-derived raw blend composed of light and heavy oils, a low- and high-severity hydrotreated product of that blend, and naphthas and fuel oils from the raw blend or from natural petroleums. Groups of 25 male and 25 female C3H/Bd$_f$ mice were exposed 3 times per week to a high, medium, and low dose of each petroleum test mixture. Thus, 75 males and 75 females were exposed to each complex mixture. Petroleum samples (50 µL) were applied evenly to the back of the mice over an area of about 1 $cm^2$. The high dose consisted of the undiluted (neat) sample, the medium was a 1:1 dilution with acetone, and the low dose was a 1:3 dilution with acetone. On a weight basis this corresponds to doses of 44, 22, and 11 mg/ application assuming a specific gravity of 0.8762. Control groups were run concurrently. Positive controls consisted of painting male and female animals 3 times per week with 50, 25, or 12.5 µg of

[4] IARCs ***"equivocal evidence of carcinogenicity"*** is used to describe the carcinogenicity of chemicals in which animal studies demonstrate a marginal increase in chemically related neoplasms.

## Table 3-8

## Chemicals Analyses of Selected Middle Distillate Fuels

| | Sample Name (Volume%) | | | | | |
|---|---|---|---|---|---|---|
| | Virgin heating oil blending base | Virgin heating oil blending base = 59% catalytically cracked liquids | Commercial heating oil | Commercial heating oil | Commercial heating oil | Light catalytic cycle oil |
| Sample No. from Table 3-7 | 1 | 9 | 6 | 7 | 8 | 10 |
| Aromatics | 19 | 46 | 46 | 29 | 40 | NM |
| • monoaromatics | 16.3 | 26.4 | NM | NM | NM | 34.5 |
| • diaraomatics | 4.8 | 20.3 | NM | NM | NM | 1.5 |
| • >3 ring aromatics | ND | ND | NM | NM | NM | ND |
| Saturates | 79 | 53 | 54 | | 60 | NM |
| Olefins | 2 | 1 | 0 | 0 | 0 | NM |

Source: Adapted from Biles et al., (1988)
NM = not measured
ND = not detected

## Table 3-9

## Polycyclic Aromatic Hydrocarbon (PAH) Content of Middle Distillate Fuels

| PAH Species | Commercial heating oil | Virgin blending stocks | Catalyticall y cracked oil boiling below 640° F | Virgin blending stocks plus catalytically cracked oils |
|---|---|---|---|---|
| | | (ppm) | | |
| Sample No from Table 3-7 | (4) | (1) | (10) | (9) |
| Fluorene | - | <130 | <121 | <100 |
| Phenanthrene | - | 195 | 2,830 | 1,450 |
| Anthracene | - | 5.4 | <1 | <1 |
| Fluoranthene | 22.2 | <20 | 4.12 | 48 |
| Pyrene | 25.8 | 14.1 | 2.78 | 264 |
| Benz[a]anthracene | 0.7 | <0.3 | <0.1 | 0.84 |
| Chrysene | 4.2 | <108 | <0.3 | 3.11 |
| Triphenylene | 2.0 | <1.0 | <0.3 | 1.54 |
| Methylbenz[a]anthracene | <0.2 | <0.4 | 1.58 | 0.94 |
| Dm/et benz[a]anthracene | <0.2 | <0.1 | <0.63 | <0.6 |
| Benzo[g,h,i]fluoranthene | 1.1 | <10 | <3 | <17 |
| Benzo[b]fluoranthene | <0.05 | <0.2 | <1 | <1 |
| Benzo[j]fluoranthene | <0.1 | <0.2 | <3 | <3 |
| Benzo[k]fluoranthene | <0.1 | <0.2 | <2 | <2 |
| Perylene | <0.05 | <0.3 | <1 | <1 |
| Benzo[a]pyrene | 0.1 | <0.3 | <0.5 | <1 |
| Benzo[e]pyrene | <0.05 | <0.3 | <1 | <1 |
| Methylbenzo[a]pyrene | <0.05 | <0.2 | <2 | <2 |
| Methylbenzo[e]pyrene | <0.05 | <0.2 | <2 | <2 |
| 1,2,3-Indeno[c,d]pyrene | - | <0.1 | <0.3 | <0.2 |
| Dibenz[a,h]anthracene | - | <0.1 | <0.4 | <0.4 |
| Benzo[g,h,i]perylene | <0.05 | <0.4 | <3 | <2 |
| Coronene | <0.01 | <0.1 | <0.2 | <0.2 |

Source: Adapted from Biles et al., (1988)

## Table 3-10 Results of Carcinogenesis Studies of Middle Distillate Fuels and Blending Stocks Tested by Biles et al. (1988)

| Material | Median survival (Weeks)[a] | No. animals with tumors/ Total No. of animals[b] | Time to first tumor (Weeks)[c] | Median time to tumor (Weeks) |
|---|---|---|---|---|
| **1. Virgin heating oil blending base** | **75** | **7/50 (5c, 2p)[d]** | **58** | **110 (99-124)** |
| **2. Lightly refined paraffinic oil** | **84** | **9/50 (9c)[d]** | **54** | **115 (103-131)** |
| **3. Commercial No. 2 heating oil** | **80** | **6/50 (5c, 1p)[d]** | **94** | **124 (108-150)** |
| **4. Commercial No. 2 heating oil** | **71** | **6/40 (5c, 1p)[d]** | **69** | **113 (100-134)** |
| **5. Commercial No. 2 heating oil** | **85** | **11/50 (9c, 2p)[d]** | **64** | **114 (103-130)** |
| **6. Commercial No. 2 heating oil** | **84** | **5/50 (3c, 2p)[d]** | **47** | **127 (110-153)** |
| **7. Commercial No. 2 heating oil** | **85** | **9/50 (8c, 1p)[d]** | **64** | **116 (105-130)** |
| **8. Commercial No. 2 heating oil** | **85** | **10/50 (7c, 3p)[d]** | **51** | **114 (103-128)** |
| 9. Virgin heating oil blending base (sample 1) + cat. cracked middle distillate | 64 | 1/50 (1p) | 113 | - |
| 10. Light catalytic cycle oil 338° c (640°F) | 78 | 2/50 (1c, 1p) | 90 | 140 (113-201) |
| Controls | | | | |
| White mineral oil | 78 | 0/50 | | - |
| HCCO (1%) | 67[e] | 9/50 (9c)[d] | 61 | 106 (96-121) |
| White mineral oil | 71 | 0/50 | | - |
| HCCO (20%) | 36[e] | 50/50 (50c)[d] | 16 | 35 (33-36)[f] |
| White mineral oil | 86 | 0/50 | | |
| HCCO (3%) | 77[e] | 39/50 (39c)[d] | 37 | 65 (62-69)[f] |
| White mineral oil | 72 | 0/40 | | - |
| HCCO (25%) | 44[e] | 39/40 (39c)[d] | 17 | 30 (29-31)[f] |

Source: Adapted from Biles et al., 1988

[a]Median survival estimated by the product-limit method

[b]Tumor response given as the most advanced tumor type in the treatment area from a test group of 40 or 50 animals (C = carcinoma; p = papilloma). [c]Median time to tumor estimated by the Weibull method. The 95% confidence limits are given in parentheses. [d]Tumor yield significantly different from control ($P<0.05$) [e]Survival significantly different from control ($P<0.05$) [f]Median latency significantly different from control (Adapted from Biles et al., 1986). Note - the data presented in bold text represents data used to evaluate the carcinogenicity of diesel fuel No. 2.

The results of the study provided no evidence that the use of cracked blending stocks significantly increased the carcinogenic potential of any of the fuel samples. The cracking process creates PAHs, and the cracked liquids typically contain more aromatic carbon and substantially higher levels of PAH than do the corresponding straight-run distillates. The carcinogenic response among middle distillates did not appear to be significantly influenced by boiling point, composition, or source of blending stocks. The authors reported the tumorigenic activity of the middle distillates duels appears to be a generic response to materials in this boiling range and was essentially independent of composition or process history. Tumor responses did not appear to have been directly related to aromatic carbon content or to the presence of specific PAHs.

Gerhart et al. (1988) conducted lifetime dermal carcinogenesis studies along with initiation/promotion studies of petroleum streams in order to investigate the correlative carcinogenic predictiveness of the initiation/promotion bioassay with conventional lifetime bioassays. The materials tested were a solvent-extracted lubricant base oil, a furnace oil, and a dewaxed heavy paraffinic distillate. Furnace oil is similar to diesel fuel No. 2. Fifty male C3H/HeN mice received twice weekly dermal applications of 50 μL (44 mg/application) of material to the clipped backs for the lifetime of the animal. Sham control groups received no test article, but were handled in the same manner as the treated groups. The results of this study are given in Table 3-11. Mice treated with furnace oil showed a statistically significant increase in the incidence of histologically confirmed malignant skin tumors (i.e., squamous cell carcinomas and fibrosarcomas) when compared to controls. Also, squamous cell carcinoma of the untreated skin was detected in 2 of the 9 mice which had malignant application-site skin tumors. A considerable increase in variety and frequency of treatment related nonneoplastic lesions were observed in mice treated with furnace oil only. These mice displayed acanthosis (27/43), dermal fibrosis (17/43), necrosis (14/43), and inflammation (4/43) as well as hyperkeratosis, hyperplasia, hyperkeratosis, increased pigmentation and dermatitis.

## Table 3-11

### Dermal Tumorigenic Activity of Petroleum Streams

| Treatment | Tumor Incidence | | | |
|---|---|---|---|---|
| | Squamous cell carcinoma | Fibrosarcoma | Squamous Cell Ademona | Total |
| Sham control(s)[a] | — | — | — | 0/99 |
| Solvent-extracted lubricant base oil | — | — | 1/47 | 1/47 |
| **Furnace oil** | **6/43** | **3/43** | **1/43** | **9/43*** |
| Dewaxed heavy paraffinic distillate | 26/48 | 1/48 | — | 27/48* |

Souce: Adapted from Gerhart et al. (1988)

[a]A single concurrent sham control of 49 mice were evaluated for the furnace oil and another 50 mice were evaluated for the lubricating base oils. These incidences, therefore, reflect a combined total of 99 histologically evaluated application-site skins. Statistical analyses were conducted with concurrently evaluated study groups only

[c]No latency

*$P \leq 0.05$, relative to control groups

Note - the data presented in bold text represents data used to evaluate the carcinogenicity of diesel fuel No. 2.

API (1989) undertook a series of lifetime dermal carcinogenesis and chronic toxicity screening bioassays of refinery streams using C3H/HeJ mice. The purpose of the study was to determine the carcinogenic and chronic toxic potential of selected petroleum refinery streams when applied dermally 2 times per week over a lifetime. The refinery streams evaluated are listed below:

1. API #81-03 - Light catalytic cracked naphtha (petroleum) [64741-55-5] - Priority refinery stream #1.

2. API #81-07 - Hydrodesulfurized kerosene [64742-81-0] - Priority refinery stream #3.

3. API #81-08 - Sweetened Naphtha (petroleum) [64741-87-3] - Priority refinery stream #4.

4. API #81-09 - Hydrodesulfurized middle distillate (petroleum) [64742-80-9] Priority refinery stream #5.

5. API #81-10 - Hydrodesulfurized middle distillate (petroleum) [64742-80-9] Priority refinery stream #5.

6. API #81-13 - Vacuum residuum (petroleum) [64741-56-6] Priority refinery stream #7.

7. API #81-14 - Vacuum residuum (petroleum) [64741-56-6] Priority refinery stream #7.

8. API #81-15 - Catalytic cracked clarified oil (petroleum) [64741-62-4] - Priority refinery stream #10.

9. API #81-24 - API PS-6 (gasoline)

10. API #83-01, Straight run diesel (VPS #5 stripper) 82-3808 No. 2 Type Fuel Oils

11. API #83-02 - Straight run diesel (VPS #5 stripper) 82-3808 No. 2 Type Fuel Oils

12. API #83-03 - Straight run diesel (VPS #5 stripper) 82-3808 No. 2 Type Fuel Oils

Seventeen hundred C3H/HeJ male mice were used to test both the carcinogenic and chronic toxicity potential of the above 12 refinery streams. The dermal cancer study lasted for the lifetime of the mice while the chronic toxicity study lasted for 1 year. Test materials were applied dermally 2 times per week in a dose of 50 μL to the shaved intrascapular region of the back. At dosing, the test materials covered at least 1 $cm^2$. All materials were applied neat except for API number 81-13, 81-14, and 81-15 which required dilution in toluene to facilitate accurate dosing. There were 50 animals per treatment except for API #81-07 and 81-09 which had 49 and 47 mice in each group, respectively. Positive controls consisted of applying 0.01% and 0.05% benzo[a]pyrene dermally to groups of 50 animals. Negative controls consisted of clipped only and toluene treated animals 50 per group.

The results of this study are given in Table 3-12. The results presented for hydrodesulfurized kerosene, hydrodesulfurized middle distillate, and straight run diesel are the only materials relevant to evaluating the carcinogenicity of diesel fuel No. 2 (see bold text Table 3-12). The percentage of mice developing dermal neoplasms in these groups were as follows: (1) Hydrodesulfurized kerosene - 14%, (2) Hydrodesulfurized middle distillate - 48, and 54%; and (3) Straight run diesel - 14, 24, and 32%. These data indicate that hydrodesulfurized kerosene, hydrodesulfurized middle distillate, and straight run diesel caused a statistically significant increased incidence in neoplasms in male C3H/HeJ mice.

## Table 3-12

## Results of the API (1989) Dermal Carcinogenicity Study of Refinery Streams: Tumor Incidence Data

| Test Material | API # | Mice Developing Dermal Neoplasms (%)[a] | | | Mean Latency[b] |
|---|---|---|---|---|---|
| | | Benign | Malignant | Total[c] | |
| **Controls** | | | | | |
| None (group 1) | | 0 | 0 | 0 | --- |
| Toluene (neat; group 2) | | 0 | 8 | 8* | 111 |
| B[a]P (0.01%) | | 8 | 56 | 64*+ | 86 |
| B[a]P (0.05%) | | 0 | 98 | 98*+ | |
| **Refinery Stream** | | | | | |
| Light catalytic cracked naphtha | 81-03 | 4 | 10 | 14* | 118 |
| **Hydrodesulfurized kerosene** | **81-07** | **2** | **47** | **49*+** | **76** |
| Sweetened naphtha | 81-08 | 4 | 2 | 6h | 113 |
| **Hydrodesulfurized middle distillate** | **81-09** | **4** | **44** | **48*+** | **73** |
| **Hydrodesulfurized middle distillate** | **81-10** | **0** | **54** | **54*+** | **72** |
| Vacuum residuum | 81-13 | 4 | 6 | 10*h | 113 |
| Vacuum residuum | 81-14 | 2 | 2 | 4h | 120 |
| Catalytic cracked clarified oil (10%) | 81-15 | 2 | 96 | 98*+ | 22 |
| Catalytic cracked clarified oil (1%) | 81-15 | 2 | 88 | 90*+ | 72 |
| Catalytic cracked clarified oil (0.1%) | 81-15 | 4 | 0 | 4h | 113 |
| API PS-6 (gasoline) | 81-24 | 0 | 4 | 4h | 123 |
| **Straight run diesel** | **83-01** | **2** | **12** | **14*** | **86** |
| **Straight run diesel** | **83-02** | **0** | **24** | **24*+** | **80** |
| **Straight run diesel** | **83-03** | **4** | **28** | **32*+** | **70** |

Source: Apdapted from API (1989)

[a]Histologically confirmed, test material site, dermal neoplasms

[b]Latency = time, in weeks, from initiation of dosing to appearance of the median tumor plus any mice that died from tumor before that time, or, when mean latency is over 60 weeks

[c]Total percent of mice developing histologically confirmed dermal neoplasms was evaluated by Chi square

*Significantly greater than Group 1, untreated controls ($P<0.05$)

+Significantly greater than Group 2, toluene controls ($P<0.05$)

Note - the data presented in bold text represents data used to evaluate the carcinogenicity of diesel fuel No. 2.

### 3.2.4 Diesel Fuels Potential Mechanism of Carcinogenesis

**Introduction of Terms: Initiators, Genotoxic Carcinogens, Promotors, Epigenetic Carcinogens**

The pioneering studies conducted by Berenblum and co-workers (Berenblum, 1941, 1974; Berenblum and Shubik, 1947), and by Rous and co-workers (Friedwald and Rous, 1944; Rous and Kidd, 1941) were the first to establish that carcinogenesis may involve a distinct number of qualitatively different stages. Through each study of the processes associated with skin neoplasia, it was found that a dose of a genotoxic carcinogen by itself was insufficient for the induction of neoplasms. However, when it is followed by administration of a second stimulus which is non-carcinogenic, tumors result. The stimulus alone was incapable of inducing skin tumors. Because the reversal of the temporal sequence failed to induce tumors, this led Friedwald and Rous (1944) to coin the terms "initiation" and "promotion", respectively, for the initial carcinogen-induced lesion and the second non-carcinogenic stimulus. It is now generally accepted that chemical-induced carcinogenesis occurs in 2 or more sequential stages. Implicit in multistage carcinogenesis are characteristics distinguishing each stage, ordering of the stages relative to each other in time and sequence, and the selective action of carcinogenic chemicals at one or more of the distinguishable stages (Pitot et al., 1987). The first stage is an initiation stage leading to a permanent genetic alteration (mutation) in the cell. The second stage, which may be a complex set of pathways, is thought to be a promotional stage in which physiological and biochemical changes facilitate the growth and expression of the initiated cell. By separating cancer induction into two distinct stages one is able to distinguish at least two distinct classes of chemical carcinogens which are operationally defined as genotoxic and epigenetic carcinogens (Weisburger and Williams, 1980). Genotoxic carcinogens are those thought to act by directly altering DNA (initiators). Genotoxicity then is largely associated with initiation and implies a modification of DNA which results in point mutations, deletions, rearrangement, and permanently altered gene expression. The features of genotoxic carcinogens include:

- occasionally active with a single exposure,

- frequently active at low (subchronic, subacute) doses,
- can be active transplacentally, and carcinogenicity often increases in neonates,
- can have additive or synergistic effects with one another, and
- subcarcinogenic effects can be made manifested by subsequent promoting activity (Williams, 1987).

Another important aspect of genotoxic carcinogens is that with increasing dose, the incidence and multiplicity of tumors increases, and the expression time for tumors to appear decreases.

Epigenetic carcinogens (promoters) are those chemicals whose mechanism does not involve direct interaction with DNA. Although one must be cautious about making generalizations concerning epigenetic carcinogens (because they seem to operate through several different mechanisms), one of the more noteworthy features of epigenetic carcinogens is their lack of interaction with DNA. The induction of low to moderate numbers of neoplasms after a lengthy expression time, their reversibility after cessation of the stimulus, and the presence of an apparent threshold. Another important aspect of epigenetic carcinogens is that the tumors produced are typically benign, occur only in specific tissues, and in certain species of laboratory animals which generally have a fairly high background spontaneous tumor incidence in the same organ that the chemical affects (e.g., liver tumors) (Williams 1987). In fact, many chemical carcinogens that are classified as epigenetic may promote cancer by increasing cell division such that tumorigenesis is likely to occur in previously initiated cells (Weisburger and Williams, 1981a;b).

Complete carcinogens by definition are able to both initiate and promote the growth of tumors. Hence, complete carcinogens can be both initiators and promotors, although not necessarily at the same dose. The most common hypothesis is that initiation involves covalent binding and/or structural changes in the genome (Harper and Morris, 1984; Pitot et al., 1981; Pitot and Sirica, 1980). At higher or chronically administered doses of the same chemical, tumors develop either as a result of a second genotoxic lesion or some separate promotional effect. An example of a complete carcinogen are some polycyclic aromatic hydrocarbons such as benzo[a]pyrene.

## Diesel Fuels Act Via A Promotional/Epigenetic Mechanism

The previous section reviewed several studies examining the dermal tumorigenic potential of diesel fuel and petroleum derived middle distillates. In general, the tumorigenic responses to these middle distillates can be characterized by low tumor frequencies and long median latencies which often exceeded 2 years. Other common responses observed in these studies were mild to severe chronic skin irritation, hyperplasia, and in some instances epidermal degeneration and necrosis. Several authors have attempted to explain the dermal carcinogenic potential of petroleum hydrocarbons on the basis of their polycyclic aromatic hydrocarbon (PAH) content (Bingham et al. 1980; Hermann et al., 1980; King, 1982; Witschi et al., 1987; Roy et al., 1988). However, the majority of PAHs with known carcinogenic potential distill at temperatures above that required to produce diesel fuel and middle distillates. Consequently the concentrations of these carcinogenic PAHs (e.g., benzo[a]pyrene, dimethylbenzanthracene, etc.) in middle distillates are normally very low. Therefore, the finding that diesel fuel and middle distillates were capable of inducing tumors was unexpected and cannot be explained entirely on the basis of their respective PAH content. In fact, in the comprehensive dermal tumorigenicity studies of Biles et al. (1988), they found no association between tumorigenic activity and aromatic content and more specifically no association with between PAH content and tumor incidence. Apparently the tumorigenic responses were not PAH dependent. The authors explained the tumorigenic effects of middle distillates by one or more of the following hypothesis:

1. The tumor responses could have been related to the presence of PAH and other carcinogenic species.

2. The middle distillates could have contained both initiating and promoting agents, and the tumor responses would then have reflected an interaction between these components. The promotional effect could have been a specific toxic response or a non-specific effect related to a chronic hyperplastic state.

3. The tumor responses could have been a secondary response to chronic skin irritation or injury and largely unrelated to the composition of the test material (i.e., recurrent cell tissue injury theory of carcinogenesis - chemicals that cause cell death which

leads to compensatory cell proliferation (hyperplasia) and tumor induction).

They indicated that the first hypothesis was unlikely because the PAH levels observed in their study and in the King (1982) study were below levels which could be detected by dermal cancer bioassays. The second hypothesis is possible based on the finding that middle distillates boil at a range that contains promotors or co-carcinogens such as $C_{10}$-$C_{20}$ alkanes and alkylated benzenes (Horton et al., 1957; Horton and Christiansen, 1974; Sice 1976; Van Duuren and Goldschmidt, 1976). These compounds may promote the initiating effect of of some of the carcinogenic PAHs present in middle distillates even though the carcinogenic PAHs are present at low levels.

The third hypothesis and most probable explanation for the tumorigenic effects of diesel fuel and middle distillates is based on the toxic effects associated with dermal application. Diesel fuel can be highly irritating to the skin, and skin irritation has been shown to be a promotor of tumors in previously initiated mouse skin (Argyris, 1983; 1985; Argyris and Slaga, 1981; Hemmings and Boutwell, 1970; Setela et al., 1959; Slaga et al., 1975). However, the authors in this study reported no direct relationship between the level of skin damage and tumorigenic response and in fact the study groups exhibiting the greatest degree of epidermal degeneration and necrosis produced the lowest tumor yields. This result is consistent with the finding that frank necrosis actually reduced tumor yield. At first glance, these findings would not support the skin irritation mechanism for tumor induction. However, analyses of the tumor incidence and hyperplasia data indicate that the highest tumor incidence was associated with those animals which developed the most severe hyperplasia. These data thus support the recurrent tissue injury mechanism as a promotor of tumorigenesis except when doses are sufficient to cause frank necrosis. This explanation is logical since cell death would prevent a transformed cell from being expressed. The site where tumors develop also supports this view as the carcinogenic activity of these compounds is confined to the site of application. The authors reported that it is likely that the irritating properties of the test samples contributed to the induction of tumors, however, the actual mechanism of tumor formation is unknown.

In a follow-up study, McKee and co-workers (1989) examined the tumorigenic mechanism of middle distillates using a lightly refined paraffinic oil (LRPO) as an example. Whole LRPO and aromatic and saturated subfractions were tested for mutagenic activity in the *Salmonella* assay and for carcinogenic initiating and promoting activities using classical two-stage mouse epidermal carcinogenesis bioassays. The results indicated there was no evidence that any of the samples (whole LRPO and aromatic and saturated subfractions) were mutagenic in *Salmonella* or carcinogenic initiating agents in mouse skin. Thus, there was no support for the first hypothesis (described above) that the complete tumorigenic activity of LRPO was related to the presence of low levels of PAHs nor to an interaction between initiating and promoting constituents (hypothesis #2). There was evidence that LRPO was a promotor for dimethylbenzanthracene (DMBA) - initiated mouse skin, but LRPO was a weak promotor as compared to the positive control 12-*O*-tetradecanoyl-phorbol-13-acetate (TPA). There was also evidence that repeated application of LRPO produced chronic irritation and hyperplasia which was suggested to have been responsible for the promotional effects.

The study by Gerhart et al., (1988) provides further support that diesel fuels are promotors. These authors conducted initiation/promotion (I/P) bioassays to assess the I/P potential of several petroleum streams including furnace oil (similar in composition to Diesel Fuel No. 2). During a 28-week initiation bioassay, groups of 30 male CD-1 mice were first treated with furnace oil or 50 μL of acetone, rested for 2 weeks, then treated twice per week for 25 weeks with 50 μL phorbol-12-myristate-13-acetate (PMA; a classical tumor promotor). Furnace oil is not a tumor initiator since it failed to induce skin tumors. In the promotional phase of the I/P bioassay groups of 30 male CD-1 mice were treated once with 50 μL of either dimethylbenzanthracene (DMBA) or acetone, rested for 2 weeks, and then treated twice per week with furnace oil for the remaining 25 weeks. The results indicated that furnace oil treatment produced significantly higher incidences of carcinomas and papillomas in DMBA-initiated mice relative to their acetone-initiated controls. Together, these I/P bioassay data indicate that furnace oil is a promotor only (not a complete carcinogen). Therefore, furnace oil induces tumors by an epigenetic mechanism.

In summary, the data presented above suggests that diesel fuels produce tumors by a promotional process. The promoting effects appear to be a result of repeated skin irritation and hyperplasia. Therefore, the biological activity of diesel fuel is due to an epigenetic mechanism related to their skin irritation properties. The negative results reported for most short term genotoxicity tests also support this view. The practical significance for being able to classify carcinogens into either one of these categories is important for purposes of quantitative risk assessment since the risk of cancer from low dose exposure to epigenetic carcinogens is presumed to be much lower than the risk from exposure to a carcinogen which acts by a genotoxic mechanism. A key concept underlying this distinction is that a threshold should exist for epigenetic carcinogens, and doses below this threshold should not induce cancer in anyone regardless of the number of persons exposed. For non-cancer toxicity, or threshold situations, models for extrapolating to low or no risk are also different than the models used for non-threshold carcinogens.

### 3.3 Hazard Evaluation: Analyses of the Dose-Response Relationships for Diesel Fuel

The cancer bioassays that were conducted by Blackburn et al. (1984, 1986) were not included for several reasons. Most importantly, details were not given concerning the time of killing, and the survival in the treated and control mice. The authors also did not report any statistical analyses of the tumor data. Furthermore, it is not clear how long the test materials were administered. Apparently, the test materials were administered for a relatively short period of time of 80 weeks, or in some cases for shorter durations such as when a papilloma larger than 1 $mm^3$ appeared. Therefore, the Blackburn studies were considered inappropriate for low-dose extrapolation of cancer risk.

All the remaining studies concerning the dermal carcinogenic potential of diesel fuel and its constituents were selected for estimating human cancer risks at low doses (Lewis et al. 1984; NTP 1986; Witschi et al., 1987; Biles et al., 1988; Gerhart et al., 1988; and API, 1989). While arguments can be made for selecting certain of these studies over others (e.g., the Witschi et al., study

provides dose-response data but the API and Biles et al. studies provide data on more types of diesel fuels), the approach taken in this report was to model the cancer risks from all the studies. We selected the remaining studies for several reasons: (1) The bioassays tested the tumorigenic potential of a wide variety of diesel fuels and middle distillates which would likely encompass the range of diesel fuels possibly encountered in the soil at the site. The cancer data from a larger number of studies also provides greater confidence in estimating human cancer risks from diesel fuels at low doses. This is true especially in light of the fact that each of the different diesel fuels (middle distillates) studied gave essentially the same results. (2) Some of the bioassays tested the tumorigenic potential of several different diesel fuel subfractions that may be present in the soil environment after "weathering". Thus, these studies provide data for possible increased or decreased toxicity of the parent material caused by "weathering", and (3) precludes any bias concerning the selection of certain studies over others.

In summary, 6 different cancer studies conducted on 20 samples of diesel fuel (and its constituents) were selected for estimating human cancer risks from low dose exposure. The tumor incidence data and other pertinent quantitative information on these studies is presented in Table 3-13. A lifespan of 104 weeks was assumed. The tumor incidence data were combined for studies which used both male and female mice. Because no one study could be selected as "most appropriate" for human cancer risk estimates at low doses for the reasons mentioned above, all data sets were used to generate separate estimates of cancer risk. A geometric mean cancer risk will be calculated from these results.

## Table 3-13 Mouse Dermal Cancer Bioassay Data Used to Estimate Unit Cancer Risks from Exposure to Diesel Fuel

| Material | Dose | Responders/ Tested | Other Data | Reference |
|---|---|---|---|---|
| Crude C Distillate (350-550° F) | 0 | 1/50 | Average bw: 0.030 kg (assumed) | Lewis et al., 1986 |
| | 44 mg | 13/43 | Exposure: 2 x week for 18 months to a lifetime | |
| Crude D Distillate (350-550° F) | 44 mg | 4/26 | Experiment: lifetime | |
| Crude C Saturate (350-550° F) | 44 mg | 29/41 | | |
| Crude D Saturate (350-550° F) | 44 mg | 26/44 | | |
| Marine Diesel Fuel | 0 | 1/100[1] | Exposure: 5 x week for 104 weeks | NTP, 1986 |
| | 250 mg/ kg/day | 3/94[1] | Experiment: 104 weeks | |
| | 500 mg/ kg/day | 5/98[1] | | |
| API No. 2 Fuel Oil | 0 | 0/100[1] | Average bw: 0.030 kg (assumed) | Witschi et al., 1987 |
| | 11 mg | 1/50[1] | Exposure: 3 x week for 98 weeks | |
| | 22 mg | 6/50[1] | Experiment: 98 weeks | |
| | 44 mg | 8/50[1] | | |
| Virgin heating oil blending base | 0 | 0/190 | Average bw: 0.030 kg (assumed) | Biles et al., 1988 |
| | 22 mg | 7/50 | Exposure: 3 x week for a lifetime | |
| Lightly refined paraffinic oil | 22 mg | 9/50 | Experiment: lifetime | |
| Commercial No. 2 heating oil | 22 mg | 6/50 | | |
| Commercial No. 2 heating oil | 22 mg | 6/40 | | |
| Commercial No. 2 heating oil | 22 mg | 11/50 | | |
| Commercial No. 2 heating oil | 22 mg | 5/50 | | |
| Commercial No. 2 heating oil | 22 mg | 9/50 | | |
| Commercial No. 2 heating oil | 22 mg | 10/50 | | |
| Furnace oil | 0 | 0/99 | Average bw: 0.030 kg (assumed) | Gerhart et al., 1988 |
| | 44 mg | 9/43 | Exposure: 2 x week for a lifetime | |
| | | | Experiment: lifetime | |
| Hydrodesulfurized kerosene | 0 | 0/50 | Average bw: 0.030 kg (assumed) | API, 1989 |
| | 44 mg | 23/47 | Exposure: 3 x week for a lifetime | |
| Hydrodesulfurized middle distillate | 44 mg | 24/50 | Experiment: lifetime | |
| Hydrodesulfurized middle distillate | 44 mg | 27/50 | | |
| Straight run diesel | 44 mg | 7/50 | | |
| Straight run diesel | 44 mg | 12/50 | | |
| Straight run diesel | 44 mg | 16/50 | | |

[1] male and female tumor incidence were combined

### 3.4 Description of the Low-dose Animal Extrapolation Model

The linearized multistage model, through the computer program Toxrisk (Crump, 1988), was applied to the data from these bioassays. This model is the preferred model of the EPA Carcinogen Assessment Group for risk extrapolation from animals to humans. The model assumes that cancer is a multistage process for which a series of events are necessary to transform a normal cell into a malignant one. The multistage model estimates the upper limit of carcinogenic potency of a substance by mathematical extrapolation of tumor incidence observed at doses generally much higher than human exposures to predict the upper-limit tumor incidence at the low levels of exposure usually experienced by people.

The output of the linearized multistage model important for quantitative risk assessment is q1 and q1* where q1 is the slope of the dose response curve or the maximum likelihood estimate (MLE) of cancer potency, and q1* is the upper bound (at low doses) of the potency of the chemical in inducing cancer. Thus, the risk estimates derived using the upper 95% confidence limit from the linearized multistage model are conservative and represent the upper-limit of risk. The upper confidence limit also illustrates how well the data fit the model at high dose-levels, but cannot determine how well the model reflects the true low-dose risks. Whenever the multistage model does not fit the data sufficiently well, the data point at the highest dose is deleted and the model is refitted to the rest of the data.

As applied to diesel fuel, use of the non-theshold linearized multi-stage model is a very conservative approach. It is conservative because the non-threshold model assumes that there is always some cancer risk attendant with exposure to diesel fuel no matter how small the dose. However, mechanistic data indicate that if diesel fuel is carcinogenic in man, it is an epigenetic carcinogen, and thus, has a threshold below which diesel fuel should not induce cancer in anyone.

### 3.5 Selection of Tumor Incidence Data

The grouping of lesions for evaluation should be based on commonality of histogenic origin. Therefore, sarcomas should not be combined with carcinomas. However, many pathologists feel that certain benign tumors (e.g., skin papillomas) should be combined with malignant tumors. While arguments can be given for and against combining benign and malignant tumors, we have combined benign and malignant tumors in this risk assessment in order to be consistent with the EPA's carcinogenic assessment group (CAG) policy. The set of data (i.e., dose and tumor incidence) used in the model should include at least one test dose level that is statistically significantly higher than the control or at least show a significant trend with respect to dose level.

### 3.6 Cancer Risk Estimates for Human Exposures

The human risk from the data given in Table 3-13 is calculated by multiplying the animal risk by several factors to adjust for experiment duration (if partial lifetime), and species differences in body weight. The risk estimate from the low-dose extrapolation is based on the average daily intake which is expressed as the time-weighted-average (TWA) daily dose over the duration of the experiment. No adjustment for experiment length was necessary since all the studies selected for quantitative risk estimation were essentially conducted for a lifetime. Often times an adjustment is necessary for studies that were conducted for a partial lifetime to allow for positive responses that would have occurred had sufficient time been allowed for the tumors to develop.

The adjustment for body weight from animal to humans uses the animals body weight divided by the average body weight of a human (70 kg). The assumed mouse body weight is 0.030 kg; therefore, the body weight scaling factor becomes 0.030/70 or 4.286E-4. The scaling factor is also multiplied by the appropriate animal risk values. Hence, the cancer risk estimates based on human equivalent doses is given in Table 3-14. The geometric mean of these studies was then taken to estimate the human cancer risk for exposure to diesel fuel. Each human risk estimate obtained

## Table 3-14

## Human Cancer Slope Factors for Exposure to Diesel Fuel

| Study | Material | MLE $(mg/kg/day)^{-1}$ | $q1^*$ $(mg/kg/day)^{-1}$ |
|---|---|---|---|
| Lewis et al. 1986 | Crude C Distillate (350-550° F) | 7.49E-04 | 1.12E-03 |
| | Crude D Distillate (350-550° F) | 3.08E-04 | 6.86E-04 |
| | Crude C Saturate (350-550° F) | 3.81E-03 | 5.23E-03 |
| | Crude D Saturate (350-550° F) | 1.83E-03 | 2.54E-03 |
| NTP, 1986 | Marine Diesel Fuel | 1.20E-04 | 2.39E-04 |
| Witschi et al. 1987 | API No. 2 Fuel Oil | 2.71E-04 | 4.34E-04 |
| Biles et al. 1988 | Virgin heating oil blending base | 4.79E-04 | 8.44E-04 |
| | Lightly refined paraffinic oil | 6.31E-04 | 1.04E-03 |
| | Commercial No. 2 heating oil | 4.07E-04 | 7.45E-04 |
| | Commercial No. 2 heating oil | 5.17E-04 | 9.47E-04 |
| | Commercial No. 2 heating oil | 7.90E-04 | 1.25E-03 |
| | Commercial No. 2 heating oil | 3.35E-04 | 6.46E-04 |
| | Commercial No. 2 heating oil | 6.31E-04 | 1.04E-03 |
| | Commercial No. 2 heating oil | 7.10E-04 | 1.15E-03 |
| Gerhart et al 1988 | Furnace oil | 5.60E-04 | 9.28E-04 |
| API, 1989 | Hydrodesulfurized kerosene | 1.60E-03 | 2.23E-03 |
| | Hydrodesulfurized middle distillate | 1.56E-03 | 2.16E-03 |
| | Hydrodesulfurized middle distillate | 1.85E-03 | 2.53E-03 |
| | Straight run diesel | 3.60E-04 | 6.33E-04 |
| | Straight run diesel | 6.55E-04 | 1.02E-03 |
| | Straight run diesel | 9.20E-04 | 1.36E-03 |
| | **Geometric Mean** | **6.70E-04** | **1.09E-03** |

MLE = maximum likelihood estimate
$q1^*$ is the upper 95% confidence limit for MLE

by fitting a low-dose extrapolation model to the animal data is presented as the maximum likelihood estimate (MLE). The MLE is the slope of the dose-response curve or cancer potency, and when possible as the upper 95% confidence limit ($q1^*$) or the upper bound 95% confidence limit of the potency of the chemical to induce cancer.

## 9.0 REFERENCES


Agency for Toxic Substances and Disease Registry (ATSDR), 1990. Toxicological Profile for Polycyclic Aromatic Hydrocarbons, February 16, 1990.

Alderson, MR and L Rushton. 1982. mortality patterns in eight UK oil refineries. Ann. NY Acad. Sci. 381:139-145.

Alderson, MR and NS Rattan. 1980. Mortality of workers in an isopropyl alcohol plant and two MEK dewaxing plants. Br. J. Ind. Med. 37:85-89.

API (American Petroleum Institute). 1989. Lifetime dermal carcinogenesis/ chronic toxicity screening bioassay of refinery streams in C3H/HeJ mice. Final report Volume 1 Lifetime Carcinogenicity Evaluation. HESD Publication No. 36-31364.

API. 1975. Laboratory studies on the effects of oil on marine organisms: An overview. Prepared by: Dr. JW Anderson, Center for Marine Resources, Texas A&M University, College Station, Texas.

API. 1978. Mutagenicity evaluation of diesel fuel, final report. Prepared by: Litton Bionetics, Inc., Kensington, Maryland.

API. 1979. Teratology study in rats: Diesel fuel. Prepared by: Litton Bionetics, Inc., Kensington, Maryland.

API. 1980. Acute toxicity studies: Diesel fuel (market place sample). Prepared by: Elars Bioresearch Laboratories, Inc., Fort Collins, Colorado.

API. 1980. Mutagenicity evaluation of diesel fuel in the mouse dominant lethal assay. Prepared by: Litton Bionetics, Inc., Kensington, Maryland.

API. 1989. Lifetime dermal carcinogenesis/chronic toxicity screening bioassay of refinery streams in $C_3H/HeJ$ mice, final report, Vol. 1. Prepared by: Primate Research Institute, Holloman AFB, New Mexico.

API. Effects of oil on aquatic organisms: A review of selected literature. Prepared by: SL Burks, Oklahoma State University, Stillwater, Oklahoma.

Argyris, TS. 1983. An analysis of the epidermal hyperplasia produced by acetic acid, a weak tumor promotor, in the skin of female mice initiated with dimethylbenzanthracene. J. Invest. Dermat., 80:430.

Argyris, TS. 1985. Promotion of epidermal carcinogenesis by repeated damage to mouse skin. Am. J. Ind. Med., 8:329.

Argyris, TS. and TJ. Slaga. 1981. Promotion of carcinomas by repeated abrasion in initiated skin of mice. Cancer Res., 41:5193.

ATSDR (Agency for Toxic Substances and Disease Registry). 1990. Health assessment for Imperial Oil Co., Inc./Champion Chemicals. Prepared by: Environmental Health Service, Marlboro Township, New Jersey.

Bailar, JC, ECC Crouch, S Rashid, and D Spiegelman. 1988. One-hit models of carcinogenesis: Conservative or not? Risk Anal. 8:485-497.

Bell, C.E. 1990. State-by-state summary of cleanup standards: A review of the new wave of state-level rules. Soils, December 1990.

Biles, RW, SC Lewis and RA Scala. 1985. Skin carcinogenic activity of middle distillate petroleum materials. The Toxicologist 5(1):18.

Biles, RW., RH. McKee, SC. Lewis, RA. Scala, and LR. DePass. 1988. Dermal carcinogenic activity of petroleum-derived middle distillate fuel. Toxicology, 53:301-314.

Bingham, E and W Barkley. 1979. Bioassay of complex mixtures derived from fossil fuels. Environ. Health Persp. 30:157-163.

Bingham, E, R Trosset and D Warshawsky. 1980. Carcinogenic potential of petroleum hydrocarbons. A critical review of literature. J. Environ. Pathol. Toxicol. 3:483-563.

Blackburn, GR, RA Deitch, CA Schreiner, MA Mehlman, and CR Mackerer. 1984. Estimation of the dermal carcinogenic activity of petroleum fractions using a modified Ames assay. Cell Biol. Toxicol. 1:67-80.

Blackburn, GR, RA Deitch, CA Screiner, and CR Mackerer. 1986. Predicting carcinogenicity of petroleum distillation fractions using a modified *Salmonella* mutagenicity assay. Cell. Biol. Toxicol. 2:63-84.

Callahan, JF, CL Crouse, GE Affleck, EG Cummings, RL Farrand, RW Dorsey, MS Ghumman, RD Armstrong, WC Starke, RJ Pellerin, DC Burnett, DH Heitkamp, C Lilly, JJ Feeney, M Rausa, EH Kandel, JD Bergmann and JT Weimer. 1986. The subchronic inhalation toxicity of DF2 (diesel fuel) used in vehicle engine exhaust smoke systems (VEESS). Chemical Research & Development Center, Aberdeen Proving Ground, Maryland. AD -A188 841.

Callahan, JF, CL Crouse, GE Affleck, RL Farrand, RW Dorsey, MS Ghumman, RJ Pellerin, DH Heitkamp, C Lilly, JJ Feeney and JT Weimer. 1983. The acute inhalation toxicity of diesel fuels ($DF_2$ and $DF_1$) used in vehicle engine

exhaust smoke systems (VEESS). Chemical Research & Development Center, Aberdeen Proving Ground, Maryland. AD B080 437.

Callahan, JF, CL Crouse, GE Affleck, RL Farrand, RW Dorsey, MS Ghumman, RJ Pellerin, DH Heitkamp, C Lilly, JJ Feeney and JT Weimer. 1983. The acute inhalation toxicity of diesel fuels, MIL-F-46162-referee grade I (arctic) and MIL-F-46162 referee grade II (regular), used in vehicle engine exhaust smoke systems (VEES). Chemical Research & Development Center, Aberdeen Proving Ground, Maryland. AD-B082 020.

Carpenter, CP, ER Kinkead, DL Geary, Jr., LJ Sullivan and JM King. 1975. Petroleum hydrocarbon toxicity studies. I. Methodology. Toxicol. & Appl. Pharmacol. 32:246-262.

Carpenter, CP, ER Kinkead, DL Geary, Jr., LJ Sullivan and JM King. 1975. Petroleum hydrocarbon toxicity studies. VI. Animal and human responses to vapors of "60 Solvent." Toxicol. Appl. Pharmacol. 34:374-394.

Carpenter, CP, ER Kinkead, DL Geary, Jr., RC Meyers, DJ Nachreiner, LJ Sullivan and JM King. 1976. Petroleum hydrocarbon toxicity studies. IX. Animal and human responses to vapors of "80 Thinner." Toxicol. Appl. Pharmacol. 36:409-425.

Chu, I, DC Villeneuve, M Cote, V Secours, R Otson and VE Valli. 1988. Dermal toxicity of a high-boiling (bp 250-450 degrees C) coal liquefaction product in the rat--II. J. Toxicol. Environ. Health 25:509-525.

Chu, I, W Rinehart, G Hoffman, DC Villeneuve, R Otson and VE Valli. 1989. Subacute inhalation toxicity of a medium-boiling coal liquefaction product (154-378C) in the rat: part III. J. Toxicol. Environ. Health 28:195-204.

Cohen, A.F. and B.L. Cohen. 1980. Protection from being indoors against inhalation of suspended particulate matter of outdoor origin. Atmospheric Environment 14:183-184.

Conaway, CC, CA Schreiner and ST Cragg. 1984. Mutagenicity evaluation of petroleum hydrocarbons. In: Applied Toxicology of Petroleum Hydrocarbons, HN MacFarland, CE Holdsworth, JA MacGregor, RW Call and ML Lane (eds.), Princeton Scientific Publishers, Inc., Princeton, New Jersey, pp 89-107.

Coomes, RM. and KA. Hazer, 1984. Statistical analyses of crude oil and shale oil carcinogenic test data. In: Advances In Modern Environmental Toxicology, Chapter 13, p. 167-185. MA. Mehlman Eds.

Cragg, ST, CC Conaway and JA MacGregor. 1985. Lack of concordance of the Salmonella/microsome assay with the mouse dermal carcinogenesis bioassay for complex petroleum hydrocarbon mixtures. Fundam. Appl. Toxicol. 5:382-390.

Crump, K.S. (ICF Clement). 1987. Toxicology risk assessment program. Version 1.0 Clement Associates Incorporated.

Dalbey, W, M Henry, R Holmberg, J Moneyhun, R Schmoyer and S Lock. 1987. Role of exposure parameters in toxicity of aerosolized diesel fuel in the rat. J. Appl. Toxicol. 7:265-276.

Dalbey, W, S Lock and R Schmoyer. 1982. Inhalation toxicology of diesel fuel obscurant aerosol in Sprague-Dawley rats, final report, phase 2: Repeated exposures. Prepared by: Oak Ridge National Laboratory, Oak Ridge, Tennessee. AD-A142-540.

Decoufle, P, WA Blatt, and A Blair. 1983. Mortality among chemical workers exposed to benzene and other agents. Environ. Res. 30:16-25.

Divine, BJ and V Barron. 1986. Texaco mortality study. II. Patters of mortality among white males by specific job groups. Am. J. Ind. Med. 10:371-381.

Divine, BJ, V Barron, and SD Kaplan. 1985. Texaco mortality study. I. Mortality among refinery, petrochemical, and research workers. JOM 27:445-447.

Doak, S, V Brown, P Hunt, J Smith and F Roe. 1983. The carcinogenic potential of twelve refined mineral oils following long term topical application. Brit. J. Cancer 48:429-436.

Dutcher, J, A Li and R McClellan. 1986. Mutagenicity of used crankcase oils from diesel and spark ignition automobiles. Environ. Res. 40:155-163.

Easley, JR, JM Holland, LC Gipson and MJ Whitaker. 1982. Renal toxicity of middle distillates of shale oil and petroleum in mice. Toxicol. Appl. Pharmacol. 65:84-91.

Edwards, WC. 1989. Toxicology of oil field wastes. Hazards to livestock associated with the petroleum industry. Vet. Clin. North Am. Food Anim. Pract. 5:363-374.

Freeman, JJ, RH McKee, RD Phillips, RT Plutnick, RA Scala and LJ Ackerman. 1990. A 90-day toxicity study of the effects of petroleum middle distillates on the skin of $C_3H$ mice. Toxicol. Ind. Health 6:475-491.

GRI (Gas Research Institute), 1988. Management of manufactured gas plant sites. GRI-87/0263.3

Gaworski, CL, JD MacEwen, EH Vernot, CC Haun, HF Leahy and A Hall. 1985. Evaluation of 90-day inhalation toxicity of petroleum and oil shale diesel fuel marine (DFM). AAMRL, Toxic Hazards Division, Dayton, Ohio. AD-A202 722.

Gerhart, JM, CA Halder, NS Hatoum, TM Warne and PJ Garvin. 1985. Tumor initiation and promotion effects of petroleum fractions in mouse skin. The Toxicologist 5(1):18.

Gerhart, JM, NS Hatoum, CA Halder, TM Warne and SL Schmitt. 1988. Tumor initiation and promotion effects of petroleum streams in mouse skin. Fundam. Appl. Toxicol. 11:76-90.

Getmanets, IY. 1967. Comparative evaluation of the carcinogenic properties of cracking residues of high- and low-paraffin petroleum (Russ.). Gig. Tr. Prof. Zabol., 11:53-55.

Gilliom, R.J., and D.R. Helsel. 1986. Estimation of distributional parameters for censored trance level water quality data: I. Estimation techniques: Water Resources Research, Vol. 22, No. 2, p. 135-146.

Gradiski, D, J Vinot, D Zissu, J Limasset, M Lafontaine and A Blachere. 1983. The carcinogenic effect of a series of petroleum-derived oils on the skin of mice. Environ. Res. 32:258-268.

Griest, W.H., CE. Higgins, and MR. Guerin. 1985. Comparative chemical characterization of shale oil and petroleum derived diesel fuels. Report by the Analytical Chemistry Division, Oak Ridge National Laboratory DE86003310.

Griest, WH, CE Higgins and MR Guerin. 1986. Comparative chemical characterization of shale oil- and petroleum-derived diesel fuels. Prepared by: Analytical Chemistry Division, Oak Ridge, Tennessee. DE86 003310.

Grimmer, G, G Detbaum, G Detbaum, J Misfield, H Brune and R Deutch-Wenzel. 1982. Quantification of the carcinogenic effect of polynuclear aromatic hydrocarbons in used engine oils by topical application onto the skin of mice. Int. Arc. Occup. Envir. Health 50:95-100.

Haas, C.N., and P.A. Scheff. 1990. Estimation of averages in truncated samples: Environmental Science and Technology. Vol. 24, No. 6, p. 912-919.

Halder, C, T Warne, R Little and P Garvin. 1984. Carcinogenicity of petroleum lubricating oil distillates: Effects of solvent refining, hydroprocessing and blending. Amer. J. Ind. Med. 5:265-274.

Haley, MV and WG Landis. 1989. Toxicity of Jet A to selected aquatic organisms. Chemical Research, Development & Engineering Center, Aberdeen Proving Ground, Maryland. AD-A208 243.

Hanis, NM, KM Stavraky, and JL Fowler. 1979. Cancer mortality in oil refinery workers. JOM 21:167-174.

Hanis, NM, LG Shallenberger, DL Donaleski, and EA Sales. 1985. A retrospective mortality study of workers in three major US refineries and chemical plants. Part I: Comparisons with US population. JOM 27:283-292.

Hanis, NM, TM Holmes, LG Shallenberger, and KE Jones. 1982. Epidemiologic study of refinery and chemical plant workers. J. Occup. Med. 24:203-212.

Hawkes, JW, EH Gruger, Jr. and OP Olson. 1980. Effects of petroleum hydrocarbons and chlorinated biphenyls on the morphology of the intestine of chinook salmon (*Oncorhynchus tshawytscha*). Environ. Res. 23:149-161.

Hawley, JK. 1985. Assessment of health risk from exposure to contaminated soil. Risk Analysis 5:289-302.

HCI, (Hydrologic Consultants) 1991. John Anthony - Personal Communication. Mean estimates of diesel fuel concentrations in soil.

Helsel, D.R., and R.J. Gilliom. 1986. Estimation of distributional parameters for censored trace level water quality data: II. Verification and applications: Water Resources Research, Vol. 22, No. 2, p. 147-155.

Helsel, D.R. 1990. Less than obvious: Statistical treatment of data below the detection limit: Environmental Science and Technology, Vol. 24, No. 12, p. 1766-1774.

Hemmings, H., and RK. Boutwell. 1970. Studies on the mechanism of skin tumor promotion. Cancer Res., 30:312.

Henderson, T.R., A.P., Li, RE. Royer, and CR. Clark. 1981. Increased cytotoxicity and mutagenicity of diesel fuel after reaction with NO2. Environ. Mutagenesis, 3:211-220.

Hendricks, NV, CM Berry, JG Lione, and JJ Thorpe. 1959. Cancer of the scrotum in wax pressmen. I. Epidemiology. Arch. Ind. Health. Occup. Med. 19:524-529.

Hermann, M, JP Durand, JM Charpentier, O Chaude, M Hofnung, N Petroff, JP Vandecasteele and N Weille. 1980. Correlation of mutagenic activity with polynuclear aromatic content of various mineral oils. In: Polynuclear Aromatic Hydrocarbons: Chemical and Biological Effects, A Bjorseth and AJ Dennis (eds.), Battelle Press, Columbus, Ohio, pp. 899-916.

Hoffman, DJ. 1979. Embryotoxic and teratogenic effects of petroleum hydrocarbons in mallards (*Anas platyrhynchos*). J. Toxicol. Environ. Health 5:835-844.

Horton, A., and G. Christiansen. 1976. Cocarcinogenic versus incomplete carcinogenic activity among aromatic hydrocarbons: Contrast between chrysene and benzo[b]triphenylene. J. Nat. Cancer Inst., 53:1017.

Horton, A., DT. Denman, and RP. Trosset. 1957. Carcinogenesis of the skin II. The accelerating properties of aliphatic and related hydrocarbons. Cancer Res. 17:758.

Hueper, WC and CC Ruchhoft. 1954. Carcinogenic studies on adsorbates of industrially polluted raw and finished water supplies. Arch. Ind. Hyg. Occup. Med. 9:488-495.

IARC (International Agency for Research on Cancer). 1984. Mineral oils: Lubricant base oils and derived products. In: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Polynuclear Aromatic Compounds, Part 2, Carbon Blacks, Mineral Oils and Some Nitroarenes. Lyon, France, Vol. 33, pp. 87-167.

IARC (International Agency for Research on Cancer). 1986. Information Bulletin on the Survey of Chemicals Being Tested for Carcinogenicity, No. 12. Lyon.

IARC (International Agency for Research on Cancer). 1989. Biological data relevant to the evaluation of carcinogenic risk to humans. In: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Occupational Exposure in Petroleum Refining, Crude Oil and Major Petroleum Fuels. Lyon, France, Vol. 45, pp. 72-77.

IIT Research Institute. 1987. Short-term dermal tumorigenesis study of selected petroleum hydrocarbons: Initiation and promotion phases (final interim report). EPA/OTS Doc #FYI-AX-1087-0547.

IIT Research Institute. 1988. Short term dermal tumorigenesis study of selected petroleum hydrocarbons in male CD-1 mice initiation and promotion phases (draft final report). EPA/OTS Doc #FYI-AX-0688-0547.

Kane, ML, EN Ladov, CE Holdsworth, NK Weaver. 1984. Toxicological characteristics of refinery streams used to manufacture lubricating oils. Am. J. Ind. Med. 5:183-200.

Kaplan, SD. 1986. Update of a mortality study of workers in petroleum refineries. JOM 28:514-516.

Karimov, MA, AS Yermolenko, and LA Artamonova. 1986. Preneoplastic and neoplastic lesions in the mouse esophagus and cardia following skin painting with heavy catalytic gas oil (Russ.). Vopr. Onkol. 32:56-61.

Karimov, MA, LA Artamonova, and AS Yermolenko. 1984. Carcinogenic effect of heavy catalytic gas oil (Russ.). Vopr. Onkol. 30:40-45.

King, R.W. 1982. Skin carcinogenic potential of petroleum fractions 1. Separation and characterization of fractions for bioassay. In: The toxicology of Petroleum Hydrocarbons Eds. H.N. MacFarland, CE. Holdsworth, JA. MacGregor, RW. Call, and ML. Kane, Eds. American Petroleum Institute, Washington, D.C. pp. 170-184.

Kizer, KW, TE Warriner, and SA Book. 1988. Sound Science in the implementation of public policy. JAMA 260:951-955.

LaGoy, PK. 1987. Estimated soil ingestion rates for use in risk assessments. Risk Analysis 7:355-359.

Laughlin, Jr. RB, GL Young and JM Neff. 1978. A long-term study of the effects of water-soluble fractions of No. 2 fuel oil on the survival, development rate, and growth of the mud crab *Rhithropanopeus harrisii*. Mar. Biol. (Berl) 47:87-95.

Lawler, GC, W-A Loong and JL Laseter. 1978. Accumulation of aromatic hydrocarbons in tissues of petroleum-exposed mallard duck (*Anas platyrhynchos*). Environ. Sci. Technol. 12:51-54.

Lee, FK., WT. Muse, and BJ. Brown. 1989. Mutagenic responses of some petroleum-base obscurants in the Ames test. Chemical Research Development and Engineering Center report #CRDEC-TR-071. 24 p.

Leung, TS and RV Bulkley. 1979. Effects of petroleum hydrocarbons on length of incubation and hatching success in the Japanese medaka. Bull. Environ. Contam. Toxicol. 23:236-243.

Lewis, SC. 1983. Curde petroleum and selected fractions. Skin cancer bioassays. Prog. Exp. Tumor. Res. 26:68-84.

Lewis, SC. RW. King, ST. Cragg, and DW. Hillman. 1984. Skin carcinogenic potential of petroleum hydrocarbons: Crude oil, distillate fractions and chemical class subfractions. In: Advances In Modern Environmental Toxicology, Chapter 11, p. 139-150. MA. Mehlman Eds.

Lock, S, W Dalbey, R Schmoyer and R Griesemer. 1984. Inhalation toxicology of diesel fuel obscurant aerosol in Sprague-Dawley rats, final report, phase 3: Subchronic exposures. Prepared by: Oak Ridge National Laboratory, Oak Ridge, Tennessee. AD-A150 100.

MacFarland, HN, CE Holdsworth, JA MacGregor, RW Call and ML Kane (eds.) 1984. Vol. VI. Applied Toxicology of Petroleum Hydrocarbons. Princeton Scientific Publishers, Princeton, New Jersey.

MacFarland, HN. 1988. Toxicology of petroleum hydrocarbons. State Art. Rev. Occup. Med. 3:445-454.

Malker, HSR, JK McLaughlin, BK Malker, BJ Stone, JA Weiner, JLE Ericsson, and WJ Blot. 1986. Biliary tract cancer and occupation in Sweden. Br. J. Ind. Med. 43:257-262.

McCraw, DS, RE Joyner, and P Cole. 1985. Excess leukemia in a refinery population. JOM 27:220-222.

McKee, R and R Przygoda. 1987. The genotoxic and carcinogenic potential of engine oils and highly refined lubricating oils. Enviro. Mutagen. (abstract) 9:72.

McKee, R.H., RT. Plutnick, and RT. Przygoda. 1989a. The carcinogenic initiating and promoting properties of a lightly refined paraffinic oil. Fundamental and Applied Toxicology 12, 748-756.

McKee, RH and RT Plutnick. 1989b. Carcinogenic potential of gasoline and diesel engine oils. Fund. Appl. Toxicol. 13:545-553.

Millemann, RE, SJ Tumminia, JL Forte and KL Daniels. 1984. Comparative toxicities of coal-derived and shale-derived crude oils and a petroleum-derived fuel oil to the fresh-water snails, *Helisoma trivolvis* and *Physa gyrina*. Environ. Pollut. Ser. A. Ecol. Biol. 33(1):23-38.

Miller, JC. 1980. Comparative data on lifethreatening risks. Tox. Subst. J. 5:3.

NAS. 1980. Lead in the human environment. Washington, DC., National Academy Press.

Nelson, NA, PFD Van Peenen, and AG Blanchard. 1987. Mortality in a recent oil refinery cohort. JOM 29:610-612.

Nesnow, S, LL Triplett and TJ Slaga. 1982. Comparative tumor-initiating activity of complex mixtures from environmental particulate emissions on SENCAR mouse skin. J. Natl. Cancer. Inst. 68:829-834.

Norell, S, A Ahlbom, R Olin, R Erwald, G Jacobson, I Lindberg-Navier, and KL Wiechel. 1986. Occupational factors and pancreatic cancer. Br. J. Ind. Med. 43:775-778.

NRC (National Research Council). 1989. Drinking Water and Health. Volume 9: Selected Issues in Risk Assessment. National Academy Press: Washington D.C.

NTP (National Toxicology Program), 1986. Toxicology and carcinogenesis studies of marine diesel fuel and JP-5 navy fuel in B6C3F1 mice (dermal studies). Technical Report Series No. 310.

NTP (National Toxicology Program). 1986. Toxicology and carcinogenesis studies of marine diesel fuel and JP-5 navy fuel in $B6C3F_1$: Dermal studies. NTP TR 310.

OSWER (Office of Solid Waste and Emergency Response). Directive.

Patton, JF and MP Dieter. 1980. Effects of petroleum hydrocarbons on hepatic function in the (mallard) duck (*Anas platyrhynchos*). Comp. Biochem. Physio. C. Comp. Pharmacol. 65:33-36.

Rice, SD, DA Moles, JF Karinen, S Korn, MG Carls, CC Brodersen, JA Gharrett and MM Babcock. 1984. Effects of petroleum hydrocarbons on Alaska aquatic organisms: A comprehensive review of all oil-effects research on Alaskan fish and invertebrates conducted by the Auke Bay Laboratory, 1970-81. NOAA Technical Memorandum NMFS F. PB85-185262.

Rossi, SS and JW Anderson. 1978. Petroleum hydrocarbon resistance in the marine worm *Neanthes arenaceodentata* (polychaeta: annelida), induced by chronic exposure to No. 2 fuel oil. Bull Environ. Contam. Toxicol. 20:513-521.

Roy, TA., SW. Johnson, GR. Blackburn, and CR. Mackerer. 1988. Correlation of mutagenic and dermal carcinogenic activities of mineral oils with polycyclic aromatic compound content. Fundam. Appl. Toxicol., 10:466-476.

Rushton, L and MR Alderson. 1980. The influence of occupation on health - some results from a study in the UK oil industry. Carcinogenesis 1:739-743.

Rushton, L and MR Alderson. 1981a. An epidemiological survey of eight oil refineries in Britain. Br. J. Ind. Med. 38:225-234.

Rushton, L and MR Alderson. 1981b. A case-control study to investigate the association between exposure to benzene and deaths from leukaemia in oil refinery workers. Br. J. Cancer 43:77-84.

Saffiotti, U and P Shubik. 1963. Studies on promoting action in skin carcinogenesis. Natl Cancer Inst.Monog. 10:489-507.

Schottenfeld, D, ME Warshauer, AG Zauber, JG Meikle, and BR Hart. 1981. A prospective study of morbidity and mortality in petroleum industry employees in the United States - a preliminary report. In: Peto, R and M Schneiderman, eds., Quantification of Occupational Cancer. (Banbury Report 9), Cold Spring Harbor, NY CHS Press, pp. 247-265.

Setala, K., L. Merenmeis, L. Stjernvall, Y. Aho, and P. Kajanne. 1959. Mechanism of experimental tumorigenesis. 1. Epidermal hyperplais in mouse cased by locally applied tumor initiator and dipole-type tumor promotors. J. Nat. Cancer Inst., 23:925.

Shapiro, DD and IY Getmanets. 1962. Blastomogenic properties of petroleum of different sources (Russ.). Gig. Sanit. 27:38-42.

Short, BG, VL Burnett, MG Cox, JS Bus and JA Swenberg. 1987. Site-specific renal cytotoxicity and cell proliferation in male rats exposed to petroleum hydrocarbons. Lab. Invest. 57:564-577.

Shu, H, D Pautenbach, FJ Murray, L Marple, B Brunck, D Dei Rossi, and P Teitelbaum. 1988. Bioavailability of soil-bound TCDD: oral bioavailability in the rat. Fund. Appl. Toxicol. 10:648-654.

Shubick, P and U Saffiotti. 1955. The carcinogenic and promoting action of low boiling catalytically cracked oils. Acta Unio Int. Contra Cancrum. 11:707-711.

Sice, J. 1976. Tumor promoting activity of n-alkanes and 1-alkanols. Tox. Appl. Pharmacol, 9:70.

Siemiatycki, J., R. Dewar, L. Nadon, M. Gerin, L. Richardson, and S. Wacholder. 1987. Associations between several sites of cancer and twelve

petroleum-derived liquids: results from a case-referent study in Montreal. Scand. J. Work Environ. Health, 13:493-504.

Slaga, TJ., GT. Bowden, and RK. Boutwell. 1975. Acetic acid, a potent stimulator of mouse epidermal macromolecular synthesis and hyperplasia but with weak tumor promoting ability. J. Nat. Cancer Inst., 55:983.

Smith, WE, DA Sunderland, and K Sugiura. 1951. Experimental analysis of the carcinogenic activity of certain petroleum products. Arch. Ind. Hyg. Occup. Med. 4:299-314

Suleiman, SA. 1987. Petroleum hydrocarbon toxicity in vitro: effect of n-Alkanes, benzene and toluene on pulmonary alveolar macrophages and lysosomal enzymes of the lung. Arch. Toxicol. 59:402-407.

Takeuchi, Y, Y Ono, N Hisanaga, J Kitoh and Y Sugiura. 1980. A comparative study on the neurotoxicity of n-pentane, n-hexane, and n-heptane in the rat. Br. J. Ind. Med. 37:241-7.

Tatem, HE and JW Anderson. 1973. The toxicity of 4 oils to *Palaemonetes-pugio* in relation to uptake and retention of specific petroleum hydrocarbons. Am. Zool. 13:1307-1308.

Tatem, HE, BA Cox, and JW Anderson. 1978. The toxicity of oils and petroleum hydrocarbons to estuarine crustaceans. Estuarine Coastal Mar. Sci. 6:365-374.

Theriault, G and S Provencher. 1987. Mortality study of oil refinery workers: five year follow-up. JOM 29:357-360.

Thomas, TL, P Decoufle, and R Moure-Eraso. 1980. Mortality among workers employed in petroleum refining and petrochemical plants. JOM 22:97-103.

Thomas, TL, RJ Waxweiler, MS Crandall, DW White, R Moure-Eraso, and JF Fraumeni. 1984. Cancer mortality patters by work category in three Texas oil refineries. Am. J. Ind. Med. 6:3-16.

Thomas, TL, RJ Waxweiler, MS Crandall, DW White, R Moure-Eraso, S Itaya, and JF Fraumeni. 1982a. Brain cancer among OCAW members in three Texas oil refineries. Ann. NY Acad. Sci. 381:120-129.

Thomas, TL, RJ Waxweiler, R Moure-Eraso, S Itaya, and JF Fraumeni. 1982b. Mortality patters among workers in three Texas oil refineries. JOM 24:135-141.

Ullrich, Jr. SO and RE Millemann. 1982. The effect of temperature on the toxicity of the water soluble fractions of diesel fuel No. 2 and H-coal crude oil to *Daphnia magna*. Oak Ridge Laboratory, Oak Ridge, Tennessee. DE82 014724.

Ullrich, Jr., SO and RE Milleman. 1983. Survival, respiration and food assimilation of *Daphnia magna* exposed to petroleum-derived and coal-derived oils at 3 temperatures. Can. J. Fish. Aquat. Sci. 40:17-26.

USEPA, 1986. Quality Criteria for Water, 1986. EPA 440/5/86-001.

USEPA. 1980. Effect of different pollutants on ecologically important polychaete worms. Prepared by: DJ Reish, Environmental Research Laboratory. PB86-168804.

USEPA. 1985b. Responses of macrobenthos colonizing estuarine sediments contaminated with drilling mud containing diesel oil. Prepared by: Tagatz, ME, GR Plaia and CH Deans. PB86-100294.

Van Duuren, BL., and BM. Goldschmidt. 1976. Cocarcinogenic and tumor promoting agents in tobacco carcinogenesis. J. Nat. Cancer Inst., 56:1237.

Vandermeulen, JH, W Silvert and A Foda. 1983. Sublethal hydrocarbon phytotoxicity in the marine unicellular alga, *Pavlova lutheri*. Aquat. Toxicol. (AMST) 4:31-50.

Wen, CP, SP Tsai, and RL Gibson. 1982. A report on brain tumors from a retrospective cohort study of refinery workers. Ann. NY Acad. Sci. 381:130-138.

Wen, CP, SP Tsai, NS Weiss, RL Gibson, O Wong, and WA McClellan. 1985. Long-term mortality study of oil refinery workers. IV. Exposure to the lubricating-dewaxing process. JNCI 74:11-18.

Wen, CP, SP Tsai, RL Gibson, and WA McClellan. 1984. Long-term mortality of oil refinery workers. II. Comparison of the experience of active, terminated and retired workers. JOM 26:118-127.

Wen, CP, SP Tsai, WA McClellan, and RL Gibson. 1983. Long-term mortality study of oil refinery workers. I. Mortality of hourly and salaried workers. Am. J. Epidemiol. 118:526-542.

Wiel, CS and NI Condra. 1977. Experimental carcinogenesis of pyrolysis fuel oil. Am. Ind. Hyg. Assoc. J. 38:730-733.

Wilson, R. 1980. Risk/benefit analysis for toxic chemicals. Ecotoxicol. Environ. Safety 4:370-383.

Witschi, HP, LH Smith, EL Frome, ME Pequet-Goad, WH Griest, C Ho and MR Guerin. 1987. Skin tumorigenic potential of crude and refined coal liquids and analogous petroleum products. Fund. Appl. Toxicol. 9:297-303.

Wong, O and GK Raabe. 1989. Critical review of cancer epidemiology in petroleum industry employees with a quantitative meta-analysis by cancer site. Am. J. Ind. Med. 15.

Wong, O, RW Morgan, WJ Bailey, RE Swencicki, K Claxton, and L Kheifets. 1986. An epidemiological study of petroleum refinery employees. Br. J. Ind. Med. 43:6-17.

Yagminas, A, P DeVries and D Villeneuve. 1988. Systemic toxicity of coal liquefaction products: Results of a 14-day dermal exposure. Bull. Enviro. Cont. & Toxicol. 40:433-438.

## 5.0 GLOSSARY

*Additive* - A substance added to e.g., *lubricating oils* to impart new or to improve existing characteristics

*Alkane* - See *Paraffin*

*Alkene* - See *Olefin*

*Aromatic* - Compound containing one or more benzene rings that also may contain sulfur, nitrogen and oxygen

*ASTM* - American Society for Testing and Materials, responsible for the issue of many of the standard methods used in the petroleum industry

*Bitumen* - A viscous liquid, semisolid or solid, consisting essentially of hydrocarbons and their derivatives, which is soluble in carbon disulfide. Bitumen is obtained from the distillation of suitable *crude oils* by treatment of the *residues* (or occasionally of the heaviest fraction). It is also a component of naturally occurring *asphalt*. According to their properties, bitumens are used for emulsions, roofing, waterproofing, insulation, road construction, binding of aggregates, etc.

*Blending* - Intimate mixing of the various components in the preparation of a product to meet a given specification

*Cetane* - n-Hexadecane, used as a reference fuel for rating *diesel fuel* ignition quality

*Cetane number* - Measure of the ignition quality of a diesel fuel, expressed as the percentage of cetane that must be mixed with liquid a-methylnaphthalene to produce the same ignition performance as the *diesel fuel* being rated, as determined by test method *ASTM* D613. A high cetane number indicates shorter ignition lag and a cleaner burning fuel

*Cracking* - A process whereby the relative proportion of lighter or more volatile components of an oil is increased by changing the chemical structure of the constituent hydrocarbons

*Cracking, catalytic* - A *cracking* process in which a catalyst is used to promote reaction

*Cracking, hydro* - A *cracking* process carried out at high temperature and pressure in the presence of hydrogen and in which a catalyst is used to promote reaction. The process combines *cracking* and hydrogenation

*Cracking, steam* - *Thermal cracking* of, e.g., *naphtha*, at high temperatures with superheated steam injection

*Cracking, thermal* - A *cracking* process in which no catalyst is used to promote reaction

*Crude oil* - Naturally occurring mixture consisting essentially of many types of hydrocarbons, but also containing sulfur, nitrogen or oxygen derivatives. Crude oil may be of paraffinic, asphaltic or mixed base, depending on the presence of *paraffin wax, bitumen* or both *paraffin wax* and *bitumen* in the *residue* after atmospheric distillation. Crude oil composition varies according to the geological strata of its origin

*Cycloalkane* - See *Naphthene*

*Cycloparaffin* - See *Naphthene*

*Deasphalting* - The removal of asphaltic constituents from *residual stock* for *lubricating oil* manufacture. A *solvent refining* process in which the *asphalt* is precipitated, for example, by liquid propane (also called *decarbonizing*)

*Dewaxing* - The removal of waxes from *lubricating oil* stocks, now usually carried out by filtration at low temperature of a mixture of the oil and a solvent such as methyl ethyl ketone

*Diesel fuel* - That portion of *crude oil* that distills out within the temperature range 200-370°C. A general term covering oils used as fuel in diesel and other compression ignition engines

*Diesel oil* - See *Diesel fuel*

*Distillate* - A product obtained by condensing the vapours evolved when a liquid is boiled and collecting the condensate in a receiver which is separate from the boiling vessel

*Distillation range* - A single pure substance has one definite boiling-point at a given pressure. A mixture of substances, however, exhibits a range of temperatures over which boiling or distillation commences, proceeds and finishes. This range of temperatures, determined by means of standard apparatus, is termed the 'distillation' or 'boiling' range

*Domestic fuel* - See *Heating oil*

*Engine oil* - *Lubricating oil* used in internal combustion and other types of engines

*Extract* - During *solvent refining* processes, other than *dewaxing* or *deasphalting*, part of the *feedstock* passes into solution in the solvent and is subsequently recovered by evaporating of the solvent. This fraction is the extract and is generally *aromatic* in character and thus referred to as an *aromatic extract*

*Feedstock* - Primary material introduced into a plant for processing

*Fractional distillation* - See *Fractionation*

*Fractionation* - A distillation process in which the *distillate* is collected as a number of separate fractions each with a different boiling range

*Fuel oil* - A general term applied to an oil used for the production of power or heat. In a more restricted sense, it is applied to any petroleum product that is burnt under boilers or in industrial furnaces. These oils are normally *residues*, but blends of *distillates* and *residues* are also used as fuel oil. The wider term, *'liquid fuel"*, is sometimes used, but the term 'fuel oil' is preferred

*Gas oil* - A petroleum *distillate* with a viscosity and *distillation range* intermediate between those of *kerosene* and light *lubricating oil*

*Gasoline (petrol)* - Refined petroleum distillate, normally boiling within the limits of 30-200°C, which, combined with certain additives, is used as fuel for spark-ignition engines. By extension, the term is also applied to other products that boil within this range

*Heating oil* - *Gas oil* or *fuel oil* used for firing the boilers of central heating systems

*Hydrocracking* - See *Cracking, hydro-*

*Hydrodesulfurization* - A desulfurization process in which the oil is treated with hydrogen

*Hydrofinishing* - A mild *hydrotreating* process used mainly for finishing solvent-extracted *lubricating oils*. It has largely replaced earth treating

*Hydrotreatment* - A general term covering treatment with hydrogen at elevated temperature and pressure, usually in the presence of a catalyst. Severity of treatment ranges from mild (*hydrofinishing*) to severe (*hydrocracking*)

*Kerosene* - A refined petroleum *distillate* intermediate in volatility between *gasoline* and *gas oil.* Its *distillation range* generally falls within the limits of 150 and 300°C. Its main uses are as a jet engine fuel, an illuminant, for heating purposes and as a fuel for certain types of internal combustion engines

*Kerosine* - European term for *kerosene*

*Light distillate* - A term lacking precise meaning, but commonly applied to *distillates,* the *final boiling-point* of which does not exceed 300°C

*Lubricating oil* - Oil, usually refined, primarily intended to reduce friction between moving surfaces

*Lubricating oil distillate* - A *vacuum distillation* cut with a *distillation range* and viscosity such that, after refining, it yields *lubricating oil*

*Middle distillate* - One of the *distillates* obtained between *kerosene* and *lubricating oil* fractions in the *refining* processes. These include light *fuel oils* and *diesel fuels*

*Naphtha - Straight-run* gasoline fraction boiling below *kerosene* and frequently used as a *feedstock* for *reforming* processes. Also known as *heavy benzine* or *heavy gasoline*

*Naphthene* - Petroleum industry term for a *cycloparaffin (cycloalkane)*

*Naphthenic oil* -A petroleum oil derived from *crude oil* containing little or no wax

*Octane number* - See *Octane rating*

*Octane rating (of gasoline)* -The percentage by volume of iso-octane in a mixture of iso-octane and n-heptane which is found to have the same knocking tendency as the gasoline under test in a CFR *engine* operated under standard conditions (also called *octane number*)

*Olefin* - Synonymous with *alkene*

*Paraffinic oil* - A petroleum oil derived from a *crude oil* with a substantial was content

*Paraffin (alkane)* - One of a series of saturated aliphatic hydrocarbons, the lowest numbers of which are methane, ethane and propane. The higher homologues are solid waxes

*Paraffin wax* - Product obtained from petroleum *distillates* consisting essentially of a mixture of saturated hydrocarbons, solid at ordinary temperatures. Fully-refined paraffin wax has a low oil content and a rather marked crystalline structure

*Refinery* - A plant, together with all its equipment, for the manufacture of finished or semifinished products from *crude oil*

*Refining* - The separation of *crude oil* into its component parts and the manufacture therefrom of products. Important processes in *lubricating oil* refining are distillation, *hydrotreatment* and *solvent extraction*

*Residual oil* - Grade No. 4 to grade No. 6 *fuel oils*

*Residue (residuum)* - The heavy fraction or *bottoms* remaining undistilled after volatilization of all lower-boiling constituents

*Straight-run product* - A product of the primary distillation of *crude oil*

*Sweetening* - Removal or conversion of undesirably acidic and malodorous constituents present in *sour feedstock* or *refinery stream*, e.g., conversion of mercaptans to disulfides

*Treatments* - Somewhat loosely used to cover all those *refining* operations in which small proportions of undesirable constituents are removed from products by chemical or physical means, e.g., *acid and earth treatment* and *sweetening*

*Vacuum distillation* - Distillation under reduced, as opposed to atmospheric, pressure, e.g., *fractional distillation* of *short residue* to produce *distillates* for *lubricating oil* manufacture