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Carcinogenic Effects of Exposure to Diesel Exhaust

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

CURRENT INTELLIGENCE BULLETIN NO. 50

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
CENTERS FOR DISEASE CONTROL
NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH
DIVISION OF STANDARDS DEVELOPMENT AND TECHNOLOGY TRANSFER

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FOREWORD

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The purpose of this bulletin is to disseminate recent information on the potential carcinogenicity of diesel exhaust. In March 1986, NIOSH issued a document entitled "Evaluation of the Potential Health Effects of Occupational Exposure to Diesel Exhaust in Underground Coal Mines." This document stated that workers exposed to diesel exhaust experienced eye irritation and reversible decrements in pulmonary function. In the document, NIOSH concluded that no causal relationship had been established between exposure to whole diesel exhaust and cancer, but that such a relationship was plausible on the basis of animal studies in which extracts of diesel exhaust were used. Since the release of that document, reports of studies in animals have confirmed the potential carcinogenicity of whole diesel exhaust.

On the basis of the results of these studies, NIOSH recommends that whole diesel exhaust be regarded as "a potential occupational carcinogen," as defined in the Cancer Policy of the Occupational Safety and Health Administration (OSHA) ("Identification, Classification, and Regulation of Potential Occupational Carcinogens," 29 CFR 1990). This recommendation is based on findings of carcinogenic and tumorigenic responses in rats and mice exposed to whole diesel exhaust. Though the excess risk of cancer in diesel-exhaust-exposed workers has not been quantitatively estimated, it is logical to assume that reductions in exposure to diesel exhaust in the workplace would reduce the excess risk.

Diesel exhaust is a complex mixture of compounds, and its composition varies greatly with fuel and engine type, load cycle, engine maintenance, tuning, and exhaust gas treatment. This complexity is compounded by a multitude of environmental settings in which diesel-powered equipment is operated. Because of limitations in currently available technology and test methods, NIOSH cannot at this time confidently offer recommendations for environmental monitoring of exposures to diesel exhaust, or for generally applicable control measures that would assure adequate reduction of the carcinogenic risks associated with occupational exposure to diesel engine emissions. Continued investigation of these issues is clearly essential.

NIOSH recommends that producers of diesel engines disseminate this current information to their customers, and that users of diesel-powered equipment disseminate this current information to their workers. NIOSH also recommends that professional and trade associations and unions inform their members of the new findings of potential carcinogenic hazards of exposure to diesel engine emissions, and that all available preventive efforts (including available engineering controls and work practices) be vigorously implemented to minimize exposure of workers to diesel exhaust. Readers seeking more detailed information on the studies cited in this bulletin are urged to consult the original publications.

J. Donald Millar, M.D., D.T.P.H. (Lond.)
Assistant Surgeon General
Director, National Institute for
Occupational Safety and Health
Centers for Disease Control

ABSTRACT

This bulletin presents recent information on the potential carcinogenicity of diesel exhaust. Included are discussions of recent animal studies that confirm the relationship between cancer and exposure to whole diesel exhaust. Also discussed is epidemiologic evidence that associates lung cancer with occupational exposure to diesel engine emissions. On the basis of the results of these studies, NIOSH recommends that whole diesel exhaust be regarded as a potential occupational carcinogen in conformance with the OSHA Cancer Policy (29 CFR 1990).

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ACKNOWLEDGMENTS

The following staff members of the Division of Standards Development and Technology Transfer (DSDTT) were responsible for preparing this CIB:

Document Manager
Jane Brown McCammon

Chief, Senior Review Activity
William D. Wagner

Senior Review Staff
David H. Groth, M.D.
G. Kent Hatfield, Ph.D.
Laurence D. Reed

Editorial Staff
Vanessa L. Becks
Ruth E. Grubbs
Anne C. Hamilton

Secretarial Staff
Denise Hill

Assistant Chief, Document Development Branch
Ralph D. Zumwalde

Chief, Document Development Branch
Bryan D. Hardin, Ph.D.

Deputy Director
Richard W. Niemeier, Ph.D.

Director, DSDTT
Richard A. Lemen

Contributions by other NIOSH staff members are also gratefully acknowledged:

William J. Moorman
Division of Biomedical and Behavioral Science

Laurence J. Doemeny, Ph.D.
Division of Physical Sciences and Engineering

John F. Gamble, Ph.D.
Michael A. McCawley, Ph.D.
Rebecca Stanevich
William Wallace, Ph.D.
Division of Respiratory Disease Studies

Nancy J. Bollinger
Division of Safety Research

Barbara Carr
Howard R. Ludwig
Susan Marksberry
June Mefford
Theodore J. Meinhardt, Ph.D.
Vlasta Molak, Ph.D.
Division of Standards Development and Technology Transfer

Kyle Steenland, Ph.D.
Dennis D. Zaebst
Division of Surveillance, Hazard Evaluation, and Field Studies

Walter M. Haag, Jr.
Anne M. Stirnkorb
Division of Training and Manpower Development

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CURRENT INTELLIGENCE BULLETIN NO. 50

CARCINOGENIC EFFECTS OF EXPOSURE TO DIESEL EXHAUST

INTRODUCTION

The purpose of this bulletin is to disseminate recent information on the potential carcinogenicity of diesel exhaust. A recent National Institute for Occupational Safety and Health (NIOSH) document entitled Evaluation of the Potential Health Effects of Occupational Exposure to Diesel Exhaust in Underground Coal Mines [NIOSH 1986] concluded that "Among workers exposed to diesel exhaust, irritation of the eyes, and reversible decrements in pulmonary function have been documented." The document also stated that "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," had not been established. Since publication of that document, results of animal studies have confirmed the potential carcinogenicity of whole diesel exhaust. This Bulletin describes the results of those animal studies and discusses the limited epidemiologic evidence of an association between lung cancer and occupational exposure to diesel engine emissions.

BACKGROUND

Diesel engines rely on heat generated during the compression cycle for ignition rather than on an electrical spark as in gasoline engines. Because of the higher compression required, diesel engines are heavier and bulkier than gasoline engines. However, diesel engines can operate with less highly refined fuel and consume less fuel per horsepower per hour. The diesel engine is the predominant source of industrial power throughout the world for units up to about 5,000 horsepower [Encyclopaedia Britannica 1987].

Composition of Diesel Engine Emissions

Diesel engines function by facilitating the combustion of liquid fuel without spark ignition. In gasoline engines, a mixture of air and fuel is drawn into a combustion chamber, compressed, and then ignited by an electric spark. In diesel engines, air alone is compressed in the combustion

chamber. Fuel is then introduced into the chamber, and ignition is accomplished by the heat of compression.

The emissions from diesel engines 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, phenol, 1,3-butadiene, acrolein, and polynuclear aromatic hydrocarbons) [Linnell and Scott 1962; Environmental Health Associates 1978; Schenker 1980; Travis and Munro 1983]. Particulates (soot) in diesel exhaust are composed of solid carbon cores that are produced during the combustion process and that tend to form chain or cluster aggregates. More than 95% of these particulates are less than 1 micrometer in size [Travis and Munro 1983; Vostal 1980; McCawley and Cocalis 1986]. Estimates indicate that as many as 18,000 different substances from the combustion process can be adsorbed onto diesel exhaust particulates [Weisenberger 1984]. The adsorbed material constitutes 15% to 65% of the total particulate mass and includes such compounds as polynuclear aromatic hydrocarbons (PAHs) [Travis and Munro 1983; Cuddihy et al. 1984].

Number of Exposed Workers

NIOSH estimates that approximately 1.35 million workers are occupationally exposed to the combustion products of diesel fuel in approximately 80,000 workplaces in the United States [NIOSH 1983]. Workers who are likely to be exposed to diesel emissions include mine workers, bridge and tunnel workers, railroad workers, loading dock workers, truck drivers, fork-lift drivers, farm workers, and auto, truck, and bus maintenance garage workers.

EXPOSURE LIMITS

Permissible exposure limits (PELs) established by the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA) for some gases typically found in diesel exhaust are listed in Table 1 along with the recommended exposure limits (RELs) established by NIOSH.

OSHA, MSHA, and NIOSH exposure limits relevant to the particulate fraction of diesel engine emissions are listed in Table 2. Because diesel emission particulates are of respirable size, the presence of diesel equipment contributes to the total burden of respirable dust present in an occupational environment. Existing limits for occupational exposures to other respirable dusts also limit exposures to the particulate fraction of diesel emissions.

As much as 15% to 65% of the mass of particulate emissions (soot) of diesel engines is made up of organic compounds adsorbed onto the surface of the particulates [Travis and Munro 1983; Cuddihy et al. 1984]. Among these organic compounds is a group of compounds known as polynuclear aromatic hydrocarbons (PAHs), several of which are carcinogens [IARC 1983]. PAHs are

Table 1.--Limits for occupational exposure to selected components of the gaseous fraction of diesel exhaust; OSHA, MSHA, NIOSH compared

Component	OSHA PEL	MSHA PELs*		NIOSH REL
		Underground coal mines	Metal and nonmetal mines	
Carbon dioxide (CO_2)	5,000 ppm (9,000 mg/m^3), 8-hr TWA†	5,000 ppm (9,000 mg/m^3), 8-hr TWA; 30,000 ppm (54,000 mg/m^3), STEL§	5,000 ppm (9,000 mg/m^3), 8-hr TWA; 15,000 ppm (27,000 mg/m^3), STEL	10,000 ppm (18,000 mg/m^3), 8-hr TWA; 30,000 ppm (54,000 mg/m^3), 10-min ceiling
Carbon monoxide (CO)	50 ppm (55 mg/m^3), 8-hr TWA	50 ppm (55 mg/m^3), 8-hr TWA; 400 ppm (440 mg/m^3), STEL	50 ppm (55 mg/m^3), 8-hr TWA; 400 ppm (440 mg/m^3), STEL	35 ppm (40 mg/m^3), 8-hr TWA; 200 ppm (230 mg/m^3), ceiling (no minimum time)
Formaldehyde	1 ppm, 8-hr TWA; 2 ppm, 15-minute STEL	1 ppm (1.5 mg/m^3), 8-hr TWA; 2 ppm (3 mg/m^3), STEL	2 ppm (3 mg/m^3), ceiling	0.016 ppm (0.020 mg/m^3), 8-hr TWA; 0.1 ppm (0.12 mg/m^3), 15-min ceiling
Nitrogen dioxide (NO_2)	5 ppm (9 mg/m^3), ceiling	3 ppm (6 mg/m^3), 8-hr TWA; 5 ppm (10 mg/m^3), STEL	5 ppm (9 mg/m^3), ceiling	1 ppm (1.8 mg/m^3), 15-min ceiling
Nitric oxide (NO)	25 ppm (30 mg/m^3), 8-hr TWA	25 ppm (30 mg/m^3), 8-hr TWA	25 ppm (30 mg/m^3), 8-hr TWA; 37.5 ppm (46 mg/m^3), STEL	25 ppm (30 mg/m^3), 10-hr TWA
Sulfur dioxide (SO_2)	5 ppm (13 mg/m^3), 8-hr TWA	2 ppm (5 mg/m^3), 8-hr TWA; 5 ppm (10 mg/m^3), STEL	5 ppm (13 mg/m^3), 8-hr TWA; 20 ppm (52 mg/m^3), STEL (5 min)	0.5 ppm (1.3 mg/m^3), 10-hr TWA

*MSHA limits are based on threshold limit values (TLVs®) of the American Conference of Governmental Industrial Hygienists (ACGIH). 1973 TLVs® are used for metal and nonmetal mines. Current TLVs® are used for underground coal mines.
†Time-weighted average.
§Short-term exposure limit.

Table 2.—OSHA, MSHA, and NIOSH limits relevant to occupational exposure to the particulate fraction of diesel exhaust

Component	OSHA PEL	MSHA PELs		NIOSH REL
		Underground coal mines	Metal and nonmetal mines	
Respirable dust*	5 mg/m^3	2 mg/m^3†	No Limit	No REL
Respirable dust when quartz content is more than 5% of total*	$\frac{10\ mg/m^3}{\%\ SiO_2 + 2}$	$\frac{10\ mg/m^3}{\%\ quartz}$†	$\frac{10\ mg/m^3}{\%\ quartz + 2}$§	REL is specific to quartz
Coal tar pitch volatiles (CTPV)	Not applicable to diesel emissions	Not considered relevant	Not considered relevant	0.1 mg/m^3, 10-hr TWA (cyclohexane-extractables)
Polynuclear aromatic hydrocarbons	No PEL	No PEL	No PEL	No REL

*These limits are not intended for diesel exhaust particulates, but they would inadvertently limit airborne concentrations because diesel particulates would be included in respirable dust samples taken where diesel engines are operating.

†MRE equivalent concentration.

§MSHA limits are based on threshold limit values (TLVs®) of the American Conference of Governmental Industrial Hygienists (ACGIH). 1973 TLVs® are used for metal and nonmetal mines.

produced as pyrolytic products during the combustion of any fossil fuel, including diesel fuel. Some readily condense onto the surface of the soot being expelled from diesel engines. Concentrations of PAHs can be determined by using solvents such as benzene or cyclohexane to extract these and other compounds from particulate samples. This analysis yields the solvent-soluble portion of the particulates (often referred to as coal tar pitch volatiles, or cyclohexane- or benzene-solubles), which can be further fractionated.

EVIDENCE OF CARCINOGENICITY IN ANIMALS

Several reports of long-term animal inhalation studies [Brightwell et al. 1986; Heinrich et al. 1986; Ishinishi et al. 1986; Iwai et al. 1986; Mauderly et al. 1987] regarding the health effects of exposure to whole diesel exhaust have been released since the publication of the NIOSH document entitled Evaluation of the Potential Health Effects of Occupational Exposure to Diesel Exhaust in Underground Coal Mines [NIOSH 1986]. Data from these reports serve as the basis for the current NIOSH conclusion that exposure to whole diesel exhaust is associated with the risk of cancer. Other health effects were examined in these studies, but only those related to carcinogenicity are presented here. The studies are summarized in Table 3 and discussed more fully in the following sections. The primary difference between the study designs of the recent positive studies and negative studies previously evaluated by NIOSH [1986] is the length of the exposure period, which was up to 30 months for the positive studies and 24 months for the negative studies.

Heinrich et al. [1986]

Results of an extensive long-term inhalation study of cancer in mice, rats, and hamsters exposed to filtered and unfiltered light-duty diesel engine exhaust were reported by Heinrich et al. [1986]. Equal numbers of male and female Syrian golden hamsters, female NMRI mice, and female Wistar rats were exposed to clean air, unfiltered diesel exhaust, or filtered diesel exhaust. Each group consisted of 96 animals. All experimental animals were 8 to 10 weeks old at the start of the study. Throughout the lifespan of the animals, exposure was for 19 hours per day, 5 days per week. The maximum duration of exposure was 120 weeks for hamsters and mice, and 140 weeks for rats.

A stationary 1.6-liter diesel engine operated according to EPA's US-72 driving cycle was used to generate the exhaust. The diesel fuel used was a European reference fuel with a sulfur content of 0.36%. The exhaust was diluted with filtered air to a volume rate of 1:17 (diesel exhaust/air) and was then directed into an exposure chamber. At this dilution rate, the measured concentration of the particulate fraction of diesel exhaust was approximately 4 mg/m^3. To remove particulates from the exhaust, the

Table 3.--Characteristics of recent studies* of carcinogenicity in animals exposed to diesel exhaust by inhalation

Study	Type of engine	Nature of exhaust	Animal species	Exposure time	Particulate exposure concentrations (mg/m^3)	Findings
Heinrich et al. [1986]	1.6-liter Volks-wagen	Unfiltered	Female Wistar rats	19 hr/day, 5 days/week, max. of 140 weeks	4	Significantly increased incidence of adenomas, benign squamous cell cysts, and squamous cell carcinoma of the lung when compared with controls.
		Filtered	Female Wistar rats	19 hr/day, 5 days/week, max. of 140 weeks	——	No significant differences in histopathological findings compared with controls.
		Unfiltered	Female NMRI mice	19 hr/day, 5 days/week, max. of 120 weeks	4	Statistically significant increase in malignant and total lung tumors (because of increases in adenocarcinomas) when compared with controls.
		Filtered	Female NMRI mice	19 hr/day, 5 days/week, max. of 120 weeks	——	Statistically significant increase in malignant and total lung tumors (because of increases in adenocarcinomas) when compared with controls.
		Unfiltered	Male and female Syrian golden hamsters	19 hr/day, 5 days/week, max. of 120 weeks	4	No significant differences in histopathological findings compared with controls.
		Filtered	Male and female Syrian golden hamsters	19 hr/day, 5 days/week, max. of 120 weeks	——	No significant differences in histopathological findings compared with controls.

(continued)

See footnotes at end of table.

Table 3 (Continued).--Characteristics of recent studies* of carcinogenicity in animals exposed to diesel exhaust by inhalation

Study	Type of engine	Nature of exhaust	Animal species	Exposure time	Particulate exposure concentrations (mg/m^3)	Findings
Mauderly et al. [1987]	5.7-liter Oldsmobile	Unfiltered	Male and female F344 rats	7 hr/day, 5 days/week, max. 30 months	0.35 3.5 7.0	High exposure led to statistically significant increases in benign squamous cysts and malignant tumors (adenocarcinomas and squamous carcinomas) compared with controls. Intermediate exposure led to a statistically significant increase in adenomas and total tumors when compared with controls. There were no statistically significant increases in benign or malignant tumors in low-exposure animals.
Brightwell et al. [1986]	1.5-liter Volks-wagen	Unfiltered	Male and female F344 rats	16 hr/day, 5 days/week, 2 years†	0.7 2.2 6.6	Statistically significant increase in undefined tumors in both male and female high-exposure animals compared with controls. Statistically significant increase in undefined tumors in female intermediate-exposure animals compared with controls.
		Filtered	Male and female F344 rats	16 hr/day, 5 days/week, 2 years†	Below the limit of detection	No increase in tumor incidence in any exposure group when compared with controls.
		Unfiltered	Male and female Syrian hamsters	16 hr/day, 5 days/week, 2 years	0.7 2.2 6.6	No increase in tumor incidence in any exposure group when compared with controls.

(continued)

See footnotes at end of table.

Table 3 (Continued).—Characteristics of recent studies* of carcinogenicity in animals exposed to diesel exhaust by inhalation

Study	Type of engine	Nature of exhaust	Animal species	Exposure time	Particulate exposure concentrations (mg/m^3)	Findings
		Filtered	Male and female Syrian hamsters	16 hr/day, 5 days/week, 2 years	Below the limit of detection	No increase in tumor incidence in any exposure group when compared with controls.
Ishinishi et al. [1986]	Light-duty, 1.8-liter, 4-cylinder, swirl chamber	Unfiltered	Male and female F344 rats	16 hr/day, 6 days/week, max. 30 months	0.1 0.4 1 2	No statistically significant increase in lung tumors. Increase in hyperplasia, squamous hyperplasia, interstitial fibrosis, hyperplastic lesions.
	Heavy-duty, 11-liter, 6-cylinder, direct injection	Unfiltered	Male and female F344 rats	16 hr/day, 6 days/week, max. 30 months	0.4 1 2 4	Statistically significant increase in lung tumors (adenoma, squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma) in the high-exposure group compared to controls.
		Filtered	Male and female F344 rats	16 hr/day, 6 days/week, max. 30 months	0.005 0.019	No statistically significant increase in lung tumors. Increase in hyperplasia, squamous hyperplasia, interstitial fibrosis, hyperplastic lesions.

(continued)

See footnotes at end of table.

Table 3 (Continued).—Characteristics of recent studies* of carcinogenicity in animals exposed to diesel exhaust by inhalation

Study	Type of engine	Nature of exhaust	Animal species	Exposure time	Particulate exposure concentrations (mg/m^3)	Findings
Iwai et al., 1986	2.4-liter	Unfiltered	Female F344 rats	8 hr/day, 7 days/week, 24 months§	4.9	Statistically significant increase in total lung tumors (adenomas, adenocarcinoma, adenosquamous carcinomas, squamous carcinoma, and large cell carcinoma) compared with controls. Statistically significant increase in splenic malignant lymphoma compared with controls. Increased incidence of tumors other than lung, and multiplicity of tumors.
		Filtered	Female F344 rats	8 hr/day, 7 days/week, 24 months§	——	Minimal histopathologic changes. Statistically significant increase in splenic malignant lymphoma compared with controls. Increased incidence of tumors other than lung, and multiplicity of tumors.

*Since 1986
†Observation period was 30 months for surviving animals
§Observation period was 30 months for some animals.

diesel emissions were passed through a centrifugal separator and/or a particle filter. The concentrations of exhaust components in the inhalation chambers for both filtered and unfiltered exhaust are shown in Table 4.

In addition, some diesel-particle-associated PAHs were measured in the unfiltered exhaust. Concentrations of 13 ng/m^3 of benzo(a)pyrene, 21 ng/m^3 of benzo(e)pyrene; and 51 ng/m^3 of a mixture of benzofluoranthenes were measured in batched samples. The authors did not specify the number of samples or the analytical method used to determine these concentrations.

Interpretation of the hamster data is complicated by the fact that the animals were treated with antibiotics for several months during the study. Control hamsters were also treated with antibiotics. No significant differences in body weight developed between control and exposed hamsters over the entire length of the study. In contrast, mice and rats exposed to unfiltered diesel exhaust showed decrements in body weight after approximately 480 days. The median survival time of animals was not affected by exposure. Tissues from the nasal cavity, sinuses, larynx, trachea, esophagus, lungs, forestomach, glandular stomach, liver, kidneys, adrenals, and urinary bladder were subjected to histopathologic examination. In some cases, the salivary glands, thyroid, thymus, aorta, heart, spleen, lymph nodes, and ovaries were also subjected to histopathologic examination.

Histopathology of hamsters exposed to diesel exhaust failed to demonstrate the induction of tumors in the lung or upper respiratory tract. Significant deposits of soot particles were evident in the hamsters exposed to unfiltered diesel exhaust. The lungs of these animals exhibited an increased incidence (measured qualitatively) of thickened septa, bronchioalveolar hyperplasia, and emphysema compared with controls. No significant differences were found between the controls and the animals exposed to filtered diesel exhaust.

Mice exposed to filtered or unfiltered diesel exhaust showed a 2.5-fold increase in lung tumor incidence compared with controls. Combined benign and malignant tumor incidences were as follows: 13% in the control group at the end of the study; 31% in the group exposed to filtered diesel exhaust; and 32% in the group exposed to unfiltered diesel exhaust. This increase was predominantly due to the induction of adenocarcinomas. Bronchioalveolar hyperplasia was more frequent (64%) in the group of mice exposed to unfiltered diesel exhaust than in mice exposed to filtered diesel exhaust (15%) and controls (5%). Furthermore, multifocal alveolar lipoproteinosis was found in 71% of the mice exposed to unfiltered diesel exhaust compared with 3% for filtered diesel exhaust and 4% for controls. Similar results were obtained for interstitial fibrosis that occurred almost exclusively in the mice exposed to unfiltered diesel exhaust.

Of the 95 rats exposed to unfiltered diesel exhaust, 15 exhibited a total of 17 lung tumors. These tumors were classified as 8 bronchiolo-alveolar adenomas and 9 squamous cell tumors (8 benign keratinizing cysts and 1

Table 4.—Concentrations of exhaust components for filtered and unfiltered diesel exhaust measured in the exposure chambers
(mean ± standard deviation)
(Adapted from Heinrich et al., 1986)

Component	Control (clean air)	Filtered exhaust	Unfiltered exhaust
Carbon monoxide (ppm)	0.16 ± 0.27	11.1 ± 1.92	12.5 ± 2.18
Carbon dioxide (vol.%)	0.10 ± 0.01	0.35 ± 0.05	0.38 ± 0.05
Sulfur dioxide (ppm)	——	1.02 ± 0.62	1.12 ± 0.89
Oxides of nitrogen (ppm)	——	9.9 ± 1.80	11.4 ± 2.09
Nitric oxide (ppm)	——	8.7 ± 1.84	10.0 ± 2.09
Nitrogen dioxide (ppm)	——	1.2 ± 0.26	1.5 ± 0.33
Alkanes (ppm)	3.5 ± 0.29	5.2 ± 0.65	5.5 ± 0.69
Methane (ppm)	2.3 ± 0.17	2.4 ± 0.20	2.6 ± 0.19
Alkanes without methane (ppm)	1.3 ± 0.15	2.9 ± 0.50	3.1 ± 0.53
Particles (mg/m^3)	——	——	4.24 ± 1.42

squamous cell carcinoma). Hyperplasia was seen in the lungs of 94 of the 95 rats exposed to unfiltered diesel exhaust, and metaplasia occurred in 62 of these animals. Other severe inflammatory changes such as thickened septa, foci of macrophages, and cholesterol crystals were found in the lungs of rats exposed to unfiltered diesel exhaust. No changes were seen in the control animals or in those exposed to filtered diesel exhaust. No exposure-related changes were observed in the upper respiratory tracts of the rats exposed to unfiltered diesel exhaust.

Exposure to filtered and unfiltered diesel exhaust resulted in a statistically significant increase in the incidence of lung adenocarcinomas in female NMRI mice. In hamsters, long-term exposure to unfiltered diesel exhaust led to broncho-alveolar hyperplasia and emphysematous lesions in the respiratory tract, but it did not produce tumors. In rats, long-term exposure to unfiltered diesel exhaust led to extensive hyperplasia and metaplasia of the broncho-alveolar epithelium and to a significantly increased incidence of adenomas and squamous cell tumors of the lung compared with controls.

Mauderly et al. [1987]

Mauderly et al. [1987] reported the results of a carcinogenicity study in which F344 male and female rats were exposed to unfiltered diesel exhaust at three concentrations for up to 30 months. Diesel exhaust was generated by stationary light-duty diesel engines (1980 model, 5.7-liter, Oldsmobile V-8) operated by computer through continuously repeating U.S. Federal Test Procedure urban certification cycles. The exhaust effluents were diluted 10:1 with filtered air, serially diluted to the final concentrations, and then directed through exposure chambers. The average particulate concentrations for the low, medium, and high exposures to diesel exhaust were 0.35, 3.5, and 7 mg/m^3, respectively. Concentrations of key components identified in the diesel exhaust are shown in Table 5.

Male and female F344 rats that were 15 weeks old were randomly divided by litter into four treatment groups. There were 365 rats in the control group, and 366, 367, and 364 rats in the low-, intermediate-, and high-exposure groups, respectively. Rats were added to all treatment groups during February 1981; a second group of rats was added to all treatment groups 1 year later. Both groups of rats were derived from the same breeding colony and were exposed in the same chambers. The two added groups of rats were treated as one study population since the groups showed no differences in body weights or survival times. All animals were exposed to unfiltered diesel exhaust for 7 hours per day, 5 days per week for up to 30 months.

All rats terminated for histopathology and all rats that died or were euthanized received a complete necropsy. All lesions except for soot macules and representative portions of each lung lobe were examined microscopically, as were samples of other respiratory tract tissues. Exposure to diesel exhaust did not cause overt signs of toxicity. No

Table 5.—Concentrations of key components of exposure atmospheres*
(Adapted from Mauderly et al., 1987)

Component	Control	Low	Medium	High
Particulate (mg/m^3)	0.010 (0.010)†	0.350 (0.070)	3.470 (0.450)	7.080 (0.810)
Carbon monoxide (ppm)	1 (1)	3 (1)	17 (7)	30 (13)
Nitric oxide (ppm)	0	0.6 (0.3)	5.4 (1.5)	10.0 (2.6)
Nitrogen dioxide (ppm)	0	0.1 (0.1)	0.3 (0.2)	0.7 (0.5)
Hydrocarbons (ppm)	3 (1)	4 (1)	9 (5)	13 (8)
Carbon dioxide (%)	0.2 (0.04)	0.2 (0.03)	0.4 (0.06)	0.7 (0.1)

*Mean of weekly mean values during 30 months of exposure.
†Figures in parentheses are standard error.

significant differences in body weight or life span were observed in either the males or females in the experimental groups compared with the controls. The physical condition of all groups of animals appeared to be similar.

Soot accumulated progressively and significantly in the lungs of all exposed rats. After 24 months of exposure, the mean lung burden of diesel exhaust particulate per rat was reported to be 0.6 $\pm$ 0.02 mg for the low exposure, 11.5 $\pm$ 0.5 mg for the intermediate exposure, and 20.8 $\pm$ 0.8 for the high exposure. These calculations were made by measuring the amount of light absorbed by lung homogenates from exposed rats and comparing those values with standard curves constructed from measurements made from known amounts of soot deposited in the lungs of unexposed rats.

Changes in the epithelial lining of the air spaces and progressive fibrosis occurred in the areas of soot accumulation. Hyperplasia and squamous metaplasia were seen in broncho-alveolar spaces.

Broncho-alveolar adenomas, adenocarcinomas, benign squamous cysts, and squamous cell carcinomas were observed in the lungs of exposed rats. Rats exposed to the high concentration of diesel exhaust for up to 30 months experienced statistically significant increases in adenocarcinomas, benign squamous cell tumors, and squamous cell carcinomas in male and female rats. The increase in total tumor incidence for the high-exposure group was also statistically significant when compared with the control group. The percentages of rats with lung tumors (males and females combined) are listed by exposure group in Table 6.

Table 6.--Percentages of rats (male and female combined) with lung tumors, by exposure group (Adapted from Mauderly et al., 1987)

Exposure group	Adenomas	Adenocarcinomas and squamous cell carcinomas	Squamous cysts only	All tumors
High	0.4	7.5*	4.9*	12.8*
Medium	2.3*	0.5	0.9	3.6*
Low	0	1.3	0	1.3
Control	0	0.9	0	0.9

*Significantly higher than controls at $p<0.05$ by z statistic.

A statistically significant increase in adenomas occurred in the intermediate-exposure group. One adenocarcinoma and two squamous cysts were also observed in female animals in that group. The increase in all tumors in the intermediate-exposure group was statistically significant when compared with the control group.

No statistically significant increases in tumor incidence occurred in the low-exposure animals.

Squamous tumors were always associated with focal areas of engine soot retention, epithelial cell alterations, and fibrosis. They are thus likely to represent a progression of squamous metaplasia. These tumors may have resulted from a generalized response to the accumulation of relatively insoluble particles.

None of the lung tumors had metastasized to pulmonary lymph nodes or other organs. Increased numbers of adducts were found in DNA extracted from the lungs of rats exposed to the highest concentration of diesel exhaust for 30 months.

Diesel exhaust inhaled chronically at the intermediate and high concentrations in this study induced a significant number of benign and malignant pulmonary tumors in male and female rats. The increased numbers of DNA adducts suggest that tumor development may have been initiated by the interaction of reactive metabolites of soot-associated organic compounds with lung cell DNA. In this study, the relationship between lung burden of diesel exhaust particulates and tumor prevalence was progressive rather than linear with time, rising rapidly late in the exposure regimen.

Brightwell et al. [1986]

Brightwell et al. [1986] reported preliminary data on the chronic toxicity of diesel engine exhaust in Fischer 344 rats and Syrian hamsters. Each group of experimental animals was made up of 144 rats and 312 hamsters with approximately equal numbers of males and females. The animals were 6 to 8 weeks old at the start of the 2-year exposure period.

The diesel exhaust emissions used in this study were generated by a 1.5-liter light-duty diesel engine. The emissions were diluted to yield particulate exposure concentrations of approximately 0.7, 2.2, and 6.6 mg/m^3. The diesel emissions were either subjected to particle filtration or they were unaltered (unfiltered). Exposures were carried out overnight for 16 hours per day, 5 days per week.

The mean concentrations for carbon monoxide (CO) and nitrogen oxides (NO_x) for both filtered and unfiltered diesel exhaust in the high-exposure groups were 32 and 8 parts per million (ppm), respectively. Concentrations of those contaminants for the controls were 1 ppm CO and 0.1 ppm NO_x. No data were presented for the concentrations of these contaminants in the intermediate- and low-exposure chambers. Similarly, no data were presented for exposure concentrations of other exhaust components, although regular

analyses were conducted for particle size distributions, aldehydes, phenols, PAHs, sulfates, and individual hydrocarbons.

Interim sacrifices of rats were conducted after 6, 12, 18, and 24 months of exposure, while hamsters had interim sacrifices at 6 and 16 months. All surviving hamsters were sacrificed at the end of 2 years of exposure. Rats that survived 2 years of exposure were maintained for up to 6 additional months without further exposure to exhaust.

Animals that died or were sacrificed were subjected to a full necropsy, and histopathology was carried out on the respiratory tracts (nasal passages, larynx, trachea, and lungs) of all animals in the high-exposure and control groups. Histologic examinations were also performed on the respiratory tracts of all animals in the groups with intermediate and low exposures to filtered and unfiltered diesel exhaust. Histopathology was carried out on all suspected tumors regardless of experimental treatment.

The major histopathologic finding in the study was an increase in the incidence of primary lung tumors in rats exposed to the intermediate and high concentrations of unfiltered diesel exhaust. Table 7 summarizes the histopathologic findings for primary benign and malignant lung tumors in rats exposed to unfiltered diesel exhaust and to air alone. The incidence of primary lung tumors was 2%, 1%, 4%, and 23% for male rats in the control, low-, intermediate-, and high-exposure groups, respectively. Lung tumor incidence in female rats was 1%, 0%, 15%, and 54% for control and for low-, intermediate-, and high-exposure groups, respectively. However, a later analysis of these data [Fouillet and Brightwell 1987] points out that tumor incidence was based on the total number of animals examined in each treatment group. Since this total included some animals sacrificed after 6, 12, 18, and 24 months of exposure, some of them clearly were not exposed long enough to induce recognizable lung tumors. When tumor incidence was recalculated using only the data for rats surviving beyond 24 months, 44% of

Table 7.--Primary benign and malignant lung tumors in rats exposed to unfiltered diesel exhaust*
(Adapted from Brightwell et al., 1986)

Exposure group	Particulate concentration (mg/m^3)	F344 rats that developed lung tumors			
		Males		Females	
		Number	%	Number	%
High	6.6	16/71†	23	39/72†	54
Intermediate	2.2	3/72	4	11/72†	15
Low	0.3	1/72	1	0/72	0
Control	0	3/140	2	1/142	1

*These figures represent calculations that included animals sacrificed after 6, 12, 18, and 24 months of exposure.
†Statistically significant compared with controls ($p<0.01$).

male and 99% of female rats exposed to unfiltered diesel exhaust developed lung tumors.

No increase occurred in the incidence of primary lung tumors in any other treatment group. Respiratory tract tumors were rare in hamsters and were not attributed to treatment.

The pathology description in this report [Brightwell et al. 1986] is very limited. It contains no specific diagnoses of the lung tumors, and no data on whether the tumors were single, multiple, lethal, or incidental. Data on degree of invasion are also absent. No comment is made on pathology of the nasal passages, larynx, or trachea. There is no description or discussion of chronic toxicity, hyperplasia, or the relationship of hyperplasia to neoplasia. Although the investigators did not present the full spectrum of their bioassay data, the information presented justifies the conclusion that long-term exposure to high concentrations of unfiltered diesel exhaust leads to a significant increase in the incidence of benign and malignant lung tumors in male and female F344 rats.

Ishinishi et al. [1986]

Ishinishi et al. [1986] studied F344 rats to determine the effects of long-term inhalation of exhausts from heavy- and light-duty diesel engines. Five-week-old female and male F344 rats were exposed to various concentrations of diesel exhausts for 6, 12, 18, 24, and 30 months, 16 hours per day, 6 days per week. Three types of exposures were administered: exposure to filtered and unfiltered diesel exhaust from 11-liter heavy-duty engines, and exposure to unfiltered diesel exhaust from 1.8-liter light-duty engines.

For the carcinogenicity experiment, five groups of animals (each consisting of 64 male and 59 female rats) were exposed for 30 months to unfiltered heavy-duty engine exhaust at a given particulate concentration originally designed to be 0, 0.4, 1, 2, and 4 mg/m^3 (see Table 8 for actual concentrations). Five additional groups (each consisting of 64 male and 54 female rats) were exposed for 30 months to unfiltered light-duty engine exhaust at a given particulate concentration originally designed to be 0, 0.1, 0.4, 1, and 2 mg/m^3 (see Table 8 for actual concentrations).

Two additional groups of 64 male rats were exposed to filtered exhaust from the heavy-duty engines. The 0.4- and 4-mg/m^3 concentrations were filtered so that the animals were exposed only to the gaseous fraction of the exhaust. For comparison, three additional groups of 64 male rats were exposed to the unfiltered diesel exhaust from the same source at particulate concentrations of 0, 0.4, and 4 mg/m^3. Table 8 presents a summary of gas and particle concentrations for each exposure atmosphere.

A concentration-dependent decrease in body weight was observed, with the greatest effect observed in the 4-mg/m^3 group exposed to exhaust from heavy-duty engines.

Table 8.—Summary of gas and particle concentrations*
(Adapted from Ishinishi et al., 1986)

Type of diesel exhaust (%)	Particle concentration (mg/m^3) Target†	Actual	Gaseous Concentration NO_x (ppm)	NO (ppm)	NO_2 (ppm)	CO (ppm)	CO_2 (%)	SO_2 (ppm)	Formaldehyde (ppm)	SO_4^{2-} ($\mu g/m^3$)	O_2 (%)
Unfiltered exhaust from heavy-duty engine	4	3.72	37.45	34.45	3.00	12.91	0.360	4.57	0.29	361	20.4
	2	1.84	21.67	19.99	1.68	7.75	0.215	2.82	0.18	198	20.6
	1	0.96	13.13	12.11	1.02	4.85	0.140	1.79	0.11	111	20.7
	0.4	0.46	6.17	5.71	0.46	2.65	0.084	0.98	0.05	62.9	20.8
	0	0.002	0.061	0.042	0.021	0.63	0.035	0.06	0.003	0.49	20.8
Filtered and unfiltered exhaust from heavy-duty engine	4 (unfiltered)	2.99	36.45	31.50	4.95	12.90	0.412	4.03	0.20	358	20.3
	4 (filtered)	0.019	36.76	32.81	3.96	13.00	0.391	4.50	0.24	1.61	20.4
	0.4 (unfiltered)	0.39	5.81	5.37	0.44	2.50	0.084	0.98	0.04	57.7	20.7
	0.4 (filtered)	0.005	5.58	5.16	0.42	2.54	0.083	0.96	0.04	1.43	20.7
	0	0.004	0.062	0.040	0.024	0.06	0.068	0.03	0.003	0.35	20.8
Unfiltered exhaust from light-duty engine	2	2.32	20.34	18.93	1.41	7.10	0.418	4.70	0.13	315	20.3
	1	1.08	10.14	9.44	0.70	3.96	0.219	2.42	0.07	151	20.5
	0.4	0.41	4.06	3.81	0.26	2.12	0.105	1.06	0.03	62.4	20.7
	0.1	0.11	1.24	1.16	0.08	1.23	0.050	0.38	0.01	18.8	20.8
	0	0.003	0.044	0.033	0.011	0.80	0.026	0.06	0.002	0.41	20.8

*Exposures were for 30 months.
†Groups are identified in the text by the design exposure.

After 6 months of exposure, "anthracosis"* was observed in all groups exposed to particle-containing exhausts. Severity was proportional to concentration and duration of exposure. Hyperplasia of type II epithelial cells and bronchiolar epithelium associated with anthracosis was observed after 18 months in the groups exposed to the higher particle concentrations. The extent of these conditions depended on exposure. Squamous metaplasia with focal interstitial fibrosis was often observed in hyperplastic lesions of the subpleural zone. Scanning electron microscopy revealed irregularity, shortening, and absence of cilia in the mucosal epithelia of the trachea and main bronchi. These lesions were also observed in rats exposed only to the gaseous components of the exhaust; the severity of the lesions increased in proportion to exhaust concentration and duration of exposure.

A statistically significant increase occurred in the incidence of lung tumors in rats (male and female combined) exposed for 30 months to heavy-duty diesel engine exhaust with particulate concentrations of 4 mg/m^3 compared with controls. Tumor incidence was 6.5% (8/124) for exposed rats and 0.8% (1/123) for controls. The majority of tumors were squamous cell carcinomas, adenosquamous carcinomas, and adenocarcinomas.

Iwai et al. [1986]

Iwai et al. [1986] studied the effects of long-term inhalation exposure to filtered and unfiltered diesel exhaust in female F344 rats. Exhaust for this experiment was generated by a 2.4-liter light-duty diesel engine. Seven-week-old female rats (initially 24 animals/exposure group) were exposed to unfiltered exhaust, filtered exhaust, or clean air for 24 months, 8 hours/day, 7 days/week. Measured concentrations (mean $\pm$ standard deviation) of exhaust components were 4.9 $\pm$ 1.6 mg/m^3 for particles, 30.9 $\pm$ 10.9 ppm for oxides of nitrogen (NO_x), 1.8 $\pm$ 1.8 ppm for nitrogen dioxide (NO_2), 13.1 $\pm$ 3.6 ppm for sulfur dioxide (SO_2), and 7.0 $\pm$ 1.4 ppm for carbon monoxide (CO). Some animals were autopsied after 3, 6, 12, and 24 months of exposure. Histologic and electron-microscopic examinations were performed on lungs, spleen, and other organs. Some of the rats exposed for 12 to 24 months were kept in clean air for an additional 3 or 6 months and then examined.

After 6 months of exposure to unfiltered diesel exhaust, phagocytotic macrophages filled with black particles were distributed in an irregular pattern in the lungs. Areas where macrophages were gathered showed proliferations of Type II alveolar epithelial cells showing adenomatous metaplasia. More lesions were found after 1 year of exposure, but no neoplastic lesions were observed. Two adenomas were found in one of five rats kept in clean air for 3 months after 1 year of exposure to unfiltered exhaust. After 2 years of exposure, the number of particles in the macrophages increased markedly. Fibrous thickening of alveolar walls was

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*Anthracosis is assumed to mean discoloration of the lung.

observed, and mast cell infiltration was found with epithelial hyperplasia where macrophages gathered. Neoplastic changes were observed after 2 years of exposure; some of these showed intra-lymphatic invasion indicative of malignant transformation. Two types of lung carcinoma (adenocarcinoma and squamous or adenosquamous carcinoma) were observed.

In the rats exposed to filtered diesel exhaust, histologic changes were minimal, and no heterotrophic hyperplasia was observed in the alveolar walls. Quantitative analysis of epithelial proliferative changes in the lung indicated an increase in affected areas that was associated with the length of exposure to unfiltered exhaust.

Rats exposed to unfiltered exhaust had a statistically significant increase in lung tumor incidence compared with controls. After 24 months of exposure, 4/14 rats had tumors, 2 of which were malignant. After an additional 6 months in clean air, four of the five remaining rats had tumors, three of which were malignant. The combined incidence of tumors was 42% (8/19) in rats exposed to unfiltered diesel exhaust compared with 0% (0/16) in rats exposed to filtered exhausts and 4.5% (1/22) in the controls. The distribution of tumor types found in rats exposed to unfiltered diesel exhaust was as follows:

Adenomas	3 rats
Adenocarcinoma	1 rat
Adenosquamous carcinomas	2 rats
Squamous carcinoma	1 rat
Large cell carcinoma	1 rat

The tumor found in the control rat was an adenoma. The authors concluded that the significantly higher incidence of lung tumors in the unfiltered exhaust exposure group could be attributed to the inhalation of particles.

Another important observation in this study was a statistically significant increase in the incidence of splenic malignant lymphoma, with or without leukemia. After 24 months, the incidence rate was 25.0% (6/24) for rats exposed to unfiltered diesel exhaust, 37.3% (9/24) for rats exposed to filtered diesel exhaust, and 8.2% (2/24) for controls. The incidence of tumors in other organs also increased in rats exposed to filtered exhaust (25%, or 6/24) and unfiltered exhaust (29%, or 7/24) compared with controls (8.2%, or 2/24). The multiplicity of tumors increased both in rats exposed to unfiltered exhaust and in those exposed to filtered exhaust, with a quadrupled incidence of tumors noted only in the unfiltered exhaust group.

HUMAN HEALTH EFFECTS

The NIOSH document entitled Evaluation of the Potential Health Effects of Occupational Exposure to Diesel Exhaust in Underground Coal Mines [NIOSH 1986] contains discussions of all pertinent epidemiologic data available at the time. Although many epidemiologic studies of diesel-exposed populations

had been conducted before 1986, the only documented health effects in humans were reversible pulmonary function changes (before and after a workshift) in salt miners [Gamble et al. 1979] and exposure-related eye irritation among men experimentally exposed to diesel exhaust [Battigelli 1965]. Past epidemiologic studies of occupational exposure to diesel exhaust and mortality from cancer have been inconclusive partly because of a myriad of methodologic problems [NIOSH 1986]. The problems included incomplete information on the extent of exposure, insufficient time from first exposure to allow for the appearance of exposure-related cancer, and confounding variables such as smoking and exposure to asbestos or ionizing radiation. These problems made it impossible to draw definitive conclusions about the cause of any observed excess of cancer incidence [NIOSH 1986].

Since the release of that document [NIOSH 1986], the final results of three epidemiologic studies have been released [Edling et al. 1987; Garshick et al. 1987a; Garshick et al. 1988]. Preliminary reports of data from each of these studies were discussed in the NIOSH document [NIOSH 1986]. Two of these recently released final reports [Garshick et al. 1987a; Garshick et al. 1988] have indicated an increased risk of death from lung cancer among railroad workers exposed to diesel engine emissions. These studies are summarized in Table 9 and discussed more fully in this section. The validity of the results obtained in the study by Edling et al. [1987] was questionable because of the small size of the cohort analyzed (694 male employees of five different bus companies), and because no exposure measurements were taken (exposures were estimated by job title). For these reasons, the study by Edling et al. [1987] will not be discussed in detail in this bulletin.

Garshick et al. [1987a]

Garshick et al. [1987a] conducted a case-control study of deaths among U.S. railroad workers to test the hypothesis that lung cancer is associated with exposure to diesel exhaust. The study included only male railroad workers who had at least 10 years of railroad service, were vested in the railroad retirement program, were born on or after January 1, 1900, and died between March 1, 1981, and February 28, 1982. The investigators collected death certificates for 87% of the 15,059 deaths reported to the U.S. Railroad Retirement Board.

Within the cohort, 1,256 workers who died from lung cancer were matched with two deceased comparison workers by age ($\pm$ 2.5 years) and date of death ($\pm$ 31 days). Deceased workers whose jobs had involved exposure to diesel exhaust (engineers and firemen, brakemen and conductors, diesel locomotive repair workers, and hostlers) were compared with deceased workers without occupational exposure to diesel exhaust (clerks and station agents).

Work histories were determined from yearly job reports filed with the U.S. Railroad Retirement Board. These reports were used to classify workers as exposed or unexposed to diesel exhaust. The classifications were confirmed

Table 9.--Characteristics of epidemiologic studies of exposure to diesel exhaust and carcinogenicity, published since 1986

Investigator	Population studied	Observation period	Findings	Comments
Garshick et al. 1987a	U.S. railroad workers born in 1900 or later with 10 or more years of service	1959-81 for diesel exhaust exposure; deaths that occurred between March 1, 1981, and February 28, 1982.	Workers exposed occupationally to diesel exhaust for 20 years had a significantly increased relative odds ratio (1.41, 95% CI*=1.06, 1.88) of lung cancer	Population-based, case-control study that included industrial hygiene characterization of exposures and multiple conditional logistic regression analysis to adjust for confounders such as smoking and asbestos exposures. Only 87% of death certificates were collected.
Garshick et al. 1988	U.S. railroad workers aged 40 to 64 in 1959 who started railroad service 10 to 20 years earlier	1959-1980 for diesel exposure; deaths that occurred before December 31, 1980	Workers aged 40-44 in 1959 had a significantly increased relative risk (1.45, 95% CI=1.11, 1.89) of lung cancer	Retrospective cohort study. Only 88% of death certificates were collected. Effects of smoking could not be eliminated. The effect of asbestos exposures was addressed by considering diesel-exposed workers separately from asbestos-exposed workers using a proportional hazards regression model.

*CI = confidence interval.

by measuring current exposures to respirable particulate matter for workers in selected jobs. Respirable particulate matter was chosen as a marker for exposure to the particulate fraction of diesel exhaust. The respirable particulate fraction was sampled because it included all of the diesel exhaust particulates and excluded some of the larger nondiesel particulates. Respirable dust exposures were corrected for cigarette smoke particulates by analyzing the nicotine content of composite samples [Woskie et al. 1988a; Woskie et al. 1988b]. An adjusted respirable particulate concentration was then calculated for each job group by subtracting the applicable average fraction of cigarette smoke from each railroad's average respirable particulate concentration. Personal exposure to respirable particulate matter was measured for 39 common jobs in four U.S. railroads over a 3-year period.

According to the authors, diesel locomotives replaced steam locomotives over a short period (from 14% diesel use in 1947 to 95% in 1959). Thus the year 1959 was chosen as the effective beginning of diesel exhaust exposure for this study. Workers who retired before that year were classified as unexposed to diesel exhaust. The authors acknowledged that some workers had additional earlier years of diesel exhaust exposure. Smoking histories were obtained by questionnaires from the deceased workers' closest relatives or by direct telephone contact if there was no response to the questionnaire. Asbestos exposures in railroad workers occurred primarily in the steam engine era. Asbestos exposure for this study was therefore categorized by the job held in 1959 (the end of the steam locomotive era) or by the last job held if retirement occurred before 1959.

The relative hazard of lung cancer attributable to diesel exhaust exposure was calculated using a multiple conditional logistic regression to adjust for smoking and asbestos exposure. A statistically significant increase in relative odds (1.41, 95% CI=1.06-1.88) was found for lung cancer among workers aged 64 or younger at the time of death who had worked in a [diesel-exposed] job with diesel exposure for 20 years. No increase was found in workers aged 65 or older. The authors felt that this finding reflected the fact that many of these men retired shortly after the transition to diesel-powered locomotives.

Garshick et al. [1988]

To confirm the results of the case-control study, Garshick et al. [1988] evaluated the risk of lung cancer as a result of exposure to diesel exhaust from railroad locomotives. These investigators conducted a retrospective cohort study of 55,407 white male railroad workers who were aged 40 to 64 in 1959 and who had started railroad service 10 to 20 years earlier. The cohort was traced until the end of 1980. Death certificates were obtained for 88% of 19,396 deaths, and 1,694 lung cancer cases were identified. Records of yearly job assignments obtained through the Railroad Retirement Board served as an index of diesel exhaust exposure. Workers were considered to be either

exposed or unexposed to diesel exhaust, depending on the yearly job code. These classifications were confirmed by measurements of current exposures to respirable particulate matter for workers in selected jobs. These measurements were analyzed as described in the earlier discussion of the 1987 case-control study [Garshick et al. 1987a]. A proportional hazards model and directly standardized rates were used to calculate the relative risk of lung cancer for a worker whose job involves diesel exhaust exposure. The group of workers aged 40 to 44 in 1959 had a relative risk of 1.45 (95% CI=1.11-1.89) for lung cancer. This group consisted of workers with the longest possible duration of diesel exposure.

To control for the confounding effects of asbestos exposures in the cohort, the relative risk of lung cancer was not considered for groups of workers with possible exposures to asbestos in the past (shop workers and hostlers). When this analysis was conducted, the relative risk for lung cancer remained elevated at 1.57 (95% CI=1.19-2.05) in the group aged 40 to 44 in 1959, and it was 1.34 (95% CI=1.02-1.76) in the workers aged 45 to 49 in 1959. These results confirmed those obtained with the proportional hazards regression model.

The effects of cigarette smoking could not be eliminated because of the retrospective nature of the study. However, the prevalence of cigarette smoking was the same for workers with and without potential diesel exhaust exposure in a group of 517 current railroad workers who were surveyed in 1982 regarding past asbestos exposure [Garshick et al. 1987b].

Epidemiologic studies of lung cancer risk in diesel-exposed workers are inherently problematic because of (1) the difficulty in defining and quantifying exposure, (2) the relatively short time between initial exposures and analysis of risk in some studies, and (3) the need to control for cigarette smoking. The reports by Garshick et al. [1987a; 1988] are the most thorough epidemiologic studies conducted to date. Data on cigarette smoking were collected in the case-control study. An attempt was made to control for the confounding exposure to asbestos. Attempts were also made to characterize exposures to diesel exhaust through the collection of industrial hygiene data. The period between the first diesel exposure and data analysis was adequate to allow the observation of exposure-related cancer for some age groups of the cohort. The fact that the findings of the two studies were both independent (the two studies based their analyses on different lung cancer deaths) and consistent fortifies the conclusion that occupational exposure to diesel exhaust is associated with an increased risk of lung cancer.

The studies of Garshick et al. [1987a; 1988] are subject to a number of limitations, some of them inherent, that preclude them from providing definitive evidence that diesel exhaust is an occupational carcinogen. Ascertainment of death certificates was incomplete in both studies (87% in the case-control study, and 88% in the retrospective cohort study). In both reports of final data, the authors presented data on lung cancer risk only for

separate-age subcohorts within the study population. Though there is merit in the authors' rationale for splitting the groups by age, the risk analysis should have considered diesel exposure for the combined cohort also. The investigators attempted to characterize exposures to diesel exhaust by collecting industrial hygiene data, but they were forced to use an experimental approach to collect them. Exposure to diesel exhaust is difficult to measure because of the complex nature of the exhaust. Measuring exposure to respirable particulate matter as a surrogate for diesel exhaust allows for a substantial error in classification of exposures, as there is no way to define the source of the particulates. Adjusting the measurements to exclude the contribution of cigarette smoke particulates eliminates only one extraneous source of respirable particulates. The classification of exposed and unexposed workers is particularly important to the outcome of the case-control study because the unexposed workers were used as the referent population. Furthermore, no attempts were made to control for potentially confounding exposures to pyrolysis products of fuels that were used to power locomotives before the use of diesel fuel.

CONCLUSIONS

Recent animal studies in rats and mice confirm an association between the induction of cancer and exposure to whole diesel exhaust. The lung is the primary site identified with carcinogenic or tumorigenic responses following inhalation exposures. Limited epidemiologic evidence suggests an association between occupational exposure to diesel engine emissions and lung cancer. The consistency of these toxicologic and epidemiologic findings suggests that a potential occupational carcinogenic hazard exists in human exposure to diesel exhaust.

Tumor induction is associated with diesel exhaust particulates. Limited evidence indicates that the gaseous fraction of diesel exhaust may be carcinogenic, as well.

RECOMMENDATIONS

Classification systems for identifying a substance as a carcinogen have been developed by the National Toxicology Program (NTP) [NTP 1984], the International Agency for Research on Cancer (IARC) [IARC 1979], and OSHA in its "Identification, Classification, and Regulation of Potential Occupational

Carcinogens" [29 CFR* 1990], also known as "The OSHA Cancer Policy." NIOSH considers the OSHA classification the most appropriate for use in identifying potential occupational carcinogens† [29 CFR* 1990]. Exposure to diesel exhaust has been shown to produce benign and malignant tumors in rats and mice. Therefore, NIOSH recommends that whole diesel exhaust be regarded as a potential occupational carcinogen in conformance with the OSHA Cancer Policy (29 CFR 1990).

The excess cancer risk for workers exposed to diesel exhaust has not yet been quantified, but the probability of developing cancer should be decreased by minimizing exposure. As prudent public health policy, employers should assess the conditions under which workers may be exposed to diesel exhaust and reduce exposures to the lowest feasible limits. Although a substantial amount of information suggests that some component (or combination of components) of the particulate fraction of diesel exhaust is associated with tumor initiation, the relative roles of the particulate and gaseous phases of emissions need further characterization.

RESEARCH NEEDS

The particulate exposures used in some of the studies summarized here may have inhibited pulmonary clearance mechanisms, resulting in unusually large particle deposits in the lung [Vostal 1986]. Research on how particle deposition and particle-associated organic compounds influence the carcinogenicity of inhaled diesel exhaust might clarify the roles of the particles themselves versus the chemicals associated with the particles. The fraction of diesel exhaust containing the causative agent (or combination of agents) needs to be further defined, and those agents need to be identified.

Engineering control techniques can be effective in reducing the production or toxicity of diesel engine emissions. Fuel and engine modifications and exhaust treatment all have been investigated, and each approach entails costs as well as benefits. No technique effectively reduces or controls all components of diesel exhaust. Research is needed to improve the efficacy of

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*Code of Federal Regulations. See CFR in references.

†"'Potential occupational carcinogen' means any substance, or combination or mixture of substances, which causes an increased incidence of benign and/or malignant neoplasms, or a substantial decrease in the latency period between exposure and onset of neoplasms in humans or in one or more experimental mammalian species as the result of any oral, respiratory, or dermal exposure, or any other exposure which results in the induction of tumors at a site other than the site of administration. This definition also includes any substance which is metabolized into one or more potential occupational carcinogens by mammals" [29 CFR 1990].

known engineering controls, to develop additional techniques, to evaluate the combined effects of engineering controls, and to identify which controls are most appropriate for various uses of diesel-powered equipment. A preferred engineering control technique is substitution (replacing a hazardous material or process with an alternative that has a lower health risk). However, the health and safety implications of any proposed alternatives to diesel power require careful evaluation before implementation.

Diesel exhaust is a very complex mixture, and its composition varies greatly with fuel and engine type, load cycle, maintenance, tuning, and exhaust gas treatment. This complexity is compounded by the multitude of environmental backgrounds in which diesel-powered equipment is operated. Gases and particulates found in the workplace may emanate from a number of sources, including diesel engines. Methods have been developed and used for apportioning the contribution of highway vehicle emissions from various sources [Hampton et al. 1983] and for apportioning sources of occupational exposure to engine exhaust [Currie et al. 1981; Johnson et al. 1981; Cantrell et al. 1986]. Although NIOSH-validated sampling and analytical methods exist for components of diesel exhaust, none of these methods can be used to apportion sources of exposure.

Quantitative risk estimates are yet to be developed for workers exposed to diesel exhaust. Studies involving measurement or careful estimation of the extent of exposure to diesel exhaust are urgently needed.

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