EVALUATION OF THE POTENTIAL HEALTH EFFECTS OF OCCUPATIONAL EXPOSURE TO DIESEL EXHAUST IN UNDERGROUND COAL MINES

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CONTENTS

I. SUMMARY

The National Institute for Occupational Safety and Health (NIOSH) has reviewed and evaluated the available data on the potential for development of adverse health effects following the exposure of workers to diesel exhaust in underground coal mines. This review included studies of the effects of exposure to diesel exhaust and solvent extracts of diesel exhaust on bacterial/cell cultures, animals, and humans. This document briefly describes the history of the development and commercial use of diesel engines, the composition of diesel exhaust, and areas in which additional studies of possible health effects are needed.

Diesel exhaust is a melange of gases, vapors, and particulate matter. Some of the individual components of diesel exhaust have been shown to cause mutations in microorganisms and cancer in animals. Other components have been demonstrated to cause a variety of adverse health effects in humans, ranging from eye irritation to respiratory disease. The evaluation of potential health effects is complex because the composition of diesel exhaust varies depending upon many factors including engine design, fuel composition, power output, fuel-to-air ratio, duty cycles, emission controls, and engine maintenance.

Based on the data reviewed in this document, few definitive conclusions are possible concerning causative associations between diesel exhaust exposure and adverse health effects in humans. A causal association between exposure to

whole diesel exhaust and cancer, although plausible on the basis of studies of extracts of diesel exhaust in animals, has not been established. In animal studies, exposure to diesel exhaust has been associated with nonmalignant respiratory disease. Among workers exposed to diesel exhaust, irritation of the eyes and reversible decrements in pulmonary function have been documented.

Based on the current scientific knowledge about the health effects of diesel exhaust, with its complexities and ambiguities, NIOSH cannot definitively affirm or condemn, at this time, the use of diesel equipment in underground coal mines. Instead, as prudent public health policy, occupational exposures to diesel exhaust should be maintained below levels specified in existing standards promulgated by the Mine Safety and Health Administration (MSHA) for regulated components of diesel exhaust or, if more protective, below NIOSH recommended exposure limits (REL's). Controlling respirable particulate is especially important given the uncertainty about the potential carcinogenicity of components of diesel particles. In order to minimize exposure to diesel exhaust, adequate ventilation in underground coal mines, as required by MSHA, is essential, as are effective environmental monitoring and proper inspection and maintenance of diesel equipment.

Important gaps in knowledge in which appropriate research is needed include: (1) well-designed and controlled epidemiologic observations of the effects of diesel exhaust on populations of workers, (2) determination of the bioavailability of organics adsorbed on diesel exhaust particles, (3)

evaluations of the ability of defense mechanisms in the lung to detoxify inhaled diesel exhaust emissions, and (4) effects of inhalation of diesel exhaust on susceptibility to infection.

II. INTRODUCTION

A. Historical Perspective on Diesel Usage

1. Development of the Diesel Engine

Invention of the diesel engine is generally credited to Rudolph Diesel, a German engineer who during 1892-1896 developed a new type of engine capable of the spontaneous combustion of liquid fuel without requiring spark ignition, as does the conventional gasoline engine. In the gasoline engine, a mixture of air and fuel is drawn into a combustion chamber, compressed, and then ignited by an electric spark. In the diesel engine, air alone is compressed in the combustion chamber; a charge of fuel is then sprayed into the combustion chamber, and ignition is accomplished by the heat of compression [1].

The first commercially useful diesel engine was built in 1897. The thermal efficiency and fuel economy of the diesel engine proved to be better than any other power plant existing at the turn of the century; therefore, it attracted considerable interest for industrial purposes. These first engines were large, heavy, and entirely unsuited for mobile or portable equipment [1].

Eventually, the diesel engine was developed into a highly efficient, lightweight power unit. Because of its high reliability and economical use

of a fuel less volatile than gasoline, it became the predominant power plant for submarines during World War I and for military equipment on the ground and at sea during World War II [1]. The first diesel engine that was small and light enough for automotive application was built in Germany in 1922 [2]. Diesel locomotives were introduced in the U.S. by the railroads in 1935 [3].

2. Use of the Diesel Engine in Mining

The first diesel-powered locomotives for underground mines were introduced in the Ruhr coal mining district of Germany in 1927 and were soon thereafter placed in service in underground coal mines in France and Belgium [4]. The use of diesel equipment in the U.S. underground mining industry has steadily increased since the introduction of a diesel naulage truck in a Pennsylvania limestone mine in 1939; the first diesel-powered locomotive was used in a U.S. coal mine in 1946 [4,5]. Today, diesel engines are used in mining operations throughout the world [6].

The use of diesel equipment in underground coal mines in the U.S. has lagged behind its use in hard-rock mines because of increased safety concerns due to the presence of potentially explosive methane gas and dusts in coal mines, because of the availability and abundance of electricity typically found near coal mining areas, and because of concerns about the possible health effects of diesel exhaust [5]. The use of diesel equipment in underground coal mines in the U.S. has also lagged behind that in many

European countries, where diesel locomotives were well established in Germany, France, and Belgium by the mid-1930's [5]. The use of diesel equipment in underground U.S. coal mines is being pursued primarily because of the associated higher levels of productivity, convenience, and durability as compared to electric units [7]. The Department of Labor estimates that in 88 underground coal mines in the U.S., there are currently about 1,100 pieces of diesel equipment [8]; this is approximately a five-fold increase since 1977 [5]. Any projected increase in usage of diesel equipment in U.S. coal mines would be primarily for coal haulage (e.g., in shuttle cars, ram cars, and load-haul-dump units) to a transfer point where a belt or car would then take the coal out of the mine. Diesel equipment is also used in the haulage of workers and materials, for cleanup, and for emergency transport situations.

B. Composition of Diesel Exhaust Emissions

Diesel exhaust emissions consist of both gaseous and particulate fractions. The gaseous constituents include carbon dioxide, carbon monoxide, nitric oxide, nitrogen dioxide, oxides of sulfur, and hydrocarbons (e.g., ethylene, formaldehyde, methane, benzene, phenols, 1,3-butadiene, and acrolein) [9,10,11,12]. Particulates (soot) in diesel exhaust are composed of solid carbon cores produced during the combustion process that tend to form aggregates, the largest of which are in the respirable range (more than 95% are less than 1 micrometer in size) [10,13]. It has been estimated that as many as 18,000 different substances can be adsorbed on diesel exhaust

particulates [14]. The adsorbed material comprises from 15 to 65% of the total particulate mass and includes such compounds as polynuclear aromatic hydrocarbons (PNA's) and polycyclic aromatic hydrocarbons (PAH's) [10,15]. The characteristics and amounts of diesel exhaust are drastically altered by changes in engine design, fuel composition, power output, fuel-to-air ratio, duty cycle, and types of emission controls. The extent of engine maintenance further modifies the nature and quantity of the emissions [16].

C. Health Concerns

Many of the individual constituents of diesel exhaust are known to be toxic at some level of exposure. For example, the following effects have been associated with some of the components found in diesel exhaust: pulmonary irritation from nitrogen dioxide [17], methemoglobin formation and central nervous system effects from nitric oxide [17], reduction in the oxygen-carrying capacity of the blood from carbon monoxide [18], irritation of the mucous membranes and eyes from sulfur dioxide [19], phenol [20], sulfuric acid [21], sulfate aerosols [22], and acrolein [23], cancer from PAH's or PNA's [24], and increased lung burden from particulates [25].

The possibility that diesel exhaust emissions can cause cancer has been a concern since 1955, when an organic solvent extract of the particulate fraction of the exhaust from an inefficiently operating diesel engine was shown to contain polycyclic organic matter capable of producing tumors in skin painting tests on strain A mice [26]. This concern about carcinogenicity

was heightened in 1978 by another observation that an organic solvent extract of diesel exhaust particulate produced mutations in the Ames bacterial assay [27]. Bacterial assays indicate that mutagenic activity from contact with diesel exhaust extract may not be due simply to the unsubstituted PAH's or PNA's in the particulate phase of diesel exhaust. Rather, it has been suggested that 50-90% of the mutagenicity of diesel emissions may be due to the nitro-substituted PAH fraction, which includes nitroarenes such as 1-nitropyrene [28].

Occupational health concerns regarding the use of diesel engines are heightened when diesel engines are used in the confined work environment of underground coal mines (where ventilation is more difficult), especially the concern of potential increased particulate burden to the lung. In addition, there are concerns about the possible interactions and potentiating effects between diesel exhaust and other exposures (e.g., coal and silica) in coal mine environments.

The growing use of diesel equipment in underground coal mines and the concerns about possible adverse health effects from occupational exposure to diesel exhaust emissions have led NIOSH to critically evaluate the current state-of-knowledge on the toxicity of diesel exhaust. This review critically evaluates the body of knowledge developed from in vivo and in vitro test systems that involve exposures to diesel exhaust or its extracts. In addition, epidemiologic studies of workers occupationally exposed to diesel exhaust are evaluated.

III. EFFECTS OF EXPOSURE ON BACTERIAL/CELL CULTURES AND ANIMALS

A. Studies of Mutagenicity

1. In Vitro

Chemical mutagens are substances that induce alterations in deoxyribonucleic acid (DNA). If the altered genes are located in mammalian sperm or egg cells, hereditary diseases or morphologic changes may result [29]. Based on the observation that many chemical carcinogens have been shown to be mutagenic in a diverse group of *in vitro* bacterial/cell culture assays, it is generally assumed that genetic alterations are a critical step in the biologic processes leading to cancer [29,30,31,32]. However, *in vitro* bacterial/cell culture assays are essentially predictive in nature and, therefore, are not definitive tests for carcinogenesis [33]. The consensus of available information suggests that short-term tests, when properly used and validated, can provide strong indications of potential carcinogenicity [34]. Confidence in positive results is increased if a mechanism of action can be deduced, if appropriate dose-response data are available, and if a compound can be tested in a battery of short-term tests [33,34,35].

The compounds adsorbed on the surface of diesel exhaust particulate (DEP) are readily extracted with organic solvents. These organic solvent extracts have caused mutagenic responses in *in vitro* bacterial/cell culture

gene mutation assays [30,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52, 53,54,55,56,57,58,59,60,61,62,63,64,65,66,67], DNA damage in bacterial and mammalian cell assays [45,50,51,58,68], and chromosomal aberrations in Chinese hamster ovary cells and human lymphocytes [45]. Although fetal calf serum extracts of DEP have caused mild mutagenic activity in S. typhimurium [61], most natural or simulated biologic fluid extracts of DEP have not demonstrated significant activity in this test system [43,61,69]. These studies suggest that most of the mutagenic compounds are either not extracted from the DEP or are bound in forms which are not mutagenically active in S. typhimurium assays. The in vitro mutagenicity studies are summarized in Table III-1.

Material extracted from alveolar macrophages obtained several days after inhalation exposures of rats to DEP demonstrated little mutagenic activity in S. typhimurium [70]. In addition, the in vitro incubation of alveolar macrophages with DEP has been shown to result in the loss of 97-98% of the mutagenic activity associated with the DEP [71]. No mutagenic activity was found in an in vitro study in which Chinese hamster ovary cells were exposed directly to only the vapor phase of diesel engine exhaust [72].

2. In Vivo

Whole diesel exhaust (i.e., both the particulate and gaseous fractions of diesel exhaust) has generally produced negative results in in vivo

mutagenesis bioassays involving insects and mammals [44,45,70,73,74,75,76,77]. However, although exposure (8 hours/day, 7 days/week) of Syrian golden hamsters to whole diesel exhaust containing 6-7 milligrams per cubic meter of air (mg/m^3) of diesel exhaust particulate (DEP) for 3 months did not increase the incidence of sister chromatid exchanges (SCE) in lung cells, exposure to 12 mg/m^3 DEP for 3.5 and 8.5 months did induce increased frequencies of SCE [73]. In addition, whole diesel exhaust has induced the formation of micronuclei (broken pieces of chromosomes) in Tradescantia (spiderwort) and has induced gene mutations in the Tradescantia stamen hair assay [45,78]. Diesel exhaust particulate (DEP) has induced increased SCE in Syrian golden hamster lung cells following intratracheal (i.t.) instillation [75] and in mouse bone marrow cells following intraperitoneal (i.p.) injection [76]. Organic solvent extracts of diesel exhaust particulate (DEE) have also induced SCE in Syrian golden hamster lung cells following i.t. instillation [73], mouse bone marrow cells following i.p. injection [76], and Syrian golden hamster fetal liver cells following i.p. injection [76]. A summary of these in vivo mutagenicity studies is given in Table III-2.

Table III-1.--Summary of results of in vitro mutagenicity studies of solvent extracts of diesel exhaust particulate*

Description of study	Reference
Positive results:	
Mutations in human lymphoblasts	Barfknecht et al., 1982 [36]
Mutations in S. typhimurium	Belisario et al., 1984 [66]
Mutations in S. typhimurium	Brooks et al., 1984 [63]
Sister chromatid exchanges in Chinese hamster ovary (CHO) cells	Brooks et al., 1984 [63]
Mutations in CHO cells	Casto et al., 1981 [37]
Enhancement of viral transformation in Syrian hamster embryo (SHE) cells	Casto et al., 1981 [37]
Mutations in CHO cells	Chescheir et al., 1981 [62]
Mutations in S. typhimurium	Choudhary & Doudney, 1981 [38]
Mutations in S. typhimurium	Clark & Vigil [39]
Mutations in S. typhimurium	Claxton, 1981 [40]
Mutations in S. typhimurium	Claxton & Barnes, 1980 [41]
Mutations in mouse BALB/c3T3 cells	Curren et al., 1981 [42]
Cell transformation in mouse BALB/c3T3 cells	Curren et al., 1981 [42]
DNA damage in E. coli	Doudney et al., 1981 [68]
Mutations in S. typhimurium	Huisingh et al., 1978 [27]
Mutations in S. typhimurium	King et al., 1981 [43]
Mutations in S. typhimurium	Lewis et al., 1985 [44]
Chromosomal aberrations in CHO cells	Lewtas, 1982 [45]
Mutations in mouse lymphoma cells	Lewtas, 1982 [45]
E. coli WP2 tryptophan reversion (gene mutation)	Lewtas, 1982 [45]
Mutations in S. typhimurium	Lewtas, 1982 [45]
Unscheduled DNA repair in liver cells	Lewtas, 1982 [45]
Chromosomal aberrations in human lymphocytes	Lewtas, 1982 [45]
Mutations in CHO cells	Li et al., 1983 [46]
Mutations in CHO cells	Li & Hoyer, 1982 [47]
Mutations in S. typhimurium	Liber et al., 1980 [48]
SCE in human lymphoblasts	Liber et al., 1980 [48]
SCE in human lymphocytes	Lockard et al., 1982 [65]

Table III-1. (Continued)--Summary of results of *in vitro* mutagenicity studies of solvent extracts of diesel exhaust particulate[a]

Description of study	Reference
Positive results--Continued:	
Mutations in S. typhimurium	Lofroth, 1981 [49]
Mutations in S. typhimurium	Loprieno et al., 1980 [50]
Mutations in S. pombe (yeast)	Loprieno et al., 1980 [50]
Gene conversion in S. cerevisiae (yeast)	Loprieno et al., 1980 [50]
Unscheduled DNA synthesis (UDS) in HUH human cells	Loprieno et al., 1980 [50]
Mutations in mouse lymphoma cells	Mitchell et al., 1981 [51]
UDS in WI-38 human cells	Mitchell et al., 1981 [51]
SCE in CHO cells	Mitchell et al., 1981 [51]
DNA damage in S. cerevisiae D3	Mitchell et al., 1981 [51]
Mutations in S. typhimurium	Nakagawa et al., 1983 [67]
Mutations in S. typhimurium	Ohnishi et al., 1980 [52]
Mutations in S. typhimurium	Pedersen & Siak, 1981 [53]
Mutations in S. typhimurium	Pitts et al., 1981 [54]
Mutations in S. typhimurium	Rannug, 1983 [55]
Mutations in S. typhimurium	Rappaport et al., 1980 [56]
Mutations in S. typhimurium	Richold et al., 1980 [57]
Mutations in S. typhimurium	Risby et al., 1980 [58]
B. subtilis comptest (induction of DNA repair)	Risby et al., 1980 [59]
Mutations in S. typhimurium	Rodriguez et al., 1980 [59]
Mutations in mouse lymphoma cells	Rudd, 1980 [60]
Mutations in S. typhimurium	Salmeen et al., 1982 [64]
Mutations in S. typhimurium	Siak et al., 1981 [61]
Mutations in S. typhimurium (extracted with fetal calf serum)	Siak et al., 1981 [61]
Negative results:	
Mutations in S. typhimurium (extracted with dog serum, lung lavage fluid, saline, dipalmitoyl lecithin, and albumin)	Brooks et al., 1980 [69]
Chromosomal aberrations in CHO cells	Brooks et al., 1984 [63]
DNA fragmentation in SHE cells	Casto et al., 1981 [37]
Mutations in CHO cells	Casto et al., 1981 [37]

Table III-1. (Continued)--Summary of results of *in vitro* mutagenicity studies of solvent extracts of diesel exhaust particulate*

Description of study	Reference
Negative results--Continued:	
Enhancement of viral transformation in SHE cells	Casto et al., 1981 [37]
Cell transformation in mouse BALB/c3T3 cells	Curren et al., 1981 [42]
Mutations in S. typhimurium (extracted with lung lavage fluid)	King et al., 1981 [43]
Mutations in E. coli	Lewtas, 1982 [45]
Mutations in human lymphoblasts	Liber et al., 1980 [48]
DNA damage in S. cerevisiae D3	Mitchell et al., 1981 [51]
SCE in CHO cells	Mitchell et al., 1981 [51]
Mutations in Chinese hamster V79 cells	Rudd, 1980 [60]
Mutations in S. typhimurium (extracted with lung surfactant, saline, and bovine serum albumin)	Siak et al., 1981 [61]

*Unless otherwise noted, the extracts were obtained with organic solvents.

Table VII-2.--Summary of results of in vivo mutagenicity studies of whole diesel exhaust, diesel exhaust particulate (DEP), and solvent extracts of diesel exhaust particulate (DEE)*

Description of study	Reference
Positive results:	
Sister chromatid exchange (SCE) in Syrian golden hamster lung cells [DEP instilled intratracheally (i.t.)]	Guerrero et al., 1981 [75]
SCE in Syrian golden hamster lung cells (DEE instilled i.t.)	Lewtas, 1982 [45]
Gene mutations in Tradescantia stamen hair assay	Lewtas, 1982 [45]
Micronucleus assay in Tradescantia (spiderwort)	Ma et al., 1981 [78]
SCE in Syrian golden hamster fetal liver cells [DEE injected intraperitoneally (i.p.)]	Pereira et al., 1982 [76]
SCE in mouse bone marrow cells (DEP injected i.p.)	Pereira et al., 1982 [76]
SCE in mouse bone marrow cells (DEE injected i.p.)	Pereira et al., 1982 [76]
SCE in Syrian golden hamster lung cells	Lewtas, 1982 [45]
Negative results:	
SCE in Syrian golden hamster lung cells	Guerrero et al., 1981 [75]
Micronucleus assay in rat bone marrow cells	Lewis et al., 1985 [44]
Micronucleus assay in mouse bone marrow cells	Lewis et al., 1985 [44]
SCE in rat lymphocytes	Lewis et al., 1985 [44]
Dominant lethal effects in rats	Lewis et al., 1985 [44]
SCE in monkey lymphocytes	Lewis et al., 1985 [44]
Chromosomal aberrations in monkey lymphocytes	Lewis et al., 1985 [44]
Mutations in S. typhimurium [urine of exposed rats]	Lewis et al., 1985 [44]
Gene mutations in fruit flies	Lewtas, 1982 [45]

Table III-2. (Continued)--Summary of results of in vivo mutagenicity studies of whole diesel exhaust, diesel exhaust particulate (DEP), and solvent extracts of diesel exhaust particulate (DEE)*

Description of Study	Reference
Negative results--Continued:	
Specific locus assay in mice (point mutation test)	Lewtas, 1982 [45]
Dominant lethal effects in mice (chromosome damage)	Lewtas, 1982 [45]
Heritable translocation test in mice (chromosome damage)	Lewtas, 1982 [45]
Micronucleus assay in mouse bone marrow cells	Pereira, 1982 [73]
Micronucleus assay in mouse bone marrow cells (DEP injected i.p.)	Pereira, 1982 [73]
SCE in mouse bone marrow cells	Pereira, 1982 [73]
Micronucleus assay in Chinese hamster bone marrow cells (DEP injected i.p.)	Pereira, 1982 [73]
Micronucleus assay in Chinese hamster bone marrow cells	Pereira, 1982 [73]
Micronucleus assay in mouse bone marrow cells (DEP injected i.p.)	Pereira, 1982 [73]
Micronucleus assay in Chinese hamster bone marrow cells (DEE injected i.p.)	Pereira, 1982 [73]
SCE in Syrian golden hamster fetal liver cells	Pereira et al., 1982 [76]
SCE in Syrian golden hamster fetal liver cells (DEP injected i.p.)	Pereira et al., 1982 [76]
Sperm-shape abnormalities in mice	Pereira et al., 1981 [77]
Dominant lethal effects in wasps (topical treatment with DEE)	Petters et al., 1983 [79]
Gene mutations in fruit flies	Schuler & Niemeier, 1981 [74]
Mutations in S. typhimurium (alveolar macrophages of rats exposed 4-7 days earlier)	Siak & Strom, 1982 [70]

*Studies used whole diesel exhaust, unless otherwise noted that DEP or DEE was used.

3. Summary

Because DNA is essentially identical in structure and function in all organisms, the demonstration of genetic alterations induced by a chemical in one organism is strongly suggestive that similar damage will be induced in other organisms if it can be established that the chemical reaches the DNA [80]. At present, these short-term tests cannot be used to determine whether or not a compound will be carcinogenic in humans or experimental animals. While negative short-term test results do not establish the safety of the agent, positive results do not establish the carcinogenicity but may suggest the need for more extensive testing of the agent in long-term animal bioassays. Results from short-term tests do make a contribution to a weight-of-evidence approach to carcinogen identification and may provide a more refined understanding of the carcinogenic process.

Studies to date confirm the mutagenic activity of the organic solvent extractable fraction of diesel exhaust particulate, but these studies generally show a lack of transmitted effect to in vivo exposure to whole diesel exhaust emissions, which could be due to differences in the bioavailability of the mutagenic compounds. The lack of mutagenic effects in studies using total DEP or biologic fluid extracts suggests the potential inability of the pulmonary fluids to extract the mutagens adsorbed on DEP and/or the potential ability of pulmonary macrophages to detoxify the mutagenic compounds.

B. Studies of Carcinogenicity

1. Skin Painting

In a study reported by Kotin et al. in 1955 [26], 25 strain A female mice were treated topically 3 times per week for 17 months with an acetone solution containing a benzene solvent extract of the particulate fraction of exhaust obtained from an inefficiently running diesel engine. No data were given on the type of diesel engine or fuel used. Skin tumors were noted in 17 of the diesel extract-treated animals over the 17-month test period. On the basis of necropsy and gross observation, 11 of the 17 tumors were determined to be carcinomas. No tumors were found in the 69 C59 black mice (sex unstated) or in the 34 strain A mice (24 females and 10 males) used as controls.

In a study reported by Mittler and Nicholson in 1957 [81], none of 36 LAF mice painted twice weekly for 11 months with a benzene extract of diesel exhaust condensate (2.26% in benzene) developed skin tumors. The diesel exhaust was generated by a 1-cylinder engine; data on the type of engine and fuel used were not specified. No tumors were noted among 24 controls treated with benzene alone. However, all 11 mice treated twice weekly with benzo(a)pyrene (BaP) and 22 of 36 mice treated twice weekly with a 4% solution of gasoline engine exhaust extract developed skin cancer.

In 1980, Misfeld [82] described a study in which three groups of 80 female CFLP mice were treated topically twice weekly with either 4.3, 8.6, or 17.15 mg of diesel exhaust condensate in an unspecified solution. It was not mentioned whether or not the condensate was from a solvent extract. There were no tumors noted in the low dose group, 2 tumors in the medium dose group, and 9 tumors in the high dose group; no tumors were noted in the 80 female CFLP mice treated twice weekly with the unspecified solvent alone. No data were given regarding tumor types, diesel engine specifications and operating parameters, or exhaust condensate collection techniques used. From results of similar testing with gasoline engine exhaust condensate, Misfeld [82] calculated that the gasoline exhaust condensate had 42-times more tumor-producing effect than the diesel exhaust condensate.

In a study of skin carcinogenesis by Nesnow et al., 1982 [83], 80 SENCAR mice were used per treatment group with 40 of each sex, aged 7 to 9 weeks. Dichloromethane extracts of particulate emissions from five different diesel engines (1973 Nissan Datsun, 1978 General Motors Oldsmobile, 1976 prototype Volkswagen Turbo Rabbit, and 1977 Mercedes 300D) and a residential furnace; all used No. 2 diesel fuel. In the tumor initiation studies, the diesel extract was suspended in acetone and applied topically in single applications (doses ranged from 0.1 to 10 mg with the 10 mg dose administered in 5 daily doses of 2 mg). This was followed 1 week later by treatment with 0.002 mg of the tumor promoter 7,12-dimethylbenz(a)-anthracene-12-O-tetradecanoylphorbol-13-acetate (TPA), which was administered twice weekly for a year. Under the complete carcinogenesis

protocol (a test for agents exhibiting both tumor-initiating and tumor-promoting activities), extracts were administered weekly for 50 to 52 weeks (doses ranged from 0.1 to 4 mg). For comparison, studies were also conducted with BaP and emission extracts from a 1977 Ford Mustang gasoline engine, a coke oven, and roofing tar. The qualitative results of these studies are summarized in Table III-3. Four of the diesel samples were positive as initiators of papillomas (Nissan, Oldsmobile, Volkswagen, and Mercedes), and one was also an initiator of carcinomas (Nissan). Only the diesel samples from the Nissan, Oldsmobile, and Caterpillar engines were evaluated in the complete carcinogen study, and none was found to be positive in the dose ranges tested.

Table III-3.--Summary of results of a dermal carcinogenesis bioassay of solvent extracts of diesel exhaust

Sample	Tumor initiation Papillomas[a] M/F[c]	Tumor initiation Carcinomas[b] M/F	Complete carcinogenesis Carcinomas M/F
Nissan engine emission	+/+	+/+	-/-
Oldsmobile engine emission	+/+	-/-	-/-
Volkswagen engine emission	+/+	-/-	I[d]
Mercedes engine emission	+/-	-/-	ND[e]
Mustang engine emission	+/+	-/+	ND
Caterpillar engine emission	-/-	-/-	-/-
Residential furnace emission	-/-	-/-	ND
Coke oven (main) emission	+/+	+/+	+/+
Roofing tar emission	+/+	+/+	+/+
Benzo(a)pyrene	+/+	+/+	+/+

[a]Scored at 6 months (positive for papilloma formation if there was evidence of a dose response and if at least two doses yielded a papilloma-per-mouse value equal to three times the background value)

[b]Cumulative score at 1 year (positive for carcinoma formation if at least one dose produced a tumor incidence of 20%)

[c]Male/Female

[d]I = Incomplete findings

[e]ND = Not determined

Adapted from Nesnow et al., 1982 [83]

Depass et al., 1982 [84], reported the preliminary findings of a dermal carcinogenesis bioassay in which 40 male C3H/HeJ mice per treatment group were exposed for life (age at initial exposure not specified). Diesel exhaust particulate (DEP) and dichloromethane extracts of diesel exhaust particulate (DEE) from an Oldsmobile engine were applied topically in 0.025 ml of acetone. Under the complete carcinogenesis protocol, a dose of 1.0 mg DEP, 2.0 mg DEP, 1.0 mg DEE, 2.2 mg DEE, 5.1 mg DEE, or 12.0 mg DEE was administered three times per week. In the tumor initiation studies, a single dose of either 2.0 mg DEP or 12.0 mg DEE was followed 1 week later by treatment 3 times per week with 0.0015 mg of the tumor promoter phorbol-12-myristate-13-acetate (PMA); the concentration of PMA was changed to 0.15 mg after 8 months of treatment. In the tumor promotion studies, a single initiating dose of 0.23 mg BaP was followed by 5 applications per week of 2.0 mg DEP, 5.1 mg DEE, or 12.0 mg DEE.

Results of the preceding study by Depass et al. [84] are as follows. In the complete carcinogenesis studies, only one tumor (a squamous cell carcinoma) was observed in groups treated with DEP and DEE (at a dose of 12.0 mg DEE), whereas 38 of the 40 positive controls treated with 0.2% BaP developed tumors; 4 of the 80 DEP-treated and 18 of the 160 DEE-treated mice were still alive at the time of reporting. In the tumor promotion study, one mouse in each of the groups treated with DEE was diagnosed as having squamous cell carcinoma, and another was grossly diagnosed as having a papilloma (no tumors were observed in the DEP

treatment group); 7 of 40 DEP-treated and 14 of 80 DEE-treated mice were still alive. In the tumor initiation studies, 3 mice in each of the DEP- and DEE-treatment groups developed tumors; the time from initial exposure to first tumor observed was 319 days in the DEP-treated mice and 395 days in the DEE-treated mice. None of the DEP- or DEE-treated mice were still alive at the time of reporting. These preliminary findings indicate that there were no statistically significant incidences of tumors from topical application of DEP or DEE in either the tumor initiation, tumor promotion, or complete carcinogenesis studies [84].

2. Intraperitoneal Injection

In a study reported by Pepelko and Peirano in 1983 involving two consecutive experiments [85], strain A mice from the Jackson Laboratories were given intraperitoneal (i.p.) injections of dichloromethane extracts of diesel exhaust particulate at 8 weeks of age, 3 times per week for 8 weeks, and were later sacrificed at 9 months of age. In the first experiment, the doses per i.p. injection (in 0.05 ml dimethylsulfoxide) were 4 mg of Nissan DEP (30 males, 30 females), 1 mg of Nissan DEE (30 males, 30 females), and 1 mg of Oldsmobile DEE (30 males). In the second experiment, the doses per i.p. injection (also in 0.05 ml dimethylsulfoxide) were 2 mg of Nissan DEP (60 males, 60 females), 1 mg of Nissan DEE (40 males, 45 females), and 1 mg of Oldsmobile DEE (35 males). The sources of the diesel exhaust were a 6-cylinder Nissan engine and an 8-cylinder Oldsmobile engine; both used No. 2 diesel fuel.

In the first experiment, only the males injected with 1 mg of Nissan DEE had a significantly higher tumor incidence than did uninjected controls; however, when the data were combined from both experiments, no significant differences were noted. The combining of results from the two experiments might have diluted any effects associated with the emissions from a given engine.

3. Inhalation

In an inhalation study by Karagianes et al., 1981 [86], 24 specific-pathogen-free male 18-week old Wistar rats per group were exposed 6 hours/day, 5 days/week for 20 months to one of the following: (1) clean air, (2) diesel exhaust alone [containing 8.3 mg/m^3 DEP, 50 parts per million (ppm) carbon monoxide (CO), 4–6 ppm nitrogen dioxide (NO_2), 26–40 ppm ammonia (NH_3), <1 ppm sulfur dioxide (SO_2), and <1 ppm aliphatic aldehydes], (3) diesel exhaust (containing the components listed above) in combination with 5.8 mg/m^3 coal dust, (4) 6.6 mg/m^3 coal dust, or (5) 14.9 mg/m^3 coal dust. The source of the diesel exhaust was a 3-cylinder, 43-brake horsepower (bhp) diesel engine that had been modified to simulate an inefficiently tuned engine; a 2-D diesel fuel oil was used. Six rats from each group were sacrificed after 4, 8, 16, or 20 months. No malignant respiratory tract tumors were observed in any of the exposure groups. According to the authors, the limited number of rats examined (24 per group) precluded definitive answers regarding the carcinogenic potential of inhalation exposure to diesel exhaust, coal

dust, or the combination of both. In addition, tumors would not have been expected among those animals sacrificed at 4 or 8 months.

In one of the most complete studies to date, reported by Lewis et al. in 1985 [44], Fischer 344 rats (120-121 males and 71-72 females per group) were exposed 7 hours/day, 5 days/week for 24 months to one of the following: (1) diesel exhaust containing 1.95 mg/m^3 DEP, (2) diesel exhaust containing 1 mg/m^3 DEP in combination with 1 mg/m^3 coal dust, (3) 2.00 mg/m^3 coal dust, or (4) clean air. The diesel exhaust (with DEP or with DEP and coal dust) also contained the following components: 10.9-11.5 ppm CO, 8.3-8.7 ppm nitrous oxide (NO), 1.5-1.6 ppm NO_2, 0.6-0.8 ppm SO_2, 0.5-0.6 ppm NH_3, 0.12 ppm total aliphatic aldehydes, <0.1 ppm acrolein, <0.1 ppm acetaldehyde, and <0.1 ppm formaldehyde. The source of the diesel exhaust was a 4-cycle, water-cooled, naturally aspirated 100-bhp Caterpillar Model 3304 diesel engine equipped with a water scrubber; a No. 2 diesel fuel containing <0.5% sulfur by mass was used. Complete gross and histopathologic examinations were performed on all the animals (i.e., those rats that died during the study or survived to the terminal kill). The incidences of neoplasia in the 50 organs examined from rats exposed to either diesel exhaust, coal dust, or diesel exhaust and coal dust combined did not differ significantly from controls exposed only to clean air.

In part I of an inhalation study by Orthoefer et al. published in 1981 [87], strain A mice from either the Strong Research Foundation (Strong) or the Jackson Laboratories (Jackson) were exposed for 20 hours/day, 7 days/week to one of the following: (1) nonirradiated diesel exhaust (containing 6.32 mg/m^3 DEP, 15.7 ppm CO, 5.9 ppm NO, 2.2 ppm NO_2, and 2.1 ppm SO_2), (2) irradiated diesel exhaust (containing 6.87 mg/m^3 DEP, 15.4 ppm CO, 4.9 ppm NO, 2.7 ppm NO_2, and 1.9 ppm SO_2), or (3) clean air. The source of the diesel exhaust was a 6-cylinder Nissan diesel engine; a No. 2 diesel fuel was used. In experiment #1, 25 male Strong A mice per group were exposed from ages 6 through 14 weeks to either nonirradiated diesel exhaust, irradiated diesel exhaust, or clean air; following these exposures, the mice were held in clean air for an additional 26 weeks and then sacrificed. In experiment #2, 40 Jackson A mice (20 males, 20 females) were exposed to either nonirradiated diesel exhaust or clean air for 8 weeks and were then sacrificed 30 weeks after cessation of exposure. There were no significant differences in tumor incidences among diesel exhaust-exposed groups in either experiment #1 or #2 as compared to their clean air controls. The small numbers of animals in the exposure and control groups might have limited the sensitivity of this study. Further, the findings might not have been negative if, following chronic inhalation of these substances, the animals had been observed for their lifetime.

In part II of the preceding study by Orthoefer et al. [87], Strong A mice were exposed 8 hours/day, 7 days/week to either clean air or to diesel exhaust containing 6.39 mg/m^3 DEP, 19.7 ppm CO, 11.2 ppm NO, 2.65 ppm NO_2, and 6.4 ppm SO_2. The source of the diesel exhaust was mentioned previously. In experiment #3, 120 female Strong A mice and 859 male Strong A mice were randomly divided into either a clean air-exposed or a diesel exhaust-exposed group. The females were exposed for 7.5 months and the males for 36 or 44 weeks; all mice were then sacrificed. In experiment #4, 120 female Strong A mice at 6 weeks of age were pretreated with a single 1-mg i.p. injection of the lung tumor initiator urethan, exposed to diesel exhaust or clean air for 7.5 months, and then sacrificed. The female mice in both experiments (#3 and #4) had significant increases in the number of tumors/mouse (0.32, $p<0.01$ and 0.39, $p<0.01$, respectively) as compared to their respective controls. There were no significant differences, however, in the tumor incidences in the male mice in either experiment. In a discussion of this study published in 1983, Pepelko and Peirano [85] discounted the positive findings in the female mice for the following reasons. First, the tumor incidence of the controls (0.09 tumors/mouse) was less than the expected value (based on historic controls) of approximately 0.25 tumors/mouse for this strain of mice; if the latter value had been used, then no significant increases would have been shown. Second, Pepelko and Peirano noted that according to Shimkin and Stoner, in 1975 [88], the increases should not have been considered significant in this type of study unless the tumor incidences had exceeded 1 tumor/mouse. Further, Pepelko and

Peirano were not able to confirm the significant increases, even at a higher level of exposure, as described in the following experiment with Strong A mice.

In part I, experiment #1 of the study reported in 1983 by Pepelko and Peirano [85], groups of 90 Strong A mice (45 males, 45 females) were exposed 8 hours/day, 7 days/week to either clean air or to diesel exhaust (containing 11.7 mg/m^3 DEP, 33.3 ppm CO, 19.5 ppm NO, 4.4 ppm NO_2, and 5.0 ppm SO_2) from the ages of 6 weeks to 9 months and were then sacrificed. The diesel exhaust was generated by the same 6-cylinder Nissan engine (using No. 2 diesel fuel) used by Orthoefer et al. [87]. In experiment #2, similar exposure treatments were administered to groups of 90 Strong A mice (45 males, 45 females) that had been pretreated with a single 5-mg i.p. injection of the lung tumor initiator urethan. Significantly lower tumor incidences were found for female and for male and female Strong A mice exposed to diesel exhaust (either with or without urethan) as compared to the clean air-exposed controls. In experiment #3 under the same conditions (except that exposures lasted until 12 months of age), 44 male Jackson A mice survived exposure to diesel exhaust, and 38 male Jackson A mice survived exposure to clean air (the initial numbers exposed were unknown). The tumor incidence in experiment #3 was significantly lower in the diesel exhaust-exposed Jackson A mice as compared to the clean-air exposed controls. In experiment #4, exposure times and conditions were identical to those in experiments #1-#3, except that the light cycle was altered such that exposures took place in the dark while the mice were presumably awake,

active, and inspiring a greater volume of air. A group of 258 Strong A mice (115 males, 143 females) was exposed to diesel exhaust and a group of 250 Strong A mice (108 males, 142 females) was exposed to clean air; the mice in both groups were exposed from 6 weeks to 9 months of age and were then sacrificed. Both male and female Strong A mice exposed to diesel exhaust in experiment #4 had significantly lower tumor incidences than their clean air-exposed controls. The significance of the findings from these four experiments is not known. The lower tumor incidences in the exposed mice as compared to the controls might have been different if chronic inhalation studies with observation periods over the lifetimes of the animals had been conducted.

In part II of the study reported in 1983 by Pepelko and Peirano [85], SENCAR mice were exposed for 8 hours/day, 7 days/week to either clean air or diesel exhaust from the age of weaning to sexual maturity and were then mated. Exposure of the dams continued through pregnancy, parturition, and weaning of offspring. The SENCAR mice offspring were assigned to three groups of 260 (130 males, 130 females). In the tumor initiation study, the mice in group A received the lung tumor promoter butylated hydroxy-toluene (BHT) in corn oil weekly by i.p. injection beginning at 7 weeks of age for 1 year; dosages of BHT were 300 mg/kg of body weight for the first week, 83 mg/kg the second week, and 150 mg/kg thereafter. In the tumor promotion study, the mice in group B received a single i.p. injection of 1 mg urethan (a lung tumor initiator) in saline

at 6 weeks of age. In the whole carcinogenesis study, the mice in group C were not injected with BHT or urethan. Exposure of the mice in all three groups to either clean air or diesel exhaust continued until 15 months of age, when all mice were sacrificed. It should be noted that exposures to diesel exhaust components (6.34 mg/m^3 DEP, 20.2 ppm CO, 11.6 ppm NO, 2.7 ppm NO_2, and 2.1 ppm SO_2) were maintained for the parental mice from the beginning of the study through mating, gestation, birth, and weaning of the offspring; when the offspring were 12 weeks of age, the exposures to diesel exhaust components (11.7 mg/m^3 DEP, 33.3 ppm CO, 19.5 ppm NO, 4.4 ppm NO_2, and 5.0 ppm SO_2) were increased and maintained at those concentrations until termination of the study. The results are as follows. In the whole carcinogenesis study (group C), the percent of pulmonary adenomas was significantly increased ($p<0.02$) in the female SENCAR mice exposed to diesel exhaust. However, in the tumor initiation study with concomitant treatment with BHT (Group A), diesel exhaust exposure resulted in a significant decrease ($p<0.01$) in tumor incidence in female SENCAR mice. No other significant between-group differences could be detected for adenoma incidence in any of the three studies. As the investigators stated, these results are of insufficient consistency to draw conclusions [85]. It is possible that the induction-latency period from first exposure to tumor development may be extremely long for animals exposed to diesel exhaust. Whether or not this is true can only be determined if the animals are observed for their entire lifetimes.

In 1982, Heinrich et al. [89] described a study in which groups of 48 Syrian golden hamsters were exposed 7-8 hours/day, 5 days/week from the age of 8 weeks for life to one of the following: (1) clean air, (2) the gaseous components of diesel exhaust alone (containing 18 ppm CO, 17 ppm NO, 1 ppm NO_2, 3 ppm methane, and 3 ppm SO_2), or (3) the gaseous components of diesel exhaust (as previously described) in combination with 3.9 mg/m^3 DEP. The diesel exhaust was generated by a 2.4-liter Daimler-Benz diesel engine using a European Reference Fuel with a sulfur content of 0.36%. No lung tumors were found in either group of diesel exhaust-exposed hamsters. The small number of animals per group limited the sensitivity of this study. In another portion of the study, groups of 48-72 hamsters were subcutaneously (s.c.) injected with 1.5 or 4.5 mg of diethylnitrosamine (DEN) per kg of body weight prior to exposures to either (1) particle-free diesel exhaust, (2) total diesel exhaust, or (3) clean air. In addition, groups of 48 hamsters received either 0.1 or 0.3 mg of dibenzo(a,h)anthracene [DB(a,h)A] by intratracheal (i.t.) instillation once a week for the first 20 weeks of exposure to either (1) particle-free diesel exhaust, (2) total diesel exhaust, or (3) clean air. Only 2 lung tumors were found in any of these experiments (one in the particle-free diesel exhaust-exposed group that received the 20 i.t. instillations of 0.1 mg DB(a,h)A and the other in the total diesel exhaust-exposed group that received s.c. injections of 1.5 mg DEN/kg). These animals with lung tumors died after experimental exposures of 75 and 76 weeks, respectively. Hamsters that were pretreated with a s.c. injection of 4.5 mg DEN/kg and then exposed to diesel exhaust (both

particle-free and total exhaust) exhibited significantly increased incidences of papillomas of the larynx and trachea as compared to hamsters that received only the s.c. injection. There were no statistical differences between the increases in the incidences of papillomas in hamsters that were exposed to only the gaseous fraction of the diesel exhaust and those that were exposed to whole diesel exhaust. The most plausible explanation, due to the similarity of the responses in both diesel-exposed groups, is that the effect may be due to the promotional properties of the irritant gases. The animals that were pretreated with a s.c. injection 1.5 mg DEN/kg also exhibited a tendency toward increased tumor incidences, but there were no significant differences among the exposure groups as compared to controls.

In an inhalation study by White et al. published in 1983 [90], Fischer 344 rats were exposed 20 hrs/day for 9 or 15 months to either clean air or diesel exhaust containing 0.25, 0.75, or 1.5 mg/m^3 DEP. One group of animals that was exposed for 15 months was permitted an 8-month recovery period. No information was given regarding other constituents in the diesel exhaust nor the type of engine or fuel used. Of the 90 rats exposed to diesel exhaust for 15 months followed by 8 months of recovery, 5 bronchoalveolar carcinomas were found (1 of the tumors was in the 0.25 mg/m^3 DEP group, 3 in the 0.75 mg/m^3 DEP group, and 1 in the 1.5 mg/m^3 DEP group). The tumors were very small, and detection required examination of serial sections. Focal pneumonia in both diesel exhaust-exposed rats and clean air-exposed controls was a possible

confounding factor. No carcinomas occurred in the 30 controls undergoing the same 23-month period in clean air or in the 180 Fischer 344 rats that were exposed to diesel exhaust for 9 or 15 months and then sacrificed (or in their 60 controls). In light of their findings, the investigators [90] decided that the study should be repeated (which is currently being done) to determine what effects pneumonia, age, and recovery period might have had on the study results.

4. Summary

Positive results obtained from three skin painting studies using solvent extracts from diesel exhaust particulate demonstrate skin tumor initiation or formation in mice [26,82,83]. The negative results in two other skin painting studies could be attributed to differences in mouse strain, composition of diesel exhaust emissions, and/or dose [81,84]. However, no conclusive evidence exists that inhalation of whole diesel exhaust results in the induction of tumors. Because chemical carcinogens are known to be contained in diesel exhaust particulate, the inability to demonstrate carcinogenic responses in animals chronically exposed appears to be associated with either low biologic availability of the chemical carcinogens or detoxification of the carcinogens prior to contact with the genetic material (or a combination of both) [44,85]. Further, the possible insensitivities of the test systems might have affected the results. A summary of the animal carcinogenicity studies is given in Table III-4.

Table III-4.--Summary of results of studies of carcinogenicity in animals

Animal studied	Result	Reference
Skin painting studies:		
Strain A mice	Positive	Kotin et al., 1955 [26]
LAF_1 mice	Negative	Mittler & Nicholson, 1957 [81]
CFLP mice	Positive	Misfeld, 1980 [82]
SENCAR mice	Positive	Nesnow et al., 1982 [83]
C3H/HeJ mice	Negative	DePass et al., 1982 [84]
Intraperitoneal injection study:		
Jackson strain A mice	Equivocal	Pepelko & Peirano, 1983 [85]
Inhalation studies:		
Wistar rats	Equivocal	Karagianes et al., 1981 [86]
Fischer 344 rats	Negative	Lewis et al., 1985 [44]
Strain A mice (Strong and Jackson)	Equivocal	Orthoefer et al., 1981 [87]
Strain A mice (Strong and Jackson)	Equivocal	Pepelko and Peirano, 1983 [85]
SENCAR mice	Equivocal	Pepelko and Peirano, 1983 [85]
Syrian golden hamsters	Equivocal	Heinrich et al., 1982 [89]
Fischer 344 rats	Equivocal	White et al., 1983 [90]

C. Toxicologic Effects

A summary of the toxicologic effects resulting from inhalation of whole diesel exhaust is presented in Table III-5. The types of engines and fuels used to generate the diesel exhaust utilized in the major studies are presented in Table III-6.

Decreased body weight gain and food intake of rats exposed to diesel exhaust containing 6 mg/m^3 DEP, 20 hours/day, 7 days/week for 2 months suggest that this exposure is near the maximum tolerated dose for the rat [85]. At lower DEP concentrations or reduced exposure schedules, studies have not demonstrated significant adverse effects of diesel exhaust on mortality, growth patterns, or organ weights (liver, kidney, spleen, or heart) in experimental animals [44,86,91,92,93,94,95]. However, increased lung to body weight ratios have been reported in rats, mice, and hamsters [92,93,94].

Accumulation of DEP in the lungs has been demonstrated to be both dose- and time-related, with the lungs and associated lymph nodes described as grey to black in color [91,96,97]. Statistically significant incidences of impaired pulmonary function (e.g., decreased lung capacity and diffusing capacity) suggestive of restrictive lung disease have been reported in rats, hamsters, and cats [97,98,99], but the impaired function (e.g., decreased expiratory flow) in monkeys was suggestive of an obstructive lung disorder [44].

Increased numbers of lavageable alveolar macrophages and white blood cells, indicative of inflammatory response in the lungs, have been reported in rats and guinea pigs [100,101,102,103]. Morphologic studies of lung tissue have revealed alveolar macrophages containing phagocytized DEP [44,86,97,103,104,105,106,107,108,109] with aggregations of these macrophages near terminal bronchioles [44,86,97,105,106,110,111], type II pneumocyte hyperplasia [44,97,105,108,110], and bronchiolar epithelial metaplasia [97,108,109]. Carbonaceous particles have been observed in associated lymph nodes [44,97,103,107]. Qualitative morphologic evidence of pulmonary interstitial fibrosis in mice, rats, guinea pigs, and cats exposed to diesel exhaust has also been reported [86,97,105,109].

Although no adverse effects have been observed on the subpopulations of lymphocytes in guinea pigs [112] nor on humoral or cellular immunities in rats [113], mice exposed to diesel exhaust have demonstrated increased mortality from infection by Streptococcus pyogenes [114] and increased severity of infection by influenza virus [115]. Rats exposed to diesel exhaust during growth and development have demonstrated reduced activity and learning ability [116]. No teratogenic or reproductive effects have been observed in mice, rats, rabbits, or monkeys [44,77,85].

Evidence of a pulmonary inflammatory response (e.g., increased protein concentrations and lysosomal enzyme activities in pulmonary lavage fluid and cells) has been reported in rats and mice exposed to diesel exhaust [102,117], although no evidence of an inflammatory response has been

reported in rats exposed to diesel exhaust under less intense exposure conditions [118]. The concentration of glutathione was decreased in the lungs of rats exposed to diesel exhaust for 18 months [117] and in the liver of rats exposed for 2 months (with a more intense exposure schedule) [119], suggesting that the glutathione had been utilized in detoxification pathways. Exposure to low concentrations of DEP for 3 months did not influence glutathione concentrations in the lungs, liver, or heart of rats or guinea pigs [119]. The activity of microsomal aryl hydrocarbon hydroxylase (AHH) was induced in the lungs, liver, and prostate of rats exposed to diesel exhaust for 42 days [120]; however, no induction (AHH) was observed in the lungs or liver of rats or mice exposed for 8-9 months [121,122]. Exposure to diesel exhaust has not been shown to produce adverse effects on microsomal cytochrome P_{450} in the lungs or liver of rats or mice [106,121,122,123]. Although some variations in serum enzyme activities have been reported in cats and hamsters exposed to diesel exhaust [85,89], most major serum enzyme and hematologic parameters in rats, guinea pigs, and cats have not been significantly altered [85,86,95,106]. Based on the biochemical, clinical chemical, and hematologic data reported in the literature, inhalation of diesel exhaust has not produced profound cytotoxicity in the respiratory tract nor hepatotoxicity in experimental animals.

Table III-5.--Summary of results of studies of toxicologic effects of inhalation of whole diesel exhaust

Effects	Species	Length of study (months)	Maximum diesel exhaust particulate (DEP) concentration (mg/m^3)	Exposure schedule		Reference
				Hours/day	Days/week	
General physiology						
Decreased body weight gain; food intake	Rat	2	6	20	7	85
No effect on body weight; mortality	Rat	18	7	7	5	91
	Rat	12	1.5	20	5.5	92
	Rat, mouse, hamster	3	1.5	20	7	93
	Rat	9	1.5	20	5.5	94
	Rat	20	8.3	6	5	86
	Rat, monkey	24	2	7	5	44
Increased lung to body weight ratios	Rat	12	1.5	20	5.5	92
	Rat, mouse, hamster	3	1.5	20	7	93
	Rat	3	1.5	20	5.5	94
No effect on liver, kidney, spleen, or heart weights	Rat	12	1.5	20	5.5	92
	Rat, mouse, hamster	3	1.5	20	7	93
	Rat, guinea pig	18	1.5	20	5.5	95
Increased liver weight	Hamster	6	6	8	7	98
Decreased lung and kidney weights	Cat	27	12[a]	8	7	108
Pulmonary physiology						
Increased lung burden of DEP (dose-related)	Rat	4.5	4.1	7	5	96
	Mouse	24	7	7	5	97
	Rat	30	7	7	5	97
	Rat	18	7	7	5	91
No effect on functional residual capacity; airway resistance	Rat	24	2	7	5	106
	Rat	30	0.35	7	5	97
	Rat	12	1.5	20	5.5	124
	Cat	24	12[a]	8	7	125
Decreased vital capacity; residual volume; carbon monoxide transfer factor	Hamster	6	6	8	7	98

Table III-5. (Continued)--Summary of results of studies of toxicologic effects of inhalation of whole diesel exhaust

Effects	Species	Length of study (months)	Maximum diesel exhaust particulate (DEP) concentration (mg/m^3)	Exposure schedule		Reference
				Hours/day	Days/week	
Increased functional residual capacity; expiratory volume and flow	Rat	20	1.5	20	5.5	124
Decreased total capacity; dynamic compliance; carbon monoxide diffusing capacity--no effect on expiratory flow	Rat	30	7	7	5	97
Increased vital capacity; total capacity--no effect on residual volume	Rat	1	6	20	7	126
Decreased vital, total, and diffusing capacities--no effect on expiratory flow	Cat	24	12[a]	8	7	99
Decreased expiratory flow--no effect on vital or diffusing capacities	Monkey	24	2	7	5	44
Decreased clearance of DEP	Mouse	24	7	7	5	97
	Rat	30	7	7	5	97
	Rat	3.5	6	20	7	104
Greater long term retention of DEP in guinea pigs than in rats	Rat, guinea pig	12	7	--[b]	--[b]	127
Increased numbers of lavageable alveolar macrophages (AM), and polymorphonuclear leukocytes, lymphocytes, or eosinophils	Rat	1	6	20	7	100
	Rat, guinea pig	12	1.5	20	5.5	101
	Rat	12	1.5	20	5.5	102
	Rat, guinea pig	11	1.5	20	5.5	103
Pulmonary morphology						
Presence of AM containing DEP	Mouse	24	7	7	5	97
	Rat	30	7	7	5	97
	Guinea pig	24	1.5	20	5.5	105
	Rat	3.5	6	20	7	104
	Rat, guinea pig	11	1.5	20	5.5	103
	Rat	20	8.3	6	5	86
	Rat	12	2	7	5	106
	Guinea pig	2	6	20	7	107
	Cat	27	12[a]	8	7	108,109
	Rat, monkey	24	2	7	5	44

Table III-5. (Continued)--Summary of results of studies of toxicologic effects of inhalation of whole diesel exhaust

Effects	Species	Length of study (months)	Maximum diesel exhaust particulate (DEP) concentration (mg/m^3)	Exposure schedule		Reference
				Hours/day	Days/week	
Probable DEP in associated lymph nodes	Mouse	24	7	7	5	97
	Rat	30	7	7	5	97
	Rat, guinea pig	11	1.5	20	5.5	103
	Guinea pig	2	6	20	7	107
	Rat, monkey	24	2	7	5	44
Type II pneumocyte hyperplasia	Rat	30	7	7	5	97
	Guinea pig	24	6	20	5.5	108
	Rat	2	6	20	5.5	110
	Rat, monkey	24	2	7	5	44
	Cat	27	12[a]	8	7	108
Aggregations of AM containing DEP near terminal bronchioles	Mouse	24	7	7	5	97
	Rat	30	7	7	5	97
	Guinea pig	24	6	20	5.5	105,111
	Rat	2	6	20	5.5	110
	Rat	20	8.3	6	5	86
	Rat	12	2	7	5	106
	Rat, monkey	24	2	7	5	44
Bronchiolar epithelial metaplasia	Mouse	24	7	7	5	97
	Rat	30	7	7	5	97
	Cat	27	12[a]	8	7	108,109
Evidence of fibrosis	Mouse	24	7	7	5	97
	Rat	24	7	7	5	97
	Guinea pig	24	6	20	5.5	105
	Rat	20	8.3	6	5	86
	Cat	27	12[a]	8	7	109
General morphology						
Structural changes in hepatic microsomes	Hamster	19	3.9	8	5	89
No effect on heart; pulmonary arteries	Rat	24	2	7	5	44

Table III-3. (Continued)--Summary of results of studies of toxicologic effects of inhalation of whole diesel exhaust

Effects	Species	Length of study (months)	Maximum diesel exhaust particulate (DEP) concentration (mg/m^3)	Exposure schedule		Reference
				Hours/day	Days/week	
Biochemistry						
Acellular pulmonary lavage fluid:						
Increased protein; lysosomal enzyme activities	Mouse, rat	18	7	7	5	117
No effect on protein; lysosomal enzyme activities	Rat	24	2	7	5	118
No effect on acid phosphatase activity	Mouse, rat	18	7	7	5	117
	Rat	24	2	7	5	118
Increased reduced glutathione (GSH); glutathione reductase activity	Mouse, rat	18	7	7	5	117
Cells from pulmonary lavage:						
Decreased aryl hydrocarbon hydroxylase (AHH) activity	Rat	1	6	20	7	100
Increased protein; β-glucuronidase; acid phosphatase	Rat	12	1.5	20	5.5	102
Increased β-N-acetylglucosaminidase	Rat	24	2	7	5	118
No effect on protein; other lysosomal enzymes; AM viability	Rat	24	2	7	5	118
GSH:						
Decreased in lung	Rat	18	7	7	5	117
Increased in lung	Rat	2	6	20	5.5	119
Decreased in liver	Rat	2	6	20	5.5	119
No effect in lung; liver; heart	Rat, guinea pig	3	0.75	20	5.5	119

Table III-5. (Continued)--Summary of results of studies of toxicologic effects of inhalation of whole diesel exhaust

Effects	Species	Length of study (months)	Maximum diesel exhaust particulate (DEP) concentration (mg/m^3)	Exposure schedule		Reference
				Hours/day	Days/week	
Microsomal AHH:						
Decreased in lung	Rat	9	1.5	20	5.5	121
Increased in lung; liver; prostate	Rat	1[c]	6	20	7	120
No effect in lung; liver	Mouse	8	6	20	7	122
No effect in liver	Rat	9	1.5	20	5.5	121
No effect on microsomal cytochrome P_{450} in lung and/or liver	Rat	12	2	7	5	106
	Rat	24	2	7	5	123
	Mouse	8	6	20	7	122
	Rat	9	1.5	20	5.5	121
Increased phospholipids and cholesterol in lung	Rat	9	1.5	20	5.5	94
Collagen in lung:						
Increased	Rat	18	7	7	5	91
No effect	Rat	9	1.5	20	5.5	94
	Rat	12	2	7	5	106
Clinical chemistry and hematology						
Increased alkaline phosphatase activity	Cat	27	12[a]	8	7	85
	Hamster	7	3.9	8	5	89
Increased carboxyhemoglobin	Rat	20	8.3	6	5	86
Increased glutamic-oxalacetic transaminase; lactic dehydrogenase; gamma-glutamyl transferase	Hamster	7	3.9	8	5	89
No effects on other major parameters	Cat	27	12[a]	8	7	85
	Rat, guinea pig	18	1.5	20	5.5	95
	Rat	20	8.3	6	5	86
	Rat	12	2	7	5	106

Table III-5. (Continued)--Summary of results of studies of toxicologic effects of inhalation of whole diesel exhaust

Effects	Species	Length of study (months)	Maximum diesel exhaust particulate (DEP) concentration (mg/m^3)	Exposure schedule		Reference
				Hours/day	Days/week	
Immunology						
No effect on humoral (hemolytic plaque assay) or cellular (lymphocyte blast transformation assay) immunity	Rat	24	2	7	5	113
No effect on B, T, or null cells in blood, spleen, or mediastinal nodes	Guinea pig	2	1.5	20	5.5	112
Increased severity of influenza virus infection	Mouse	6	2	7	5	115
Increased susceptibility to *Streptococcus pyogenes*	Mouse	11	6	8	7	114
No effect (mortality) with viral pathogen (A/PR8-34)	Mouse	11	6	8	7	114
Reproduction and teratology						
No effect on numbers of abnormally shaped sperm	Mouse	10	6	8	7	77
No effect on sperm motility, velocity, density, or morphology	Monkey	24	2	7	5	44
No effect on fetal visceral or skeletal abnormalities	Rat, rabbit	--[d]	6	8	7	85
No effect on fertility or survival through three generations	Mouse	--[e]	6	8	7	85

Table III-5. (Continued)--Summary of results of studies of toxicologic effects of inhalation of whole diesel exhaust

Effects	Species	Length of study (months)	Maximum diesel exhaust particulate (DEP) concentration (mg/m^3)	Exposure schedule		Reference
				Hours/day	Days/week	
Behavioral						
Decreased spontaneous locomotor activity	Rat	4	6	8	7	116
Decreased acquisition of learning task in adult animals	Rat	--[f]	6	20	7	116

[a] 6 mg/m^3 from weeks 1-61; 12 mg/m^3 thereafter

[b] Single exposure to 7 mg ^{14}C-labeled DEP/m^3 for 45 min, or 2 mg/m^3 for 140 min

[c] 42 days

[d] Rats exposed during days 5-16 of gestation; rabbits, days 6-18

[e] Mice exposed from 100 days prior to mating through maturity of F_2 generation

[f] Exposed as neonates (1-17 days), tested as adults (15 months)

Table III-6.--Engines and fuels used to generate diesel exhaust for inhalation studies of toxicologic effects

Investigators	Generation of diesel exhaust: Engine	Generation of diesel exhaust: Fuel	References
Lovelace Biomedical and Environmental Research Institute	5.7-liter, General Motors Oldsmobile	No. 2 diesel fuel	91,96,97
National Institute for Occupational Safety and Health	4-cylinder, 4-cycle, 100-bhp, 7.0-liter displacement, Caterpillar model 3304	No. 2 diesel fuel	44,106,113,115,118,123
U.S. Environmental Protection Agency	6-cylinder, 92-bhp, 3.24-liter displacement, Nissan CH 6-33	No. 2 diesel fuel	77,85,98,99,107,108,109 114,116,120,122,125,126
General Motors Research Laboratories	4-cycle, 5.7-liter displacement, indirect injection, 1978 General Motors Oldsmobile	Type 2D fuel	92,93,94,95,100,101,102, 103,104,105,110,111,112, 119,121,124,127,128

IV. EFFECTS IN HUMANS OF EXPOSURE TO DIESEL EXHAUST

A. Studies of Effects other than Cancer

This section evaluates studies concerning the relationship between diesel exhaust exposure and adverse health effects primarily to the respiratory system. The populations described in these studies were exposed in both experimental and occupational settings. The studies describing occupational exposures attempted to ascertain the nature and extent of adverse health effects among railroad roundhouse workers, bus garage workers, non-coal mine workers, and coal mine workers. The studies are presented in order of increasing environmental complexity, beginning with a report of experimental exposure and ending with studies that evaluate the effects of diesel exhaust on coal miners.

1. Experimental Exposures

Katz et al., 1959 [129], described the experience of 14 chemists and their assistants who were exposed to diesel exhaust emitted from diesel-powered locomotives inside a 6,032-foot railroad tunnel. Air sampling stations were located at seven points in the tunnel. Each station was occupied by one chemist and one assistant. Over a three-day period, 104 separate trains passed through the tunnel. Air samples were collected and analyzed for oxides of nitrogen (NO_x), NO_2, CO, formaldehyde, and total particulate matter; the ranges of the mean concentrations were 0.4-2.8

parts per million (ppm) NO_2, 9.1-38.4 ppm NO_x, 1.3-8.6 ppm CO, 1.2-5.8 ppm formaldehyde, and 0.9-2.3 milligrams per cubic meter (mg/m^3) total particulate. Samples analyzed for SO_2 revealed a concentration range of "zero to 0.13 ppm."

The authors [129] reported that the 14 chemists and assistants were given brief physical examinations; however, they did not indicate when the examinations were conducted or whether pre-exposure examinations were administered. Pulse rates and blood pressures were within normal limits; there were no complaints of impaired vision or tearing and no unusual findings following chest examinations. On three "brief occasions" some workers complained of minor eye and throat irritation. Blood samples obtained from the group were analyzed for carboxyhemoglobin. With two exceptions, all samples indicated an increase in carboxyhemoglobin following an 8-hour workshift; this finding was correlated with cigarette smoking, however, and not with exposure to diesel exhaust. Although the complaints of eye and throat irritation were correlated with exposure to diesel exhaust, they were not correlated with concentrations of any particular diesel exhaust component. The authors [129] did note that on several occasions the locomotives were allowed to idle at the midpoint of the tunnel, but they did not mention if this practice was correlated with the eye and throat irritation.

In a 1965 [130] follow-up to a 1964 study of 364 enginehouse workers [131], Battigelli described additional studies conducted on 18 volunteers exposed

to dilute diesel exhaust obtained from a 7-horsepower, 1-cylinder, 4-cycle diesel engine; the fuel type was not specified. The amounts of NO_2, SO_2, CO, acrolein, total hydrocarbons, total aldehydes, and formaldehyde for the three dilutions of diesel exhaust are presented in Table IV-1. One of the dilutions (unspecified by the authors) was selected to mimick the worst conditions found in the enginehouse in 1964. It should be noted that Battigelli [130] did not specify how the air samples were analyzed, nor did he state the units of concentration in which the values are expressed.

Table IV-1.--Composition of diluted diesel exhaust

	Average "Concentration"*		
	Dilution A	Dilution B	Dilution C
NO_2	1.3	2.8	4.2
SO_2	0.2	0.5	1
CO	<20	30	55
Total aldehydes	<1.0	<1-2	1-2
Acrolein	<0.05	<0.05	<0.05
Formaldehyde	<0.1	<0.1	<0.1
Hydrocarbons	<2.0	2.5	3.2

*Values undefined, expressed as in original manuscript

Adapted from Battigelli [130]

By simultaneously recording esophageal pressure and air flow determined by electrical differentiation of the volume signs from spirometry, Battigelli [130] was able to estimate that there was no significant

resistance to pulmonary flow as a result of a 1-hour exposure to the diluted diesel exhaust, nor did any subject complain of adverse effects, except for a slightly unpleasant taste that disappeared following cessation of exposure. In a separate experiment, eye irritation was reported after 6 minutes of exposure to "Dilution A," after 3 minutes and 20 seconds of exposure to "Dilution B," and after 40 seconds of exposure to "Dilution C."

2. Railroad Enginehouse Workers

In 1964, Battigelli et al. [131] investigated the prevalence of adverse effects among a group of 210 male workers exposed to diesel exhaust in three enginehouses. An additional 154 male workers matched for age, body size, and "past extrapulmonary medical history" (no explanation of this phrase was provided) served as a comparison population. The exposed workers at the time of the study had an average age of 49.8 years and an average exposure to diesel exhaust of 9.6 years. The comparison population had an average age of 50.0 years and no present or prior diesel exhaust exposure.

Exposure to diesel exhaust showed great seasonal variation. Battigelli et al. [131] reported that during the summer months when the doors of the enginehouse were open, the concentration of diesel exhaust a "few feet" away from the engine exhaust domes was 70 times less than at the domes themselves. Winter and summer concentrations of NO_2, SO_2, acrolein,

total aldehydes, and total hydrocarbons are presented in Table IV-2. The sampling duration was not specified by Battigelli et al. [131].

Table IV-2.--Estimated concentrations of diesel exhaust components as measured in the summer and in the winter (expressed in ppm)

	Winter		Summer	
	Median	Maximum	Median	Maximum
NO_2	0.5	1.8	<0.5	1.5
SO_2	<1	4	<<<2	<<<2
Acrolein	<0.1	0.1	<<0.1	0.15
Total aldehydes	<0.5	1.7	<0.5	1
Total hydrocarbons	2	5	<2	>2

Values were derived from Figure 1 of Battigelli et al. [131].

Battigelli et al. [131] found no significant clinical differences in pulmonary function nor in prevalence of dyspnea (difficult or labored breathing), cough, or sputum production between the exposed workers and the unexposed comparison population; the prevalence of eye irritation was not studied.

3. Bus Garage Workers

In a 1966 report, El Batawi and Noweir [132] described the prevalence of a variety of complaints and clinical findings among 161 workers from two garages where diesel-powered buses were serviced and repaired. The workers ranged in age from 20 years to more than 60 years; 72% of the workers were described as "heavy smokers." Although the authors did not define "heavy smokers," they did note that most used a tobacco mixed with molasses, a practice that produces a tobacco known to irritate the throat and cause an increase in coughing and phlegm production. Concentrations of diesel exhaust components in the two garages are described in Table IV-3.

Table IV-3.—Ranges of mean concentrations of diesel exhaust component in two diesel bus garages

	Garage 1*	Garage 2*
NO_2 (ppm)	0.4–1.3	0.4–1.4
Aldehydes (ppm)	0.6–44.1	0.7–35.4
SO_2 (ppm)	0.14–0.81	0.13–0.71
Particulate (mg/m^3)	2.15–4.25	1.34–4.51

*Highest values obtained close to exhaust

Adapted from El Batawi and Noweir [132]

As noted in Table IV-3, the highest contaminant concentrations were obtained close to the exhaust of buses. Therefore, it is not possible to determine how these exposures contributed to the prevalence of symptoms described by El Batawi and Noweir [132]. Complaints of headache were made by 37% of workers, dizziness by 30%, throat irritation by 19%, cough and phlegm by 11%, and eye irritation by 42% of the workers. There were no clinical findings of adverse pulmonary function. Because of the unusual smoking characteristics of these workers, it is not possible to draw any conclusions concerning the prevalence of symptoms associated with exposure to diesel exhaust.

In 1982, Fredga et al. [133] reported the results of an investigation of the nature and frequency of chromosome changes among male drivers of both diesel- and gasoline-powered vehicles in Sweden. The workers studied by Fredga et al. were matched by age, length of time at work, and smoking habits. There were 12 workers (6 smokers and 6 nonsmokers) who drove 8- to 10-ton diesel trucks and 12 workers (6 smokers and 6 nonsmokers) who were exposed to gasoline fumes from a variety of conventionally-powered vehicles (Ford Tanus, Volkswagen van, "light 8-cylinder vehicles," and "private cars" used as taxis). A group of 12 automobile inspectors (6 smokers and 6 nonsmokers) was also studied, and a final group of 12 office workers and prison guards (6 smokers and 6 nonsmokers) was used as the referent population. Information was solicited by questionnaire concerning past employment, recent radiographic examination, recent viral infection, and exposure to solvents and to other substances known to

cause chromosome damage. Although Fredga et al. [133] reported that three blood samples were collected from each subject during May and June of 1978, they provided no information on the protocol for collection, nor did they specifically mention whether alcohol use was considered.

No statistically significant group differences in the frequencies of chromosome aberrations (gaps and breaks) or sister chromatid exchanges were observed, except when smokers were compared to nonsmokers within the same group. One exception (based on one of 18 different statistical analyses) was a statistically significant increase in chromosome breaks among diesel exhaust-exposed nonsmokers, but the authors concluded that this might have occurred by chance.

4. Workers in Mines other than Coal Mines

A 1978 report by Gamble et al. [134] identified a cohort of 246 salt miners (236 male; 10 female) from five salt mines. Pulmonary function data were obtained for 187 workers; however, it was not specified how many were women. The population was divided into nonsmokers (18%), ex-smokers (23%), and smokers (59%). The characteristics of the miners for whom pulmonary function data was available and of the mines in which they worked are presented in Table IV-4.

Table IV-4.--Some characteristics of salt miners exposed to diesel exhaust and of their work environments

	Nonsmokers	Ex-smokers	Smokers
Mean age (years)	37.4	42.6	37.0
Mean NO_2 (ppm)	1.71	2.04	1.87
Mean respirable particulate (mg/m^3)	0.62	0.80	0.70
Number of miners	35	44	108

Adapted from Gamble et al. [134]

For the total group of salt miners, NO_2 concentrations ranged from nondetectable to 5.76 ppm, and respirable particulate ranged from 0.01 mg/m^3 to 6.2 mg/m^3. Based on results obtained using indicator tubes, SO_2 concentrations were reported to be below 1 ppm, and formaldehyde was reported to be below 0.5 ppm [134]. Gamble et al. [134] indicated that diesel equipment was not used in one of the mines, and the number of diesel units in use in the remaining 4 mines ranged from 1 to 50. No associations between miners and mines were provided.

Gamble [134] recorded pulmonary function by measuring preshift forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) for each of the 187 workers, and he used those values to obtain peak flow forced expiratory flow rate at 25% of FVC (FEF_{25}), peak flow forced expiratory flow rate at 50% of FVC (FEF_{50}), and peak flow forced expiratory flow rate at 75% of FVC (FEF_{75}). After-shift pulmonary

function values were determined from total lung capacity and flows at preshift percentages of FVC. Change in pulmonary function test (PFT) results was obtained from the difference between pre- and post-shift results. No statistically significant associations between changes in pulmonary function and in NO_2 and respirable particulate combined were detected. When NO_2 was used as the only significant variable, over-the-shift decrements in pulmonary function were observed. The slopes of the regressions of NO_2 and changes in FEV_1, FEF_{25}, FEF_{50}, and FEF_{75} were significantly different from zero. Based on other studies of acute pulmonary function effects over a workshift among miners exposed to respiratory irritants, Gamble et al. [135] expected to find either no change or a slight increase in the change in pulmonary function. The authors [134] concluded that the observed effects were due to variations in NO_2 within each mine.

In a series of 1983 reports by Gamble et al. [135] and Gamble and Jones [136,137], the respiratory morbidity was investigated for a group of 259 white male salt miners working in five sodium chloride mines; two of the mines used diesel extensively. In the first report, 1983 [135], Gamble et al. attempted to determine whether or not respiratory symptoms, radiographic findings, and pulmonary function were correlated with NO_2, respirable particulate, or years worked underground. They also attempted to determine if there was an increased prevalence of morbidity among the salt miners as compared to others having no diesel exposure.

The five mines studied were identified as A, B, C, D, and E. In mine A, diesels were introduced during the years 1963 to 1967; in mine B, they were introduced in 1963; in mine D, in 1956; and in mine E, in 1957. No diesels were used in Mine C. Some estimates of contaminant concentrations were also provided, but the raw data were not supplied; the authors described these as "relatively rough" estimates [135]. All samples collected for SO_2 and formaldehyde were below the limits of detection (1 ppm and 0.5 ppm, respectively) for the indicator tubes used. Table IV-5 presents approximate values for NO_x, NO_2, and CO. Average concentrations for NO_2 and respirable particulates are provided in Table IV-6, but it is not clear how these values were generated because no information was provided to indicate that they were based on any values other than indicator tube estimates. The characteristics of the study population are also presented in Table IV-6.

Table IV-5.--Approximate mean concentrations of NO_x, NO_2, and CO in the atmospheres of five sodium chloride mines (expressed in ppm)

	Mine				
	A	B	C	D	E
NO_x	2	4	1	8	4
NO_2	<0.5*	2	<0.5*	5	2
CO	10	10	<5*	12	6

*Non-detectable

Values derived from Figure 3 of Gamble et al. [135]

Table IV-6.--Some characteristics of white male salt miners exposed to diesel exhaust and of their work environments

	Nonsmokers	Ex-smokers	Smokers	Total
Mean age (years)	36.9	45.2	37.7	39.3
Mean years worked	9.7	14.8	9.3	10.6
Mean respirable particulate (mg/m^3)	0.59	0.56	0.57	0.57
Mean NO_2 (ppm)	1.26	1.40	1.32	1.33
Number of miners with <10 years experience	32	26	100	158
Number of miners with ≥10 years experience	18	33	50	101
Number of miners	50	59	150	259

Adapted from Gamble et al. [135], characteristics of miners from individual mines were not provided.

Several working populations were compared to the salt miner populations. All comparisons were adjusted for age, smoking, and (for pulmonary function test values) height. White male miners from six potash mines, all of which were diesel-equipped, were used for comparison. A non-mining comparison population was also constructed. This group (referred to as the blue collar group) consisted of male and female workers from the electronics industry, synthetic textile manufacturing, bakeries, and bottling plants. These groups were compared to both surface and underground coal miners.

The characteristics of the comparison populations are presented in Table IV-7. It was not stated by the authors why the values for dust and NO_2 were expressed as means when the values for the salt mining population were expressed as averages.

Table IV-7.--Characteristics of comparison populations and of their work environments

	Potash workers	Aboveground coal miners	Underground coal miners	Blue collar workers
Mean age (years)	41	44	39	38
Mean years worked	16	18	15	12
Mean total dust (mg/m^3)	3.45	NA*	NA	NA
Mean respirable dust (mg/m^3)	NA	1.44	1.36	NA
Mean NO_2 (ppm)	0.90	NA	NA	NA
Nonsmokers	178	105	1112	207
Ex-smokers	244	150	1234	194
Smokers	451	214	3023	442
Number of miners	875	509	5722	843

*NA = Not available

Adapted from Gamble et al. [135]

Each of the salt miners was administered a questionnaire and given a chest x ray and a spirometry test. Complete work histories were also

obtained from questionnaires or personnel records "when available." The effects of age, smoking, and exposure on symptom prevalence were analyzed using a logistic analysis and presented by age category (those fewer than 40 years, those 40 or more years) and smoking category (nonsmokers, ex-smokers, and smokers). In order to determine if a dose relationship existed, Gamble et al. [135] classified the salt miners into groups of high, medium, and low respirable particulate and NO_2 exposures. Comparison populations were adjusted for the salt mining population on the basis of age and smoking category. The overall symptom prevalence (by percentage) for the salt mining populations is presented in Table IV-8.

Table IV-8.--Overall prevalence of symptoms among salt miners by mine

	Mine					
	A	B	C	D	E	Total
Cough (%)	0	22.7	18.5	29.6	24.7	24.3
Dyspnea (%)	5.9	0	0	8.3	10.6	7.3
Phlegm (%)	0	13.6	14.8	37.0	30.6	28.2
Number of miners	17	22	27	108	85	259

Adapted from Gamble et al. [135], values were based on questionnaire response.

Further analysis by Gamble et al. [135] revealed that the prevalence of cough and phlegm was related to age and smoking. Dyspnea was related only to age, not to smoking or diesel exhaust exposure.

The authors stated [135]: "In summary, there were no consistent differences in age- and smoking-adjusted symptom prevalence among the salt, potash, blue collar, and aboveground coal populations. The underground population consistently had an elevated symptom prevalence."

The authors did note, however, that the prevalence of phlegm was elevated and was exposure-related among salt miners, but only when compared to the blue collar workers. As noted previously, the salt miners were all males, while the blue collar comparison group consisted of both males and females. The effect that this difference might have had on the results was not discussed.

Gamble et al. [135] also made an extensive evaluation of the salt miners' pulmonary function by measuring FEV_1, FVC, FEF_{50}, and FEF_{75}. While these parameters were uniformly lower for salt miners in relation to all the comparison populations, the differences were small (not statistically significant), and there were no correlations with diesel exhaust exposure.

As the authors [135] stated:

> "Problems that make the assessment of risk [in the salt miner population] difficult include: relatively rough estimates of exposure, imperfect measure of effect, undocumented role of selection, high correlation of age and estimated exposure, and lack of contemporary regional comparison groups."

In the second report, 1983 [136], Gamble and Jones continued to explore the respiratory health of the same cohort of 259 salt miners using tenure in jobs with diesel exhaust exposure as the exposure variable. The comparison population used for this study was the "blue collar" group described above. As in the first report [135], only the prevalence of phlegm was exposure-related; the average FVC and FEV_1 were both about 96% of expected, well within the normal range.

In the third report, 1983 [137], Gamble and Jones stated that the prevalence of phlegm was increased in both the "intermediate" and the "high" diesel exhaust-exposed categories and that FVC in the "high" exposure category (>90% tenure in jobs with diesel exhaust exposure) was reduced as compared to the "low" exposure category. However, considering the authors' own caveats given in the first report [135] concerning the accuracy of the exposure data, these trends are difficult to interpret.

Considered either individually or as a group, these reports [135,136,137] do not demonstrate any consistent adverse respiratory effects that can be clearly attributed to diesel exhaust exposure. The dose-related finding of an increase in phlegm may be due to mine dust rather than to diesel exhaust exposure.

In a similar type of study published in 1982, Attfield et al. [138] explored the effects of diesel exhaust on the respiratory health of 630

potash miners from 6 potash mines. Questionnaire, chest x ray, and spirometric data were collected in 1976. Characteristics of the miners and mines are presented in Table IV-9.

Table IV-9.--Characteristics of 630 potash miners and 6 potash mine environments

	Mine						
	A	B	C	D	E	F	Total
Mean age (years)	43	40	39	31	43	42	39
Mean pack-years of smoking	29	26	29	19	32	29	27
Mean years of mining potash	14	13	11	5	17	15	12
Mean years of diesel exposure	14	13	10	5	8	14	10
Mean full-shift NO_2 (ppm)	0.7	0.7	3.3	0.5	0.1	0.3	--
Mean total dust (mg/m^3)	9	23	23	11	18	19	--
Mean CO (ppm)	5	7	9	7	5	5	--
Mean aldehydes (ppm)	0.7	4.0	3.2	0.8	0.7	0.1	--
Start of mine operations	1964	1952	1940	1964	1934	1964	--
Year of diesel introduction	1964	1952	1950	1964	1966	1964	--
Number of workers	56	103	122	121	121	107	630

Adapted from Attfield et al. [138]

The prevalence of respiratory symptoms was related only to smoking (Table IV-10). No correlation was found between symptoms and tenure, dust exposure, NO_2, CO, or aldehydes.

Table IV-10.--Prevalence of symptoms among potash miners (expressed as percentage)

	Mine					
	A	B	C	D	E	F
Nonsmokers						
Cough	8	15	23	3	8	11
Dyspnea	8	11	3	0	3	6
Phlegm	25	19	23	28	19	14
Smokers						
Cough	48	33	43	34	44	22
Dyspnea	16	12	8	9	14	10
Phlegm	52	33	52	31	43	24

Adapted from Attfield et al. [138], values were based on questionnaire response.

Attfield, 1978 [139], described a study of silica and diesel exhaust exposure on underground metal and nonmetal miners. The study was conducted during a 21-month period; 2,659 miners from 21 mines were studied. Of the 21 mines, 8 were metal, 6 were potash, 5 were salt, and 2 were trona. Attfield [139] noted that diesels were used in only 18 of the mines, but he did not indicate the types of the 3 mines that did not use diesels. Means of the mine averages for contaminants found in the mines are presented in Table IV-11. Characteristics of the miners are presented in Table IV-12.

Table IV-11.--Concentrations of airborne contaminants by type of mine

	Type of mine			
	Metal	Potash	Salt	Trona
Respirable dust (mg/m^3)	0.94	3.45	1.22	6.24
Respirable quartz (%)	4.58	0.89	0.56	1.55
NO_2 (ppm)	0.20	0.90	1.25	0.16
CO (ppm)	6.1	7.5	11.2	8.1
Aldehydes (ppm)	0.68	1.63	0.46	0.36

Adapted from Attfield [139], values are means of mine averages.

Table IV-12.--Characteristics of miners and mines by type of mine

	Type of mine			
	Metal	Potash	Salt	Trona
Mean age (years)	41	39	40	30
Smokers (%)	63	67	71	75
Years of diesel use in mines	10	16	13	8
Number of miners	1709	532	150	268

Adapted from Attfield [139]

The years of diesel usage in the mines were used as a surrogate for diesel exposure. It is also notable that about 70% of these miners were tobacco smokers. The prevalence of respiratory symptoms was determined by questionnaire. Clinical evaluation of respiratory health was conducted using spirometry and posterior-anterior chest x ray. Based on the questionnaire, an increase in the prevalence of persistent cough was associated with aldehyde exposure, but this finding was not supported by spirometric data. No adverse symptoms or pulmonary function decrements were related to NO_2, CO, CO_2, dust, or quartz. No comment was made by the authors [139] as to whether the prevalence of persistent cough was related to the 70% of this population that smoked.

5. Coal Mine Workers

In this section, reports of studies that have addressed acute and chronic effects of diesel exhaust on underground coal miners are examined.

Nordenson et al., 1981 [140], described the chromosomal aberrations in a group of 14 male miners from Sweden who were exposed to diesel exhaust. The mine was not specified as being aboveground or underground. The results from the miners were compared to a group of 15 office workers who ranged in age from 26 to 60 years (mean = 45.9 years). The miners ranged in age from 20 to 57 years (mean = 37.4 years), and their work experience underground ranged from 2 to 36 years (mean = 11.6 years). Diesel engines were first introduced in the mine in 1973; therefore, at the time

of the study the miners had eight or fewer years of exposure. Five of the miners and five of the office workers were cigarette smokers.

Using a man-year of 1,700 hours, Nordenson et al. [140] estimated that the miners had an annual exposure to diesel fumes of about 150 hours. Concentrations of CO ranged from 5-10 ppm, NO_2 ranged from 0.5-1 ppm, and radon gas was less than 0.4 becquerel/liter (using an equilibrium ratio of 50% for radon gas, 0.4 Bq/l is equivalent to about 0.054 working levels).

Chromosomal aberrations were recorded according to the recommendations of classification made by the World Health Organization, and statistical analysis was performed using the chi-square test [140]. After examining 1,400 cells from each miner and 1,500 cells from each referent, Nordenson et al. [140] found a slightly greater incidence of aberrations ($p<0.05$) among the referents and a significantly greater frequency of total aberrations ($p<0.001$), breaks ($p<0.01$), and gaps ($p<0.025$) among the smokers. Diesel exhaust exposure was not found to correlate with either total aberrations, gaps, or breaks.

In a study published in 1982, Ames et al. [141] examined a group of 60 miners from six diesel-equipped coal mines for evidence of acute respiratory effects associated with exposure to diesel exhaust. Changes over the workshift in FVC, FEV_1, and FEF_{50} were used as hallmarks of acute respiratory effects.

The study population was developed by identifying 10 male miners from each of the 6 diesel-equipped coal mines. A comparison group of 90 miners was generated from existing NIOSH data bases and from non-diesel coal mines in the vicinity of the 6 diesel-using mines. The exposed miners and comparison miners were matched for geographic area, smoking status, race, age, and years worked underground. However, the authors [141] stated that matching on these characteristics was not "optimal." Therefore, matching was based on time of year, calendar year, geographic location of the mine, time of shift, and race. The characteristics of the study and comparison groups are presented in Table IV-13.

Table IV-13.--Characteristics and symptoms of coal miners and characteristics of their working environments

	Diesel-equipped mines	Non-diesel mines
Mean age (years)	29.3 ± 10.1	44.4 ± 12.6
Mean time underground (years)	4.8 ± 7.1	20.7 ± 12.6
Mean respirable dust (mg/m^3)	2.0 ± 1.7	1.4 ± 1.5
Mean NO_2 (ppm)	0.2 ± 0.1	--
Smokers (%)	45.0	43.0
Miners with coal workers' pneumoconiosis (%)	1.7	2.2
Phlegm (%)	23.3	34.4
Number of miners	60	90

Adapted from Ames et al. [141], mean values are ±1 standard deviation.

The investigators found that there was an "overall significant" decline in FVC and FEV_1 over the workshift in both the exposed and the comparison groups. In addition, smokers had greater decrements in FVC, FEV_1, and maximal expiratory flow than nonsmokers. However, there were no statistically significant differences in any of these parameters when diesel-exposed miners were compared to those having no diesel exposure. Inspection of Table IV-13 reveals that there was great disparity (about 15 years) between the ages of the diesel-exposed miners and the miners having no diesel exposure. A similar difference (about 15 years) existed between the time spent underground by the diesel-exposed miners and by those with no diesel exposure. This may not be significant because acute changes in pulmonary function are usually not age dependent.

In a cross-sectional study of miners in these same mines, Reger et al. [142] evaluated the respiratory health status of 823 male coal miners from 6 diesel-equipped mines. An additional 823 coal miners from neighboring coal mines that were not diesel-equipped served as a matched comparison population. The exposed and comparison miners were matched on age, height, geographic area, smoking status, race, and years spent underground. To characterize their exposures to the mine air contaminants, area samples were collected and analyzed for CO, CO_2, NO_x, NO_2, SO_2, formaldehyde, respirable dust, and total dust. Full-shift personal sample data for NO_2 and respirable dust and, also, short-term area detector tube sample data for CO, NO_x, and NO_2 are presented in Table IV-14.

Table IV-14.--Concentrations of mine air contaminants in six underground diesel-equipped coal mines

Mine	Full-shift personal samples	
	NO_2 (ppm)	Respirable dust (mg/m^3)
A	0.15 ± 0.10	0.93 ± 0.93
B	0.28 ± 0.07	2.73 ± 1.04
C	0.22 ± 0.14	1.30 ± 0.94
D	0.19 ± 0.08	1.20 ± 0.87
E	0.15 ± 0.07	1.94 ± 1.72
F	0.13 ± 0.07	1.62 ± 1.30

Mine	Short-term area detector tube samples		
	CO (ppm)	NO_x (ppm)	NO_2 (ppm)
A	3.4 ± 3.4	4.3 ± 2.8	0.6 ± 0.6
B	21.3 ± 12.6	5.2 ± 5.3	0.1 ± 0.2
C	8.3 ± 1.5	2.0 ± 1.1	0.0
D	13.6 ± 6.5	4.6 ± 1.5	0.2 ± 0.3
E	23.3 ± 23.6	0.0	0.0
F	9.1 ± 8.7	4.2 ± 3.6	0.3 ± 0.4

Adapted from Reger et al. [142], all values are means ±1 standard deviation.

Reger et al. [142] divided their study and comparison groups into underground workers and surface workers; however, details concerning the selection of surface workers were not provided. Therefore, it is not

clear how much time the surface workers had previously spent underground. Furthermore, it is not clear if the exposure data presented by the authors [142] reflect underground exposure alone or if the data are combinations of underground and surface samples. From Table 2 of their report, it appears that there were totals of 550 underground workers and 273 surface workers, some having had diesel exposure and some not, but the exact numbers of underground and surface workers with or without diesel exposure were not provided.

The prevalence of cough, phlegm, and dyspnea were reported as described in Table IV-15. The authors presented prevalence data for other symptoms, but the differences between diesel and non-diesel workers were small or nonexistent. The differences in prevalences of symptoms observed by the authors [142] were not statistically significant.

Table IV-15.--Prevalence of symptoms among underground and surface coal miners (expressed as percentage)

	Underground		Surface	
	Diesel	Non-diesel	Diesel	Non-diesel
Cough	23.6	16.5	20.1	17.6
Dyspnea	9.3	23.8	6.3	6.6
Phlegm	26.5	22.8	23.6	21.8

Adapted from Reger et al. [142]

Reger et al. [142] also evaluated the effect of diesel exhaust on the pulmonary function of the miners. The authors [142] reported that on the average, the underground miners at diesel-using mines had lower FVC, FEV, FEF_{50}, FEF_{75}, and FEF_{90} than their matched controls. These differences, however, were not statistically significant, and no consistent relationships between these findings and the prevalence of cough, dyspnea, or phlegm existed. Neither the pulmonary function data nor the symptom prevalence data were related to NO_2, CO, respirable particulate, or any other component of diesel exhaust determined by the investigators. Because only 4 cases of simple coal workers' pneumoconiosis (CWP) and no cases of progressive massive fibrosis were found, the authors felt that analysis of these factors was unwarranted.

The results of a 5-year prospective study on chronic respiratory effects experienced by underground coal miners exposed to diesel exhaust were presented by Ames et al. [143] in 1984. Their study is a follow-up of a portion of the miners discussed in the previous paragraph; 280 underground coal miners who were first examined in 1977 were re-examined in 1982. All the miners in this group had had at least one year of underground mining experience in 1977. The miners were evaluated for changes in FVC, FEV_1, FEF_{50}, and prevalence of respiratory symptoms, including chronic cough, phlegm, and dyspnea. For purposes of comparison, 838 coal miners who were from neighboring mines and who had had no exposure to diesel exhaust were selected.

Although no data were provided, Ames et al. [143] stated that the "levels of diesel combustion gases and mine dust particulate" were found to be "very low." In general, the authors [143] could find no adverse health effects (as indicated by either decrement in pulmonary function or prevalence of symptoms) that were related to exposure to diesel exhaust. In fact, the 5-year incidences of cough, dyspnea, and phlegm were greater among those miners who had had no exposure to diesel exhaust than among those miners who were exposed to diesel exhaust.

Robertson et al. [144] explored the relationship between respiratory symptoms and lung function among 560 British coal miners from 9 mines who were exposed to NO_x as a result of either diesel use in the mines or shot-firing (use of explosives). The 560 miners examined by Robertson et al. [144] were identified by exploring records obtained from the National Coal Board's Pneumoconiosis Field Research.

Based on a minimum of five shifts and average measurements of NO_2 and NO_x, Robertson et al. [144] divided their study group into 126 workers with "high" exposures and 434 workers with "low" exposures. High and low exposures were determined from indices according to ACGIH recommendations for calculating Threshold Limit Values (TLVs®) of mixtures. An NO_x index of less than 0.4 was defined as a low exposure and greater than 0.9 as a high exposure. A miner had to have spent at least 80% of the time between 1972 and 1979 in either a high- or a low-exposure environment to be placed in either group. Characteristics of the miners are listed in Table IV-16.

Table IV-16.--Characteristics of British coal miners exposed to NO_x and respirable dust concentrations in the mine environment

	Low NO_x	High NO_x
Mean age (years)	46.7	45.9
FEV_1 (liters)	3.08	3.29
Mean respirable dust (gh/m^3)*	148	174
Number of miners	434	126

*gh/m^3=gram·hour per cubic meter

Adapted from Robertson et al. [144]

Average full-shift NO concentrations in mines in which diesel locomotives were not used ranged from 0.07-0.68 ppm; NO_2 ranged from 0.03-0.07 ppm. In those mines in which diesel locomotives were used, concentrations of NO ranged from 0.48-3.74 ppm. NO_2 concentrations ranged from 0.05-0.84 ppm inside the cabins of the locomotives. The highest peak concentration of NO recorded after shot-firing was 94 ppm, with a NO_2 peak concentration of 10.5 ppm. In locomotive cabins, the highest peak concentration of NO was 100 ppm, and the highest NO_2 concentration was 14 ppm. The sampling durations of these measurements were not specified.

Robertson et al. [144] found no statistically significant correlation between occurrence of persistent cough, sputum production, or dyspnea and exposure to oxides of nitrogen. Smoking, however, was related to the

prevalence of cough and sputum production, but not to dyspnea. Decrements in FEV_1 were related to age, height, smoking, and dust exposure, but not to NO_x, nor were there any significant differences between the high and the low exposure groups.

6. Summary

Considered either individually or collectively, the reports described above fail to demonstrate a consistent pattern of adverse effects on respiratory morbidity as a result of exposure to diesel exhaust. Two studies described the frequencies of chromosomal aberrations among truck drivers [133] and coal miners [140]. In the study of truck drivers [133], aberrations were related only to smoking, and in the study of coal miners [140], the referent population had a higher frequency of aberrations than the group exposed to diesel exhaust. One description of chemists who manned air sampling stations inside a railroad tunnel [129] showed increased levels of carboxyhemoglobin, but this effect was reported to be related to smoking and not to diesel exhaust.

No increase in prevalence of cough, dyspnea, or phlegm nor decrement in pulmonary function was found among a group of workers exposed to diesel exhaust in a railroad engine repair shop as compared to railroad workers not exposed to diesel exhaust [131]. Workers in a bus garage [132] complained of headache, dizziness, throat irritation, cough, and eye

irritation, but 72% of them were "heavy smokers," "most" of whom smoked a tobacco known to be especially irritating to the throat and to cause coughing and excess phlegm production.

A number of studies of underground non-coal miners [134,135,136,137, 138,139] described both acute and chronic respiratory effects among miners exposed to diesel exhaust. None of the studies detected any statistically significant decrements in baseline pulmonary function as a result of diesel exposure. One study [134] did report reversible decrements in pulmonary function over a workshift, but the authors did not attribute this finding to diesel exhaust. A group of these studies [135,136,137] did reveal an exposure-related increase in phlegm among salt miners, but other indicators of acute effects due to diesel exhaust (cough and dyspnea) were no different in prevalences than among populations not exposed to diesel exhaust. As the authors [135,136,137] stated, these studies suffered from "rough estimates of exposure, imperfect measure of effect, undocumented role of selection, high correlation of age and estimated exposure, and lack of contemporary regional comparison groups."

A study of potash miners [138] did show a smoking-related increase in the prevalence of adverse respiratory system effects, and another study of miners from a variety of mines [139] reported that the frequency of

persistent cough was related to aldehyde exposure. These latter findings were not supported by spirometric data, nor were there any symptoms of reduced PFT that could be related to NO_2, CO, CO_2, or quartz exposure.

Several studies described the relationship between adverse respiratory system effects and diesel exhaust exposure among underground coal miners [140,141,142,143,144]. One of these [141] showed that there was an "overall" decline in FVC and FEV_1 over a workshift and that this finding was dust-related, although it was not different than among coal miners not exposed to diesel exhaust. In addition, the exposed workers were about 15 years younger than the non-exposed group. There was a similar disparity in total years of underground work; therefore, interpretations concerning these results are confounded. In another study [142], the authors reported that the prevalence of dyspnea was elevated (but not in a statistically significant manner) among underground miners having no diesel exposure, a finding contrary (at least qualitatively) to that reported for non-coal miners [135,136,137,138,139]. No excesses in other symptoms or decrements in pulmonary function were detected [142]. A five-year prospective study [143] failed to show any adverse health effects, and a study of British coal miners [144] revealed an excess of cough and phlegm that was related to smoking.

Only one study has reported an effect that was related to diesel exposure. In this study [130], the investigators determined that the onset of eye irritation was inversely related to increasing concentrations of diesel exhaust.

Thus, except for eye irritation, these studies have failed to document any consistent pattern of acute or chronic adverse health effects as a result of exposure to diesel exhaust. The reports of increased phlegm production among salt miners were not corroborated by similar findings among metal, potash, trona, or coal miners, which leads to the possibility that this effect could be attributed to NaCl exposure and not to diesel exhaust. Therefore, the current studies are not useful for deriving a recommended exposure limit for diesel exhaust.

B. Epidemiologic Studies Addressing Carcinogenicity:

The following studies describe epidemiologic investigations which provide information about the possible association between occupational exposure to diesel exhaust and cancer [145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171]. They include data on morbidity and mortality, on cancer, and, in some instances, on non-cancer disease categories. To facilitate discussion, these studies have been classified as retrospective cohort studies or as case-control studies. Brief summaries of the studies pertinent to human carcinogenicity follow,

including the measures of associations such as standard mortality ratio (SMR), relative risk (RR), observed/expected ratio (O/E), and odds ratio (OR), all of which are presented as percentages.

1. Retrospective Cohort Studies

Hueper, 1955 [157]: A descriptive review of crude employment and mortality data of railroad workers employed between 1939 and 1950 in two companies revealed an apparent disproportionate amount of lung cancer observed in operating workers (e.g., engineers, firemen, brakemen, conductors, switchmen, and roundhouse personnel) as compared to nonoperating workers. The data imply that the operating workers, who represented approximately 20% of the railroad employment, represented 81% (83/103) of the lung cancers that could be assigned to one of the two employment categories. Comments: No exposure measurements were made; therefore, exposures were estimated by job title. Exposure duration and latency might have been inadequate because the period of observation began well before complete use of diesel engines by U.S. railroads. This cohort had potential exposures to asbestos, coal dust, and coal combustion products. No smoking histories were given. Limited employment and mortality data did not permit stratification by confounding factors such as sex and age.

Raffle, 1957 [161]: A cohort mortality study of male London Transport Authority (LTA) workers (aged 45 to 64 years) who drove and serviced

diesel bus equipment between 1950 and 1954 showed no excess lung cancer attributable to diesel exhaust exposures. Comments: The measured diesel exhaust exposures were inadequate; therefore, exposures were estimated by job title. Exposure duration and latency might have been inadequate because diesels were gradually introduced during the period from 1935 to 1952. In addition to active-worker deaths, the study also included retirements and transfers due to lung cancer; there was no follow-up of other workers who left the LTA. No smoking histories were given.

Kaplan, 1959 [158]: A cohort mortality study of Baltimore and Ohio Railroad workers who died between 1953 and 1958 found 6,506 deaths from "all causes," with 154 deaths from cancer of the lung and/or bronchus as compared to 192 deaths expected on the basis of age-specific rates. There were no excesses in lung cancer SMR's as compared to national rates in any of the three groups studied: operating personnel (49 cases, SMR=88%, p--not reported), nonoperating personnel with limited exposures (67 cases, SMR=72%, p--not reported), and nonoperating personnel rarely exposed (38 cases, SMR=89%, p--not reported). Overall, the rates were slightly lower than national rates. Comments: No exposure measurements were made; therefore, exposures were estimated by job title. Exposure duration and latency might have been inadequate because conversion from steam to diesel engines took place during the period from 1935 to 1958. Effects of job transfers and retirements were not considered. Potential exposures included asbestos, coal dust, and coal combustion products. No

smoking histories were given. No rates for other causes of deaths were given for comparison. All lung cancers occurred in men, although women comprised 4% of the workforce.

Waxweiler et al., 1973 [165]: A cohort mortality study of 2,743 underground potash miners who had worked between 1940 and 1967 showed no differences in causes of death between miners who worked with diesel equipment and those who did not (31 deaths occurred in mines using diesel equipment). Comments: No exposure measurements were made; therefore, exposures were estimated by job title. The exposure latency might have been inadequate because one mine had used diesels for transportation only since 1949 and the other only since 1957.

Ham, 1976 [154]: A cohort mortality study of 15,094 Canadian uranium miners who worked at least one month during the period between 1955 and 1974 revealed a significant excess of lung cancer deaths (81 cases, O/E=180%, p--significant, but not reported). Comments: Although the mines used diesel equipment, the excess of lung cancer was attributed by the author to exposure to radon daughters for an average of 75 working level months (WLM), range 0 to 375. NIOSH defines 1.0 WLM as an exposure for 170 hours to any combination of short-lived radon decay products per liter of air that will result in the emission of 1.3×10^5 million electron volts of alpha energy [172].

Menck and Henderson, 1976 [160]: This study does not completely fit into the category of retrospective cohort studies; rather, it is a period prevalence study of the Los Angeles County Cancer Surveillance Program mortality and morbidity data from white males aged 20 to 60 years. This investigation revealed 2,161 lung cancer deaths occurring between 1968 and 1970 and 1,777 incident lung cancer cases observed between 1972 and 1973. Investigation by occupation showed an excess of lung cancer in truck drivers (109 cases, SMR=165%, $p<0.01$). Analysis by industry sector for lung cancer showed excesses in the following two categories: auto repair workers (28 cases, SMR=146%, $p<0.01$) and transportation workers (166 cases, SMR=127%, $p<0.01$). Comments: No exposure measurements were made; therefore, exposure was estimated by job title or industry (last job used for each case). No exposure duration or latency data were given. No smoking histories were given.

Hannunkari et al., 1978 [155]: An analysis of mortality in Finnish railroad workers (aged 30 to 52 years) from 1955 to 1973 indicated that an excess of tumors occurred in 4,347 engineers (47 cases, O/E=121%, $p<0.05$) as compared to the expected from the mortality experience of the control groups, which included 1,575 trainmen and 1,224 railroad clerks (all members of this study were employed on December 1, 1955). Air concentrations measured in roundhouses and locomotive cabs were within Finnish threshold limit values. Comments: Exposures were estimated by job title. No smoking histories were given. Specific tumor types were not analyzed due to the few cancer deaths observed.

Luepker and Smith, 1978 [159]: A cohort mortality study of 183,791 members of the International Brotherhood of Teamsters employed during a three-month period in 1976 showed a significant deficit in all deaths among males (249 cases, SMR=74%, $p<0.01$) as compared to the general population. Respiratory tract cancer death rates per 100,000 were in slight excess in the 40- to 49-year and the 60- to 69-year age categories and significantly higher in the 50- to 59-year age category as compared to general U.S. respiratory cancer death rates per 100,000 (in the latter group, the worker rate was 184.4/100,000, O/E=137%, $p<0.001$). Comments: Inclusion in the study was based on union membership only, and no specific occupations were given. The study did not deal with mortality among retirees, individuals on disability who died after termination of their life insurance, or persons who left employment for other reasons. No exposure duration or latency data and no exposure measurements were given. The study period was only three months. No smoking histories were given.

Waller, 1981 [164] (a follow-up to the 1957 Raffle study [161]): A cohort mortality and morbidity study of male London Transportation Authority (LTA) workers (aged 45 to 64 years) who drove and serviced diesel bus equipment (from 1950 to 1974) revealed SMR's for lung cancer cases below those expected in each of five occupational groupings. The SMR for engineers in the garages (the presumed highest exposure group) had a deficit in lung cancer mortality (177 cases, SMR=90%, p--not reported). Other exposure groups studied included the following deficits

in lung cancer mortality: bus conductors (130 cases, SMR=75%, p--not reported), bus drivers (259 cases, SMR=75%, p--not reported), engineers in the central works (42 cases, SMR=66%, p--not reported), and motormen and guards (59 cases, SMR=87%, p--not reported). Comments: The measured diesel exhaust exposures were inadequate; therefore, exposures were estimated by job title. In addition to deaths from active-duty workers, the study also included retirements and transfers due to lung cancer. There was no follow-up of workers who left the LTA voluntarily or upon normal retirement. No smoking histories were given.

Ahlberg et al., 1981 [147]: A case-control study based on the Cancer and Environment Register from 1961 to 1973 and the 1960 census from Sweden demonstrated a significant RR of lung cancer for truck drivers (RR=133%, p=0.001), derived from the mortality experience of 34,027 truck drivers (excluding tank truck drivers) and 696,708 controls whose occupations did not include exposure to petroleum products or other chemicals. The incidence of leukemia was shown to be increased (RR=114%, p=0.08), as were all forms of cancer combined (RR=104%, p=0.13). No significant results were obtained by comparing 865 tank truck drivers with the control group. Comments: No exposure measurements were made; therefore, exposures were estimated by job title (job titles were obtained through a 1960 census). Inclusion into either the truck driver or the non-exposed control group was based on the occupation listed during the 1960 census. No exposure duration or latency data were reported. No individual

smoking histories were given, although an investigation of 470 current professional drivers revealed that 31% of Swedish drivers of "ordinary" trucks smoked, whereas 78% of the drivers of tank trucks and about 40% of the people in Stockholm smoked.

Howe et al., 1983 [156]: A cohort mortality study of 43,826 male Canadian National Railway Company pensioners who died between 1965 and 1977 revealed the following differing patterns of excesses and deficits in mortality by death category: total deaths (17,838 cases, SMR=95%, $p<0.001$), cancer deaths (3,573 cases, SMR=99%, p--not significant, but not reported), and cancer of the trachea, bronchus, and lung (933 cases, SMR=106%, p--not significant, but not reported). When individuals were grouped according to presumed diesel exposure (non-exposed, possibly exposed, and probably exposed), lung cancer was the only cancer cause of death with a statistically significant trend ($p<0.001$) and with the relative risk consistently increased with increasing exposure (the relative risks being 100%, 120%, and 135%, respectively); the relative risks were calculated by comparison to the non-exposed group. A similar significant trend ($p<0.001$) resulted when analyses were conducted for coal dust exposure, considering the non-exposed, possibly exposed, and probably exposed categories (the relative risks being 100%, 121%, and 135%, respectively). Comments: Exposure to diesel fumes, coal dust, and other fumes, dusts, or gases were estimated by job title at retirement. No exposure duration data and no exposure measurements were given. Only

pensioners were studied; those workers who left employment prior to retirement were not studied. There were possible asbestos exposures. No smoking histories were given.

As a part of the mortality study by Roberts and Julian, 1983 [171], mines of the International Nickel Company (INCO) were evaluated by the use of diesel equipment. The earliest use of diesel equipment underground was in 1968, when a diesel-powered scooptram for moving ore was introduced. This scooptram replaced the slushing operation. In this study, which ended in 1976, the mortality patterns in miners in the years prior to and following the move to diesel power were compared. For all causes of death reported according to the World Health Organization International Classification of Diseases, eighth revision (ICDA), all SMR's were less than expected (Neoplasia, ICDA-8-140.0-239.9; Circulatory Disease, ICDA-8-390.0-458.9; Respiratory Disease, ICDA-8-460.0-519.9; Digestive Disease, ICDA-8-520.0-577.9; Accidents/Violence, ICDA-8-800.0-999.9). This was also true for the All Causes category. The authors attributed this less-than-expected pattern of mortality to an "extreme healthy worker effect created by an influx of new young miners to work with the new procedures." In a similar cohort of new miners (having less than 15 years since first exposure), the authors also observed less-than-expected mortality patterns, except for the Respiratory Disease, Accident/Violence, and All Causes categories. Comments: Because the observation period was at the maximum only 8 years after first exposure to diesel exhaust, it is not surprising that the neoplasia category is

less than expected; this is because such cancers arising from environmental exposures generally do not occur until at least 20 to 30 years after initial exposure. Smoking histories and exposure measurements were not given.

Rushton et al., 1983 [168]: A mortality study of 4,671 maintenance men employed at least one year between 1967 and 1975 at 71 London Transport bus garages and the engineering works at Chiswick showed much lower mortality from all causes than expected, based on the mortality experience of the male population of England and Wales (705 cases, O/E=87%, $p<0.0001$). Mortality from cerebrovascular disease, ischemic heart disease, and bronchitis was also much lower than expected. Mortality from neoplasms was slightly less than expected overall (216 cases, O/E=95%, $p=0.46$). The observed deaths from lung cancer were approximately the same as those expected on the basis of national rates (102 cases, O/E=101%, $p=0.94$). However, a deficit of deaths from lung cancer was obtained after use of a crude adjustment for the higher mortality from this disease in Greater London (102 cases, O/E=87%, p--not significant, but not reported). Raised mortality was found in subgroups of the cohort for several malignant disease groups, but it was based on small numbers of deaths [e.g., brain and central nervous system cancer in bus mechanics (4 cases, O/E=320%, $p=0.04$)]. Comments: Occupational groupings were based on job titles, and only 27% of the cohort (2,313) were bus mechanics. There was a short follow-up time (mean of 5.9

years), with 50,008 person-years of observation. There was a limited cohort size and a low number of deaths. No smoking histories or industrial hygiene measurements were given.

Edling et al., 1984 [151]: A pilot cohort mortality study of 129 male Swedish bus company workers employed anytime between 1950 and 1959 and observed through 1978 resulted in 3,161.5 man-years of observation. The study showed a significant excess mortality due to cardiovascular diseases (12 cases, O/E=184%, $p<0.05$). Seventy-nine workers with at least 10 years of service and at least 15 years of latency (total of 1,093.5 man-years) were subdivided by assumed exposure (clerks--no exposure, bus drivers--low exposure, and garage workers--high exposure). After correcting for smoking, there were significant increases in deaths among the garage workers (high exposure) due to all causes (6 cases, O/E=310%, $p<0.05$) and cardiovascular disease (4 cases, O/E=420%, $p<0.05$). No increased mortality due to cancer was found for the entire cohort nor for any of the subcohorts. Comments: No exposure measurements were given; therefore, exposures were estimated by job title. The latency period was 10 to 28 years. The cohort was small, and there were only 6 cancers. Smoking histories were collected from 352 current bus company employees.

Schenker et al., 1984 [162]: A pilot study of 2,519 white male subjects (aged 45 to 64 years) who had at least 10 years of railway service by 1967 and who were followed through 1979 revealed a deficit for all causes

of death (532 cases, SMR=87%, $p<0.05$). There were no significant differences from expected numbers of deaths for any specific neoplasm, including the categories of lung cancer, respiratory cancer, and bladder cancer. Calculating and comparing the rates for respiratory cancer in subjects who were either exposed or not exposed to diesel exhaust yielded a nonsignificant RR (RR=142%, $p>0.05$). Comments: No exposure measurements were given (industrial hygiene measurements planned for full study); therefore, exposures were estimated by job title. The duration of exposure and latency might have been inadequate. There were possible asbestos exposures. Individual smoking histories were not available. The RR of 142% was obtained by comparing statistically insignificant SMR differences. The study discussed above was a pilot study, but a larger retrospective cohort study is underway. A case-control study has already been completed by Garshick et al., 1984 [152], and is summarized in the next section.

Wong et al., 1985 [167]: A mortality study of 34,156 male members of a heavy construction equipment operators union (employed for at least one year between 1964 and 1978) revealed an overall mortality rate below that expected (3,345 cases, SMR=81%, $p<0.01$), a deficit in all cancers (817 cases, SMR=93%, $p<0.05$), and a number of lung cancer deaths close to that expected (309 cases, SMR=99%, $p>0.05$)). However, an increase in deaths due to cancer of the liver was observed (23 cases, SMR=167%, $p<0.05$). Because about 75% of liver cancers occur in association with cirrhosis (according to Wong et al., 1985 [167]), the investigators found it

"interesting" that mortality from cirrhosis of the liver for the entire cohort was significantly low (107 cases, SMR=80%, $p<0.05$). The total cohort experienced a significant excess in mortality due to emphysema (116 cases, SMR=165%, $p<0.01$). When 4,075 retirees who worked to age 65 or older were considered, the following were found: overall mortality (796 cases, SMR=91%, $p<0.01$); all cancers (224 cases, SMR=115%, $p<0.05$); cancer of the lung (86 cases, SMR=130%, $p<0.05$); lymphosarcoma and reticulosarcoma (8 cases, SMR=267%, $p<0.05$); and emphysema (59 cases, SMR=275%, $p<0.01$). It should be noted, however, that although the preceding excesses were observed in the retirees, there were no significant excesses detected in cause-specific SMR's for cohort members categorized as having either high, low, or unknown exposures to diesel exhaust emissions. There was an increasing trend for lung cancer with duration of union membership. Analysis by latency clearly indicated an upward trend of mortality with latent periods for all causes, all cancers, and lung cancer. Comments: No exposure measurements were given; therefore, exposures were estimated by job title. Partial work histories were available from union dispatch records. There were no smoking histories; however, a random sample by the authors of 107 active union members showed that 25.2% had never smoked as compared to 30.7% in a National Center for Health Statistics' Health Interview Survey.

2. Case-Control Studies

Doll, 1953 [149,150]: In this study, 1,357 men with bronchial carcinoma and 1,357 men with other diseases were interviewed; all occupations for men aged 20 or more years for which employment had been 3 or more years (resulting in 2,281 occupations for the men with lung carcinoma and 2,415 for the comparison group, which were reduced into 76 occupational categories) were recorded. No significant positive association was observed between lung cancer and employment in a specific occupation, although two occupations, coal miners and policemen, were less common among lung cancer patients than their respective controls. Comments: The author suggested that the finding regarding policemen, in the absence of other evidence, may be attributable to chance. The authors did not explain how many of the groups were exposed to diesel exhaust.

Decoufle et al., 1978 [148]: A retrospective survey of cancer as related to the occupations of 24,416 individuals admitted to Roswell Park Memorial Institute was conducted. The survey showed no significant increases in RR for cancer of any site (with five or more cases) either for patients who had ever been employed as locomotive engineers or firemen or for patients who had been employed at least 5 years in either occupation. Truck and tractor drivers showed a significant decrease in RR only for colon and rectum cancer (RR=60%, p=0.04), a RR for lung cancer close to that expected if exposure had no effect (RR=107%, p>0.05), and an increased RR for bladder cancer which was not significant

(RR=166%, $p>0.05$). Hospital patients who did not have cancer were used as controls. Comments: No exposure measurements were made; therefore, exposures were estimated from job title. No exposure duration or latency data were given. Smoking histories were considered in the analyses.

Wegman and Peters, 1978 [166]: A case-control morbidity study using the Massachusetts Tumor Registry (1965 to 1972) was undertaken to evaluate the reported occupations of persons known to have oat cell cancer of the lung. An excess number of transportation equipment operators (i.e., eight, 10%, vs. one, 1%, in the controls) was found among 91 cases of oat cell cancer as compared to an equal number of controls with central nervous system tumors. However, when more detailed information of the occupations was incorporated, this difference was essentially eliminated. Comments: No exposure measurements were made; therefore, exposures were estimated by job title. Of the oat cell cancer patients, 94% were or had been cigarette smokers (vs. 77% in the control group). No exposure duration or latency data were reported. Smoking histories were considered in the analyses.

In a 1983 mortality and case-control study of metal miners, Costello [170] found that 11 of the 50 mines studied used diesel equipment of some type. The type of diesel equipment used ranged from single diesel truck or haulageway locomotives to several pieces of equipment. In the case-control portion of the study, one-for-one and two-for-one matches were made for those cases of cancer of the trachea, bronchus, and lung.

The author stated that for deaths due to "lung cancer," the one-for-one comparison showed an elevated mortality RR of 150% in those exposed to diesel; for the two-for-one match, the RR was 110%. Comments: While the author did find some effect when the one-for-one match was performed, it was not confirmed in the two-for-one match. No exposure levels for those exposed to diesel exhaust were given, and any indications of confounding exposures were not discussed. Smoking histories for the cases and their matches were also not given.

Silverman et al., 1983 [163]: A population-based case-control study was performed of 303 white male patients with cancer of the lower urinary tract (primarily the bladder) and 296 white male controls from the general population. Of 32 industries, only "trucking service" had a significantly higher RR (RR=220%, $p<0.05$). Of 47 occupations, only "truck drivers" had a significantly higher RR (RR=210%, $p<0.05$). An increased RR for truck drivers employed for at least 10 years was observed (RR=550%, $p<0.05$). Truck drivers with a history of operating vehicles with diesel engines had the highest risk observed in this study when the unexposed control group included only males never employed as truck drivers (RR=1190%, $p<0.05$) or when the control group was comprised of truck drivers who had never operated diesel vehicles (RR=720%, $p>0.05$). Among truck drivers employed since 1950, there was a trend in increasing risk with increasing duration of employment. Comments: No exposure measurements were made; therefore, exposures were estimated by job title or industry. Lifetime occupational histories were obtained for both groups. Most diesel exposure in truck drivers occurred during

employment in non-trucking occupations. Evaluation of an association between risk and duration of diesel exposure was not possible because only one control had ever been exposed to diesel exhaust. The authors commented that the high risk observed in diesel exhaust-exposed truck drivers might have been partly due to recall bias. The findings of only 1 of 32 industries and only 1 of 47 occupations with increased cancer incidences could have been by chance. Smoking was clearly associated with bladder cancer in this study.

Schoenberg et al., 1984 [145]: In a New Jersey case-control study of bladder cancer cases that considered a broad range of occupational environments, the authors reported a significantly increased OR for garage and/or gas station workers (OR=235%, $p<0.05$) as well as a nonsignificantly increased OR for drivers and/or deliverymen (OR=116, $p>0.05$). The authors thought that both results were noteworthy in view of the Silverman et al. report [163]. Comments: Direct personal interviews of the cancer cases and their respective controls were possible, and information was obtained about occupation and potential exposure. This limited data evidently did not permit consideration of the potential for or the extent of exposure to diesel exhaust. Because numerous comparisons were made, some of the differences might have been due to chance occurrence.

Hoar and Hoover, 1985 [146]: This study showed a nonsignificantly increased OR for bladder cancer cases in truck drivers from New Hampshire

and Vermont as compared to controls (OR=150%, $p>0.05$). In further analyses, the authors reported a statistically significant, but "inconsistent" trend between the number of years worked as truck drivers and the observed OR, with a significant OR for those truck drivers who had worked 5 years or more in this latter group of drivers (OR=230%, $p<0.05$). Additionally, the authors reported the greatest OR for men who began driving in the 1930's and 1940's (OR=260%, $p<0.05$). Information on employment and other variables of interest were obtained from next-of-kin. These limited data permitted the researchers to stratify the analysis by whether or not the driver was exposed to diesel exhaust. The OR of drivers exposed to diesel exhaust as compared to controls was slightly higher than the OR of the drivers without diesel exhaust exposure as compared to controls; neither value was statistically significant, nor were the values statistically different from one another. Comments: The number of bladder cancer cases that fit into this stratified analysis was relatively small; therefore, the study had limited power to evaluate whether the observed effect was associated with diesel exhaust exposure or truck driving in general.

Taken together, the latter three studies (i.e., Silverman et al., Schoenberg et al., and Hoar and Hoover) corroborate the potential association between increased bladder cancer incidence and truck drivers. The data are not sufficient, however, to determine if this association can be attributed, at least in part, to diesel exhaust exposure.

Hall and Wynder, 1984 [153]: A case-control study of 502 male lung cancer patients and 502 control patients without tobacco-related diseases was conducted to investigate the association between occupational diesel exhaust exposure and lung cancer. No association was found between diesel exhaust exposure and the risk of developing lung cancer. Comments: No exposure measurements were made; therefore, exposures were estimated by job title. No exposure duration or latency data were given. The study controlled for age, smoking, and socioeconomic class. A strong association was found between smoking and lung cancer.

Garshick et al., 1984 [152]: A case-control study of railroad workers showed that workers who were age 64 or younger at the time of death due to lung cancer had an increased OR (OR=120%-140%, $p<0.05$) of having been exposed to diesel exhaust in their jobs (after adjusting for smoking and asbestos exposure). Lung cancer cases (1,319) and age-matched controls were identified out of 15,000 deaths among railroad workers who had at least 10 years of service and who were born in 1900 or later. No increase in OR was seen in workers who were age 65 or older at the time of death. Comments: Information was from an abstract only; no final paper was available. The pilot cohort mortality study of these railroad workers was discussed in the previous section (Schenker et al., 1984 [162]).

Wynder et al., 1985 [169]: A case-control study compared 194 bladder cancer patients (aged 20 to 80 years) to 582 control patients who were hospitalized during the same period (January 1981 to May 1983) with diseases that were not tobacco-related. The study found no difference in the proportion of bladder cancer patients employed in occupations with exposure to diesel exhaust as compared to controls. Bladder cancer patients were significantly more likely to be current smokers than were controls. Comments: No exposure measurements were made; therefore, exposures were estimated by job title. No exposure duration or latency data were given. The study controlled for age, smoking habits, and socioeconomic status.

3. Summary

The epidemiologic studies exploring the relationship between exposure to diesel exhaust and the incidence of mortality from cancer among exposed workers are inconclusive. Almost without exception these investigations suffer from a myriad of methodologic problems including (1) incomplete information on the extent of exposure to diesel exhaust, requiring estimations of these exposures from job titles, (2) insufficient passage of time from first exposure to diesel exhaust until one could reasonably expect the appearance of cancer, and (3) confounding variables such as smoking and exposure to asbestos or ionizing radiation, which make it almost impossible to draw definitive conclusions as to the cause of any excess of cancer observed. In this review, the results of the epidemiologic studies have been classified as either negative (i.e.,

studies that provided no evidence of elevated cancer risks associated with diesel exhaust exposure), equivocal (i.e., studies that were inconclusive because of limited size or inadequate data such as the lack of exposure data or clear categorization of exposure), or positive (i.e., studies that demonstrated an association between diesel exhaust and site-specific cancer or cancer in general). These classifications can be found in Table IV-17. Two of these epidemiologic studies showed positive results and specifically related the increased cancer risks with diesel exhaust exposure, but even in both of these studies, confounding variables made it very difficult to interpret these results [152,156].

Table IV-17.--Summary of results of epidemiologic study results

Cohort or cases studied	Result	Reference
Retrospective cohort studies:		
Railroad workers	Equivocal	Hueper, 1955 [157]
Transit workers	Equivocal	Raffle, 1957 [161]
Railroad workers	Negative	Kaplan, 1959 [158]
Potash miners	Equivocal	Waxweiler et al., 1973 [165]
Uranium miners	Equivocal	Ham, 1976 [154]
Workers in Los Angelas County	Equivocal	Menck & Henderson, 1976 [160]
Railroad workers	Equivocal	Hannunkari et al., 1978 [155]
Teamster union members	Equivocal	Luepker & Smith, 1978 [159]
Transit workers	Negative	Waller, 1981 [164]
Truck drivers	Equivocal	Ahlberg et al., 1981 [147]
Railroad workers	Positive	Howe et al., 1983 [156]
Nickel miners	Equivocal	Roberts & Julian, 1983 [171]
Transit workers	Negative	Rushton et al., 1983 [168]
Bus workers	Equivocal	Edling et al., 1984 [151]
Railroad workers	Equivocal	Schenker et al., 1984 [162]
Heavy construction equipment operators	Equivocal	Wong et al., 1985 [167]
Case-control studies:		
Bronchial cancer	Equivocal	Doll, 1953 [149,150]
Cancer (all sites)	Equivocal	Decoufle et al., 1978 [148]
Lung cancer (oat cell)	Negative	Wegman & Peters, 1978 [166]
Lung cancer	Equivocal	Costello, 1983 [170]
Bladder cancer	Equivocal	Silverman et al, 1983 [163]
Bladder cancer	Equivocal	Schoenberg et al., 1984 [145]
Lung cancer	Negative	Hall & Wynder, 1984 [153]
Lung cancer	Positive	Garshick et al., 1984 [152]
Bladder cancer	Equivocal	Hoar & Hoover, 1985 [146]
Bladder cancer	Negative	Wynder et al., 1985 [169]

V. EVALUATIONS OF RISK ASSESSMENTS WHICH FOCUS ON CARCINOGENICITY

The research on the health effects associated with exposure to diesel exhaust, which could serve as a basis for quantitative risk assessment, has been reviewed in the two previous sections. Several authors have addressed the hypothesized risk between non-cancerous health outcomes and exposure to diesel exhaust [10,15]. Specifically, diesel exhaust in combination with other sources of pollutants may exceed air quality standards and contribute to the development of long-term damage to respiratory health. Data are currently insufficient to thoroughly address the potential respiratory hazards of diesel exhaust [10]. However, NIOSH is exploring the data needs for doing a credible risk assessment of the non-cancerous effects of diesel exhaust as well as determining what type of assessment can be conducted with the available data. The remainder of this section will discuss the issues which pertain to cancer risk. To date, no epidemiologic study has shown a definitive increase in cancer risk that could be associated with exposure to diesel exhaust. There are several epidemiologic studies that provide limited evidence of an association between exposure to diesel exhaust and human carcinogenicity. These include the following: Howe et al, 1983 [156], observed a significant trend of increasing lung cancer relative risks when the mortality experience of pensioned railway workers was stratified by presumed diesel exhaust exposure (both the relative risks of those possibly exposed and those probably exposed were significantly greater than those non-exposed); Garshick et al., 1984 [152], described a case-control study that gave a significant odds ratio for exposure to diesel exhaust in

railroad workers who died from lung cancer at 64 years of age or younger as compared to exposure of similar railroad workers who evidently died of causes other than lung cancer.

Chronic animal carcinogenesis studies have provided only limited evidence of carcinogenicity from exposure to whole diesel exhaust. Heinrich et al. [89] demonstrated that diesel exhaust exposure increased the incidence of papillomas of the larynx and trachea in animals initially treated with the primary carcinogen diethylnitrosamine as compared to animals similarly treated but not exposed to diesel exhaust. The authors indicated that their data provided evidence of "co- or syn-carcinogenicity." A preliminary communication by White et al. [90] indicated an apparent increase of bronchoalveolar carcinoma in animals exposed to diesel exhaust as compared to controls; however, this study was subject to a number of experimental problems, was considered to be inconclusive, and is being repeated.

Because no definitive association between diesel exhaust exposure and cancer has been demonstrated in humans or in animals, dose-response data are not available. Therefore, any direct quantitative cancer risk assessment is not possible.

Several investigators, however, have used innovative techniques to generate bounds for cancer risk based on available epidemiologic data or to generate human cancer risk estimates using indirect quantitative methods. Harris [173] reanalyzed the data presented by Raffle [161] and Waller [164] on the

cancer incidence of London Transport Authority employees who had varying potential exposures to diesel exhaust. Analyses of these data by Raffle and by Waller had not demonstrated any excess cancer risk associated with diesel exhaust. However, the employees with the greatest potential for exposure experienced the highest rates of lung cancer among all employees, although still less than that expected as compared to Greater London cancer rates. The original data for the London Transit Authority study are limited by numerous methodologic problems, which were discussed by Harris [173] and Cuddihy and McClellan [174]. These include the lack of any follow-up of terminated employees, which alone is reason to believe that the lung cancer risk in this study could have been underestimated, especially if a selective survival bias operated against the continued employment of affected people. Despite these shortcomings, Harris [173] conducted a sensitivity analysis based on these epidemiologic data in an attempt to quantitate the upper limit for a possible undetected risk of lung cancer. Harris [173] used a relative risk model for this analysis that implied that for any given smoking status, the proportional increase in lung cancer incidence would be a linear function of cumulative lifetime exposure to excess diesel engine emissions (excess assumed to mean above ambient). This model incorporated the possible variations in the extent, duration, and time course of exposure and in smoking practices. The analysis was conducted using maximum likelihood methods to solve for lung cancer potency of diesel exhaust. This resulted in an estimated 95% upper confidence limit of 5×10^{-4} for the increment in lung cancer incidence risk (i.e., lung cancer cases) per unit of cumulative lifetime exposure, with a unit of cumulative lifetime exposure

defined as one microgram of particles per cubic meter of air for one year ($\mu g/m^3/yr$). It should be noted that if the incidence of lung cancer was underestimated in the original study, then this estimated 95% upper confidence interval could have resulted in the underestimation of the maximum undetected lung cancer incidence experienced by the exposed study members.

Indirect estimates of human lung cancer risk associated with diesel exhaust exposure have been generated by Harris [173] and Albert et al. [175]. They did this by combining the results of epidemiologic studies of environmental exposures related to diesel exhaust with the results from biologic test systems using solvent extracts of diesel exhaust and solvent extracts of the related environmental exposure agent. The related exposures included coke oven emissions, roofing tar emissions, and cigarette smoke condensate. Both of these analyses are based on the assumption of constant relative potencies for various endpoints; that is, the relative potencies of diesel exhaust and of any one of the related exposures remain the same whether derived from human epidemiologic studies or from one of the biologic test systems. Therefore, the potency of diesel exhaust necessary to induce lung cancer can be estimated if the potency for one of the other exposures necessary to induce lung cancer is known and if the relative potency of diesel exhaust to that of the other exposure in one of the biologic test systems is known. The various biologic test systems considered by Harris [173] and Albert et al. [175] include the following: reverse mutation in Salmonella typhimurium TA98 (with and without metabolic activation), forward mutation at the

thymidine kinase locus in L5178Y mouse lymphoma cells, sister chromatid exchanges in Chinese hamster ovary cells, enhancement of viral transformation in Syrian hamster embryo cells, and mouse skin tumor initiation in a sensitive mouse strain (SENCAR). The assessments by Harris [173] and Albert et al. [175] used different subsets of the biologic test systems and different mathematical models to derive the potency of diesel exhaust for the induction of lung cancer. Because several types of diesel exhaust were considered, it is not surprising that some discrepancies exist between the results of the two analyses.

The following discussion describes some of the uncertainties and issues that can arise from using these risk assessment strategies. Selecting among the available data sets and the mathematical models to construct a quantitative risk assessment based on the assumption of constant relative potency is an exercise in professional judgement, expertise, and intuition. Harris [173] has referred to the constant relative potency approach as "at best an approximation" of quantitative risk estimation because of all the assumptions inherent in the underlying concept of constant relative potency. In a subsequent communication [176], the second group of researchers (including Albert) described risk assessment as "crude and uncertain but it can be useful, particularly when the estimated risks are either very low or relatively high."

Decisions made while conducting innovative assessments before the individual researchers or the scientific community has had the opportunity to accumulate experience with the approach could lead to overestimates or underestimates of risk and also to loss of important insight into the disease modeling process. For example, neither assessment included the estimated potencies of diesel exhaust solvent extracts based on the reverse mutation assay without activation; this is because they were unexpectedly high and inconsistent with the relative potencies derived for the epidemiologic data and some of the other test systems. Using these estimated relative potencies could have resulted in different estimates of lung cancer risk due to diesel exhaust exposure. In a subsequent communication, Harris [177] stated that although he did not use the reverse mutation data, he recognized that "the idiosyncratic responses of certain emissions in certain species give us some information about the probability of idiosyncratic responses in humans." Another uncertainty which confounds these quantitative risk estimates of the lung cancer potency of diesel exhaust is that the lung cancer potencies derived from the epidemiologic data relate to the whole diesel exhaust particulate, whereas the potencies derived from the biologic test systems relate to the solvent extract of diesel exhaust particulate. Discrepancies in these potencies could result because of differences in chemical composition, bioavailability, tissue adhesion of the particulate, and many other factors.

Travis and Munro [10] attempted to standardize into equivalent units the risk estimates that were generated by Harris [173] and Albert et al. [175]. The percentage lifetime excess lung cancer risk for a continuous lifetime exposure of one microgram of particles per cubic meter derived by Albert et al. was 0.09%, and the estimate derived by Harris was 0.25% (this last estimate was originally reported by Harris as 0.35×10^{-4} excess lung cancer cases per $\mu g/m^3/yr$, which was in the same units and less than the upper bound excess lung cancer cases per $\mu g/m^3/yr$ that Harris derived as the possible undetected risk from the epidemiologic data analysis of 5×10^{-4}). The comparability of the two estimates can be disputed based on several issues, one of which was pointed out by Harris [177]. His estimate was based on the cancer risk for men during their working lifetimes, whereas the estimate of Albert et al. was based on the lifetime risk from continuous lifetime exposure.

Novel risk assessment approaches such as those based on the constant relative potency assumption may provide useful insight about the potential risks posed by agents such as diesel exhaust, although such risk estimates are subject to even greater uncertainties than are those derived from traditional quantitative risk assessment approaches. Harris [177] has pointed out that such assessments must additionally contend with the uncertainties of which experiments are relevant; these uncertainties are qualitatively different from the uncertainty of measurement error familiar to risk assessors. A consensus opinion [174,176] has developed from these assessments; that is, the relative potencies of solvent extracts of diesel

exhaust particulate are similar to the potencies of solvent extracts of other combustion products such as coke oven emissions, roofing tar emissions, and cigarette smoke condensates. It can then be inferred that the lung cancer potency of diesel exhaust emission is similar to those of the other combustion products (subject to the uncertainties of differences in chemical composition, bioavailability, tissue adhesion of the particulate, etc. mentioned earlier). However, although the potencies may be similar, the exposure levels are not. The usual ambient or occupational exposure levels to these various combustion products are 3 to 6 orders of magnitude higher than the usual occupational exposure levels to diesel exhaust [174]; therefore, the risks resulting from such exposure conditions to diesel exhaust should be at least several orders of magnitude lower than the risks from such exposure conditions to these other combustion products.

The available data are inadequate to reach definitive conclusions about the quantitative cancer risks associated with exposure to diesel exhaust. Nonetheless, from a qualitative standpoint, the available assessments and the isolated reports mentioned at the beginning of this section suggest the possibility of a carcinogenic risk from exposure to diesel exhaust.

VI. CONCLUSIONS

Most epidemiologic data point to a lack of excess risk of lung cancer or chronic respiratory effects associated with diesel exhaust emissions. There are some suggestive findings of increased cancer risks in humans, but because of previously mentioned limitations such as lack of dose analyses, lack of smoking histories, poor study designs, and inadequate observation periods for cancer, it is questionable as to whether the risk is due to diesel exhaust [152,156]. Further, there is no convincing evidence that the inhalation of whole diesel exhaust is mutagenic or carcinogenic in laboratory animals.

However, the fact that diesel exhaust does contain toxic compounds (such as nitrogen dioxide, carbon monoxide, particulates, PAH's, aldehydes, phenols, nitric oxide, and sulfur dioxide) is cause for concern. In particular: (1) organic extracts of diesel exhaust particulates have been found to be mutagenic and carcinogenic in animal cell and whole animal skin application studies; (2) studies of laboratory animals suggest that diesel exhaust alters the various defense mechanisms of the lung, leading to impaired dust clearance and enhanced susceptibility to infection; (3) pulmonary function impairment that is indicative of restrictive lung disease has been reported in animal studies at high doses of diesel exhaust; in addition, responses consistent with obstructive lung disease were noted in one study of monkeys at lower doses; and (4) reversible pulmonary changes (before and after a workshift) have been noted in salt miners, and exposure-related eye irritation has been noted among men experimentally exposed to diesel exhaust. A summary of the effects associated with diesel exhaust is given in Table VI-1.

Table VI-1.--Summary of effects associated with exposure to diesel exhaust

	Number	Positive	Negative	Equivocal
Mutagenicity Effects				
In vitro studies using solvent extracts of diesel exhaust	65	52	13	--
In vivo studies				
Whole diesel exhaust	22	3	19	--
Diesel exhaust particulate	6	2	4	--
Solvent extract of diesel exhaust	5	3	2	--
Effects in Animals				
Susceptibility to infection	3	2	1	--
Restrictive lung disease	6	3	3	--
Obstructive lung disease	6	1	5	--
Tumorigenesis				
Skin painting	5	3	2	--
Intraperitoneal injection	1	0	0	1
Inhalation exposure	7	0	1	6
Effects in Humans				
Acute lung disease	12	1	4	7
Chronic lung disease	9	0	6	3
Retrospective cohort studies	16	1	3	12
Case-control studies	10	1*	3	6

*Only an abstract is available for this study.

Based on the current scientific knowledge about the health effects of diesel exhaust, with its contradictions and ambiguities, NIOSH at this time can neither affirm nor condemn the use of diesel equipment in underground coal mines. Instead, as prudent public health policy, occupational exposures to diesel exhaust should be maintained below the levels specified in existing Mine Safety and Health Administration (MSHA) standards or, if more protective, below NIOSH recommended exposure limits (REL's) for occupational exposures to all contaminants found in diesel exhaust. Controlling respirable particulate is especially important given the uncertainty about its potential carcinogenicity. In order to minimize exposures to diesel exhaust, adequate ventilation in underground coal mines, as required by MSHA, is essential, as are effective industrial hygiene monitoring programs and proper inspection and maintenance of diesel equipment.

The following discussion describes some of the areas in which additional studies are needed of the possible health effects of exposure to diesel exhaust. Well-designed and controlled epidemiologic studies are needed of populations that are occupationally exposed to diesel exhaust. In these studies, the extent of exposure of the cohort to the individual components of diesel exhaust, as well as to concomitant exposures, should be ascertained. These studies must carefully control for such confounding factors as cigarette smoking.

Additional data are needed concerning the bioavailability in animals and humans of mutagenic and carcinogenic substances from inhaled or ingested diesel exhaust particulate, as well as the ability of the defense mechanisms of the lung to detoxify the various components of diesel exhaust.

The increased susceptibility of animals to infection following inhalation of diesel exhaust needs to be further evaluated. Additionally, studies are needed to determine if resistance to a bacterial and/or viral challenge is modified primarily by the gas phase or by the particulate fraction of diesel exhaust. A study of the incidence of infection-related absences from work among populations occupationally exposed to diesel exhaust may be useful.

Further identification of the components of the diesel exhaust particulate fraction that contain mutagenic and carcinogenic activity is needed, as well as the possible carcinogenicity (and other toxic effects) of the gas phase component of diesel exhaust. Questions remain about possible synergism among the many components of diesel exhaust.

The possible long-term consequences of diesel exhaust inhalation in animals, such as the development of fibrotic and emphysematous changes in the lung, should be further investigated. In addition, the possible reversibility in decrements of pulmonary function should be studied.

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