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ADEQUACY OF EXISTING DATA TO ASSESS HEALTH EFFECTS OF DIESEL EXHAUST

Submitted by the
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ADEQUACY OF EXISTING DATA TO ASSESS HEALTH EFFECTS OF DIESEL EXHAUST

INTRODUCTION

The purpose of this review is to demonstrate that sufficient data exists to adequately evaluate the health effects of diesel exhaust and that no additional testing should be required under Tier Two of Section 211(b)of the Clean Air Act (CAA). To date, there have been thousands of studies on the health effects of diesel exhaust compiled in six major reviews: 1) NIOSH's "Current Intelligence Bulletin 50: Carcinogenic Effects of Exposure to Diesel Exhaust", 1988, 2) US EPA's "Health Assessment Document for Diesel Emissions", 1994 (Draft), 3) California EPA's, Air Resource Board's, "Technical Support Document: Proposed Identification of Diesel Exhaust as a Toxic Air Contaminant", 1994 (Draft), 4) American Health Foundation's (AHF) "The Health Effects of Exposure to Diesel Engine Exhaust", 1994, 5) Health Effects Institute's (HEI) "Diesel Exhaust: A Critical Analysis of Emissions, Exposure, and Health Effects", 1995, and 6) ACGIH's TLV Documentation on Diesel Exhaust, 1995. The California, USEPA, ACGIH and HEI documents reviewed multiple end-points in both animals and humans whereas the AHF and NIOSH reports examined carcinogenicity only.

Table 1 of this report provides an overview of the adequacy of the diesel exhaust health effects data as summarized and compared to EPA's criteria for determining adequacy of existing data in lieu of Tier 2. Subsequent text sections further explain the basis for our "adequacy" determination by endpoint. Additional detail of selected studies for specific endpoints is provided in attachments 1-7. Based on review of existing diesel exhaust toxicology literature, it is concluded that sufficient data is available for EPA to adequately evaluate the health effects of diesel exhaust using the criteria specified in Section 79.53(d) (*Federal Register 59 #122 June 27, 1994 p. 33102*) of the rule and summarized on page 16 of this document, and that no additional 90-day screening tests as described in Section 211(b) Tier 2 should be required. A comprehensive review of toxicological studies on diesel fuel, constituents and relevant fractions will be provided to EPA in compliance with the Section 211(b) Tier 1 literature search requirements.

Table 1. Adequacy of Existing Data

Endpoint	Minimum requirement for adequacy[1]	Adequacy of existing data	Acceptability of study protocols	Conclusion
Carcinogenicity	Salmonella assay plus two other assays (at least one of which shall be *in vivo*).	1. Over 20 lifetime studies in rats, mice or hamsters have been completed. 2. Mauderly's chronic study (Attachment 1) is the most quoted study to date and is the study used by EPA to identify the cancer risk of diesel exhaust. 3. Over 20 epidemiology retrospective cohort or case control studies have been completed. The Garshick studies have been identified as the most comprehensive (Attachment 2).	1. Animal studies - The majority of the studies meet standard criteria of animal testing. 2. Epidemiology - The two Garshick studies have been identified as the best studies.	**Data exceed the requirements** with respect to length of exposure and number of studies (≥ 2 yr vs 90 d; number of studies, number of animals, etc.) as outlined in the preamble to section 211(b) of 40 CFR 79 and column 2 of this table.
Mutagenicity	Salmonella assay plus one *in vivo* assay	Over 100 mutagenicity assays have been completed on diesel exhaust, its particulate phase and gaseous phase, and organic extracts of the particulate phase. Types of assays include the following: Salmonella, mammalian cell assays, gene mutation in yeast, and cell transformation assays. In vivo assays include chromosome aberrations, sister chromatid exchange, micronuclei formation, and heritable mutations assessment of DNA damage (Attachment 3).	Genotoxic endpoints have been adequately covered. Also, it was noted that over 20 lifetime bioassays using three species have been completed on diesel exhaust.	**Data exceed the requirements** with respect to length of exposure and number of studies (≥ 2 yr vs 90 d; number of studies, diversity of assays, number of rodent strains/species, etc.) as outlined in the preamble to section 211(b) of 40 CFR 79 and column 2 of this table.

[1] Taken from EPA Table 2. - Criteria for Determining Adequacy of Existing Data in Lieu of Tier 2 (T2) Tests (F.R. 59 #122, June 27, 1994, p 33080).

Table 1. Adequacy of Existing Data (cont'd)

Endpoint	Minimum requirement for adequacy[1]	Adequacy of existing data	Acceptability of study protocols	Conclusion
Teratogenicity	FDA/Phase II (gd6-15) Study.	Several studies have been completed to address this endpoint. Two studies, one in rats and one in rabbits, were published by EPA (Attachment 4).	These studies were not done in accordance with today's standards; only a single dose level was used. However, the dose level was very high and likely would have elicited an effect if diesel was teratogenic. Additionally, studies were conducted in rats, mice and rabbits.	**Data meet minimum requirements** as outlined in the preamble to section 211(b) of 40 CFR 79 and column 2 of this table.
Adult Reproductive Effects	T2[2] fertility/teratology assessment with 90-day exposures	Several studies have evaluated the developmental and reproductive toxicity of diesel exhaust. As an example, EPA completed a two generation study in mice. (Attachment 5).	These studies were not done in accordance with today's standards; only a single dose level was used. However, the dose level was very high and likely would have elicited an effect if diesel was, in fact, a reproductive toxin. Additionally, studies were conducted in rats, mice and rabbits.	**Data meet minimum requirements** as outlined in the preamble to section 211(b) of 40 CFR 79 and column 2 of this table.

[1] Taken from EPA Table 2. - Criteria for Determining Adequacy of Existing Data in Lieu of Tier 2 (T2) Tests (F.R. 59 #122, June 27, 1994, p 33080).

[2] T2; Tier 2

Table 1. Adequacy of Existing Data (cont'd)

Endpoint	Minimum requirement for adequacy[1]	Adequacy of existing data	Acceptability of study protocols	Conclusion
Neurotoxicity	GFAP assay and neurohistopathology with 90-day exposure	Several studies have been completed to evaluate this endpoint. (Attachment 6). Additionally, the numerous lifetime diesel exhaust animal studies that have been performed are considered scientifically adequate for the assessment of neurotoxicity.	Several studies were conducted in Sprague-Dawley rats, with *in utero* and/or neonatal exposure up to 49 days of age, or adult exposures for 16 wk. Neurobehavioral and/or neurophysiological changes were assessed. Exposures were at a single, high dose level which did elicit changes. **Note** -The use of GFAP as a screen is a relatively recent assay, so it is unrealistic to expect it to be conducted in earlier studies.	**Data meet minimum requirements** as outlined in the preamble to section 211(b) of 40 CFR 79 and column 2 of this table.
Pulmonary Function	T2 respiratory tract pathology after 90-day exposure	Along with approximately 20 life-time animal carcinogenicity studies which included lung histopathology, there have been a number of studies in both animal and humans that have addressed the effects of diesel exhaust on pulmonary function. (Attachment 7).	Numerous life-time studies that meet the standard criteria of animal testing have been completed. In addition, there are studies in both animals and humans that are acceptable for assessing the pulmonary function effects of diesel exhaust.	**Data exceed the requirements** with respect to length of exposure and number of studies (≥ 2 yr vs 90 d; number of studies, number of animals, etc.) as outlined in the preamble to section 211(b) of 40 CFR 79 and column 2 of this table.

[1] Taken from EPA Table 2. - Criteria for Determining Adequacy of Existing Data in Lieu of Tier 2 (T2) Tests (F.R. 59 #122, June 27, 1994, p33080).
[2] T2; Tier 2

REVIEW OF STUDIES ADDRESSING SPECIFIC ENDPOINTS OF DIESEL EXHAUST TOXICITY

Carcinogenicity

1. Animal Studies

Over 20 lifetime studies have assessed carcinogenicity of diesel exhaust with and without the particulate phase. Lung tumors developed in rats when the study was longer than 24 months, and the ability of the rats lung to remove particles was compromised at an exposure level greater than 2.0 mg/M^3. In mice, previous studies report conflicting results of the response of mice, which is presently considered equivocal (Muscat and Wynder, 1995; Mauderly et al., 1996). All studies were negative in hamsters. Consequently, many authors concluded that the carcinogenic effect in the rat was "species-specific" and should not be used to extrapolate to humans. There is general consensus that the carcinogenicity of diesel exhaust has been sufficiently studied in test animals.

Based on the results of these animal studies and results of the mutagenicity testing on extracts of the organic fraction of the diesel particulates (covered below), investigators questioned whether it was the organic fraction or the particles themselves that were causing the tumors. This led to studies in rats using carbon black, a material which is essentially devoid of organic material.

Two studies have been completed on carbon black; one was conducted at the Inhalation Toxicology Research Institute and one was conducted at the Fraunhofer Institute for Toxicology Aerosol Research in Germany (Mauderly, 1994; Nikula et al., 1995; Heinrich et al., 1990). In both studies, the results were essentially the same and were comparable to the results on diesel exhaust exposure. In other words, lung tumors developed in rats if the study duration or exposure period was greater than 24 months, the particle clearance mechanism was disrupted, and the exposure level was greater than 2.0 mg/M^3.

Joe Mauderly of the Inhalation Toxicology Research Institute, author of the most pivotal study (described in Attachment 1), concluded that "These results suggest strongly that the soluble organic fraction of soot is not primarily responsible for the carcinogenicity of diesel exhaust in rats. Further, the results tend to support the view that the rat's response to diesel exhaust may be a species-specific, general response to heavy particle loading of the rat lung, and that such data might be of little or no value for predicting human lung cancer risk at lower exposure rates." (Mauderly, 1994; Nikula et al., 1995)

Following is a list of animal carcinogenicity studies that were cited in the US EPA "Health Assessment Document for Diesel Emissions" (1994) and provides the most relevant and comprehensive list of studies to date. Three papers published after 1994 have also been included.

Carcinogenicity References:

Brightwell, J. et al.; (1986) Neoplastic and functional changes in rodents after chronic inhalation of engine exhaust emissions. In: Carcinogenic and mutagenic effects of diesel engine exhaust; W. Stober, ed.; Elsevier Science Publishers; pp. 471-485.

Brightwell, J. et al.; (1989) Tumors of the respiratory tract in rats and hamsters following chronic inhalation of engine exhaust emissions. J. Appl. Toxicol. 9: 23-31.

Heinrich, U. et al.; (1990) Results of long-term inhalation exposure of rats to carbon black "Printex 90" [Letter to Dr. Lester D. Grant]. Presented at: U.S. Environmental Protection Agency peer review workshop on the Health Assessment Document for Diesel Emissions; July; Research Triangle Park, NC.

Heinrich, U. et al.; (1986) Chronic effects on the respiratory tract of hamsters, mice and rats after long-term inhalation of high concentrations of filtered and unfiltered diesel engine emissions. J. Appl. Toxicol. 6: 383-395.

Heinrich, U. et al.; (1986) Comparison of chronic inhalation effects in rodents after long-term exposure to either coal oven flue gas mixed with pyrolized pitch of diesel engine exhaust. In: Ishinishi, N.; Koizumi, A.; McClellan, R.O.; Stober, W., eds, Carcinogenic and mutagenic effects of diesel engine exhaust: proceedings of the international satellite symposium on the toxicological effects of emissions from diesel engines; July; Tsukuma Science City, Japan. Amsterdam, Holland: Elsevier Science Publishers B. V.; pp. 441-457. (Developments in toxicology and environmental science: v. 13)

Ishinishi, N. et al.; (1988b) Long-term inhalation experiments on diesel exhaust. In: Diesel exhaust and health risks: results of the HERP studies. Tsukuoba, Ibaraki, Japan: Japan Automobile Research Institute, Inc. Research Committee for HERP Studies; pp. 11-84.

Iwai, K. et al.; (1986) Long-term inhalation studies of diesel exhaust on F344 SPF rats. Incidence of lung cancer and lymphoma. In: Ishinishi, N.; Koizumi, A.; McClellan, R.O.; Stober, W., eds, Carcinogenic and mutagenic effects of diesel engine exhaust: proceedings of the international satellite symposium on the

toxicological effects of emissions from diesel engines; July; Tsukuma Science City, Japan. Amsterdam, Holland: Elsevier Science Publishers B. V.; pp. 349-360. (Developments in toxicology and environmental science: v. 13)

Kaplan, H. L. et al.; (1982) A subchronic study of the effects of exposure to three species of rodents to diesel exhaust. In: Lewta, J., ed., Toxicological effects of emissions from diesel engines: proceeding of the Environmental Protection Agency diesel emission symposium; October, 1981; Raleigh, NC. New York, NY: Elsevier Biomedical: pp. 161-182. (Developments in toxicology and environmental science: v. 10)

Kaplan, H. L. et al.; (1983) Studies of potential health effects of long-term exposure to diesel exhaust emissions. San Antonio, TX: Southwest Research Institute; SWRI project no. 01-0750-103.

Karagianes, M.T. et al.; (1981) Effects of inhaled diesel emissions and coal dust in rats. Am. Ind. Hyg. Assoc. J. 42: 382-391.

Lewis, T. R. et al.; (1986) A chronic inhalation toxicity study of diesel engine emissions and coal dust, alone and combined. In: Ishinishi, N,:Koizumi, A.; McClellan, R.O.; Stober, W., eds, Carcinogenic and mutagenic effects of diesel engine exhaust: proceedings of the international satellite symposium on the toxicological effects of emissions from diesel engines; July; Tsukuma Science City, Japan. Amsterdam, Holland: Elsevier Science Publishers B. V.; pp. 361-380. (Developments in toxicology and environmental science: v. 13)

Mauderly, J.L. et al.; (1987) Diesel exhaust is a pulmonary carcinogen in rats exposed chronically by inhalation. Fund. Appl. Toxicol. 9:208-221.

Mauderly, J.L.; (1994) Health effects of diesel emissions. Reformulated Diesel Symposium Proceedings. Reformulated Diesel Symposium, Chestnut Park Hotel, Toronto, Ontario September 14-15, 1994.

Mauderly, J.L.; (1996) Diesel exhaust is not a pulmonary carcinogen in CD-1 mice exposed under conditions carcinogenic to F344 rats. Fund. Appl. Toxicol 30:233-242.

Muscat, J.E. and Wynder, E.L.; (1995) Diesel engine exhaust and lung cancer: an unproven association. Environ. Hlth. Perspect. 103:812-818.

Nikula, K.J.; Snipes, M.B.; Barr, E.B.; Griffith, W.C.; Henderson, R.F.; and Mauderly, J.L.; (1995). Comparative pulmonary toxicities and carcinogenicities of chronically inhaled diesel exhaust and carbon black in F344 rats. Fund. Appl. Toxicol. 25:80-94.

Orthoefer, J. G.; et al.; (1981) Carcinogenicity of diesel exhaust as tested in strain A mice. Environ. Int. 5: 461-471.

Pepelko, W. E.; et al.; (1983) Health effects of exposure to diesel engine emissions: a summary of animal studies conducted by the US Environmental Protection Agency's Health Effects Research Laboratories at Cincinnati, Ohio. J. Am. Coll. Toxicol. 2: 253-306.

Stober, W. (1986) Experimental induction of tumors in hamsters, mice and rats after long-term inhalation of filtered and unfiltered gazelle engine exhaust. In: Ishinishi, N.; Koizumi, A.; McClellan, R.O.; Stober, W., eds, Carcinogenic and mutagenic effects of diesel engine exhaust: proceedings of the international satellite symposium on the toxicological effects of emissions from diesel engines; July; Tsukuma Science City, Japan. Amsterdam, Holland: Elsevier Science Publishers B. V.; pp. 421-439. (Developments in toxicology and environmental science: v. 13)

Takaki, Y. et al.; (1989) Long-term inhalation studies of exhaust from diesel engine in F-344 rats: the quantitative relationship between pulmonary hyperplasia and anthracosis. Exp. Pathol. 37:56-61.

Takemoto, K. et al.; (1986) Effects of chronic inhalation exposure to diesel exhaust on the development of lung tumors in di-isopropanol-nitrosamine-treated F344 rats and newborn C57BL and ICR mice. In: Ishinishi, N,; Koizumi, A.; McClellan, R.O.; Stober, W., eds, Carcinogenic and mutagenic effects of diesel engine exhaust: proceedings of the international satellite symposium on the toxicological effects of emissions from diesel engines; July; Tsukuma Science City, Japan. Amsterdam, Holland: Elsevier Science Publishers B. V.; pp. 311-327. (Developments in toxicology and environmental science: v. 13)

2. Epidemiology Studies

An excellent summary of the epidemiological evidence on diesel exhaust was provided by Muscat and Wynder (1995) and is as follows: "The risk of lung cancer associated with diesel exhaust has been calculated from 14 case-control or cohort studies. We evaluated the finding from these studies to determine whether there is sufficient evidence to implicate diesel exhaust as a human lung carcinogen. Four studies found increased risks associated

with long-term exposure, although two of the four studies were based on the same cohort of railroad workers. Six studies were inconclusive due to missing information on smoking habits, internal inconsistencies, or inadequate characterization of diesel exposure. Four studies found no statistically significant association. It can be concluded that, short-term exposure to diesel engine exhaust (<20 years) does not have a causative role in human lung cancer. There is statistical but not causal evidence that long-term exposure to diesel exhaust (>20 years) increases the risk of lung cancer for locomotive engineers, brakemen, and diesel engine mechanics. There is inconsistent evidence on the effects of long-term exposure to diesel exhaust in the trucking industry. There is no evidence for a joint effect of diesel exhaust and cigarette smoking on lung cancer risk. Using common criteria for determining causal association, the epidemiologic evidence is insufficient to establish diesel engine exhaust as a human lung carcinogen."

The Garshick studies (cited below) are considered the most comprehensive to date on the correlation between diesel exhaust and lung cancer. See Attachment 2 for a short description of the two reports.

Epidemiology References:

Benhamou, S. et al.; (1988) Occupational risk factors of lung cancer in a French case-control study. Br. J. Ind. Med. 45:231-233.

Boffetta, P. et al.; (1989) Diesel exhaust exposure and lung cancer risk. Exp. Pathol. 37:32-38.

Boffetta, P. et al.; (1988) Diesel exhaust exposure and mortality among males in the American Cancer Society prospective study. Am. J. Ind. Med. 14:403-415.

Damber, L. and Larsson, L.G.; (1985) Professional driving, smoking and lung cancer: a case referent study. Br. J. Ind. Med. 42:246-252.

Emmelin, A. et al.; (1993) Diesel exhaust exposure and smoking: a case-referent study of lung cancer among Swedish dock workers. Epidemiology 4:237-244.

Garshick, E. et al.; (1987) A case-control study of lung cancer and diesel exhaust exposure in rail-road workers. Am. Rev. Resp. Dis. 135:1242-1248.

Garshick, E. et al.; (1988) A retrospective cohort study of lung cancer and diesel exhaust exposure in rail-road workers. Am. Rev. Resp. Dis. 137:820-825.

Gustavsson, P. et al.; (1990) Lung cancer and exposure to diesel exhaust among bus garage workers. Scand. J. Environ. Health 16:348-354.

Hall, N.E.L. and Wynder, E.L.; (1984) Diesel exhaust exposure and lung cancer: a case-control study. Environ. Res. 34:77-86.

Hayes, R.B. et al.; (1989) Lung cancer in motor exhaust-related occupations [erratum appears in Am. J. Ind. Med. 19:136 (1991)]. Am. Ind. Med. 16:685-695(1989).

Howe, G.R. et al.; (1983) Cancer mortality (1965-77) in relation to diesel fume and coal exposure in a cohort of retired railway workers. J. Natl. Cancer Inst. 70:1015-1019.

Muscat, J.E. and Wynder, E.L.; (1995) Diesel engine exhaust and lung cancer: an unproved association. Environ. Health Perspect., 103:812-818.

Siemiatychi, J. et al.; (1988) Associations between several sites of cancer and ten types of exhaust and combustion products. Results from a case-referent study in Montreal. Scand. J. Work Environ. Health 14:79-90.

Steenland, N.K. et al.; (1990) Case-control study of lung cancer and truck driving in the Teamsters Union. Am. J. Public Health 80:670-674.

Swanson, M.G. et al.; (1993) Diversity in the association between occupation and lung cancer among black and white men. Cancer Epidemiol. Biomarkers Prev. 2:313-320.

Mutagenicity

There were numerous data regarding the in vitro toxicity of diesel exhaust. During the past 20 years, over 100 publications have appeared in the literature in which genotoxicity assays were conducted with diesel emissions and organic or physiological fluids extracts of diesel emissions. In general, positive results were observed with the organically extracted material. However, these data are not considered relevant to human exposure because they were collected using strong, organic solvents not comparable to physiological systems. When physiological fluids were used to extract diesel particulates, the results were mixed. These studies, plus a host of other studies have been described in the International Agency for Research on Cancer (IARC) monograph No. 46 (1989), Claxton et al. (1983), Lewtas (1982), Ishinishi et al. (1986) and the proceedings of symposia on the health effects of diesel emissions (USEPA,1980). In particular, the IARC Monograph (1989) contained an

exhaustive description of the available studies, which will not be listed here. Attachment 3 provides a description of several example mutagenicity studies.

Mutagenicity References:

Claxton, L. et al.;(1983) Characterization of automotive emissions by bacterial mutagenesis bioassay: a review. Environ. Mutagen. 5:609-631.

International Agency for Research on Cancer; (1989) Diesel and gasoline engine exhausts and some nitroarenes. Lyon, France: World Health Organization: pp. 41-185. IARC monographs on the evaluation of carcinogenic risks to humans, Volume 46.

Ishinishi, N. et al.; (1986) Carcinogenic and mutagenic effects of diesel engine exhaust: proceedings of the international satellite symposium on toxicological effects of emission from diesel engines; July: Tsukuba Science City, Japan. Amsterdam, The Netherlands: Elsevier Science Publishers B. V. (Developments in toxicology and environmental science: v. 13).

Lewtas, J.; (1982) Mutagenic activity of diesel emissions. In: Lewtas, J., ed., Toxicological effects of emissions from diesel engines: proceeding of the Environmental Protection Agency 1981 diesel emissions symposium; October 1981; Raleigh, NC. New York NY: Elsevier Biomedical; pp 243-264. (Developments in toxicology and environmental science: v. 10).

Lewis, T.R. et al.; (1989) A chronic inhalation toxicity study of diesel engine emissions and coal dust, alone and combined; J. Am.. College of Tox. 2: 345-375.

Pepelko, W.E. et al.,; (1980) Health effects of diesel engine emissions: Proceedings of an international symposium held at Cincinnati, Ohio on December 3-5, 1979, V.2. Cincinnati, Ohio: US Environmental Protection Agency, Health Effects Research Laboratory; EPA report no. EPA-600/9-80-057b. Available from NTIS, Springfield, VA, document PB81-173817.

Reproductive and Developmental Effects

Inhalation of diesel exhaust did not effect male or female reproductive parameters in a two generation mouse study (Pepelko et al., 1983). Effects on sperm morphology and sperm number were reported in hamsters, but these effects were not seen in mice or monkeys (Lewis et al., 1989). No teratogenic, embryotoxic or fetotoxic effects were seen in rats, mice or rabbits (Pepelko et al., 1983). Likewise, no effects were reported in a heritable point mutation or a dominant lethal study.

Regarding developmental effects, a single study reported fetotoxic effects (delayed ossification) in rats exposed to 6.0 mg/m^3 diesel particles (Callahan et al., 1986).

In all of the reported studies, a single dose of diesel exhaust was administered. However, the dose levels were very high ranging from 6.0 to 12.0 mg/M^3. Sufficient numbers of animal were used, and the appropriate parameters were studied. For details of the EPA Study (Pepelko et al., 1983), see Attachments 4 and 5. The authors concluded "Based on the available data, exposure to diesel exhaust at a particulate concentration of 12 mg/M^3 did not affect reproduction."

Reproductive and Developmental Effects References:

Callahan, J.F. et al.; (1986) The subchronic inhalation toxicity of DF2 (diesel fuel) used in vehicle engine exhaust smoke systems (VEESS) pp 1-152; NTIS No. ADA166841.

Lewis, T.R. et al.; (1989) A chronic inhalation toxicity study of diesel engine emissions and coal dust, alone and combined; J. Am.. College of Tox. 2: 345-375.

Pepelko, W.E. et al.; (1983) Health effects of exposure to diesel engine emissions. J. Am. College of Tox. 2: 253-306.

Pereira, M.A. et al.;(1983) The effect of diesel exhaust on sperm-shape abnormalities in mice; Environ. Int. 5: 459-460.

Werchowski, K.M., et al.; (1980) Teratologic effects of long-term exposure to diesel exhaust emissions (rats). Cincinnati, OH; US Environmental Protection Agency, Health Research Laboratory; EPA report number EPA-600/1-80-010. Available from NTIS, Springfield, Va.; PB80-159965.

Werchowski, K.M., et al.; (1980) Teratologic effects of long-term exposure to diesel exhaust emissions (rabbits). Cincinnati, OH; US Environmental Protection

Agency, Health Research Laboratory; EPA report number EPA-600/1-80-011. Available from NTIS, Springfield, Va.; PB80-168529.

Neurotoxicity

Several studies which examined this health effect have been reported in the literature. Reported findings included effects on somatosensory and visual evoked potential (SEPs and VEPs, respectively), spontaneous locomotor activity and bar pressing tasks (Callahan et al., 1986; Pepelko et al., 1983; Laurie et al., 1980, 1981a, 1981b). Relevant studies are briefly summarized in Attachment 6. Additionally, the numerous lifetime diesel exhaust animal studies that have been performed are considered scientifically adequate for the assessment of neurotoxicity.

Neurotoxicity References:

Callahan, J.F. et al.; (1986) The subchronic inhalation toxicity of DF2 (diesel fuel) used in vehicle engine exhaust smoke systems (VEESS) pp 1-152; NTIS No. ADA166841.

Laurie, R.D. et al.; (1980) Behavioral alterations due to diesel exhaust exposure. In: Pepelko, W.E. et al.,; (1980) Health effects of diesel engine emissions: Proceedings of an international symposium held at Cincinnati, Ohio on December 3-5, 1979, v.2. Cincinnati, Ohio: US Environmental Protection Agency, Health Effects Research Laboratory; pp.698-712;EPA report no. EPA-600/9-80-057b. Available from NTIS, Springfield, VA, document PB81-173817.

Laurie, R. et al.; (1981a) Neurophysiological alterations due to diesel exhaust exposure during neonatal life of the rat. Environ. Intern. 5: 363-368.

Laurie, R. et al.; (1981b) Behavioral alteration due to diesel exhaust exposure. Environ. Intern. 5: 357-361.

Pepelko, W.E. et al.; (1983) Health effects of exposure to diesel engine emissions. J. Am. College of Tox. 2: 253-306.

Pulmonary Effects

Pulmonary function has been studied in both animals and humans. No consistent results were evident in the species that have been studied including: monkeys, cats, rats, hamsters and guinea pigs. However, it was observed that for an effect to occur, the necessary exposure period was at least one year of continuous exposure. Lewis et al. (1989), "demonstrated small airway obstructive responses in monkeys exposed to diesel exhaust. The obstructive impairment was most detectable in the diesel exhaust treatment using the forced expiratory flow at 40% of the total lung capacity instead of the forced expiratory flow as a percentage of the vital capacity." Two studies are described in Attachment 7.

In humans, all studies had clear limitations in that "there were small numbers of subjects, limited information on historical exposure levels, possible confounding from exposure to other substances, and potential for selection bias due to the possibility that the most affected workers had already left their employment before the beginning of the studies." (California Health Risk Assessment, 1995).

Pulmonary Effects References:

Animal

See all references to animal carcinogenicity as listed above in carcinogenicity section.

Barnhart, M.I. et al.; (1981) Ultrastructure and morphometry of the alveolar lung of guinea pigs chronically exposed to diesel engine exhaust : six month's experience. J. Appl. Tox. 1: 88-103.

Lewis, T.R. et al.; (1989) A chronic inhalation toxicity study of diesel engine emissions and coal dust, alone and combined. J. Am. Coll. Toxicol. 8: 345-375.

Pepelko, W.E. et al.; (1983) Health effects of exposure to diesel engine emissions: a summary of animal studies conducted by the US Environmental Protection Agency's Health Effects Research Laboratories at Cincinnati, Ohio. J. Am. College of Tox. 2: 253-306.

Vinegar, A. et al.; (1981) Pulmonary function changes in Chinese hamsters exposed six months to diesel exhaust. Environ. Intern.. 5: 369-371.

Wallace, M.A. et al.; (1987) Analysis of the effects on inhaled diesel exhaust on the alveolar intravascular and interstitial cellular component of rodent lungs. Scanning Microscopy 1: 1387-1395.

Human

Ames, R.G. et al.; (1982) Acute respiratory effects of exposure to diesel emissions in coal miners. Am. Rev. Respir. Dis. 125, 39-42.

Ames, R.G. et al.; (1984) Chronic respiratory effects of exposure to diesel emissions in coal miner. Arch. Environ. Health 39: 389-394.

Ames, R.G. et al.; (1988) Effects of exposure to diesel emissions among coal miners: a prospective evaluation. An .Occup. Hyg. 32: 635-643, Supplement 1.

Battigelli, M.C.. et al.; (1964) Environmental and clinical investigation of workmen exposed to diesel exhaust in railroad engine houses. Indust. Med. Surg. 33: 121-124.

Gamble, J. et al.; (1983) Respiratory effects of diesel exhaust in salt miners. Am. Rev. Resp. Dis. 128: 389-394.

Gamble, J. et al.; (1983) Chronic health effects of exposure to diesel emissions among salt miners. Ann. Am. Conf. Ind. Hyg. 4: 73-83.

Gamble, J. et al.; (1983) An epidemiology study of salt miners in diesel and nondiesel mines. Am. J. Ind. Med. 4: 435-458.

Gamble, J. et al.; (1987) Epidemiological environmental study of diesel bus garage workers: acute effects of NO_2 and respirable particulate on the respiratory system. Environ. Res. 42: 201-214.

Purdham, J.T. et al.; (1987) Environmental and medical assessment of stevedores employed in ferry operations. Appl. Ind. Hyg. 2: 133-139.

Reger, R. et al.; (1982) Coal miners exposed to diesel exhaust emissions. Ann Occup. Hyg. 26: 799-815.

Reger, R. et al.; (1983) Diesel emissions and associated respiratory health effects in mining. In: Health Issues Related to Metal and Nonmetallic Mining, Eds. W.L. Wagner, W. N. Rom, J.A. Mercent, pp. 393-412.

Robertson, A. et al.; (1984) Exposure to oxides of nitrogen: respiratory symptoms and lung function in British coal miners. Brit. J. Ind. Med. 41: 214-219.

Ulfvarson, U. et al.; (1987) Effects of exposure to vehicle exhaust on health. Scand. J. Work Environ. Health 13: 505-512.

Ulfvarson, U. et al.; (1990) Reduction in adverse effect on pulmonary function after exposure to filtered diesel exhaust. Am. J. Ind. Med. 17: 341-347.

Ulfvarson, U. et al.; (1991) Pulmonary function in workers exposed to diesel exhaust: The effect of control measures. Am. J. Ind. Med. 19: 283-289.

CONCLUSION

Existing data specifically and adequately address diesel exhaust carcinogenicity, mutagenicity, teratogenicity, adult reproductive effects, neurotoxicity and pulmonary effects. These studies, as indicated by key studies summarized in the following attachments, provide the EPA with sufficient information to determine that these previously conducted tests were adequately performed and documented according to the criteria as specified in Section 79.53(d) (*Federal Register 59 #122 June 27, 1994 p. 33102*) and summarized below:

1. The age of the data;
2. The adequacy of documentation of procedures, findings, and conclusions;
3. The extent to which the testing conforms to generally accepted scientific principles and practices;
4. The type and number of test subjects;
5. The number and adequacy of exposure concentrations, *i.e.*, emission dilutions;
6. The degree to which the tested emissions were generated by procedures and under conditions reasonably comparable to those set forth in §79.57;
7. The degree to which the test procedures conform to the testing guidelines set forth in §79.60 through 79.68 and/or furnish information comparable to that provided by such testing.

Based on the information presented above, it is the Section 211(b) Research Group's opinion that there is overwhelming evidence to support our position that sufficient data is available to adequately evaluate the health effects of diesel exhaust and no additional 90-day screening tests as described in Section 211(b) Tier 2 should be required.

Attachment 1

DIESEL EXHAUST PULMONARY CARCINOGENICITY

The following is a review of a study published in the open literature on the effects of diesel exhaust in rats exposed for over two years. Title "Diesel Exhaust is a Pulmonary Carcinogen in Rats Exposed Chronically by Inhalation", Mauderly et al.; (1987) Fund. Appl. Tox. 9: 208-221.

Methods

Material: Diesel Exhaust

Species: Rat/F344/Crl

Number of Animals per Group: 221 to 230 males and females

Exhaust Source: Generated by a 1980 model 5.7-L Oldsmobile V-8 engines.

Fuel: D-2 diesel control fuel (Phillips Chemical Company) met USEPA certification standards and contained approximately 30% aromatic hydrocarbons and 0.3% sulfur.

Dose Levels:

	Control	Low	Mid	High
Soot (ug/m3)	10(10)*	350(70)	3470(450)	7080(810)
CO (ppm)	1(1)	3(1)	17(7)	30(13)
NO (ppm)	0	0.6(0.3)	5.4(1.5)	10.0(2.6)
NO2 (ppm)	0	0.1(0.1)	0.3(0.2)	0.7(0.5)
Hydrocarbon Vapor (ppm)	3(1)	4(1)	9(5)	13(8)
CO2 (%)	0.2(0.04)	0.2(0.03)	0.4(0.06)	0.7(0.1)

* Numbers in parentheses represent standard error of weekly mean during 30 months of exposure.

Duration: 30 months. Animals were exposed five days per week, 7 hrs/day from about 15 weeks of age until death or 30 months of age.

Laboratory: Lovelace Biomedical and Environmental Research Institute, Albuquerque, NM.

Results

Body Weights: There were no significant exposure related differences in body weight among either the male or female rats.

Life Expectancy: Exposure did not significantly affect the life span of either sex.

Physical Condition: The physical condition of all groups appeared similar, except for soot discoloration of the haircoat of exhaust-exposed groups.

Lung Burden of Soot: The increase in lung burden of soot was significant for all groups, although the accumulation was very slight at the lowest exposure level. The amounts for each group were as follows:

Control	0.0
Low Dose	0.6 + 0.02 mg
Middle Dose	11.5 + 0.5 mg
High Dose	20.8 + 0.8 mg

Note: The middle and high exposures caused lung disease which progressed parallel to the accumulation of soot in the lung.

Tumor Incidence (percentage of rats with lung tumors):

Control	0.9 %
Low	1.3 %
Middle	3.6 %*
High	12.8 %*

* Significantly higher than controls p> 0.005

Tumor Types:

	BENIGN TUMORS		MALIGNANT TUMORS	
	Squamous Cell Cyst	Adenoma	Adenocarcinoma	Squamous Cell Carcinoma
Male				
Control	0	0	2	0
Low	0	0	1	0
Mid	0	3	1	0
High	4	1	6	2
Female				
Control	0	0	0	0
Low	0	0	2	0
Mid	2	2	0	0
High	8	2	6	0

* One animal with two different types of tumors

Discussion

The results of this study demonstrate a clear dose-response relationship between concentration received and the degree of carcinogenic response. There was also a correlation between the amount of soot in the lung and the carcinogenic response. However, it is not clear if the carcinogenic response was due to the diesel exhaust particles or the PNAs attached to the particles.

Studies done by other investigators demonstrated that experimental animals exposed to diesel exhaust with the particles removed did not demonstrate a carcinogenic response, thus indicating that the response is in some way associated with the particulate phase of the diesel exhaust.

One of the most interesting findings was that the carcinogenic response developed late in the study. Of all the rats observed to have tumors, only 19% were identified at or before the 24 month time period, the remaining 81% were identified later. It maybe that the carcinogenic response is related to the age of the animal, i.e., that the animal's recuperative powers are lower.

Conclusion: These results demonstrate that diesel exhaust, inhaled chronically at a high concentration, is a pulmonary carcinogen in the rat.

Attachment 2

EPIDEMIOLOGY OF DIESEL EXHAUST

1. From Garshick, E. et al.; (1987) A case-control study of lung cancer and diesel exhaust exposure in rail-road workers. Am. Rev. Resp. Dis. 135:1242-1248.

Study Type:	Case-control
Design and sample size:	1,250 lung cancer deaths among railroad workers.
Exposure measurements:	Air samples.
Bias:	Minimal
Relative risk:	1.41 (1.05-1.88)
Adjusted for smoking:	Yes

2. From Garshick E. et al.; (1988) A retrospective cohort study of lung cancer and diesel exhaust exposure in rail-road workers. Am Rev Resp Dis 137:820-825.

Study Type:	Retrospective cohort
Design and sample size:	55,407 railroad workers 1,694 lung cancer cases identified.
Exposure measurements:	Air samples.
Bias:	Minimal
Relative risk:	1.45 (1.11-1.89)
Adjusted for smoking:	No

Attachment 3

MUTAGENICITY/GENOTOXICITY OF DIESEL EXHAUST

A chronic inhalation toxicity study of diesel engine emissions and coal dust, alone and combined, reported on several toxicology end-points. (Lewis, T.R. et al.; (1989) A chronic inhalation toxicity study of diesel engine emissions and coal dust, alone and combined; J. Am. Coll. Tox.2: 345-375). This paper provides a good representation of several genotoxic assays which are outlined below.

1. Salmonella

Strains:	TA98 and TA100.
Dose:	Dichloromethane extract of diesel particulates.
Activation:	With and without S-9 activation.
Conclusion:	Diesel exhaust extract was mutagenic and caused an approximate 10-fold increase in the number of revertants per plate over background controls.

2. Bone Marrow

Species:	Female Swiss Webster CD-1 mice. Male F344 rats.
Exposure:	Females exposed for 6 months Males exposed for 24 months
Dose:	2.0 mg/M3 diesel exhaust
Conclusion:	Diesel exhaust-exposed mice exhibited twice the micronuclei in polychromatic erythrocytes over controls. Rats did not exhibit an increase.

3. The following studies were also reported in this paper:
   Sister chromatid exchange,
   Dominant lethal effects in rats.

   No diesel exhaust effect was demonstrated in either study.

In a report on the "Health Effects of Exposure to Diesel Engine Emissions, A summary of Animal Studies Conducted by the US Environmental Protection Agency's Health Effects Research Laboratories at Cincinnati, Ohio; Pepelko and Peirano; J of the Am. College of Toxicology, 1993, numerous studies on different genotoxic end-points were reported. The following were some of those studies.

General Methodology

Exposure Scenario:	6 cylinder Nissan diesel engine operated 8 hours/day, 7 days/wk, during the 2 year, 4 month study.
Fuel:	Diesel No. 2.
Particulate level:	6 to 12 mg/M^3.

1. Metaphase analysis:

Species:	Swiss Webster mice.
No./group:	10
Exposure:	6 mg/M^3 diesel exhaust or clean air for 7 wks; 1.0 mg/kg colcemid (i.p.) was injected 30 min. before sacrifice.
Sample:	Marrow was taken from one femur.

2. Micronucleus Test:

Species 1:	2 month old Chinese hamsters and Swiss Webster mice.
No./group:	10

Exposure:	6 mg/M^3 for 1, 3 and 6 months; additional groups of Chinese hamsters and B6C3F1 mice were exposed for 1 month at a particulate concentration of 12.0 mg/M^3.
Sacrifice:	Immediately after last exposure.
Sample:	Bone marrow.
Species 2:	Three month old Chinese hamsters and B6C3F1 mice.
Number:	10 males/group
Exposure:	i.p. injection of diesel exhaust particles or methylene chloride extract of the diesel exhaust particles.
Dose:	Diesel exhaust particles - 80, 160, 320, and 640 mg/kg Diesel exhaust particle extracts - 80, 160, 320, 640 and 800 mg/kg for hamsters. Diesel exhaust particle extracts - 200, 400, 800 and 1000 mg/kg for mice.
Sacrifice:	30 or 54 hours or 1 week after injection.
Sample:	Bone marrow.

3. Sister Chromatid Exchange

Species 1:	2 month old male mice.
No./group:	10 mice 6 hamsters
Exposure:	Clean air or 6 mg/M^3 for 1, 3 or 6 months; additional groups of Chinese hamsters and B6C3F1 mice were exposed for 1 month at a particulate concentration of 12.0 mg/M^3.

Sacrifice:	24 hr prior to sacrifice, a 60 mg pellet of bromodeoxyuridine was implanted under the skin. Two hr. prior to sacrifice the animals were injected with colchicine (10 mg/kg).
Sample:	Femoral bone marrow cells.
Species 2:	Three month old male mice.
Number:	6 males/group
Exposure:	i.p. injection of diesel exhaust particles or methylene chloride extract of the diesel exhaust particles.
Dose:	Diesel exhaust particle extracts - 300 mg/kg, Diesel exhaust particles - 800 mg/kg, B(a)P mg/kg.
Sacrifice:	1, 2 5 or 14 days after injection.
Sample:	Femoral bone marrow.

4. The following studies were also reported in this paper:

SCE in fetal liver cells
SCE analysis of hamster lung
Heritable effects in Drosophila
Heritable effects in mice
- Heritable point mutations in male mice
- Test for induction of Dominant Lethal in male mice
- Test for heritable translocations in male mice
- Test for induction of genetic effects and oocyte killing in female mice
- Test for dominant-lethal induction in female mice
- Test for spermatogonial survival in the mouse

Conclusions: "Exposure to diesel emissions did not result in detectable genotoxic effects as measured by increases in sister chromatid exchange (SCE), micronucleus testing and metaphase analysis in Chinese hamster and mouse bone marrow cells or in the morphology of cat sperm. SCE in lung cells from Syrian hamsters, however, was increased at the higher exposure level. The incidence of heritable mutation was not increased in mice."

Attachment 4

TERATOGENICITY OF DIESEL EXHAUST

The following describes Teratogenicity testing by EPA and reported by Pepelko (Pepelko, W.E. et al.; (1983) Health effects of exposure to diesel engine emissions. J. Am. College Tox .2: 253-306).

Methods:

Study 1

Material:	Diesel Exhaust
Species:	Rat (Sprague-Dawley)
Number of Animals per Group:	20
Exhaust Source:	Generated by a 6 Cylinder Nissan diesel engine operating 8 hr./day, 7 days/week.
Fuel:	Diesel fuel No. 2
Gestation days of exposure:	5 through 16
Dose Level:	6 mg/M^3
Examinations:	1/3 - soft tissue examination 2/3 - skeletal examination
The following parameters were recorded:	Numbers of fetuses, live and dead fetuses, resorbed, implants, corpora lutea, distribution of fetuses in uterine horns, gross pathology in the dam, fetal weights and sex of fetuses.

Study 2

Material:	Diesel Exhaust
Species:	Rabbits (New Zealand white)
Number of Animals per Group:	20
Exhaust Source:	Generated by a 6 Cylinder Nissan diesel engine operating 8 hr./day, 7 days/week
Fuel:	Diesel fuel No. 2
Gestation day of exposure:	6 through 18
Dose Level:	6 mg/M^3
Examinations:	1/3 - soft tissue examination 2/3 - skeletal examination
The following parameters were recorded:	Numbers of fetuses, live and dead fetuses, resorbed, implants, corpora lutea, distribution of fetuses in uterine horns, gross pathology in the dam, fetal weights and sex of fetuses.

Conclusion: "Under the conditions of the experiment inhalation of diesel exhaust did not cause any teratogenic effects".

Attachment 5

REPRODUCTIVE EFFECTS OF DIESEL EXHAUST

The following describes reproductive testing by EPA and reported by Pepelko (Pepelko, W.E. et al.; (1983) Health effects of exposure to diesel engine emissions. J. Am. Coll. Tox. .2: 253-306).

Methods

Material:	Diesel Exhaust
Species:	Mice (CD-1)
Number of Animals per Group:	25 (1 male housed with 1 female for mating); vaginal smears were taken for 15 days prior to mating.
Desired Number Pregnant	20
Exhaust Source:	Generated by a 6 cylinder Nissan diesel engine operating 8 hr./day, 7 days/week
Fuel:	Diesel fuel No. 2

F_0 Generation

Group 1	CA* female, CA male
Group 2	CA female, DE** male
Group 3	DE female, CA male
Group 4	DE female, DE male

* CA = Clean Air
** DE= Diesel exhaust

F_1 Generation

Group 5	CACA female, CACA male
Group 6	CADE female, CADE male
Group 7	DECA female, DECA male
Group 8	DEDE female, DEDE male

Dose Level:	12 mg/M^3
Exposure:	100 days prior to breeding through maturity of the F_2 generation, 8 hr./day, 7 days/week
Examination:	Viability counts and individual pup weights were recorded at birth, days 4, 7, 14 and 21 (weaning). Litters were randomly reduced to 6 pups (3 male and 3 female when possible) on day 4.
The following tissues were weighed:	Adrenals, brain, colon, heart, kidneys, liver, lungs, ovaries, pancreas, pituitary , spleen, testes, thyroids and uterus.
In addition to the above, the following were examined and collected for histopathology:	Bladder (urinary), epididymis intestine (duodenum) lymph nodes (mesenteric and bronchial), mammary glands, nasal turbinates, prostate, skeletal muscle (psoas), skin (back)and thymus. Histology was not reported.

Conclusion: "Based on available data, exposure to diesel exhaust at a particulate concentration of 12 mg/M^3 did not affect reproduction."

Attachment 6

NEUROTOXICITY OF DIESEL EXHAUST

1. Neurobehavioral study (Laurie, R.D., et al.; (1980) Behavioral alterations due to diesel exhaust exposure. In: Pepelko, W.E. et al.,; (1980) Health effects of diesel engine emissions: Proceedings of an international symposium held at Cincinnati, Ohio on December 3-5, 1979, v.2. Cincinnati, Ohio: US Environmental Protection Agency, Health Effects Research Laboratory; pp.698-712;EPA report no. EPA-600/9-80-057b. Available from NTIS, Springfield, VA, document PB81-173817.)

Methods

Material:	Diesel Exhaust
Species:	Rat, Sprague Dawley
Exhaust Source:	Generated by a 6 cylinder Nissan diesel engine operating 8 hr./day, 7 days/week.
Fuel:	Diesel fuel No. 2
Dose Level:	6 mg/M^3 from 10 to 25 wks of age (16 week exposure total)
No of animals:	13 at 6 mg/M^3 13 controls (very high and very low runners were excluded from a baseline group of 50 to reduce variability)
Age at test:	8-27 wks of age (6 wks postpartum through 2 wks post-exposure)
End-point:	Spontaneous locomotion activity (SLA)

Results: " Exposure to diluted diesel exhaust lowered the SLA of adult rats. . . .rats exposed to diesel exhaust 8 hrs/day did show a typical increase and subsequent decrease in SLA over time, and were significantly less active than controls for 1 or 4 weeks of the experiment, depending on the data analysis."

2. Neurobehavioral study (Laurie, R. et al.; (1981) Behavioral alteration due to diesel exhaust exposure. Environ. Intern. 5: 357-36.)

Methods

Material:	Diesel Exhaust
Species:	Rat, Sprague Dawley
Exhaust Source:	Generated by a 6 cylinder Nissan diesel engine operating at 8 hr/day, 7 days/week or 20 hr/day, 7 days/week.
Fuel:	Diesel fuel No. 2
Dose Level:	6 mg/M^3 (≈ 1:20 dilution of raw exhaust with filtered air)
No of animals:	12 neonates from day 1 of age to day 17 (20 hr/day, 7 days/week) 15 neonates from day 1 of age to day 21 (8 hr/day, 7 days/week) 28 neonates from day 1 of age to day 28 or day 42 (8 hr/day, 7 days/week)
Age at test 1:	Six or seven weeks postpartum
End-point:	Spontaneous locomotion activity,
Age at test 2:	15 months
End-point:	Bar press task

Results: "As adults, the two groups of animals exposed to diesel exhaust during development were significantly less active than their respective control groups. In addition, it can be seen that the differences between the control groups and exposed groups were greater for the 20 h/day exposure versus the 8 hr/day exposure."

3. Neurophysiological study (Laurie, R. et al.; (1981) Neurophysiological alterations due to diesel exhaust exposure during neonatal life of the rat. Environ. Intern. 5: 363-368.)

Methods

Material:	Diesel Exhaust
Species:	Rat, Sprague Dawley
Exhaust Source:	Generated by a 6 Cylinder Nissan diesel engine operating 8 hr./day, 7 days/week
Fuel:	Diesel fuel No. 2
Dose Level:	6 mg/M^3, 8 hr/day, 7 day/wk
Exposure:	From post-conception to birth, 28, 35, 42, and 49 day or birth, day 7, 14, 21 or 28 of age.
End-points:	Somatosensory Evoked Potentials (SEP). Visual Evoked Potentials (VEP).

Results: Some delays in response were observed during the study.

Attachment 7

PULMONARY EFFECTS OF DIESEL EXHAUST

1. From Lewis, 1989 (Lewis, T.R. et al.; (1989) A chronic inhalation toxicity study of diesel engine emissions and coal dust, alone and combined. J. Am.. Coll. Tox. 8: 345-375.)

Methods

Material:	Diesel Exhaust
Species:	Cynomolgus monkeys
Number of animals:	15 per group
Exhaust Source:	Generated by a 425 cu-in displacement four-cycle, water cooled, naturally aspirated diesel engine (Caterpillar model 3304) equipped with a water scrubber.
Dose level:	2.0 mg/ M^3 diesel exhaust with particulates. Unexposed controls
Duration:	2 years, 7 hr/day,5 days/wk.
Pulmonary function:	Prior to exposure and every 6 months thereafter.

Results: Demonstrated small airway obstructive responses. The obstructive impairment was most detectable using the forced expiratory flow at 40% of the total lung capacity instead of the forced expiratory flow as a percentage of the vital capacity.

2. From Pepelko, W.E. et al.; (1983) Health effects of exposure to diesel engine emissions: a summary of animal studies conducted by the US Environmental Protection Agency's Health Effects Research Laboratories at Cincinnati, Ohio. J. Am. Coll. of Tox. 2: 253-306.

Methods

Material:	Diesel Exhaust
Species:	Cats
Number of animals:	25 per group
Exhaust Source:	Generated by a 6 cylinder Nissan diesel engine operating 8 hr./day, 7 days/week.
Dose level:	6.0 mg/ M^3 diesel exhaust with particulates during the second year of exposure. 12.0 mg/m3 diesel exhaust with particulates during the second year of exposure. Unexposed controls
Duration:	2 years, 8 hr/day,7 days/wk.
Pulmonary function:	At 1 and 2 years after exposure

Results: No compound related effect after the first year of exposure. After the second year of exposure, "the reduction in inspiratory capacity, vital capacity, and total lung capacity compared with normal values for ventilatory function indicated that a lesion was present that restricted breathing but did not cause airway obstruction of loss of elasticity."

Summary Table of Diesel Exhaust Toxicity Studies

(Compiled for compliance with Section 211(b) Tier 1 literature search requirements)

SUMMARY TABLE
INHALATION STUDIES - DIESEL EXHAUST
TABLE OF CONTENTS

TABLE 1. INHALATION STUDIES - *Diesel Exhaust*

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
I. NON-CANCER STUDIES					
1. Acute					
a. Human					
Human Coal miners (M)	8 hrs (single workshift)	Little changes in respiratory function (decreased lung volumes and flows in relation to diesel exposure among non- and ex-smokers)	2.0 mg/m^3	0.2 ppm NO_2, 12 ppm CO, and 0.8 ppm formaldehyde also present	Ames, Attfield, Hankinson et al. 1982
Human Bus garage workers (M)	8 hrs (single workshift)	No readily interpretable changes in respiratory function in workers tested before and after work	0.24 mg/m^3	<1.5 ppm NO_2 also present	Gamble, Jones, and Minshall 1987
Human (13 Coal Miners)	Acute	Miners had mucous membrane irritation, headache, and light headedness; nausea, sensation of unreality; heartburn; weakness, numbness, and tingling in extremities, vomiting, chest tightness and wheezing symptoms.	Dose not stated	Diesel exhaust to Utah and Colorado miners. Symptoms resolved within 24-48 hrs	Kahn, Orris, and Weeks 1988.
I. Lethality					
No studies located.					

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
ii. Non-Lethality					
No studies located.					
b. Animal					
I. Lethality					
CR/CD-1 Mouse (Female)	8 h/day, 7 days/wk, 2 h up to 46 weeks	Enhanced susceptibility to lethal effects of *Streptococcus pyogenes* infections at all exposure durations (2 and hrs; 8, 15, 16, 307, and 321 days); inconclusive result with *S. typhimurium* because of high mortality rates in controls; no enhanced mortality when challenged with A/PR8-3 influenza virus	5.3 to 7.9 mg/m^3	Varying levels of CO, NO_2, and SO_2	Campbell, George, Washington 1981
CD-1 Mouse (Female)	7 h/day, 5 days/wk, 4 weeks	Mice inoculated intranasally with influenza virus had smaller increases in ethylmorphine demethylase activity on Days 2 to 4 postvirus infection and abolition of Day 4 postinfection increase in NADPH-dependent cytochrome c reductase	2.0 mg/m^3	0.2-0.36 µm, MMD	Rabovsky, Judy, Rodak et al. 1986
ii. Non-Lethality					

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
Rat	Single or multiple acute exposures	Transient depression in mucociliary clearance of excised tracheas	8 or 17 mg/m^3		Battigelli, Hengstenberg, Mannella et al., 1966
Rat	<1 hr	No effect of mucociliary transport rates	6 mg/m^3		Chan, Lee, and Hering 1981
2. Chronic/Sub-Chronic					
a. Human					
i. Pulmonary					
Human 1,118 U.S. Coal Miners (M)	Occupational (5-yr symptom incidence for miners with >1 yr underground work)	Respiratory symptoms (decreased prevalence of dyspnea, cough, and phlegm) and decreased respiratory function (decreased FVC, FEV_1, FEF_{50})[1] compared to workers in nondiesel mines	Diesel mines vs. nondiesel mines	Smoking adjusted for in study	Ames, Attfield, Hankinson et al. 1982
Human 630 Potash miners (M)	Occupational	Respiratory symptoms (increased prevalence of dyspnea, cough, and phlegm) and changes in respiratory function (slight elevation of FVC and FEV_1) compared to other blue-collar workers	Miners vs. Other blue-collar workers	Smoking adjusted	Attfield, Trabant, and Wheeler 1982
Human 364 U.S. railroad workers (M)	Occupational	Respiratory symptoms (dyspnea, cough, and phlegm) and decreased respiratory function (decreased FVC and FEV_1) compared to unexposed workers	Exposed jobs vs.unexposed jobs	Smoking not adjusted	Battigelli, Mannella, and Hatch, 1964

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
Human 283 U.S. bus garage workers (M)	Occupational	Respiratory symptoms (dyspnea, cough, and phlegm) and changes in respiratory function (FVC, FEV_1, FEF_{50}, FEF_{75})	Bus garage workers vs. reference population	Smoking adjusted	Gamble, Jones, and Marshall 1987
Human 1,646 U.S. Coal miners (M)	Occupational	Respiratory symptoms (decreased prevalence of dyspnea, increased prevalence of cough and phlegm) and changes in respiratory function (FVC, FEV_1, FEF_{50}, FEF_{75}) compared to nondiesel miners	Diesel miners vs. nondiesel miners	Smoking adjusted	Reger, Hancock, Hankinson et al. 1982
ii. Mortality					
Human U.S. male volunteers	Chronic	•Death caused by emphysema (total number = 10); COPD[2] (23); pneumonia/influenza (14) and other (5) •Relative risk for emphysema was 1.21, COPD was 1.18, pneumonia/influenza was 1.97, and other was 0.43	Self-reported regular exposure via questionnaire	Smoking adjusted	Boffetta, Stellman, and Garfinkel 1988
Human U.S. Railroad workers (M)	Occupational ($\geq$ 5 yrs exposure on job)	Death from chronic respiratory diesease (total number = 575), relative risk of 1.23.	Exposure classified from job titles from records	Smoking adjusted	Garshick, Schenker, Munoz et al. 1987
Human Canadian Railroad workers (M)	Occupational	Death caused by emphysema and chronic bronchitis (numbers not available) with an estimated relative risks for both of 1.00	Exposure classified from job titles from records (last job held)	Smoking not adjusted for in study	Howe, Fraser, Lindsay et al. 1983

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
Human U.S. Bus drivers (M)	Occupational	Death caused by nonmalignant respiratory diseases (total number = 16) with a relative risk of 0.61	Exposure classified from employment from union records	Smoking not adjusted for in study	Michaels and Zoloth 1991
Human U.S. Railroad Workers (M)	Occupational	Death from all respiratory dieseases (total number = 21) with a relative risk of 0.54	Exposure classified from job titles from records in low and high exposure	Smoking not adjusted for in study	Schenker, Smith, Munoz et al. 1984
Human U.S. Heavy Equipment Operators	Occupational	Death from all nonmalignant dieseases (total number = 196) with a relative risk (RR[3]) of 0.84; from emphysema (116) with an RR of 1.65; from pneumonia (41) with an RR of 0.54	Exposure classified from union work histories	Smoking not adjusted for in study	Wong, Morgan, Kheifets et al. 1985
b. Animal					
i. Hepatic					
F-344 Rat (Male and Female)	7 h/day, 5 days/wk, 52 weeks	No changes in absolute liver weight or liver/body weight ratio	2.0 mg/m^3	0.23-0.36 µm, MMD[4] (12.7 ppm CO, 1.6 ppm NO_2, and 0.83 ppm SO_2)	Green, Boyd, Danner-Rabovsky et al. 1983

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
Sprague-Dawley Rat (Male)	20 h/day, 7 days/wk, 1-7 weeks	AHH[5] induction occurred in lung, liver, and prostate gland but not in testes; maximum significant activities occurred at different times; liver has greatest overall activity, percent increase highest in prostate; epoxide hydrase activity was unaffected	6.3 mg/m^3	(17.4 ppm CO, 2.3 ppm NO_2, and 2.1 ppm SO_2)	Lee, Suzuki, Lee et al. 1980
Syrian Hamster	7-8 h/day, 5 days/wk, 22 weeks	Enlarged sinusoids, with activated Kupffer's cells and slight changes of nuclei; fatty deposits; mitochondria, loss of cristae and pleomorphic character; gap junctions between hepatocytes had wide range in structural diversity	4.0, 8.0 and 11.0 mg/m^3	Varying levels of CO, NO_2, SO_2 also present	Meiss, Robenek, Schubert et al. 1981
Syrian golden Hamster	5 months (frequency unspecified)	•Liver toxicity: enlarged sinusoids with activated Kupffer's cells with frequently fragmented or irregularly shaped nucleoli; fat deposition in sinusoids; microbodies in hepatocytes; disturbed gap junction between hepatocytes.	Dilution of 1:5 and 1:10 in air (particles unspecified)		Meiss, Robenek, Schubert et al. 1981.
A/J Mouse (Male)	8 h/day, 7 days/wk, 26 or 35 weeks	No effect on liver and lung AHH activities and liver cyt. P-448 or P-450 levels.	6.0 mg/m^3	17.4 ppm CO, 2.3 NO_2, and 2.1 ppm SO_2 also present	Pepelko and Peirano 1983

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
Sprague-Dawley Rat	Up to 6 mo.	No increase in foci (γ-glutamyl transpeptidase-positive foci) or induced liver toxicity	5 mg/m^3 diesel particles	Rats were partially hepatectomized.	Pereira, Shinozuka, Lombardi et al. 1981a.
Inbred Cat (Male)	8 h/day, 7 days/wk, 124 weeks	No change in the absolute liver weight	6.0[a] and 12.0[b] mg/m^3	[a]Exposure wks 1-61 [b]Exposure wks 62-124	Plopper, Hyde, Weir 1983
F-344 Rat (Female)	7 h/day, 5 days/wk, 12, 26, or 104 weeks	No effect on benzo[a]pyrene hydrolase or 7-ethoxycoumarin deethylase activity in the liver	2.0 mg/m^3	0.23-0.36 µm, MMD (11.5 ppm CO, 1.5 ppm NO_2, and 0.8 ppm SO_2)	Rabovsky, Petersen, Lewis et al. 1984
ii. Hematological/Cardiovascular					
Syrian Hamster	16 h/day, 5 days/wk, 104 weeks	•Elevated red and white cell counts, hematocrit, and hemoglobin; increased heart/body weight and right ventricular/heart weight ratios; lower left ventricular contractility; changes in blood chemistry; obstructive and restrictive lung disease •No effects from filtered diesel	•0.7 mg/m^3 •2.2 mg/m^3	Unfiltered diesel	Brightwell, Fouillet, Casdsano-Zoppi et al. 1986

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
F-344 Rat (Male and Female)	16 h/day, 5 days/wk, 104 weeks	•Elevated red and white cell counts, hematocrit, and hemoglobin; increased heart/body weight and right ventricular/heart weight ratios; lower left ventricular contractility; changes in blood chemistry; obstructive and restrictive lung disease •No effects from filtered diesel	•0.7 mg/m^3 •2.2 mg/m^3	Unfiltered diesel	Brightwell, Fouillet, Casdsano-Zoppi et al. 1986
F-344 Rat	16 h/day, 5 days/wk, 104 weeks (0.7, 2.2 and 6.6 mg/m^3)	Reduction in blood glucose, blood proteins, triglycerides and cholesterol; increase in BUN[6], alkaline phosphate alanine and aspartate amino-transferases (SGPT and SGOT)	6.6 mg/m^3	32.0 ppm CO at high dose	Brightwell, Fouillet, Casdsano-Zoppi et al. 1986
Syrian Hamster	16 h/day, 5 days/wk, 104 weeks (0.7, 2.2 and 6.6 mg/m^3)	Decrease in potassium, LDH, aspartate amino-transferase; increase in albumin and gamma-glutamyl transferase	6.6 mg/m^3	32.0 ppm CO at high dose	Brightwell, Fouillet, Casdsano-Zoppi et al. 1986
Syrian Hamster (Male, Female)	7-8 h/day, 5 days/wk, 75 weeks	At 29 weeks, lower erythrocyte count; increased MCV; reduced leukocyte count	3.9 mg/m^3	0.1 µm, MMD (18.5 ppm CO, 1.2 ppm NO_2, 0.8 ppm SO_2 also present)	Heinrich, Peters, Funcke et al. 1982
Syrian Hamster (Male, Female)	7-8 h/day, 5 days/wk, 75 weeks	After 29 weeks, increases in SGOT, LDH, alkaline phosphatase, gamma-glutamyl transferase, and BUN	3.9 mg/m^3	0.1 µm, MMD (18.2 ppm CO, 1.2 ppm NO_2, and 3.1 ppm SO_2 also present)	Heinrich, Peters, Funcke et al. 1982

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
Wistar Rat (Male)	6 h/day, 5 days/wk, 78 weeks	3% increase in carboxyhemoglobin (COHb)	8.3 mg/m^3	0.71 µm, MMD (50 ppm CO and 4-6 ppm NO_2 also present)	Karagianes, Palmer, Busch 1981
F-344 Rat (Male and Female)	7 h/day, 5 days/wk, 104 weeks	Increase in banded neutrophils; no effect on heart or pulmonary arteries	2.0 mg/m^3	0.23-0.36 µm, MMD	Lewis, Green, Moorman et al. 1989; Vallyathan, Virmani, Rochlani et al. 1986
Cynomolgus Monkey (Male)	7 h/day, 5 days/wk, 104 weeks	Increased mean corpuscular volume	2.0 mg/m^3	0.23-0.36 µm, MMD (11.5 ppm CO, 1.5 ppm NO_2, and 0.8 ppm SO_2 also present)	Lewis, Green, Moorman et al. 1989
F-344 Rat (Male and Female)	7 h/day, 5 days/wk, 104 weeks	Decreased phosphate, LDH, SGOT, and SGPT; increased sodium in females but not males	2.0 mg/m^3	0.23-0.36 µm, MMD (11.5 ppm CO, 1.5 ppm NO_2, and 0.8 ppm SO_2 also present)	Lewis, Green, Moorman et al. 1989
F-344 Rat	20 h/day, 5.5 days/wk, 78 weeks	No changes in heart mass or hematology at any exhaust level or duration of exposure	0.25, 0.75 and 1.5 mg/m^3	0.19 µm, MMD	Penney, Baylerian, Fanning et al. 1981
Hartley Guinea Pig	20 h/day, 5.5 days/wk, 78 weeks	No changes in heart mass or hematology at any exhaust level or duration of exposure	0.25, 0.75 and 1.5 mg/m^3	0.19 µm, MMD	Penney, Baylerian, Fanning et al. 1981
Inbred Cat (Male)	8 h/day, 7 days/wk, 124 weeks	Increases in banded neutrophils; significant at 12 mo, but not 24 mos. BUN unaltered; SGOT and SGPT unaffected; LHD increase after 1 year of exposure.	6.0[a] and 12.0[b] mg/m^3	[a]Exposure wks 1-61 [b]Exposure wks 62-124	Pepelko and Peirano 1983

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
F-344/Jcl Rat (Male and Female)	16 h/day, 6 days/wk, 130 weeks	Lower cholinesterase activity in males; elevated gamma globulin and electrolyte levels in males and females; at higher concentrations, RBC, Hb, Hct slightly elevated; MCV and mean corpuscular hemoglobin and concentration were lowered.	0.11[a], 0.41[a], 1.08[a], 2.31[a], and 3.72[b] mg/m^3	0.1 µm, MMD [a]Light-duty engine [b]Heavy-duty engine (CO, NO_2, SO_2 also present)	Research Committee for HERP Studies 1988
Hartley Guinea Pig (Male and Female)	20 h/day, 7 days/wk, 8 weeks	No effect on heart mass or ECG; small decrease in heart rate (IE only)	6.3 and 6.8 mg/m^3		Wiester, Iltis, Moore 1980
iii. Immunological					
Fischer 344 rat	Up to 24 months	Exposure related pathological changes in lung-associated lymph nodes: •at 6 months, number of lymphoid cells in lymph nodes was significantly increased •at 6 months, immunized rats had significantly elevated total number of IgM antibody-forming cells in lymph nodes. •at 12 months, all immunized rats had elevated total number of IgM antibody-forming cells; Antibodies in serum not altered	•0.35, 3.5, and 7.0 mg/m^3 •Critical dose not stated •7.0 mg/m^3 •All doses: 0.35, 3.5, and 7.0 mg/m^3	Rats immunized by intratracheal instillation of sheep RBCs (red blood cells) and IgM in lymphoid cells and IgM, IgC, and IgA in serum analyzed	Bice, Mauderly, Jones et al. 1985

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
F-344 Rat	7 h/day, 5 days/wk, 104 weeks	Total number of anti-sheep red blood cell IgM AFC in the lung-associated lymph nodes was elevated in rats exposed to 3.5 or 7.0 mg/m^3 DP (no such effects in mice); total number of AFC per 10^6 lymphoid cells in lung-associated lymph nodes and level of specific IgM, IgG, or IgA in rat sera were not altered	0.35, 3.5 and 7.0 mg/m^3	0.25 µm, MMD (Varying levels of CO an d NO_2)	Bice, Mauderly, Jones et al. 1985
CD-1 Mouse	24 mon (Up to)	Exposure related pathological changes in lung-associated lymph nodes: •at 6 months, number of lymphoid cells in lymph nodes was significantly increased •at 6 months, mice immunized with sheep RBCs, had increased number of antibody-forming cells in lymphs	•0.35 mg/m^3, 3.5 mg/m^3 7.0 mg/m^3 (not stated) •Critical dose not stated	Rats immunized by intratracheal instillation of sheep RBCs (red blood cells) and IgM in lymphoid cells analyzed	Bice, Mauderly, Jones et al. 1985.
CD-1 Mouse	7 h/day, 5 days/wk, 104 weeks	Increased number of lymphoid cells	3.5 or 7.0 mg/m^3		Bice, Mauderly, Jones et al. 1985

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
Hartley Guinea Pig (Male)	20 h/day, 5.5 days/wk, 4 or 8 weeks	Increased lymphoid cell numbers, but no alterations in number of B, T, and null lymphocytes or cell viability among lymphocytes isolated from tracheobronchial lymph nodes, spleen, or blood	1.5 mg/m^3	0.19 µm, MMD (7.5 ppm CO)	Dziedzic 1981
CD-1 Mouse (Female)	7 h/day, 5 days/wk, 4, 12, or 26 weeks	Mortality similar at each exposure duration when challenged with Ao/PR/8/34 influenza virus; in mice exposed for 3 and 6 mo, but not 1 mo, there were increases of lung consolidation, higher virus growth, depressed interferon levels and a 4-fold reduction in hemagglutin antibody levels	2.0 mg/m^3	0.23-0.36 µm, MMD (11.5 ppm CO, 1.5 ppm NO_2, and 0.8 ppm SO_2)	Hahon, Booth, Green et al. 1985
Hamster	19 hrs/day, 5 days/wk, for 2 years	Increased number of lymphocytes	4.2 mg/m^3		Heinrich, Muhle, Takenaka et al. 1986
Cats	8 hrs/day, 7 days/wk, 27 mos	Lymphocytes observed in lung interstitium; subpopulations of lymphocytes not known.	6.3 mg/m^3 (1-62 wks); 11.7 mg/m^3 (62-124 wks)		Hyde, Plopper, Weir et al. 1985

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
F-344 Rat (Male)	7 h/day, 5 days/wk, 52 or 104 weeks	Neither-humoral immunity (assessed by enumerating antibody-producing cells) nor cellular immunity (assessed by the lymphocyte blast transformation assay) were markedly affected	2.0 mg/m^3	0.23-0.36 μm, MMD (11.5 ppm CO, 1.5 ppm NO_2, and 0.8 ppm SO_2)	Mentnech, Lewis, Olenchock et al. 1984
Rat	20 hrs/day, 5 days/wk, for 1 yrs	Increased number of lymphocytes in bronchoalveolar lavage fluid	0.75 or 1.5 mg/m^3	May be artifactual based possible extraction from enlarge epithelial lymphoid tissues.	Strom 1984
iv. Nervous System					
Sprague-Dawley Rat (Male)	8 h/day, 7 days/wk, 1-4 weeks	Somatosensory and visual evoked potentials revealed longer pulse latencies in pups exposed neonatally	6.0 mg/m^3	19 ppm CO, 2.5 ppm NO_2, and 1.8 SO_2	Laurie, Boyes 1980 1981
Sprague-Dawley Rat (Male)	8 or 20 h/day, 7 days/wk, 3, 4, 6, or 16 weeks	Reduction in spontaneous locomotor activity (SLA) in adults; neonatal exposures for 8 or 20 h/day caused reductions in SLA; Neonates exposed for 20 hrs/day for 17 days resulted in a slower rate of a bar-pressing task to obtain food	6.0 mg/m^3	19 ppm CO, 2.5 ppm NO_2, and 1.8 ppm SO_2	Laurie, Boyes 1980
Sprague-Dawley Rat (Male)	20 h/day, 7 days/wk, 6 weeks	Reduction in adult spontaneous locomotor activity and in neonatal pivoting	6.0 mg/m^3	19 ppm CO, 2.5 ppm NO_2, and 1.8 ppm SO_2	Laurie, Lewkowski, Cooper et al. 1978

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
v. Pulmonary					
Hartley Guinea Pig (Male)	20 h/day, 5.5 days/wk, 104 weeks	•Minimal response •Ultrastructural changes at 0.75 mg/m^3; increase in PMN at 0.75 mg/m^3 and 1.5 mg/m^3; •Thickened alveolar membranes, cell proliferation, fibrosis.	•0.25 mg/m^3 •0.75, 1.5 mg/m^3 •6.0 mg/m^3		Barnhart, Chen, Salley 1981; Barnhart, Salley, Chen 1982; Vostal, Chan, Garg et al. 1981
Hartley guinea-pigs	>6 mos (0.25-6 mg/m^3)	•Alveolar septa thickening •Fibrotic changes in lungs •Dose-dependent ultrastructural changes	•0.25 mg/m^3 particulate conc. •0.75 mg/m^3 part. conc. •0.25-6 mg/m^3		Barnhart, Chen, Salley et al. 1981 1982.
A/HEJ Mouse (Male)	8 h/day, 7 days/wk, 39 weeks	Increase in lung protein content and collagen synthesis; a decrease in overall lung protein synthesis.	6.0 mg/m^3		Bhatnagar, Hussain, Sorensen et al. 1980; Pepelko 1982a
F-344 Rat (Male and Female)	7 h/day, 5 days/wk, 104 weeks	Multifocal histiocytosis; inflammatory changes; Type II cell proliferation, fibrosis	2.0 mg/m^3	0.23-0.36 µm, MMD (11.5 ppm CO, 1.5 ppm NO_2, and 0.8 ppm SO_2 also present)	Bhatnagar, Hussain, Sorensen et al. 1980; Pepelko 1982a
Sprague-Dawley Rat (Male)	8 h/day, 7 days/wk, 39 weeks	Increase in lung protein content and collagen synthesis; a decrease in overall lung protein synthesis; prolylhydroxylase activity increased in rats in utero	6.0 mg/m^3		Bhatnagar, Hussain, Sorensen et al. 1980; Pepelko 1982a

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
F-344 Rat (Male)	7 h/day, 5 days/wk, 104 weeks	Little effect on viability, cell number, oxygen consumption, membrane integrity, lyzomal enzyme activity, or protein content of AMs; decreased cell volume and ruffling of cell membrane and depressed luminescence of AM	2.0 mg/m^3	0.23-0.36 µm, MMD (11.5 ppm CO, 1.5 ppm NO_2, and 0.81 ppm SO_2)	Castranova, Bowman, Reasor et al. 1985
Fischer 344 Rat	2 yrs	•Decreased phagocytic activity of macrophages	2 mg/m^3		Castranova, Bowman, Reasor et al. 1985
F-344 Rat (Male)	20 h/day, 5.5 days/wk, 4, 13, 26, or 39 weeks	•No significant effect on liver AHH[2] activity •Lung AHH activity was slightly reduced after 6-mo exposure to 1.5 mg/m^3 •Cytochrome P-450 was unchanged in lungs and liver following inhalation or i.p. administration.	0.75 and 1.5 mg/m^3	0.19 µm, MMD (4.8 and 7.5 ppm CO, respectively) NOTE: An intra-peritoneal (i.p.) dose of particulate extract, estimated to be equivalent to inhalation exposure, had no effect on AHH activity.	Chen and Vostal 1981
Hartley Guinea Pig	20 h/day, 5.5 days/wk, 8 weeks	No significant changes in absolute numbers of alveolar macrophages (Ams)	0.25 and 1.5 mg/m^3	0.19 µm, MMD (2.9 and 7.5 ppm CO, respectively)	Chen, Weller, Barnhart 1980

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
Wistar rat (F)	19 hrs/day, 5 days/wk, for 24 mos.	•Lung burdens of ~40 mg •Highly elevated lung weights and histological exam showed pronounced proliferation •Proliferation caused alteration in breathing pattern of tracer aerosols, which deposited much higher in the tracheobronchial region of the lung resulting in apparently accelerated clearance rate.	1 mg/m^3	Whole body exposure chambers of diesel exhaust.	Creutzenberg, Bellmann, Heinrich, et al. 1990.
Fischer 344 Rat	2 wks	•Macrophages with diesel particles present 6 wks post exposure	6 mg/m^3 particles		Garg 1983
Hamster	19 hrs/day, 5 days/wk, for up to 18+ clean air mos	•Minimal macrophage accumulation •Aggregates of macrophages	•3.7 mg/m^3 for 6 and 10.5 mos •3.7 mg/m^3 for 15 and 18+ mos		Heinrich, Mohr, Fuhst et al. 1989
Rats [Wistar]	19 hr/day, 5 days/wk for life	•Wet and dry weights of lungs of mice exposed to unfiltered diesel were 2-3 times higher than controls •Increased enzyme levels, collagen, and total protein in lavage fluid	4.24 mg/m^3 unfiltered diesel particles; Controls received clean air	Exhaust from 1.6-L engine (US-72 test cycle) diluted 1:17 Note: Effects observed after 2 years	Heinrich, Muhle, Takenaka et al. 1986a
Wistar Rat (Female)	19 h/day, 5 days/wk, 140 weeks	Thickened alveolar septa; AM aggregation; inflammatory changes; hyperplasia; lung tumors	4.24 mg/m^3		Heinrich, Muhle, Takenaka et al. 1986a

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
NMRI mouse	19 hr/day, 5 days/wk for life	•Wet and dry weights of lungs of mice exposed to unfiltered diesel were 2-3 times higher than controls	4.24 mg/m^3 unfiltered diesel particles; Controls received clean air	Exhaust from 1.6-L engine (US-72 test cycle) diluted 1:17 Note: Effects observed after 2 years	Heinrich, Muhle, Takenaka et al. 1986a
Syrian golden Hamster (M, F)		•Increased lung weights by 50% and 70% •Increased enzyme levels, collagen, and total protein in lavage fluid •Inflammatory changes; thickened alveolar septa; bronchoalveolar hyperplasia; emphysema (diagnostic methodology not described)	4.24 mg/m^3 unfiltered diesel particles	Exhaust from 1.6-L engine (US-72 test cycle) diluted 1:17 (12.5 ppm CO, 1.5 ppm NO_2, and 1.1 ppm SO_2 also present)	Heinrich, Muhle, Takenaka et al. 1986a
Wistar Rat	19 h/day, 5 days/wk, 120 to 140 weeks	•Decreased body weight •Decreased lung compliance and increased airway resistance •Differences in lung lavage enzymes and cell counts and lung histopathology and collagen content among rats, hamsters, and mice, with effects most pronounced in rats; •Filtered exposure: no effect on glucose-6-phosphate dehydrogenase, total protein and lung collagen	4.24 mg/m^3	Unfiltered diesel (Varying levels of CO, NO_2, and SO_2 in unfiltered)	Heinrich, Muhle, Takenaka et al. 1986a

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
Syrian Hamster	19 h/day, 5 days/wk, 120 to 140 weeks	•Decreased lung compliance and increased airway resistance •Differences in lung lavage enzymes and cell counts and lung histopathology and collagen content among rats, hamsters, and mice, with effects most pronounced in rats; •Filtered exposure: no effect on glucose-6-phosphate dehydrogenase, total protein and lung collagen	4.24 mg/m^3	Unfiltered diesel (Varying levels of CO, NO_2, and SO_2 in unfiltered)	Heinrich, Muhle, Takenaka et al. 1986a
NMRI Mouse (Female)	19 h/day, 5 days/wk, 120 to 140 weeks	•Decreased body weight; •Increased mortality; •Differences in lung lavage enzymes and cell counts and lung histopathology and collagen content among rats, hamsters, and mice, with effects most pronounced in rats; •Filtered exposure: no effect on glucose-6-phosphate dehydrogenase, total protein and lung collagen	4.24 mg/m^3	Unfiltered diesel (Varying levels of CO, NO_2, and SO_2 in unfiltered)	Heinrich, Muhle, Takenaka et al. 1986a
NMRI Mouse (Female)	19 h/day, 5 days/wk, 120 weeks	Inflammatory changes; broncholoalveolar hyperplasia; alveolar lipoproteinosis; fibrosis	4.24 mg/m^3	12.5 ppm CO, 1.5 ppm NO_2, and 1.1 pp, SO_2	Heinrich, Muhle, Takenaka et al. 1986a

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
Syrian Hamster	7 h/day, 5 days/wk, 104 weeks	Increases in pulmonary adematous proliferation, with unfiltered significantly higher than filtered or control	3.9 mg/m^3	Unfiltered diesel (Varying levels of CO, NO_2, SO_2 also present)	Heinrich, Peters, Funcke et al. 1982
Wistar Rat (Female)	7 h/day, 5 days/wk, 104 weeks	No effect on pulmonary function or heart rate	3.9 mg/m^3	Unfiltered diesel (Varying levels of CO, NO_2, SO_2 also present)	Heinrich, Peters, Funcke et al. 1982
Syrian Hamster (Male, Female)	7-8 h/day, 5 days/wk, 120 weeks	Inflammatory changes, 60 % adenomatous cell proliferation	3.9 mg/m^3	0.1 µm, MMD (18.5 ppm CO, 1.2 ppm NO_2, and 3.1 ppm SO_2 also present)	Heinrich, Peters, Funcke et al. 1982
F-344/Crl Rat (Male and Female)	7 h/day, 5 days/wk, for 6, 12, 18, or 21 mos	•No effect level •Inflammatory response, as indicated by a dose-dependent increase in macrophages and neutrophils in BAL and hydroxyproline content; lung GSH increased in a dose-dependent manner •Significant increases of AM exposed to 7.0 mg/m^3 for 24 months •Decreased lung cyt. P-450 content	•0.35 mg/m^3 •3.5 and 7.0 mg/m^3 •7.0 mg/m^3 •0.35, 3.5, and 7.0 mg/m^3	0.25 µm, MMD (Varying levels of CO and NO_2) GSH = glutathione	Henderson, Pickrell, Jones, et al. 1988.

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
CD-1 Mouse (Male and Female)	7 h/day, 5 days/wk, for 6, 12, and 18 mos	•No effect level •Inflammatory response, as indicated by a dose-dependent increase in macrophages and neutrophils in BAL and hydroxyproline. •Significant increases of AM exposed to 7.0 mg/m^3	•0.35 mg/m^3 •3.5 and 7.0 mg/m^3 •7.0 mg/m^3	0.25 µm, MMD (Varying levels of CO, NO_2, and SO_2)	Henderson, Pickrell, Jones, et al. 1988.
Cats	8 hrs/day, 7 days/wk, 27 mos	•Elevated collagen level in lungs, more than 2x after 6 mos post-exposure; •Increased aggregates of macrophages at 11.7 mg/m^3	•6.3 mg/m^3 (1-62 wks); 11.7 mg/m^3 (62-124 wks) •11.7 mg/m^3		Hyde, Plopper, Weir et al. 1985
Rat	16 hrs/day, 6 days/wk, up to 30 mos	•Dose-dependent irregularity, shortening, and loss of cilia in respiratory tract, trachea and bronchi. •Aggregates of macrophages	•1 or 2[a] mg/m^3, or 2 or 4[b] mg/m^3 •2.0, 2.0, and 4.0[a] mg/m^3, or 0.4, 1.0, and 2.0[b] mg/m^3	[a] Light-duty engine [b] Heavy-duty engine	Ishinishi, Kuwabara, Nagase et al. 1986

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
F-344 Rat (Female)	8 h/day, 7 days/wk, 104 weeks	•Lung/body rate weight rate higher in both groups at 24 mos; fibrosis and epithelial hyperplasia in lungs of unfiltered; type II cell proliferation; nominal lung and spleen histological changes; minimal macrophage aggregates •Body weight decrease after 6 mos in unfiltered, 18 mos in filtered	4.9 mg/m^3	Unfiltered diesel (7.0 ppm CO, 1.8 ppm NO_2, and 13.1 ppm SO_2 also present in unfiltered; none in filtered)	Iwai, Udagawa,Yamagishi et al. 1986
Rat	Chronic exposure	Decrease in functional activity of alpha-1-proteinase inhibitor	3.5 mg/m^3		Johnson, Winters, Lee, and Smith 1989
Syrian Hamster (Male)	20 h/day, 7 days/wk, 12-13 weeks	Inflammatory changes; increase in lung weight; increase in thickness of alveolar walls; no species difference between hamsters and rats and mice.	1.5 mg/m^3 6.9, .49, -	0.19 µm, MMD CO, N02, SO_2 present	Kaplan, MacKenzie, Springer et al. 1982
A/J Mouse (Male)	20 h/day, 7 days/wk, 12-13 weeks	Inflammatory changes; increase in lung weight; increase in thickness of alveolar walls; no species difference between mice and hamsters and rats.	1.5 mg/m^3	0.19 µm, MMD CO, N02, SO_2 present	Kaplan, MacKenzie, Springer et al. 1982
F-344 Rat (Male)	20 h/day, 7 days/wk, 12-13 weeks	Inflammatory changes; increase in lung weight; increase in thickness of alveolar walls; no species difference between rats and hamsters and mice.	1.5 mg/m^3	0.19 µm, MMD CO, NO_2, SO_2 present	Kaplan, MacKenzie, Springer et al. 1982

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
Wistar Rat (Specific-pathogen free Male)	6 h/day, 5 days/wk, 4 or 20 mos	•Macrophage accumulation •Alveolar cell hypertrophy •Interstitial fibrosis and alveolar emphysema (diagnostic methodology not described)	8.3±2.0 mg/m^3 soot	0.71 µm, MMD (50.0 ppm CO, 4.0-6.0 ppm NO_2)	Karagianes, Palmer, Busch 1981
Sprague-Dawley Rat (M)	4 hrs/day, 5 days/wk, for 1, 5, or 20 days.	•Type-1 and type-2 lesions. •5 days: Significantly inhibited macrophage Fc receptor binding and phagocytic activity •20 days: Significant increased in macrophage phagocytic activity but no effect on binding •1 or 5 days: Greater bronchoalveolar permeability than controls	•230 or 520 µg/m3 •500 µg/m3	0.15 µm, size (Nose-only exposure) No SO_2, CO, and NO_2	Kleinman, Bhalla, Ziegler, et al. 1993
Cynomolgus Monkey (Male)	7 h/day, 5 days/wk, 104 weeks	Decrease in flow rates; AM aggregation; no fibrosis, inflammation or emphysema (at 6, 12, 18, and 24 mos)	2.0 mg/m^3	0.23-0.36 µm, MMD	Lewis, Green, Moorman et al. 1989
F-344 Rat (M, F)	7 h/day, 5 days/week 19 weeks	No effects on lung function; increase in PMNs and proteases and AM aggregation in both F-344 rats and CD-1mouse.	0.21 mg/m^3	No presence of CO, NO_2, SO_2 was observed	Mauderly, Benson, Bice et al. 1981

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
CD-1 Mouse (M, F)	7 h/day, 5 days/week 19 weeks	No effects on lung function; increase in PMNs and proteases and AM aggregation in both F-344 rats and CD-1mouse.	0.21 mg/m^3	No presence of CO, NO_2, SO_2 was observed	Mauderly, Benson, Bice et al. 1981
F-344 Rat (M, F)	7 h/day, 5 days/wk, 130 weeks	•NOAEL •Alveolar and bronchiolar epithelial metaplasia at 3.5 and 7.0 mg/m^3; fibrosis at 7.0 mg/m^3; •Progressive, focal inflammation (decrease in lung compliance)	•0.35 mg/m^3 •3.5, and 7.0 mg/m^3	0.23 µm, MMD (Varying levels of CO and NO_2 also present)	Mauderly, Bice, Carpenter et al. 1987a; Mauderly, Jones, Griffith et al. 1987b; Henderson, Pickrell, Jones et al. 1988
CD-1 Mouse (Male and Female)	7 h/day, 5 days/wk, 130 weeks	•NOAEL •Fibrosis at 7.0 mg/m^3; inflammatory cells in lungs and increased number of neutrophils	•0.35 mg/m^3 •3.5, and 7.0 mg/m^3	0.23 µm, MMD (Varying levels of CO and NO_2 also present)	Mauderly, Bice, Carpenter et al. 1987
Rat	7 hrs/day, 5 days/wk, for 12, 18, or 24 mos	•Inflammatory cells in lungs for all exposure time periods; •Decreased number of macrophages and increased number of neutrophils in BAL at 18 and 24 mos	3.5 mg/m^3		Mauderly, Bice, Cheng et al. 1989
Fischer 344 Rat (Specific-pathogen free)	up to 30 mos (0.35, 3.5, or 7.0 mg/m^3)	•Dose-dependent focal accumulation of soot and fibrosis •Active inflammation of alveolar macrophages near terminal bronchioli	0.35, 3.5, or 7.0 mg/m^3 soot	Diesel exhaust diluted with soot	Mauderly, Jones, Griffith et al. 1987

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
Rat	16 hrs/day, 5 days/wk, for 3, 6, 12, 18, or 23 mos	•Aggregates of macrophages present at all exposure times; •Increased number of neutrophils in BAL at 18 and 23 mos. •Increased number of macrophages in BAL at 18 mos, and increased neutrophils at 12 and 18 mos.	•2.5 and 6.5 mg/m^3 •2.5 mg/m^3 •6.5 mg/m^3		Mauderly, Snipes, Barr et al. 1994
Cat	8 hrs/day, 7 days/wk, for 27 mos	Decreased lung volume (statistically different from control)	11.7 mg/m^3		Moorman, Clark, Pepelko et al. 1985
F-344 Rat (Male)	20 h/day, 5.5 days/wk, 8-53 weeks	•After 8 weeks, no induction of P-450, P-448, or NADPH-dependent cyt c reductase; •After 1 year, liver microsomal oxidation of benzo[a]pyrene was not increased; •1 year of exposure to either 0.25 or 1.5 mg/m^3 impaired lung microsomal metabolism of benzo[a]pyrene.	0.25 and 1.5 mg/m^3	0.19 µm, MMD	Navarro , Charboneau, McCauley 1981
Sprague-Dawley Rat (M)	20 h/day 7 days/week 4 weeks	Decreased body weight; arterial blood pH reduced; vital total lung capacities increased	6.4 mg/m^3 6.8[a] mg/m^3	CO, NO_2, SO_2 present in varying concentrations [a] Irradiated exhaust	Pepelko 1982a

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
Chinese Hamster (Male)	8 h/day, 5 days/wk, 26 weeks	Inflammatory changes; AM accumulation; thickened alveolar lining, Type II cell hyperplasia; edema; increase in collagen	6.0 and 12.0 mg/m^3		Pepelko 1982b
Inbred Cat (M)	20 h/day 7 days/week 4 weeks	Few effects on lung function; focal pneumonitis or alveolitis	6.4 mg/m^3	CO, NO_2, SO_2 present	Pepelko, Mattox, Yang et al. 1980a, as cited in USEPA 1994
Inbred Cat (Male)	8 h/day, 7 days/wk, 124 weeks	Inflammatory changes; AM aggregation; bronchiolar epithelial metaplasia; Type II cell hyperplasia; peribronchiolar fibrosis	6.0[a] and 12.0[b] mg/m^3	[a]Exposure wks 1-61 [b]Exposure wks 62-124 (Varying levels of CO, NO_2, and SO_2)	Plopper, Hyde, Weir et al. 1983; Hyde, Plopper, Weir et al. 1985
F-344/Jcl Rat (Male and Female)	16 h/day, 6 days/wk, 130 weeks	Inflammatory changes; Type II cell hyperplasia and lung tumors seen at >0.4 mg/m^3, shortening and loss of cilia in trachea and bronchi	0.11[a], 0.41[a], 1.08[a], 2.31[a], and 3.72[b] mg/m^3	[a]Light-duty engine [b]Heavy-duty engine (Varying levels of CO, NO_2, and SO_2)	Research Committee for HERP Studies 1988

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
F-344 Rat (Male)	20 h/day, 5.5 days/wk, 48 or 52 weeks	AM cell counts proportional to concentration of particles at 0.75 and 1.5 mg/m^3; AM increased in lungs in response to rate of particle mass entering lung rather than total burden in lung; increased PMNs were proportional to inhaled concentrations and/or duration of exposure; PMNs affiliated with clusters of aggregated AM rather than particles •Elevated protein content and enzyme activities in lavage fluid cells	0.75[a] and 1.5[b] mg/m^3	0.19 µm, MMD [a]52-wk exposure [b]48-wk exposure (4.8 and 7.5 ppm CO, respectively)	Strom 1984
Rat	20 hrs/day, 7 days/wk for 3.2, 6.5, and 12 mos	Aggregates of macrophages	0.5 mg/m^3		Strom, Garg, Johnson et al. 1990
Hamster	8 hrs/day, 7 days/wk, 6 mos	Decreases in lung volume(statistically significant)	6.3 and 11.7 mg/m^3		Vinegar, Carson, Pepelko, et al. 1981.
Guinea-pigs	1 day-12 mos	•Enzyme (acid phosphatase) activity reduced	0.25-6 mg/m^3	Effects directly related to duration and doses	Weller, Chen, Barnhart 1981
Rat	1 day-12 mos	•Enzyme (acid phosphatase) activity reduced	0.25-6 mg/m^3	Effects directly related to duration and doses	Weller, Chen, Barnhart 1981

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
F-344 Rat (M)	20 h/day, 5.5 days/week, 4 weeks	Macrophage aggregation; increase in PMNs; Type II cell proliferation; thickened alveolar walls	6.0 mg/m^3	6.8 µm, MMD	White & Garg 1981
Fischer 344 Rat	20 hrs/day, 5 days/wk for 2 mos	•Increased numbers of alveolar macrophages with diesel particles •Increase type II pneumocytes and inflammatory cells in alveoli	6 mg/m^3 particles		White and Garg 1981, as cited in IARC 1989
Hartley Guinea-pig (M, F)	•20 h/day 7 days/week 4 weeks •20 h/day 7 days/week 8 weeks	•Exposure started when animals were 4 days old; increase in pulmonary flow; bradycardia •Increase in relative lung wt; AM aggregation; hypertrophy of goblet cells; focal hyperplasia of alveolar epithelium	•6.8[a] mg/m^3 •6.3 mg/m^3	[a] Irradiated exhaust 1:13 dilution of diesel:air (CO, NO_2, SO_2 present)	Wiester, Iltis, Moore 1980
Fischer 344 Rat	20 hrs/day, 7 days/wk, for up to 14 days	•DNA synthesis in lung tissue had 4-fold increase after 2 days exposure •Total lung fatty acid content decreased 23% after 1 day	6 mg/m^3 particles	DNA synthesis returned to normal after 7 days	Wright 1986
vi. Reproduction/Development					
Cynomolgus Monkey (Male)	7 h/day, 5 days/wk, 104 weeks	No effects on sperm motility, velocity, density, morphology, or incidence of abnormalities	2 mg/m^3	11.5 ppm CO, 1.5 ppm NO_2, and 0.8 ppm SO_2	Lewes, Green, Moorman et al. 1989

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
CD-1 Mouse (Male and Female)	8 h/day, 7 days/wk, 6 to 28 weeks	Overall fertility and survival rates were unaffected in the three generation reproductive study; only consistent change noted, an increase in lung weights, was diagnosed as anthracosis	12 mg/m^3	33 ppm CO, 4.4 ppm NO_2, and 5.0 ppm SO_2	Pepelko and Peirano 1983
Chinese Hamster	6 months	3-fold increase in sperm abnormalities as compared to controls	Diesel particle dose not specified	Controls exposed to "fresh air"	Pereira, Shinozuka, Lombardi 1981a; Pereira, Sabharwl, Kaur et al., 1981b.
A/Strong Mouse (Male)	8 h/day, 7 days/wk, 31 or 38 weeks	No effect on sperm morphology; high rate of spontaneous sperm abnormalities may have masked small effects	6 mg/m^3	20 ppm CO, 0.8 ppm NO_2, and 2.1 ppm SO_2	Periera, Sabharwal, Gordon et al. 1981b
[C57B1]/[6XC3H]F1 Mouse (Male)	5 days (ip injection)	Dose related increase in sperm abnormalities; decrease in sperm number at highest dose; testicular weights unaffected	50, 100 or 200 mg/kg		Quinto and DeMarinis 1984 1981
New Zealand Albino Rabbit (Female)	8 h/day, 7 days/wk, 1.9 weeks	No adverse effects on maternal weight gain or fertility; no skeletal or visceral teratogenic effects in the fetuses	6 mg/m^3	20 ppm CO, 2.7 ppm NO_2, and 2.1 ppm SO_2	Werchowski, Chaffee,Briggs 1980a; Pepelko and Peirano 1983
Sprague-Dawley Rat (Female)	8 h/day, 7 days/wk, 1.7 weeks	No signs of maternal toxicity or decreased fertility; no skeletal or visceral teratogenic effects in 20-day-old fetuses	6 mg/m^3	20 ppm CO, 2.7 ppm NO_2, and 2.1 ppm SO_2	Werchowski, Chaffee,Briggs 1980a; Pepelko and Peirano 1983
II. CANCER STUDIES					

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
1. HUMAN					
Human: U.S. highway maintenance workers (54)	Occupational	Lung cancer relative risk (RR) of 0.69	Exposure assessment via employment department records	Cohort mortality study; Smoking not controlled	Bender, Parker, Johnson et al. 1989
Volunteers in the American Cancer Society's Prospective Mortality Study of Cancer in 1982 (46,981 M: 40 to 79 years old)	Chronic	•Lung cancer relative risk was 1.18 for exposed population, 1.59 for railroad workers, and 1.24 for truckers •Total mortality elevated for railroad workers, heavy equipment operators, miners, and truck drivers and lung cancer mortality elevated for miners and heavy equipment operators (both statistically significant) •Relative risks of cancers other than lung are: stomach = 0.9; colon = 1.0; rectal = 1.0; liver = 1.1; pancreatic = 1.4; prostate = 0.9; kidney = 1.2; bladder = 1.0; brain = 0.9; leukemia = 1.3; lymphoma = 0.9; and malignant melanoma = 1.7.	•Exposure assessment via questionnaire •Self-reported occupations were coded into 70 job categories •Employment in high diesel exhaust exposure jobs were compared with nonexposed jobs	•Cohort Mortality study •Exposure information based on self-reported occupation for which no validation was done •Volunteer population, probably healthy population •First 2-year follow-up	Boffetta , Stellman, and Garfinkel 1988
Human: U.S. hospital-based population (489)	Occupational	Lung cancer relative risk of 1.21 for self-reported exposed population and of 2.39 for self-reported exposed population with 31 yrs of exposure	Exposure assessment via interviews	Case-control incidence; smoking controlled for in study	Boffetta, Harris, and Wynder 1990

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
Human: 15 mechanics, 23 truck drivers	Occupational	Bladder cancer RR of 1.2 for mechanics and of 2.7 for truck drivers (high-grade vs. low-grade tumors); Bladder cancer RR of 2.4 for mechanics and of 0.8 for truck drivers (late-stage vs. early stage tumors)	Not stated	Case-control study	Brooks, Geller, Chang et al. 1992
Human: U.S. population (118 mechanics, 35 railroad workers; 166 truck drivers)	Occupational	Lung cancer relative risk of 1.72 for mechanics; RR of 1.37 for railroad workers; and RR of 2.31 for truck drivers	Exposure assessment via interviews with individual or proxy	Case-control incidence study; smoking controlled	Burns and Swanson 1991
Human: General Population (87)	Occupation	Bladder cancer RR for any exposure to diesel was 1.0 and for high exposure to diesel was 1.7	Not stated	Case-control study	Coggin, Pannett, and Acheson 1984
Human: Hospital-based Worker (66)	Occupational	Lung cancer relative risk of 0.92 for truck, bus, taxi drivers; RR of 0.97 for railroad workers	Exposure assessed questionnaire	Case-control mortality; Smoking controlled	Decoufle, Stanislawczyk, Houten et al. 1977

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
Male Bus Garage Employees (694 Males)	Chronic	No statistically significant differences were observed between observed and expected for any cancers by different exposure groups	•High exposure: bus garage workers •Intermediate exposure: bus drivers •Low exposure: clerks	•Small sample size •No validation of exposure •No data on confounders •Follow-up from 1951 through 1983 •Mortality of these men were compared with mortality of general population of Sweden	Edling, Anjou, Axelson et al. 1987
Human: U.S. Railroad workers (335≤64 yr; 480 ≥ 65 yr))	Occupational	Lung cancer relative risk of 1.41for workers ≤64 yrs-old and 20+ yrs work; RR of 0.91 for workers ≥ 65 yrs and 20+ yrs work experience	Exposure assessment via job record and particle level measurements	Case-control mortality study; smoking controlled	Garshick, Schenker, Muñoz et al. 1987
White Railroad Workers (55,407 M:40 to 64 yrs in 1959)	Chronic	Lung cancer RR of 1.45 (40 - 44 yrs); RR of 1.33 (45 - 49yrs), both were statistically significant •Excluding workers exposed to asbestos, RR were 1.57 (40 - 44 yrs) and 1.34 (45 -49 yrs), both were statistically significant •Dose response indicated by increasing lung cancer risk with increasing cumulative exposure	Industrial hygiene data correlated with job titles to dichotomize the jobs as "exposed" or "not exposed"	•Years of exposure used as surrogate for dose •Not possible to separate the effect of time since first exposure and duration of exposure •Workers started work 10-20 yrs earlier than 1959	Garshick, Schenker, Moñoz et al. 1988
Human: U.S. hospital-based population (45)	Occupational	Lung cancer relative risk of 1.4	Exposure assessment via interviews	Case-control incidence; Smoking controlled	Hall and Wynder 1984

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
Human: U.S. hospital-based population (112 truckers and 18 mechanics)	Occupational	Lung cancer relative risk of 1.5 truckers and of 2.1 for mechanics	Exposure assessment via interviews	Case-control incidence; smoking controlled for in study	Hayes, Thomas, Silverman et al. 1989
Human 35 truck drivers, 40 related to truck driving	Occupational	Bladder cancer RR of 1.5 for truck driver; of 1.5 for diesel exposure in truck-driving job; and of 1.8 for diesel fuel or engine exposure	Not stated	Case-control study	Hoar and Hoover 1985
Human 9 Railroad workers and 11others	Occupational	Bladder cancer RR of 9.0 for railroad workers and of 2.8 for other exposed to diesel and traffic "fumes"	Not stated	Case-control study	Howe, Burch, Miller et al. 1980

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
Pensioners of the Canadian National Railway Company (48,826 M)	Occupational	•Lung cancer relative risk (RR) of 1.2 ($p = 0.013$) and 1.3 ($p = 0.001$) for possible and probable exposure, respectively •A highly significant dose-response relationship demonstrated by trend test ($p < 0.001$) •Relative risks of cancers other than lung are: stomach = 0.9; colorectal = 1.0; kidney = 1.3; bladder = 1.0; brain = 1.1; leukemia = 0.8; and lymphatic = 1.1.	Possibly and probably exposed (exposure assessment via job held at retirement)	•Incomplete exposure assessment due to lack of lifetime occupational history •Mixed exposures due to coal dust and diesel exhaust •No validation of method was used to categorize exposure •No data on smoking •No latency analysis •Mortality between 1965 and 1977 among these pensioners was compared with mortality of general Canadian population	Howe, Fraser, Lindsay et al. 1983
Human	Chronic (diesel exhaust)	IARC categorized diesel as probably carcinogenic to humans, Group 2A, based on sufficient evidence in animals (whole and extracts of diesel), and on limited evidence in humans.	Not stated.		IARC 1989
Human 20 Truck or railway drivers	Occupational	Bladder cancer relative risk of 4.3	Not stated	Case-control study	Iscovich, Castelletto, Esteve et al. 1987

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
Human: 42 Bus, taxi, or truck drivers	Occupational	Bladder cancer relative risk of 1.3	Not stated	Case-control study	Jensen, Wahrendorf, Knudsen et al. 1987
Human: Railroad workers (154 total; 49 most exposed)	Occupational	Total cohort: 0.80 relative risk; 0.88 most exposed	Exposure assessment: Job records	Cohort mortality study; Smoking not controlled	Kaplan 1959
Human: U.S. Mechanics (7)	Occupational	Lung cancer relative risk of 0.6 for mechanics (5) and for total exposed (7)	Exposure assessment via interviews	Case-control incidence study	Lerchen, Wiggins, and Samet 1987
Human: U.S. Teamsters Union Workers (34)	Occupational	Lung cancer relative risk ratio of 1.21	Exposure assessment via union records	Cohort mortality	Leupker and Smith 1978
Human: LA County Truckers	Occupational exposure	Lung cancer relative risk = 1.65	109 cases or deaths	Cohort mortality study: exposure assessed from death certificates; hospital records	Menck and Henderson 1976
Human: U.S. Truckers	Occupational	Lung cancer relative risk of 1.6	Exposure assessment via death certificates	Case-control mortality study	Milne, Sandler, Everson et al. 1983
Human	Chronic (not stated)	Relative potency of respiratory cancer (coke oven emissions = 1.0) was 0.075, which was highly correlated to mouse skin tumor data and human lung cancer risks	Not stated	Data were fitted to a linear regression	Nesnow 1990

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
Human: Railway workers, mechanics, and other	Occupational	Bladder cancer risk ration of 1.2 for railway workers; of 1.0 for mechanics; and of 1.7 for those exposed to diesel or traffic "fumes"	Not stated	Case-control study	Risch, Burch, Miller et al. 1988
Human: U.S. Railroad workers (2,519 total)	Occupational	•Lung cancer relative risk of 1.4 •Relative risks of cancers other than lung are: stomach = 0.7; colorectal = 0.9; kidney = 1.7; bladder = 0.8; brain = 1.3; leukemia = 1.5; and lymphatic = 1.0.	Exposure assessment via job records	Cohort mortality; Smoking not controlled	Schenker, Smith, Muñoz et al. 1984
Human: Canadian hospital-based population (81 cases)	Occupational	•Lung cancer relative risk of 1.2 •Relative risks of cancers other than lung were: esophagus = 0.6; stomach = 0.9; colon = 1.3; rectosigmoid = 1.1; rectal = 1.1; pancreatic = 0.6; prostate = 1.2; kidney = 0.9; bladder = 1.0; malignant melanoma - 1.1; non-Hodgkin's lymphoma = 0.7.	Exposure assessment via interviews and job/exposure matrix	Case-control incidence	Siemeatycki, Gerin, Stewart et al. 1988
Human: 96 Vehicle operators	Occupational	Bladder cancer relative risk of 2.1 for truck drivers, 1.8 for deliverymen, and 11.9 for operators of vehicles with diesel engines	Not stated	Case-control study	Silverman, Hoover, Albert et al. 1983

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
Human (Caucasian M, 1909 cases, 3569 controls)	• Variable past occupational exposure	• Males employed as truck drivers or delivery men have a statistically significant (50%) increase in risk of bladder cancer; risk ratio of 1.5. • Significant trend in increased risk with duration of truck driving. • Risk elevation also suggested for taxicab and bus drivers; bladder cancer risk ratio of 6.3 for taxi drivers or chauffeurs and 1.5 for bus drivers.	• Unknown	• Stratified for other risk factors such as smoking. • Assumed diesel exhaust exposure specifically.	Silverman, Hoover, Mason et al. 1986
Human: Auto or truck mechanics	Occupational	Bladder cancer relative risk of 1.2 for mechanics (smokers) and of 1.3 for mechanics (nonsmokers)	Not stated	Case-control study	Smith, Miller, Woolson et al. 1985
Human: 6 Truck drivers and 22 railroad workers	Occupational ($\geq$ 20 hrs)	Bladder cancer relative risk of 12.0 for truck drivers and of 2.2 for railroad workers	Not stated	Case-control study	Steenland, Burnett, and Osorio 1987
Human: U.S. Teamster Union Workers (730 truckers, 50 mechanics)	Occupational	Lung cancer relative risk of 1.27 for long-haul truckers; RR of 1.31 for short-haul truckers; and RR of 1.69 for mechancis	Exposure assessment via union record, next-of-kin interviews, and particle level measurements	Case-control mortality; smokingcontrolled for in study	Steenland, Silverman, and Hornung 1990
Human: 16 truck drivers	Occupational ($\geq$ 6 mos)	Bladder cancer relative risk 1.3	Not stated	Case-control study	Vineis and Magnani 1985

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
Human: (31 Potash Miners)	Occupational exposure	No lung cancer relative risk reported	Diesel use in mines	Cohort mortality	Waxweiler, Wagoner, and Archer 1973
Human: US Cancer Survey of Truckers (22)	Occuptationl	Lung cancer relative risk ratio of 1.52	Exposure assessed by interviews	Case-control incidence study; Smoking controlled	Williams, Stegens, and Goldsmith 1977
Human: Heavy Construction Equipment Operators (34, 156 M)	Occupational	•SMR[7] = 166 ($p < 0.05$) for liver cancer for total cohort •SMR = 343 (observed = 5, $p < 0.05$) for lung cancer for high exposure bulldozer operators with 15 - 19 years of membership, 20+ years of follow-up •SMR = 119 (observed = 141, $p < 0.01$) for workers with no work histories •Lung cancer relative risk of 0.98 for total population and 1.07 for workers with 20+ years in the union •Relative risks of cancers other than lung are: stomach = 1.2; colon = 0.9; rectal = 0.5; liver = 1.7; pancreatic = 1.0; prostate = 0.9; kidney = 0.7; bladder = 1.2; leukemia = 0.8; and lymphatic = 0.9.	High, low, and unknown exposure groups; exposure assessment via job title from union records	Cohort mortality study Weaknesses included: no validation of exposure categories, which were based on surrogate information; incomplete employment records; employment history other than from the union not available; no data on confounders; smoking not controlled; members of the local union for at least 1 year between January 1 1964 and December 1 1978	Wong, Morgan, Kheifets et al. 1985

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
Human General population exposed to diesel	Occupational	Bladder cancer relative risk of 0.9 for those exposed to more than minimal diesel exhaust exposure; of 0.8 for warehousemen (n=2); of 0.9 for bus or truck drivers (n=10); of 2.0 for railroad workers (n=2); and of 0.8 for heavy equipment operators or mechanics (n=2)	Not stated	Case-control study	Wynder, Dieck, Hall et al. 1985
2. ANIMAL					
F344 Rat (143-144 M + F per group)	16 hrs/day, 5 days/wk, up to 24 mo (+ 6 mos of clean air)	•9.7% tumor incidence (statistically significant, $p<0.05$) •38.5% tumor incidence (statistically significant, $p<0.05$)	•2.2 mg/m^3 •6.6 mg/m^3	•Whole exhaust from 1.5-L Volkswagon engine	Brightwell, Fouillet, Cassano-Zoppi, et al. 1989.
Golden Syrian Hamster (102 M, 102 F)	16 hrs/day, 5 days/wk, 24 mos	No difference in tumor incidence among control and exposed groups (no numbers given)	6.6 mg/m^3	Whole exhaust from 1.6 L Volkswageon diesel engine	Brightwell, Fouillet, Cassano-Zoppi, et al. 1989.
Syrian Golden Hamster	19 hrs/day, 5 days/wk, for 6, 10.5, 15, or 18 mos.	•Focal metaplasia and dysplasia of the respiratory epithelium seen in the oldest animals •Increased tumor rate in upper respiratory tract of males exposed to total diesel exhaust and single s.c. injection of 6 mg/kg diethylnitrosamine	Dose not stated	Total exhaust Filtered exhaust	Heinrich, Mohr, Fuhst, et al. 1990.

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
NMRI Mouse (80 F/group)	18 hrs/day, 5 days/wk, for 13.5 mos (+ 9.5 mos clean air)	Tumor incidence of 32.1%	7.0 mg/m^3	1.6-L Volkswagon	Heinrich et al. 1995 as cited in HEI 1995
Wistar Rats (100-200 F/group)	18 hrs/day, 5 days/wk, for 24 mos	Tumor incidence of 6% and 22%, resp.	2.5 and 7.0 mg/m^3	1.6-L Volkswagon	Heinrich et al. 1995 as cited in HEI 1995
Wistar Rat (96 Females)	19 hrs/day, 5 days/wk, up to 32 mo	15.8% tumor incidence (statistically significant, $p<0.05$)	4.2 mg/m^3	Whole exhaust from 1.6-L Volkswagon engine	Heinrich, Muhle, Takenaka et al. 1986; Heinrich, Pott, Rittinghausen 1986
Syrian Golden Hamster (96 M+F)	19 hrs/day, 5 days/wk, up to 28 mo	No difference in tumor incidence among controls and exposed group	4.2 mg/m^3	Whole exhaust from 1.6-L engine	Heinrich, Muhle, Takenaka et al. 1986; Heinrich, Pott, Rittinghausen 1986
NMRI Mouse (96 F/group)	19 hrs/day, 5 days/wk, up to 26 mos	•Significant increase in number of animals with lung tumors; 32% tumor incidence in exposed group •Significant increase in number of animals with adenocarcinomas •No increase in number of animals with adenomas	4.24 mg/m^3 particles; Controls received clean air (Exhaust diluted with air: 1:17)	Unfiltered or filtered exhaust from 1.6-L Volkswagon engine (US-72 test cycle) engine Controls were exposed to filtered exhaust	Heinrich, Muhle, Takenaka et al. 1986; Heinrich, Pott, and Rittinghausen 1986

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
Wistar Rat (96F/group)	19 hrs/day, 5 days/wk for life	•Significant increased incidence of lung tumors in animals exposed to unfiltered exhaust (17/95 and 0/96 in controls) •No lung tumors in rats exposed to filtered exhaust	Exhaust diluted with air: 1:17 and contained 4.24 mg/m^3 particles; Controls received clean air	Unfiltered or filtered exhaust from 1.6-L engine (US-72 test cycle) •Decreased body weight in rats exposed to unfiltered vs. filtered exhaust	Heinrich, Muhle, Takenaka et al. 1986a
Syrian golden Hamster (48M, 48F)	19 hrs/day, 5 days/wk for life	•Median lifespan was 72-74 weeks in all groups •No lung tumors reported	Exhaust diluted with air: 1:17 and contained 4.24 mg/m^3 particles; Controls: clean air	Unfiltered or filtered exhaust from 1.6-L engine (US-72 test cycle)	Heinrich, Muhle, Takenaka et al. 1986a
Syrian golden Hamster (48F/group)	7-8 hrs/day, 5 days/wk, for life	•No effect on survival; median lifespan was 72-74 weeks in all groups •No lung tumors reported	Unfiltered diluted (1:7) 3.9±0.5 mg/m^3 (0.1 µm) Controls: clean air	2.4-L displacement engine operating at steady-state	Heinrich, Peters, Funcke et al. 1982.
Animals	Chronic (diesel exhaust)	IARC categorized diesel as probably carcinogenic to humans, Group 2A, based on sufficient evidence in animals (whole and extracts of diesel), and on limited evidence in humans.	Not stated.		IARC 1989.
F344 Rat (5-13, Non-specified)	16 hrs/day, 6 days/wk, up to 12 mos	0% tumor incidence	0.1 - 1.8 mg/m^3	Whole exhaust	Ishinishi, Kuwabara, Takaki et al. 1988

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
F344 Rat (123-124 Males and Females/group)	16 hrs/day, 6 days/wk, up to 30 mos (0, 0.5, 1.0, 1.8, and 3.7 mg/m^3)	6.5% tumor incidence (statistically significant, $p<0.05$)	3.7 mg/m^3	Whole exhaust from 11-L engine	Ishinishi , Kuwabara, Takaki et al. 1988
Fischer 344 Rat (64M, 59F; specific-pathogen-free)	16 hrs/day, 6 days/wk, for 30 months	•No statistically significant increase in lung tumor incidence in rats exposed to light-duty exhaust •Incidence of lung tumor in 3.72 mg/m^3 dose group (5/64M, 3/60F) exposed to heavy-duty exhaust was statistically significant	0.11, 0.41, 1.08, or 2.32 mg/m^3 particle conc; 0.46, 0.96, 1.84, or 3.72 mg/m^3 particle conc.	Exhaust from 1.8-L displacement, 4-cyl engine (light-duty); Exhaust from 11-L displacement 6-cyl engine (heavy-duty)	Ishinishi, Kuwabara, Nagase et al. 1986
F344 Rat (22, 19 F/group)	8 hrs/day, 7 days/wk, up to 24 mo	42.1% tumor incidence (statistically significant, $p<0.05$)	4.9 mg/m^3	Whole exhaust from a 2.4-L truck	Iwai, Udagawa, Yamagishi et al. 1986
Fischer Rat (24F/group specific-pathogen-free)	8 hrs/day, 7 days/wk, for 24 months (some killed at 24 months; some exposed to clean air for 6 mo)	•Incidences of lung tumors significantly higher in group exposed to whole diesel exhaust, with or without 6-mo clean air post-exposure (8/19 rats) •No lung tumors reported in rats exposed to filtered diesel exhaust •Incidences of malignant lymphomas and tumors at other sites did not differ among groups.	Exhaust diluted 10:1 with clean air to 4.9±1.6 mg/m^3 particles; Clean air (controls for 30 mo)	Unfiltered and filtered diluted exhaust from 2.4-L displacment small truck engine.	Iwai, Udagawa, Yamagishi et al. 1986

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
F344 Rat 30 Males	20 hrs/day, 7 days/wk, 15 mo	3.3 - 10.0% Bronchoalveolar carcinomas Incidence	0.25 - 1.5 mg/m^3	Whole exhaust	Kaplan, Springer, and MacKenzie 1983, White, Vostal, Kaplan et al. 1983
A/J Mouse 388-396 Males	20 hrs/day, 7 days/wk, 8 mo	25.0 - 33.8% Pulmonary Adenomena Incidence	0.25 - 1.5 mg/m^3	Whole exhaust	Kaplan, Springer, and MacKenzie 1983, White, Vostal, Kaplan et al. 1983
A/J Mouse 485 Males	20 hrs/day, 7 days/wk, 3 mo	34.2% Pulmonary Adenomena Incidence	1.5 mg/m^3	Whole exhaust	Kaplan, MacKenzie, Springer et al. 1982
Wistar Rat 40 Males	6 hrs/day, 5 days/wk, 20 mo	16.6% adenoma incidence	8.3 mg/m^3	Whole exhaust	Karagianes, Palmer, Busch 1981
Wistar Rat (M specific-pathogen-free; # not stated)	6 hrs/day for 20 months (6/group sacrificed at 4, 8, 16, and 20 mo)	•Significant non-neoplastic lesions in respiratory tract, increasing in severity with exposure duration •2 bronchiolar adenomas observed after 20 months: 1from diesel exhaust only and 1 from diesel exhaust and coal dust	8.3±2.0 mg/m^3 soot from diesel; 8.3±2.0 mg/m^3 soot from diesel and 5.8±3.5 mg/m^3 coal dust; 6.6±1.9 mg/m^3 coal dust; 14.9±6.2 mg/m^3 coal dust; Clean air (controls).	3-cyl, 43-brake HP diesel engine driving a 15 kW electric generator with a modified fuel-injection system simulating engines in mines (dilution of ~35:1).	Karagianes, Palmer, Busch 1981
F344 Rat 288 Males and Females	7 hrs/day, 5 days/wk, up to 24 mo	0 % tumor incidence	2.0 mg/m^3	Whole exhaust	Lewis, Green, Moorman et al. 1986

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
Fischer 344 Rat (72M, 72F)	7 hrs/day, 5 days/wk, for 24 months (10M/group removed at 3, 6, 12, and 24 mo for ancillary studies)	•No difference in survival •No difference in tumor incidence (NOTE: Data on survival was unavailable as was data on tumor incidence)	2 mg/m^3 coal dust; 2 mg/m^3 diesel particles; 1 mg/m^3 diesel part and 1 mg/m^3 coal dust; Clean air (controls)	Exhaust generated by 7-1 displacement, 4-cyl, water-cooled open-chamber engine; Exhaust diluted 27:1 before exposures	Lewis, Green, Moorman et al. 1986.
Monkey (Cynomolgus) (15M/group)	7 hrs/day, 5 days/wk, for 24 months	•No significant difference in tumor incidence in groups (NOTE: Inadequate reporting of study noted by IARC working group)	2 mg/m^3 coal dust; 2 mg/m^3 diesel particles; 1 mg/m^3 diesel part and 1 mg/m^3 coal dust; Clean air (controls)	Exhaust generated by 7-1 displacement, 4-cyl, water-cooled open-chamber engine; Exhaust diluted 27:1 before exposures	Lewis, Green, Moorman et al. 1986.
F344 Rat •221 M+F •227 M+F	7 hrs/day, 5 days/wk, up to 30 mo	•3.6% tumor incidence •12.8% tumor incidence (statistically significant, $p<0.05$)	•3.5 mg/m^3 •7.1 mg/m^3	•Whole exhaust •Whole exhaust (from 5.7-L engine)	Mauderly et al. 1987
Fischer 344 Rat (221-230 M and F specific-pathogen-free)	7 hrs/day, 5 days/wk for 30 months (subgroups at 6, 12, 18, and 24 mo removed for ancillary studies)	•Survival not significantly affected •4 tumor types found (81% after 2 years): bronchoalveolar adenomas, adenocarcinomas, squamous cysts, and squamous-cell carcinomas. None metastasized to other organs •Prevalences at 3.5 and 7.0 mg/m^3 dose groups were significantly increased ($p<0.05$)	Unfiltered diluted conc: 0.35 mg/m^3; 3.5 mg/m^3; 7.0 mg/m^3	Exhaust from 1980 5.7-L V8 engine operated via US FTP cycles	Mauderly, Jones, McClellan et al. 1986; Mauderly, Jones, Griffith et al. 1987.

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
F344 Rat (105-109 M, F per group)	16 hrs/day, 5 days/wk, for 24 mos	•2.5 % and 7.6% tumor incidence in M and F, resp. •8.5 % and 27.4 % tumor incidence in M and F, resp.	•2.5 mg/m^3 •6.5 mg/m^3	6.2-L GM engine. Carbon black may play significant role in tumor formation	Mauderly, Snipes, Barr et al. 1994; Nikula, Snipes, Barr et al. 1995
Jackson A Mouse •60 F •430 M	20 hrs/day, 7 days/wk, 7 mo	•25.0 - 37.3% Lung Tumor Incidence (0.32 - 0.39 Tumors/Mouse) •17.9% Lung Tumor Incidence (0.20 Tumors/Mouse)	•6.4 mg/m^3 •6.4 mg/m^3	•Whole exhaust •Whole exhaust	Orthoefer et al. 1981, Pepelko and Peirano 1983
Strong A Mouse 25 Males	20 hrs/day, 7 days/wk, 7 weeks	27.3 - 36.8% Lung Tumor Incidence (0.27 - 0.63 Tumors/Mouse)	6.4 mg/m^3	Whole exhaust	Orthoefer et al. 1981, Pepelko and Peirano 1983
Jackson A Mouse 40 M + F	20 hrs/day, 7 days/wk, 8 weeks	32.3% Lung Tumor Incidence (0.4 Tumors/Mouse)	6.4 mg/m^3	Whole exhaust	Orthoefer et al. 1981, Pepelko and Peirano 1983
Strain A Mouse 90 Males and Females	Continuous for 15 mo	0.95 - 12.5 % tumor incidence (0.10 -0.95 Tumors/Mouse)	12 mg/m^3	Whole exhaust	Pepelko and Peirano, 1983
Sencar Mouse (101 Males and 104 Females)	8 hrs/day, 7 days/wk, for 15 mos	5.9% (M) and 16.3% (F) tumor incidence	6 mg/m^3 (wks 1-12); 12 mg/m^3 (wks 12-15mos)	Whole exhaust	Pepelko and Peirano, 1983
Wistar Rat 123-124 Males and Females	16 hrs/day, 6 days/wk, up to 30 mo	2.4 - 4.1% tumor incidence	0.1 - 2.3 mg/m^3	Whole exhaust	Takaki et al. 1988

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
IRC Mouse 56 Males and Females	4 hrs/day, 4 days/wk, 13 to 28 mo	8.7% adenoma incidence and 4.3% carcinoma incidence; 25% tumor incidence	2-4 mg/m^3	Whole exhaust from 269 cc Yanmar engine	Takemoto et al. 1986
F344 Rat 18 Females	4 hrs/day, 4 days/wk, 18 to 24 mo	66.7% adenoma incidence and 38.9% carcinoma incidence	2-4 mg/m^3	Whole exhaust	Takemoto et al. 1986
F344 Rat 38 Males and Females	4 hrs/day, 4 days/wk, 18 to 24 mo	21.1% adenoma incidence and 7.9% carcinoma incidence	2-4 mg/m^3	Whole exhaust	Takemoto et al. 1986
Fischer Rat (26F specific-pathogen-free)	4 hrs/day, 5 days/wk, for 24 months	•No lung tumor in the 26 exposed or 20 control animals •15 exposed and 12 control animals survived beyond 18 mo.	Exhaust diluted 1:2 to 1:4 in air to 2-4 mg/m^3 particles (0.32 µm size) Control s received clean air	Small diesel engine (269 cm^3 displacement, idling speed)	Takemoto, Yoshimura, Katayama 1986
C57Bl/6N Mouse (297 alive at 3 mo., initial # and sex not stated)	4 hrs/day, 4 days/wk, at least 28 months (exposed within 24 hrs after birth)	•Lung tumors found in 17/150 (11%) exposed mice vs. 1/51 (2%) control mice (not statistically significant)	2-4 mg/m^3 particles Controls received clean air	Small diesel engine (269 cm^3 displacement, idling speed) Exhaust diluted 1:2 to 1:4 in air (0.32 µm size)	Takemoto, Yoshimura, Katayama 1986.
ICR Mouse (315 alive at 3 mo., initial # and sex not stated)	4 hrs/day, 4 days/wk, at least 28 months	•Lung tumors (adenomas and adenocarcinomas) found in 14/56 exposed mice vs. 7/60 control (not statistically significant)	Exhaust diluted 1:2 to 1:4 in air to 2-4 mg/m^3 particles (0.32 µm size); Control s received clean air	Small diesel engine (169 cm^3 displacement, idling speed)	Takemoto, Yoshimura, Katayama 1986, IARC 1989.
III. MUTAGENICITY/GENOTOXICITY					

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
1. HUMAN					
a. In Vivo					
Human (8 Nonsmokers)					Rudell, Sandstrom, Stjernberg, et al. 1990.
2. ANIMAL					
a. In Vivo					
Fischer 344 Rat	3 to 24 months (exp. frequency not stated)	•Urine not mutagenic to *Salmonella typhimurium*	1.9 mg/m^3		Green, Boyd, Danner-Rabovsky et al. 1983; Ong, Whong, Xu et al. 1985.
Syrian Hamster	3.5 months	•Increased incidence of SCE[1] in lung cells	12 mg/m^3 particles	Whole diesel exhaust	Guerrero, Rounds, Orthoefer 1981.
ICR Mouse	Up to 18 months	•No increase in frequency of micronuclei in bone marrow	0.4 and 2.0 mg/m^3	Mice exposed to whole exhaust of light-duty engine	Morimoto, Kitamura, Kondo et al. 1986.
Rat	Up to 30 months	•No increase in frequency of SCE[1] in bone-marrow cells	4 mg/kg whole emissions	•Rats exposed to emissions from light- or heavy-duty engines	Morimoto, Kitamura, Kondo et al. 1986.
Fischer 344 Rat	3 months	•No increase in frequency of SCE[2] in peripheral lymphocytes	1.9 mg/m^3 particles	•Rats exposed to whole diesel exhaust	Ong, Whong, Xu et al. 1985.
Fischer 344 Rat	2 years	•No increase in frequency of micronuclei in bone marrow	1.9 mg/m^3	Whole emission	Ong, Whong, Xu et al. 1985.

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
Swiss-Webster CD-1 Mouse	6 months	•No increase in frequency of micronuclei in bone marrow	1.9 mg/m^3	Whole emission	Ong, Whong, Xu et al. 1985.
•T-stock Mouse (M) •(101XC3H)F_1 Mouse (F)	•3 hr/day, 7 days/wk, for 7.5 wks •3 hr/day, 7 days/wk, for 7 wks	•No increase in incidence of lethal mutations when treated M mice mated to untreated F; •No increase in frequency of heritable point mutations after mating; no oocyte killing in (SECXC57B1)F_1 female mice after 8 wks prior to mating	6 mg/m^3	Diesel particles	Pepelko and Peirano 1983.
Syrian Hamster	From gestation Day 1 to 12	•No increase in frequency of SCE[3] in fetal liver (determined on Day 13)	12 mg/m^3	Pregnant hamsters exposed to whole diesel emissions	Pereira 1982
B6C3F1 Mouse	1 month	•No increase in frequency of SCE[8] in bone-marrow cells	12 mg/m^3	Whole diesel exhaust emission	Pereira 1982.
Swiss Mouse (F)	8 hr/day, 5 days/wk, 7 wks	•Urine not mutagenic to *Salmonella typhimurium*	6-7 mg/m^3	Whole diesel exhaust diluted 1:18	Pereira, Connor, Meyne et al. 1981c.
Chinese Hamster	•1-6 months •1 month	•Increase in frequency of micronuclei in bone marrow at 6 months •No increase in frequency of micronuclei in bone marrow	•6 mg/m^3 particles •12 mg/m^3 particles (1mo.)	Exhaust emissions	Pereira, Sabharwal, Kaur et al. 1981b; Pereira, Connor, Meyne et al. 1981c; Pereira 1982; Pepelko and Peirano 1983.

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
B6C3F1 Swiss Mouse	•1-6 months •1 month	No increase in frequency of micronuclei in bone marrow	•6 mg/m^3 particles •12 mg/m^3 particles (1mo.)	Exhaust emissions	Pereira, Sabharwal, Kaur et al. 1981b; Pereira, Connor, Meyne 1981c, Pereira 1982, or Pepelko and Peirano 1983.
IV. METABOLISM					
A. HUMAN					
B. ANIMAL					
Rat • nasal tissue • perfused lungs	• Nasal tissue exposed 10 min to 1-nitropyrene • Lung 90 min exposure • Diesel pretreatment: 4 weeks; 5 days/wk; 7 hr/day	• Nasal tissue: diesel exposure caused 2-fold increase of metabolites found after 1-nitropyrene exposure. • Lung tissue: diesel exhaust particles caused 2 fold increase of nitropyrene metabolism. • Major metabolites found in both tissue 3-,6- and 8-hydroxy-1-nitropyrene; 4,5-dihydro-4,5-dihydroxy-1-nitropyrene.	• Nasal tissue 20 uM [^{14}C] 1-nitropyrene • Perfused lung 25 uM	• LOAL of diesel particles= 7400 particles/m^3 • Prior exposure to diesel particles.	Bond, Mauderly, Henderson et al. 1985
Fischer 344/Crl Rat	4 wks	•Metabolism of 1-nitropyrene in nasal tissue and perfused lung increased by 2 •Amount of ^{14}C covalently bound to lung macromolecules increased by 4	7.4 mg/m^3		Bond, Mauderly, Henderson et al. 1985

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
F344/N-Rat (M)	7 hrs/day, 5 days/wk, 12 wks	•Unique DNA adduct patterns in each of the respiratory tract regions. •Highest levels of DNA adducts and exhaust induced adducts were in the peripheral lung	10 mg/m^3 particles	Diluted diesel exhaust (Rats exposed to filtered air also.)	Bond, Wolff, Harkema, et al. 1988.
Wistar Rat (F)	18 hrs/daily for 2 or 6 mos, or 2 years	•Particulate burden of 63.9 mg per lung for 2-yr exposure •Incidence of lung tumors was 22% for 2-yr exposure •Two DNA adducts detected: Adduct I increased significantly over exposure time vs. controls; Adduct II did not increase with exposure time.	7.5 mg/m^3	Diesel particles contained 33.9% extractable organic matter	Gallagher, Heinrich, George, et al. 1994
F344/N-Rat B6C3F1-Mouse	7 hrs/day, 5 days/wk, for up to 17 days	Significant increases in lung lavage fluid and greater amounts of arachidonic-acid metabolites in rats than mice. Increased lung fibrosis in rats relative to mice.	3.5 mg/m^3	Diluted diesel	Henderson, Leung, Harnsen and McClellan 1988.
V. PHARMACOKINETICS					
A. HUMAN					
B. ANIMAL					

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
Sprague-Dawley Rat	4-6 hrs/day, 7 days/wk, 0.1-14.3 weeks	Impairment of tracheal mucociliary clearance in a concentration-response manner	0.9, 8.0, and 17.0 mg/m^3	(Varying levels of NO_2 and SO_2)	Battigelli et al. 1966
Rat	20 hrs/day, 7 days/wk, 0.23 - 3.7 mos	Decreased alveolar clearance	6.0 mg/m^3		Chan, Lee, and Hering 1984 as cited in HEI 1995
Rat (F)	19 hrs/day, 5 days/wk, for 24 mos.	Decreased alveolar clearance	0.8, 2.5, and 7.5 mg/m^3		Creutzenberg, Bellmann, Heinrich, et al. 1990.
F-344 Rat (Male and Female)	7 hrs/day, 5 days/wk, 18 weeks	Lung burdens of DP were concentration-related; clearance half-time of DP almost double in 4.1 mg/m^3 group compared to 0.15 mg/m^3 group •Decreased alveolar clearance	•0.15, 0.94, and 4.1 mg/m^3 •4.1 mg/m^3	<0.5 µm, MMD	Griffis et al. 1983
Rat	19 hrs/day, 5 days/wk, for 3, 8, 12 or 19 mos	Decreased alveolar clearance for all exposure periods	4.2 mg/m^3		Heinrich, Muhle, Takenaka et al. 1986
Hamster	19 hrs/day, 5 days/wk, for 12 mos	No effect of clearance	4.2 mg/m^3		Heinrich, Muhle, Takenaka et al. 1986

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
F-344 Rat (Male)	7 hrs/day, 5 days/wk, 26-104 weeks	No difference in clearance of $^{59}Fe_3O_4$ particles 1 day after tracer aerosol administration; 120 days after exposure tracer aerosol clearance was enhanced; Lung burden of DP increased significantly between 12 to 24 months of exposure	2.0 mg/m^3	0.23-0.36 μm, MMD (11.5 ppm CO, 1.5 ppm NO_2, and 0.8 ppm SO_2)	Lewis et al. 1989
Rat	7 hrs/day, 5 days/wk, 6 mos	Decreased alveolar clearance	3.5 mg/m^3		Mauderly, Bice, Carpenter et al. 1987
Rat	7 hrs/day, 5 days/wk, for 24 mos	Decreased alveolar clearance	3.5 mg/m^3		Mauderly, Bice, Cheng et al. 1989
Rat	16 hrs/day, 5 days/wk, for 3 or 18 mos	Decreased alveolar clearance at 3 and 18 mos	2.5 and 6.5 mg/m^3		Mauderly, Snipes, Barr et al. 1994
Rat	7 hrs/day, 5 days/wk, 12 weeks	•Reduced clearance of tracer aerosol at 12 weeks •Indication of a lower percentage of ciliated cells at the 1.0 and 4.5 mg/m^3 levels •Evidence of apparent speeding of tracheal clearance after 1 week of ^{99m}Tc macroaggregated-albumin	•0.2, 1.0, and 4.5 mg/m^3 •1.0 and 4.5 mg/m^3 •4.5 mg/m^3	0.25 μm, MMD	Wolff and Gray 1980

Species (N)	Duration	Effect(s)/Endpoint(s)	Dose/Critical Concentration	Comments	Reference
F-344 Rat (Male and Female)	7 hrs/day, 5 days/wk, 130 weeks	No changes in tracheal mucociliary clearance after 6, 12, 18, 24, or 30 mo of exposure; increases in lung clearance half-times as early as 6 mo at 7.0 mg/m^3 level and 18 mo at 3.5 mg/m^3 level; no changes seen at 0.35 mg/m^3 level; after 24 mo of diesel exposure, long-term clearance half-times were increased in the 3.5 and 7.0 mg/m^3 level groups.	0.35, 3.5, and 7.0 mg/m^3	0.25 µm, MMD (Varying levels of CO and NO_2)	Wolff et al. 1987 Wolf, Henderson, Snipes et al. 1987
VI. IRRITATION					
A. HUMAN					
No studies found					
B. ANIMAL					
No studies found					

ENDNOTES

1. FVC = forced vital capacity; FEV_1 = force expiratory volume in 1 sec; FEF_{50} = Force expiratory flow at 50%

2. COPD = Chronic obstructive pulmonary disease

3. RR = Relative risk

4. MMD = Mean Mass Diameter

5.AHH = Aryl hydrocarbon hydroxylase

6.BUN = Blood urea nitrogen

7. SMR = Standardized Mortality Ratio

8.SCE = Sister chromatid exchange