

Toxicological and Epidemiological Evidence for Health Risks from Inhaled Engine Emissions

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Information from toxicological and epidemiological studies of the cancer and noncancer health risks from inhaled diesel engine exhaust (DE) and gasoline engine exhaust (GE) was reviewed. The toxicological database is more extensive for DE than for GE. Animal studies have shown that heavy, chronic exposures to both DE and GE can cause lung pathology and associated physiological effects. Inhaled GE has not been shown to be carcinogenic in animals. Chronically inhaled DE at high concentrations is a pulmonary carcinogen in rats, but the response is questionable in mice and negative in Syrian hamsters. The response in rats is probably not attributable to the DE soot-associated organic compounds, as previously assumed, and the usefulness of the rat data for predicting risk in humans is uncertain. Experimental human exposures to DE show that lung inflammatory and other cellular effects can occur after single exposures, and sparse data suggest that occupational exposures might affect respiratory function and symptoms. Epidemiology suggests that heavy occupational exposures to exhaust probably increase the risks for mortality from both lung cancer and noncancer pulmonary disease. The small magnitudes of the increases in these risks make the studies very sensitive to confounding factors and uncertainties of exposure; thus, it may not be possible to resolve exposure-response relationships conclusively by epidemiology. Our present knowledge suggests that heavy occupational exposures to DE and GE are hazardous but does not allow quantitative estimates of risk with a high degree of certainty. — *Environ Health Perspect* 102(Suppl 4):165–171 (1994).

Key words: automotive emissions, air pollution, diesel exhaust, epidemiology, gasoline exhaust, inhalation, inhalation toxicology, lung cancer, lung disease, rat

Introduction

This paper provides an overview of information from toxicological studies in animals and experimental and epidemiological studies in humans of the cancer and noncancer pulmonary effects of inhaling gasoline engine exhaust (GE) and diesel engine exhaust (DE). This review focuses on the effects of inhaled whole, diluted exhaust, rather than on individual exhaust constituents or reaction products. Because of the scope of this paper, published information is only summarized; original reports could be consulted for details. Recent views are noted, and information not recently reviewed is treated in more detail. The health effects of DE were recently reviewed (1,2), but there is no good recent

summary on GE. The 1989 monograph on engine exhaust by the International Agency for Research on Cancer (3) is another key information source.

Lung Cancer from Engine Exhaust

Toxicological Evidence: Gasoline Engine Exhaust

There have been few cancer bioassays of animals exposed chronically to GE, but there is little evidence that GE causes lung cancer in animals.

In 1936, Campbell (4) reported exposing groups of 75 mice, males and females, strain unspecified, 7 hr/day, 5 days/week for 750 days to exhaust from either a 1.0-L engine burning "ordinary petrol" or a 3.0-L engine burning leaded gasoline. The carbon monoxide (CO) concentration in the statically operated chambers varied from 6 to 12%. A slight, but questionably significant, increase in lung tumor incidence resulted from both exposures with a greater incidence for leaded than for unleaded GE. The microbial status of the exposed or control mouse lungs was not indicated.

In 1978, Hyde et al. (5) reported the pulmonary histopathology of dogs exposed, beginning in the mid-1960s, in the study conducted by the U.S. National Air Pollution Control Administration, often called the "Cincinnati Beagle study." Groups of 12

female Beagles were examined 32 to 36 months after the end of exposures 16 hr/day, 7 days/week for 68 months to exhaust from a 2.3-L engine burning leaded gasoline and operated on an urban cycle to produce chamber concentrations of approximately 110 ppm CO (6). Although the small group sizes preclude a good test of carcinogenicity, no lung tumors were observed in the dogs.

In 1981, Roggendorf et al. (7) reported exposing 100 Wistar rats (both sexes) 8 hr/day, 5 days/week for up to 28 months to exhaust from an idling engine that was diluted to 90 ppm CO. Inflammation, pneumonia, and emphysema of the lungs were attributed to infections in both control and exposed rats, but no lung tumors were described.

Heinrich et al. (8) exposed groups of 80 female Wistar rats and 80 Syrian hamsters 19 hr/day, 5 days/week for 24 months to exhaust from a 1.6-L engine burning leaded fuel and operated on an urban cycle to produce chamber concentrations of either 112 ppm CO (1:61 dilution) or 207 ppm CO (1:27 dilution). The particle concentrations at these dilutions were approximately 0.05 and 0.10 mg/m³, respectively. No increase in lung tumor incidence was observed.

Brightwell et al. (9) exposed groups of 144 F344 rats or 312 Syrian hamsters (males and females) 16 hr/day, 5 days/week for 24 months to exhaust from 1.6-L engines oper-

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ated on an urban cycle and burning unleaded fuel, either with or without an exhaust catalytic converter. Exhaust was diluted to 1:29 or 1:83 to produce CO concentrations of 6 to 21 ppm (catalyst) and 67 to 224 ppm (nuncatalyst). No increase in lung tumors was observed in either species.

Toxicological Evidence: Did Engine Exhaust

The extensive data from cancer bioassays of DE in rats, Syrian hamsters, and mice were reviewed recently (2), and the most recent studies, noted below, have reproduced these findings. There is clear evidence of the pulmonary carcinogenicity of DE in rats. Studies by several laboratories in four countries clearly demonstrated by the mid-1980s that repeated exposure of rats for 24 months or longer to whole, diluted DE at soot concentrations of 3.5 mg/m³ or greater increases the incidence of lung tumors. Studies by Brightwell et al. (9) and Heinrich et al. (10), using filtered and unfiltered DE, demonstrated that the carcinogenicity of DE in rats requires the presence of soot. Although few studies have been done, there is some evidence that inhalation of DE might act as a co-carcinogen by increasing the lung tumor response of rats to chemical carcinogens (1).

There is no evidence for carcinogenicity of DE in Syrian hamsters from five studies conducted in four laboratories, including three studies in which hamsters were exposed for 24 months or longer. There is mixed evidence for the carcinogenicity of DE in mice. Pepelko and Peirano (11) found increased lung tumors in female Strong A and Sencar mice exposed 8 hr/day, 7 days/week to DE at 6 to 12 mg soot/m³ for 7.5 to 15 months. These mouse strains are particularly sensitive to cancer induction. Heinrich et al. (10) found DE to be carcinogenic in female NMRI (Swiss) mice exposed 19 hr/day, 5 days/week for 28 months at 4.2 mg soot/m³; however, both filtered and unfiltered DE caused tumors in mice, unlike rats. Because of these confusing results and the fact that other studies found no lung tumor induction in mice, the carcinogenicity of DE in mice is questionable. The few studies that have been done do not suggest that DE is a co-carcinogen in mice or hamsters (1).

Several questions remain unanswered concerning the interpretation of the carcinogenicity of DE in rats and its implication for human health risk. Concern for DE carcinogenesis originated because of the mutagenic and carcinogenic organic compounds adsorbed to DE soot. Increased levels of lung-DNA adducts in exposed rats support-

ed the view that the tumors were caused by chemical carcinogenesis via DNA adduction (2). Further, unit lung cancer risks derived from the rat data are generally similar to those predicted earlier by comparing the bacterial mutagenic potency of DE soot extract to those of known human carcinogens (2). These facts led some to propose extrapolation of human unit risks for DE-induced lung cancer from the rat carcinogenesis data on the basis of the delivered dose of soot-associated organic compounds.

Other facts suggested that DE-induced lung cancer in rats might occur by mechanisms that may not be directly applicable to human risk. Statistically significant increases in lung cancer incidence have been observed only in rats exposed sufficiently to cause an overloading of particle clearance from the deep lung by macrophages, which results in a progressive sequestration of soot in the lung. This increasing lung burden of soot is accompanied by chronic inflammation, alveolar epithelial hyperplasia, and multifocal fibrosis. Slight increases in lung tumor incidence have occurred in rats exposed to lower DE concentrations that do not cause the proliferative and fibrotic changes, but the group sizes (up to approximately 200) have not allowed the significance of the smaller increases to be evaluated with confidence. It also has become apparent that the inhalation or instillation of high doses of a wide range of poorly soluble particles without mutagenic chemical compounds can cause a syndrome of particle sequestration, inflammation, cell proliferation, fibrosis, and tumors in rat lungs indistinguishable, as of yet, from that caused by DE (12,13). Further, although DE soot particles accumulate in lungs of mice and hamsters as they do in rats, those species do not characteristically respond by developing lung tumors. These facts suggested that the tumor response of rats to inhaled DE may not be very specific to the chemical nature of DE soot. It is not known whether the response of human lungs to DE might be more like that of rats or like that of mice and hamsters. The differences among species, however, suggest the possibility that tumors might occur in rats by mechanisms that might not occur in humans.

Two laboratories, the Fraunhofer Institute in Hannover, Germany, and the Inhalation Toxicology Research Institute (ITRI) in Albuquerque, New Mexico, have recently completed similar studies of the importance of the soot-associated mutagenic organic compounds in the lung tumor response of rats to DE. Both laboratories compared the pulmonary carcinogenicity in rats of DE and

carbon black (CB), which simulated DE particles without the mutagenic organic compounds. Although the studies varied in design and neither has been fully published, preliminary information indicates that the findings of the studies are consistent with their major points, and that these have important implications for interpreting the earlier carcinogenicity data (14-16).

At ITRI, groups of approximately 100 male and 100 female F344/N rats were exposed 16 hr/day, 5 days/week for 24 months to whole DE at 6.5 or 2.5 mg soot/m³, to CB at the same concentrations, or to clean air as controls. The DE was generated by 1988 model General Motors 6.2-L engines burning EPA certified fuel and operated on the FTP urban cycle. Cabot Elftex-12 CB, which has a particle size and specific surface area similar to that of DE soot, was aerosolized in an air jet mill. Approximately 8% of the soot mass consisted of solvent-extractable organic material having a bacterial mutagenic potential similar to that of DE. Only approximately 0.04% of the CB was extractable, and the extract was not mutagenic. In addition to carcinogenesis, lung burdens of particles, clearance of radiolabeled tracer particles, bronchoalveolar lavage fluid (BALF) markers of inflammation, and histopathology were evaluated serially.

The DE exposures at ITRI reproduced the findings of previous studies. In addition, exposures also caused an overloading of particle clearance; progressive accumulation of particles in the lungs; and inflammation, proliferative, and fibrotic changes. Because of differences in the particle distributions of the two materials, the lung burdens of DE soot were higher than those of CB, and the noncancer effects were greater in DE-exposed rats. At similar particle exposure levels, DE and CB caused nearly identical prevalences of benign and benign lung tumors among rats sacrificed for observation during the study. The types of tumors caused by DE and CB were the same as those observed in previous studies. Because the lung burdens of CB were lower than those of DE soot, the response to DE per unit of accumulated particle lung burden.

The results of the recent DE and CB studies suggest that the soot-associated mutagenic organic compounds are not important in the induction of DE-induced lung cancer in rats. These results suggest that extrapolation to human risks derived from the rat studies

basis of the delivered dose of soot-associated organic material is not warranted. Follow-up research is examining the role of lung DNA adduction in the tumor response, the relationship between epithelial proliferation and tumor formation, and whether or not differences exist at the gene level between the DE- and CB-induced tumors. Of course, it is possible that soot-associated organic compounds or their metabolites might affect organs other than the lung. There is epidemiological evidence suggesting a slight increase in risk for bladder cancer among workers with heavy occupational exposures to DE, but there is little toxicological evidence for effects of inhaled DE in organs other than the lung (2).

Epidemiological Evidence: Gasoline and Diesel Exhaust

The epidemiological evidence for human lung cancer from exposures to engine exhaust is taken from a recent review (2) of 30 published studies. The 15 cohort studies, 14 case-control studies, and one combined analysis of 12 studies focused on DE exposures, but many of the occupations also involved substantial exposures to GE. Importantly, no study to date has included actual measurements of the exposures of the subjects studied. Two studies estimated previous exposures from measurements in contemporary workplaces, and three questioned the subject or immediate family directly about DE exposure. Exposure classification in other studies was based on job history, general occupation, or union membership.

Fourteen retrospective and one prospective cohort study were reported between 1957 and 1988. Cohort sizes ranged from 700 to 477,000, and the study periods range from 3 months to 32 years. Notably, only two of these studies attempted controls for smoking as a confounding variable. The relative risks (RR) for lung cancer for specific cohorts among these studies ranged from less than 1.0 to 2.7. Ten of the 15 studies reported at least one exposed subcohort with a RR for cancer of 1.2 or greater.

Perhaps the most robust of the cohort studies were those of Boffetta et al. (17) and Garshick et al. (18), both published in 1988. Boffetta et al. reported the results of the first two years of follow-up in the prospective mortality study of U.S. males conducted by the American Cancer Society. Occupation, DE exposure, and smoking history were obtained interviewing living subjects during enrollment. They calculated a RR for lung cancer among DE-exposed subjects of 1.6 for railroad workers, 2.6 for heavy equipment operators, and 2.7 for

miners who worked in mines where diesel equipment was operated. Garshick et al. conducted a retrospective study of U.S. railroad workers by inferring exposure from job title, assuming that workers with the greatest DE exposures were the youngest at the time railroads were converted to diesel engines and judging that smoking prevalence was the same among workers in relatively exposed and unexposed jobs. Garshick et al. calculated a RR for lung cancer of 1.5 for the group which was youngest at the time of diesel conversion and calculated lower RR values for groups older at that time.

Fourteen case-control studies were reported between 1976 and 1990. The number of cases ranged from 376 to 6434, typically with the same or greater numbers of controls. The study periods ranged from 1 to 10 years. Notably, all but two of these studies used some form of control for smoking. The RR for lung cancer among these studies ranged from less than 1.0 to 2.4 for exhaust-exposed groups. Twelve of the 14 studies reported a RR of 1.2 or greater.

The two most robust case-control studies were probably also those of Boffetta et al. (19) and Garshick et al. (20). In 1987, Garshick et al. studied 1256 cases of lung cancer and 2512 controls among railroad workers dying during a 1-year period in 1981 to 1982. DE exposure was inferred from job title. After adjusting for smoking and asbestos exposure, they calculated a RR for cancer of 1.4 among 251 cases and 496 controls under 64 years of age (with longer DE exposures than older workers) and a RR of 1.6 for workers with 20 years or more of exposure. In 1990, Boffetta et al. conducted a hospital-based study of 2584 lung cancer cases and 5099 controls divided into occupations with different exposures to DE. They analyzed separately a subgroup of 477 cases and 946 controls entered after subjects began to be questioned directly about DE exposure. The smoking-adjusted RR for lung cancer for self-reported exposure was 1.3 and that for self-reported exposures of 31 years or longer was 2.4.

Dubrow and Wegman (21) performed a combined analysis of 12 epidemiological studies in a manner that gave equal weighting from each study to the combined RR for occupations thought to have the greatest exposures. They calculated a combined RR of 1.3 for heavy equipment operators and truck drivers and 1.2 for professional drivers of buses, taxis, and other motor vehicles.

The weight of the above epidemiological evidence suggests that heavy occupational

exposure to DE probably increases the RR for lung cancer in the range of 1.2 to 2.0. In considering this information, it is important to keep three facts in mind. First, the database contains no individual studies that cannot be sharply criticized in terms of exposure discrimination and potential confounding factors. Second, because the lower limit of the 95% confidence intervals for many of the elevated risk ratios overlapped 1.0, the possibility of increased risk was precluded for many groups. Third, because elevations of risk in the range of 20 to 50% (RR of 1.2 to 1.5) are at the approximate lower limit of practical detectability by epidemiology, it may be that the true human lung cancer risk from DE will never be resolved conclusively.

Summary of Evidence for Exhaust-induced Lung Cancer

Epidemiology suggests that past long-term occupational exposures to DE have slightly increased the risk for lung cancer. It is plausible that GE also contributed to this effect, but present information does not allow partitioning of the effect between the two materials. It is clear that inhaled DE can act as a pulmonary carcinogen in rats, but it is uncertain that other species, including humans, respond similarly. The mechanism of the effect in rats is unknown, but it does not appear to require the soot-associated mutagenic organic compounds that were the original agent of concern. It is not presently clear how, or if, the cancer results from rats can be used to estimate cancer risk for humans. There is no good toxicological evidence for the carcinogenicity of inhaled GE.

Noncarcinogenic Pulmonary Effects of Engine Exhaust

Toxicological Evidence: Gasoline Exhaust

Perhaps the study with the most direct relevance to the long-term, noncancer effects of GE in humans is the Cincinnati Beagle study mentioned above. This is because the dog has a lower airway structure more similar than rodents to that of humans, the exposures of this long-lived species were longer than those of other species, the detailed serial physiological evaluations were performed during and after the exposures, and the final evaluations occurred at a considerable time after exposures ceased. Female Beagles were exposed to GE as described above (6) for over 5 years. Respiratory function was evaluated extensively throughout exposure (22). After exposures, the dogs were transferred to the University of California, Davis, where more

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extensive functional evaluations were performed [(23)]. Gillespie, personal communication], followed by detailed histopathological evaluations at 32 to 36 months after the end of exposure (5).

Little effect on respiratory function was observed during exposure (22). Subsequent tests revealed increases in lung volumes, deadspace ventilation, and dynamic lung compliance, and a decrease in alveolar-capillary gas exchange efficiency (23). Distinct, although not severe, histopathology included squamous metaplasia and some loss of cilia in large airways, epithelial hyperplasia in small bronchioles, and emphysema in proximal alveoli (5). These findings indicated that, in lungs morphologically similar to those of humans, long-term DE exposure induced functional and structural changes in airways and alveoli that persisted after exposures ceased.

The most extensive study of the noncancer pulmonary effects of GE on lungs of rodents was that of Heinrich et al. [(8); personal communication] who exposed rats and Syrian hamsters for 24 months to GE diluted 1:27 or 1:61 as described above. Evaluations included respiratory function, airway reactivity to acetylcholine, chemistry of BALF, clearance of inhaled ferric oxide ($^{59}\text{Fe}_2\text{O}_3$) particles, and histopathology. GE did not cause any substantial histopathology or alterations of lavage fluid chemistry in either species. The higher concentration of GE increased lung weight, retarded particle clearance, reduced dynamic lung compliance, and increased acetylcholine sensitivity in rats. No significant functional changes were found in rats at the lower concentration or in hamsters at either concentration.

Other toxicological data on the noncancer effects of GE are sparse. The cancer study by Brightwell et al. (9) of rats and hamsters exposed to GE, mentioned above, also included limited evaluations of respiratory function (24), but no significant alterations were observed. In 1966, Hueter et al. (25) reported limited measurements of the respiratory function of guinea pigs during 20 months of exposure to GE at 100 ppm CO, but found no significant effects. In 1979, Pepelko et al. (26) reported exposing rats 16 hr/day for 90 days to GE at a dilution of 1:10. They observed alveolitis and increases in lung volume and weight in both exposed and control rats; thus, the results are inconclusive.

Toxicological Evidence of Diesel Exhaust

In the only DE study involving animals with airway morphology similar to that of

humans, the EPA exposed male cats 8 hr/day, 5 days/week to DE from a 3.2-L engine operated on an urban cycle diluted to 6 mg soot/ m^3 for 61 weeks, then 12 mg soot/ m^3 for the remainder of 27 months (II). A restrictive respiratory function impairment with nonuniform gas distribution was observed at the end of exposure (27). Accompanying histopathology included peribronchiolar fibrosis and epithelial metaplasia in terminal and respiratory bronchioles (28). Interestingly, the epithelial changes lessened, but the fibrosis worsened during 6 months after exposure ended.

There are extensive data on noncancer pulmonary effects of DE in rodents, but most are from heavily exposed animals, and the majority are from rats. In all species, most soot deposited in alveoli is phagocytized by macrophages that, at low exposure rates, remain largely unaggregated and clear most of the soot from the lung. In rats exposed repeatedly at a high rate, the macrophages become loaded with soot and tend to form aggregates in alveoli instead of clearing from the lung. Under these conditions, macrophage-mediated particle clearance from alveoli is slowed, although mucociliary clearance in airways is not (29). The general phenomenon of overwhelming macrophage-mediated clearance by high rates of particle deposition is not specific to DE soot, and has been termed dust overload (30). This term is sometimes wrongly used to include the other functional and morphological (including cancer) abnormalities that are characteristic for rats with continued macrophage overloading caused by chronic exposure.

The time course and exposure-response relationships of the DE-induced, noncarcinogenic changes in animals, particularly at early times and low exposures, are not well-defined. White and Garg (31) exposed F344 rats 20 hr/day, 5.5 days/week to DE from a 5.7-L engine operated at constant load at 6 mg soot/ m^3 and examined lungs serially. After only one exposure, soot was found in epithelial cells as well as macrophages, and the number of Type II cells was slightly increased. By 3 days of exposure, soot was in peribronchiolar and mediastinal lymphoid tissue, and Type II cell hyperplasia was evident. After 2 weeks of exposure, macrophage aggregates, an influx of inflammatory cells, and some alveolar septal thickening were seen. Several studies have shown that, with long-term exposure of rats, many of these aggregates become the focus of progressive Type II cell hyperplasia, squamous epithelial metaplasia, and fibrosis. The lowest chronic exposure rate

for which soot lung burdens have been measured in rats was that of the ITRI in which F344 rats were exposed 7 hr/day, 5 days/week to DE from a 5.7-L engine operated on an urban cycle at 0.35 mg soot/ m^3 . Soot accumulated progressively in the rat lungs at that exposure rate and only reached 0.6 mg/lung after 24 months of exposure (29). At that exposure rate, few macrophage aggregates were observed and no significant inflammatory response, particle clearance (29), respiratory function (33), pulmonary immune function, or morphological changes (32) occurred.

Heavier exposures of rats cause significant abnormalities which have been reported in several laboratories. These effects are represented by the results of the above study which also included rats exposed to 3.5 and 7.1 mg soot/ m^3 . These exposures caused a dose-related overload of macrophage-mediated particle clearance (29) and a progressive accumulation of soot, reaching lung burdens of 11 and 20.5 mg/lung (32). Serial analysis of these rats demonstrated a progressive inflammatory and cytotoxic response, paralleled by increases in lung weight, lung tissue collagen, and histological multifocal changes (32). A progressive restrictive respiratory function impairment with gas distribution and gas exchange abnormalities followed accompanied the lung pathology. Although soot also accumulated in lung-associated lymph nodes, the inflammatory responses in these nodes to intratracheally instilled particulate antigen were not observed (34). Thus, chronic lung disease was induced in rats by chronic exposure to 3.5 and 7.1 but not at 0.35 mg soot/ m^3 . It is not known if there is a threshold for these effects.

It is of interest to compare the noncancer responses of rats to DE to responses of mice. At ITRI, CD-1 (Swiss) mice were exposed 7 hr/day, 5 days/week to 3.5, or 7.1 mg soot/ m^3 . Lung weights, burdens of soot, BALF chemistry, histology, and lung tissue collagen, acetylcholinesterase, reduced glutathione, and histopathology were evaluated at 1, 3, 6, and up to 18 months. The lung burden per gram of lung was slightly greater in mice than in rats (32), and although particle clearance was measured in mice, it was probably slower than in rats. Less of the retained soot was contained in macrophage aggregates; more was in single macrophages in the alveoli of rats. Except for glutathione, concentrations of cells, enzymes, and proteins in BALF of mice were increased proportionally to those in rats.

throughout exposure, reflecting inflammatory and cytotoxic responses as great as those of mice. The glutathione in BALF was increased 3- to 10-fold in a dose-related manner in mice but increased only slightly in rats. Reduced glutathione in lung tissue was not decreased by exposure in mice but was decreased in a dose-related manner in rats. Lung collagen was not increased in mice or in rats, and only occasional collagen fibrils in thickened alveolar septae were observed in mice, even at the highest exposure level, although DE soot accumulated similarly and causes similar inflammation in lungs of mice and rats, there is no aggregation, no depletion of tissue glutathione, and little fibrosis in mouse lungs.

There also are data for noncancer effects of DE in Chinese and Syrian hamsters. The U.S. Environmental Protection Agency studies (17) included measurements of the respiratory function of Chinese hamsters exposed 8 hr/day, 7 days/week for 6 months to DE from a 3.2-L engine operated on an urban cycle at 6 or 12 mg soot/m³. Accumulations of soot-laden macrophages, hyperplasia of alveolar Type I cells, and early fibrosis were reflected by increased lung weight, reduced maximal tidal volume, and reduced alveolar-capillary exchange efficiency (CO-diffusing capacity). These responses are similar to those observed in mice but because of the short exposure in the Chinese hamsters, it is not clear if they also respond with lung

The Brightwell et al. (24) cancer study evaluated the respiratory function of Syrian hamsters after exposure 16 hr/day, 5 days/week for 16 months to DE at 6.6 mg soot/m³. No significant abnormalities were found. Nontumor histopathology was not described. The Heinrich et al. (10) cancer study evaluated lung weight, lung function, and BALF chemistry of Syrian hamsters exposed 19 days/week for 2 years to DE at 1.7 mg soot/m³, or to filtered DE. Lung weight increased 50%, and the clearance of ⁵⁹Fe₂O₃ was increased (significant) after 1 year of exposure. High BALF parameters reflected inflammatory and cytotoxic effects. Significant effects on respiratory function were observed after 2 years of exposure. Histopathology included bronchiolitis, epithelial hyperplasia, alveolar septal thickening, and emphysema. There is little information available on the effects of acute low-level exposures to DE. Repeated exposure of

animals to DE at high concentrations causes a slowing of macrophage-mediated particle clearance and persistent inflammation. Continued exposure causes epithelial hyperplasia and fibrosis, which may vary in degree among species. Present data suggest that the rat, and possibly the Chinese hamster, might be more prone to developing focal proliferative and fibrotic changes than the other species.

Experimental and Epidemiological Evidence from Humans

There are few reports of experimental exposures of humans to DE and no reports of experimental GE exposures. In 1965, Battigelli (35) reported exposing 13 subjects for up to 1 hr to DE from a 7 hp single-cylinder engine. Soot concentrations were not reported, but the highest of three DE concentrations included 55 ppm CO, 4.2 ppm NO_x, and 1 ppm SO₂. No effect was found on pulmonary flow resistance measured during exposure. In 1987, Ulfvarson et al. (36) reported exposing six subjects for 3.7 hr to DE at 0.6 mg soot/m³ generated by a 2.4-L engine operated at constant speed at 0.6 mg soot/m³. No significant changes were found in forced exhalation and single-breath nitrogen washout parameters. Rudell, Sandstrom, and colleagues in Umeå have done the most recent studies. In 1990, Rudell et al. (37) reported exposing eight nonsmoking subjects for 1 hr to DE from an idling truck engine at approximately 1 mg soot/m³ (4.3×10^6 particles/cm³). The cytology of BALF and *in vitro* phagocytosis of opsonized yeast by macrophages obtained by lavage were measured before and 18 hr after exposure. The DE exposure increased BALF neutrophils, decreased mast cells, increased the T-helper and suppressor lymphocyte ratio, and depressed macrophage phagocytosis.

There are a few data on workshift changes in respiratory function in occupations with heavy exhaust exposures. In 1982, Ames et al. (38) reported that the workshift decrement in forced expiratory function did not differ significantly between workers in mines where DE was present or absent. In 1987, Ulfvarson et al. (36) reported studies of workshift decrements in forced expiratory function of workers with heavy exhaust exposures. They found significant decrements in roll-on, roll-off ship workers during loading and unloading operations in which the primary exposure was DE at 0.13 to 0.59 mg soot/m³, but no significant decrements in bus garage or car ferry workers exposed to both GE and DE at 0.10 to 0.46 mg soot/m³.

A few studies have examined longer term effects of heavy exhaust exposures on respiratory function and respiratory symptoms. In 1984, Ames et al. (39) reported that the maximal expiratory flow-rate at 50% of forced vital capacity was lower in workers in mines using diesel engines but found no differences in other forced expiratory parameters or in symptoms. In 1987, Gamble et al. (40) reported that bus garage workers had a higher age and smoking-adjusted incidence of cough, phlegm, and wheezing than controls, but found no association between symptoms and length of employment and no differences in respiratory function. Also in 1987, Purdham et al. (42) reported comparing the respiratory function and symptoms of 17 stevedores exposed to exhaust at 0.06 to 1.72 mg soot/m³ to those of 11 office worker controls. After adjusting for smoking, they found that the forced expiratory function of the stevedores was lower than that of the controls, but that there was no difference in symptoms.

Three of the epidemiological studies of lung cancer reviewed above also evaluated mortality from noncarcinogenic chronic respiratory disease (CRD). In their case-control study of railroad workers, Garshick et al. (42) found 575 cases of CRD mortality among exposed workers and calculated a RR of 1.2 for workers exposed 5 years or longer. In their retrospective cohort study, the same group (43) calculated a RR of 1.6 for CRD mortality among railroad workers aged 40 to 49 in 1959 (those with the longest DE exposures). In their prospective mortality study of 476,648 U.S. males, Boffetta et al. (44) observed 1242 noncancer respiratory deaths during 1983 to 1984, and calculated RRs for DE-exposed subjects of 1.2 for emphysema, 1.2 for other chronic obstructive lung disease, and 1.7 for pneumonia and influenza.

Summary of Evidence for Exhaust-Induced Noncancer Lung Disease

The experimental and epidemiological data base giving evidence for noncancer pulmonary effects of exhaust exposure in humans is small, but it suggests that heavy exposures probably affect respiratory function and contribute to symptoms and development of CRD. Experimental exposures have shown that a single exposure can cause lung inflammation and other cellular changes. Repeated exposures might therefore be expected to affect lung function, symptoms, and disease, and the plausibility of these effects is supported by the toxicological data. An impairment of particle clearance and sig-

nificant noncancer histopathology can occur in animals with repeated exposures, and the histopathology is reflected by impairments of respiratory function. Present information suggests that the effects in humans have small magnitudes; however, the data do not lend themselves to accurate quantitative estimates of risk.

Conclusions

Other than studies of individual exhaust components such as CO, nitrogen oxides (NO_x), etc., most attention to health risks from inhaled exhaust has been given to its potential for causing cancer. For this reason, DE exhaust has been given greater attention than GE. There is a very large toxicological data base on the cancer and noncancer

effects of DE and much less information on GE. Animal studies have shown that heavy chronic exposures to DE cause cancer and noncancer lung disease in rats, but the exposure conditions in these studies and the potential uniqueness of the lung tissue responses of this species make derivation of human risk factors from these data highly questionable.

Data from humans suggest that heavy occupational exposures to DE can cause acute inflammation and other cellular effects and that chronic exposures probably incur small increases of similar magnitude in the risks for lung cancer and other chronic lung disease. At present, the toxicological data demonstrate that engine exhaust can present a health hazard and support the plausibility

of both cancer and noncancer pulmonary effects in humans. The magnitude of these effects are such that the direct effects of exhaust as a single material are of concern primarily for occupational exposures. At present, quantitative estimates of unit risk for exhaust-induced cancer and noncancer disease are difficult to make with a high degree of confidence. Our information leaves little doubt, however, that repeated exposures to high concentrations of engine exhaust are hazardous and should be minimized. Engine exhaust is a complex material and a ubiquitous component of urban air pollution; thus, it undoubtedly contributes to the adverse health effects of the pollution mixture.

REFERENCES

- Mauderly JL, Griffith WC, Henderson RF, Jones RK, McClellan RO. Evidence from animal studies for the carcinogenicity of inhaled diesel exhaust. In: Nitroarenes (Howard PC, ed). New York: Plenum Press, 1990;13.
- Mauderly JL. Diesel exhaust. In: Environmental Toxicants - Human Exposures and Their Health Effects, Chap 5 (Lippmann M, ed). New York: Van Nostrand Reinhold, 1992;119-162.
- IARC. Diesel and gasoline engine exhausts and some nitroarenes. In: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol 46. Lyon: International Agency for Research on Cancer, 1989.
- Campbell JA. The effects of exhaust gases from internal combustion engines and of tobacco smoke upon mice, with special reference to incidence of tumours of the lung. *Br J Exp Pathol* 27:146-158 (1936).
- Hyde D, Orthoefer J, Dungworth D, Tyler W, Carter R, Lum H. Morphometric and morphologic evaluation of pulmonary lesions in beagle dogs chronically exposed to high ambient levels of air pollutants. *Lab Invest* 38:455-469 (1978).
- Hinners RG. Engineering the chronic exposure of animals to laboratory produced automobile exhaust. *J Air Pollut Control Assoc* 12:527-530 (1962).
- Roggendorf W, Neumann H, Thron HL, Schneider H, Sarasa-Corral JL. Histological examination of the rat after long-term exposure to subtoxic automotive exhaust gas. *Arch Toxicol* 47:247-256 (1981).
- Heinrich U, Peters L, Mohr U, Bellmann B, Fuhst R, Ketkar MB, König J, König H, Pott F. Investigation of subacute and chronic effects of gasoline engine exhaust on rodents. FAT Series No. 55. Frankfurt am Main: Forschungsvereinigung Automobiltechnik, V, 1986.
- Brightwell J, Fouillet X, Cassano-Zoppi A L, Bernstein D, Crawley F, Duchosal F, Gatz R, Perczel S, Pfeifer H. Tumours of the respiratory tract in rats and hamsters following chronic inhalation of engine exhaust emissions. *J Appl Toxicol* 9:23-31 (1989).
- Heinrich U, Muhle H, Takenaka S, Ernst E, Fuhst R, Mohr U, Pott F, Stober W. 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 (1986).
- Pepelko WE, Peirano WB. Health effects of exposure to diesel engine emissions. *J Am Coll Toxicol* 2:253-306 (1983).
- Mauderly JL, Cheng YS, Snipes MB. Particle overload in toxicological studies: friend or foe? *J Aerosol Med* 3:S169-S187 (1990).
- Poa F, Dungworth DL, Heinrich U, Muhle H, Kamino K, Germann PG, Roller M, Rippe RM. Lung tumours in rats after intratracheal instillation of dusts. In: Proceedings of the Seventh International Symposium on Inhaled Particles, 16-21 September 1991, Edinburgh, Scotland. *Ann Occup Hyg* (in press).
- Mauderly JL, Barr EB, Griffith WC, Henderson RF, Nikula KJ, Snipes MB. Importance of soot-borne organic mutagenic compounds in pulmonary carcinogenicity of diesel exhaust. *Toxicologist* 13:69 (1993).
- Nikula KJ, Snipes MB, Barr EB, Griffith WC, Henderson RF, Mauderly JL. Influence of particle-associated organic compounds on the carcinogenicity of diesel exhaust. In: Proceedings of the 4th International Inhalation Symposium on Toxic and Carcinogenic Effects of Solid Particles in the Respiratory Tract, 1-5 March 1993, Hannover, Germany. Washington: ILSI Press, (in press).
- Heinrich U, Fuhst R, Dasenbrock C, Muhle H, Koch W, Mohr U. Long-term inhalation exposure of rats and mice to diesel exhaust (DE), carbon black (CB), and titanium dioxide (TiO_2). In: Proceedings of the 4th International Inhalation Symposium on Toxic and Carcinogenic Effects of Solid Particles in the Respiratory Tract, 1-5 March 1993, Hannover, Germany, (in press).
- Boffetta P, Stellman SD, Garfinkel L. Diesel exhaust exposure and mortality among males in the American Cancer Society prospective study. *Am J Ind Med* 14:403-415 (1988).
- Garshick E, Schenker MB, Munoz A, Segal M, Smith TJ, Wolk S, Hammond KS, Speizer FE. A retrospective cohort study of lung cancer and diesel exhaust exposure in railroad workers. *Am Rev Respir Dis* 137:820-825 (1988).
- Boffetta P, Harris RE, Wynder EL. Case-control study on occupational exposure to diesel exhaust and lung cancer risk. *Am J Ind Med* 15:577-591 (1990).
- Ganham E, Schenker MB, Munoz A, Segal M, Smith TJ, Wolk S, Hammond KS, Speizer FE. A case-control study of lung cancer and diesel exhaust exposure in railroad workers. *Am Rev Respir Dis* 135:1242-1248 (1987).
- Dubrow R, Wegman DH. Setting priorities for occupational cancer research and control: synthesis of the results of occupational disease surveillance studies. *J Natl Cancer Inst* 71:1123-1142 (1983).
- Lewis TR, Moorman WJ, Yang YY, Stara JF. Long-term exposure to auto exhaust and other pollutant mixtures. *Arch Environ Health* 29:102-106 (1974).
- Hyde D, Gillespie J, Carter R, Orthoefer J. Correlations of pulmonary structural and functional changes in dogs after long-term exposure to auto exhaust and other air pollutants. *Am Rev Respir Dis* 117:243 (1978).
- Brightwell J, Fouillet X, Cassano-Zoppi AL, Bernstein D, Pott F, Duchosal F. Neoplastic and functional changes in rodents after chronic inhalation of engine exhaust emissions. In: *Carcinogenesis*

- and Mutagenic Effects of Diesel Engine Exhaust (Ishinishi N, Koizumi A, McClellan RO, Stober W, eds). Amsterdam:Elsevier, 1986;471-485.
25. Hueter FG, Contner GL, Busch KA, Hinners RG. Biological effects of atmospheres contaminated by auto exhaust. *Arch Environ Health* 12553-560(1966).
 26. Pepelko WE, Orthoefer JG, Yang YY. Effects of 90 days exposure to catalytically treated automobile exhaust in rats. *Environ Res* 1991-101 (1979).
 27. Moorman WJ, Clark JC, Pepelko WE, Mattox J. Pulmonary function responses in cats following long-term exposure to diesel exhaust. *J Appl Toxicol* 5:301-305 (1985).
 28. Plopper CG, Hyde DM, Weir AJ. Centriacina alterations in lungs of cats chronically exposed to diesel exhaust. *Lab Invest* 49:391-399 (1983).
 29. Wolff RK, Henderson RF, Snipes MB, Griffith WC, Mauderly JL, Cuddihy RG, McClellan RO. Alterations in particle accumulation and clearance in lungs of rats chronically exposed to diesel exhaust. *Fundam Appl Toxicol* 9:154-166 (1987).
 30. Morrow PE. Dust overloading of the lungs: update and appraisal. *Toxicol Appl Pharmacol* 113:1-12 (1992).
 31. White HJ, Garg BD. Early pulmonary response of the rat lung to inhalation of high concentration of diesel particles. *J Appl Toxicol* 1:104-110 (1981).
 32. Henderson RF, Pickrell JA, Jones RK, Sun JD, Benson JM, Mauderly JL, McClellan RO. Response of rodents to inhaled diluted diesel exhaust: biochemical and cytological changes in bronchoalveolar lavage fluid and in lung tissue. *Fundam Appl Toxicol* 11:546-567 (1988).
 33. Mauderly JL, Gillett NA, Henderson RF, Jones RK, McClellan RO. Relationships of lung structural and functional changes to accumulation of diesel exhaust particles. *Ann Occup Hyg* 32:659-669 (1988).
 34. Bice DE, Mauderly JL, Jones RK, McClellan RO. Effects of inhaled diesel exhaust on immune responses after lung immunization. *Fundam Appl Toxicol* 5:1075-1086 (1985).
 35. Battigelli MC. Effects of diesel exhaust. *Arch Environ Health* 10:165-167 (1965).
 36. Ulfvarson U, Alexandersson R, Aringer L, Svensson E, Hedenstierna G, Hogstedt C, Holmberg B, Rosen G, Sorsa M. Effects of exposure to vehicle exhaust on health. *Scand J Work Environ Health* 13:505-512 (1987).
 37. Rudell B, Sandstrom T, Stjernberg N, Kolmodin-Hedman B. Controlled diesel exhaust exposure in an exposure chamber: pulmonary effects investigated with bronchoalveolar lavage. *J Aerosol Sci* 21:411-5414 (1990).
 38. Ames RG, Attfield MD, Hankinson JL, Hearl FJ, Reger RB. Acute respiratory effects of exposure to diesel emissions in coal miners. *Am Rev Respir Dis* 125:39-42 (1982).
 39. Ames RG, Hall DS, Reger RB. Chronic respiratory effects of exposure to diesel emissions in coal mines. *Arch Environ Health* 39:389-394 (1984).
 40. Gamble J, Jones W, Minshall S. Epidemiologic-environmental study of diesel bus garage workers: chronic effects of diesel exhaust on the respiratory system. *Environ Res* 44:6-17 (1987).
 41. Purdam JT, Holness DL, Pilger CW. Environmental and medical assessment of stevedores employed in ferry operations. *Appl Ind Hyg* 2:133-139 (1987).
 42. Garshick E, Schenker MB, Smith TJ, Speizer FE. A case-control study of respiratory disease mortality and diesel exhaust exposure in railroad workers. *Am Rev Respir Dis* 135:A339 (1987).
 43. Garshick E, Segal MR, Schenker MB, Woskie SR, Smith TJ, Speizer FE. A retrospective cohort study of respiratory disease mortality and diesel exhaust exposure in railroad workers. *Am Rev Respir Dis* 137:252 (1988).
 44. Boffetta P, Stellman SD, Garfinkel L. Diesel exhaust exposure and mortality among males in the American Cancer Society prospective study. *Am J Ind Med* 14:403-415 (1988).

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