Diesel Exhaust

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Citation for most recent IARC review

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Current evaluation

Conclusion from the previous Monograph:
DE is *probably carcinogenic to humans (Group 2A)* because of limited evidence of carcinogenicity in humans coupled with sufficient evidence of the carcinogenicity of whole engine exhaust in experimental animals.

Exposure and biomonitoring

Environmental exposure to DE is ubiquitous in urban areas, with substantial DE exposure to those who commute on highways for years. Occupational exposure to DE is widespread, affecting 1.4 million workers in the United States (Steenland et al., 1996) and 3 million workers in the European Union (Kauppinen et al., 2000).

Occupational exposure

Because of the ubiquitous nature of environmental exposure to DE, it is difficult to measure environmental DE exposure for risk estimation in epidemiologic studies. In contrast, DE exposure is potentially quantifiable among the some of the following DE-exposed occupational groups: miners, professional drivers (truck drivers, bus drivers, taxicab drivers), railroad workers, vehicle mechanics, heavy equipment operators, dockworkers, tunnel workers, firefighters, farmers and shipping engineers. Since the last Monograph, industrial hygiene (IH) surveys of DE exposure have been conducted in truck drivers and underground miners.

For truck drivers, two IH surveys have been carried out. In the late 1980s, NIOSH (Zaebst et al., 1991; Steenland et al., 1992) measured elemental carbon, the primary surrogate for DE, in the cabs of long haul truck drivers and pick-up & delivery (P&D) drivers. The investigators reported the following elemental carbon levels: 5.1 μ/m^3 for in-cab long haul truckers; 5.4 μ/m^3 for in-cab local drivers; 3.4 μ/m^3 for roadway background; and 1.4 μ/m^3 for residential background in urban areas. In 2001-05, a second IH survey was conducted to determine elemental carbon levels in the trucking industry. Davis et al. (2007) reported lower levels of EC exposure for in-cab long haul truckers (1.1 μ/m^3) and in-cab P&D drivers (1.2 μ/m^3) than those reported by Zaebst et al. (1991). They attribute the recent lower levels to a downward trend in ambient particulate levels and tighter regulations on fuel composition and emissions over time. However, missing data on a number of factors, including trucker driving patterns, are needed in order to build a comprehensive model of driver exposure for epidemiologic analysis. Thus, results to date of both these IH surveys have not provided the data needed to estimate quantitative DE exposure among truck drivers in epidemiologic studies.

For underground miners, two IH surveys have been completed. In 1992-94, NIOSH and NCI conducted an IH survey of a New Mexico potash mine (Stanevich et al., 1997) to determine the feasibility of conducting retrospective exposure assessment for DE in a cohort and nested case-control study of lung cancer in DE-exposed underground nonmetal miners. The survey results indicated that DE exposure is higher in the mining industry than in other industries. Underground worker average EC levels ranged from 53-345 μ/m^3 and surface worker EC levels ranged from 12-31 μ/m^3. IH surveys in the six other US nonmetal mines in the epidemiologic study have been completed and results are expected to be published soon. In 1992, an industrial hygiene survey of German potash miners in underground jobs was conducted (Neumeyer-Gromen et al., 2009). Total carbon (TC) was used as the surrogate for DE because more data were available for TC than for EC. (Typically, EC is roughly 40 - 60% of TC.) The reported average TC exposure was 0.120-0.244 mg/m^3, which is similar to underground levels reported for the New Mexico potash miners. The German investigators assumed that the 1992 TC estimates were representative of DE exposure in the period from 1970 (when diesel equipment began to be introduced in the study mines) through 1992 because diesel technology had not changed during the 20-year timeframe. Thus, factors that affect level of DE, such as changes in number of pieces of equipment in operation, maintenance of diesel equipment, ventilation, and fuel composition, were not taken into account. In contrast, the retrospective exposure assessment in the U.S. study has included an intensive effort to incorporate all factors affecting DE exposure over time in the study mines.

In addition to IH surveys in truck drivers and miners, retrospective assessments of DE exposure have been conducted for a number of other occupational groups, including railroad workers (Laden et al., 2006), Swedish bus garage workers (Gustavsson et al., 1990) and Swedish dockworkers (Emmelin et al., 1993), since the last Monograph. However, these exposure assessments were based on virtually no measurement data, and thus, it is difficult to compare DE exposure levels in these occupational groups to levels reported for truck drivers and miners.

Cancer in humans

(*limited,* Vol 46, 1989)

Lung cancer

Much relevant research on the relation between DE exposure and risk of dying from lung cancer has been published since the last Monograph. Two meta-analyses have estimated the summary risk to range from 1.33 (95%CI = 1.24-1.44)(Bhatia et al., 1998) to 1.47 (95%CI=1.29-1.67)(Lipsett and Campleman, 1999). Although each meta-analysis was based on about 30 studies, most of the studies inferred DE exposure based on job title rather than from data on individual exposure, which may have led to misclassification of exposure and estimates of risk biased towards the null.

A small number of studies in the past 20 years have included a retrospective assessment of DE exposure. In the German study of potash miners (Neumeyer-Gromen et al., 2009), 5,862 potash miners were followed from 1970 to 2001, yielding 61 lung cancer deaths. A non-significant, positive trend with increasing cumulative TC exposure was observed after adjustment for age and smoking. Relative risks (RR) were 1.13(0.46-2.75), 2.47(1.02-6.02), 1.50(0.56-4.04) and 2.28(0.87-5.97) for cumulative TC up to 2.04, 2.73, 3.90 and >3.90 (mg/m^3)*years, respectively. This study was based on only 61 lung cancer deaths and none of the reported trends achieved statistical significance. Other limitations include possible residual confounding by smoking and an inability to adjust for other confounders, such as employment in other high-risk occupations for lung cancer; and a relatively short latent period since DE exposure was not introduced in the study mines until 1970 or later.

Two epidemiologic studies of DE exposure and lung cancer risk have been conducted among truck drivers. A nested case-control study of 996 cases and 1,085 controls in a Teamsters Union cohort (Steenland et al., 1990; Steenland et al., 1992) reported a significant trend in risk with increasing duration of employment (based on union records) as a long-haul truck driver after 1959 (the year when many trucking companies had completed dieselization of their fleets)(p=0.04), with the odds ratio (OR) peaking at 1.55 for 18 or more years duration of employment after adjustment for age, smoking and asbestos exposure. Next-of-kin interviews also indicated that drivers of primarily diesel trucks for 35 years or more had increased risk (OR of 1.89 (95%CI=1.04-3.42)). In a cohort study of 31,135 male truck drivers followed from 1985 to 2000 (Garshick et al., 2008), long-haul truckers with 20 years of employment had an hazard ratio (HR) of 1.40 (95%CI=0.88-2.24) and P&D drivers had an HR of 2.21 (95%CI=1.38-2.52) for 20 years of employment after adjustment for age in 1985,

decade of hire, calendar time, race, census region, the healthy worker-survivor effect, and indirect adjustment for smoking. The reason for the higher risk among P&D drivers compared to long haul truck drivers is unclear since the IH survey indicated that the in-cab EC exposure levels measured for the two groups were virtually the same. The investigators indicate that their findings suggest that driver exposure comes predominantly from surrounding vehicles and from background air pollution, as well as from the driver's own vehicle. Both studies of truck drivers are limited because the IH surveys of DE exposure were conducted at the same time as the epidemiologic studies, and no historical measurement data were available to quantify individual truck driver DE exposures in either study.

For railroad workers, Garshick et al. (2004) extended follow up through 1996 on the original 54,973 US railroad workers in the cohort included in the last Monograph, identifying 4,351 lung cancer deaths. They reported a RR of 1.4 (95%CI=1.30-1.51) for workers in jobs associated with operating trains, but risk did not increase with increasing years employed at these jobs. Lung cancer mortality was elevated in selected DE-exposed jobs such as conductor and engineer, but risk did not increase with increasing years of employment in these DE-exposed jobs. Although historical measurement data on DE exposure in this cohort were unavailable, Laden et al. (2006) obtained extensive historical information on diesel locomotive use by railroad. They found that workers hired after 1945 (when diesel locomotives began to be introduced) had a RR of 1.77 (95%CI=1.50-2.09), with increasing risk with increasing duration of employment in a DE-exposed job. In contrast, railroad workers hired before 1945 had an RR of 1.30 (95%CI=1.19-1.43) for any diesel exposure and no evidence of a trend in risk with duration of employment. However, no trend in risk with increasing cumulative DE exposure was apparent. Findings reported by Laden et al. (2006) were not adjusted for smoking despite the fact that indirect adjustment for smoking in the earlier analysis reported by Garshick et al. (2004) did attenuate estimates of risk.

Studies of Swedish bus garage workers (Gustavsson et al., 1990) and Swedish dock workers (Emmelin et al., 1993), based on retrospective exposure assessments in the absence of historical measurement data on DE levels, yielded elevated ORs for heavily exposed bus garage workers (2.4, 95%CI=1.3- 4.5) and for heavily exposed dock workers (2.9, 95%CI=0.8-10.7). However, both studies were small, with only 20 and 50 lung cancer deaths among the bus garage workers and the dock workers, respectively. In addition, smoking was not taken into account in the bus garage workers study.

Other cancers

Epidemiologic studies of the carcinogenicity of DE have focused primarily on lung cancer. In addition, DE exposure has been linked to a number of other neoplasms including cancers of the bladder, kidney, pancreas, colon and rectum, prostate and multiple myeloma and leukemia (IARC, 1989; Boffetta and Silverman, 2001; Seidler et al., 1998; Lee et al., 2003). Following lung cancer, the strongest evidence of increased risk associated with DE is apparent for bladder cancer. A meta-analysis (Boffetta and Silverman, 2001) yielded a summary of RR of 1.44 (95%CI=1.18-1.76) for high DE exposure. However, some evidence of publication bias was apparent, with a paucity of small studies with null or negative results.

Cancer in experimental animals

(*sufficient,* Vol 46, 1989)

Diesel emissions research was initiated in 1977 by scientists at the US EPA to evaluate the health impact of increasing diesel vehicle emissions (US EPA/625/9-79-004), 1979. The first diesel studies designed to characterize the chemical and bioassay characterization led to the discovery that diesel particles contained a relatively large quantity of mutagenic organic compounds (Lewtas et al., 1979). Animal studies were initiated to characterize the tumor potency of different diesel emissions and determine which diesel extracts, fractions, and specific chemicals were carcinogenic (Nesnow et al., 1982). Mutagenesis and carcinogenesis studies of a range of diesel particles was published in the early 1980s (Lewtas, 1982, Nesnow et al, 1982) as well as inhalation (Pepelko, 1982) (Pepelko et al., 1983) and toxicology studies (Lewtas, 1982). Comparative cancer potency studies of diesel and gasoline particle extracts were compared to a series of organic extracts from known human carcinogens (coal tar, a coke oven, tobacco smoke) with respect to chemical composition (Williams et al., 1986), mutagenicity (Lewtas, 1983), and animal tumor potency (Nesnow,1982). The tumor initiation potency of the three known human carcinogens compared to the tumor potency of a series of diesel combustion emissions and one gasoline combustion emission sample was used to estimate the range of relative cancer unit risks from diesel emissions (Albert et al., 1983, Lewtas et al., 1983). Lung implantation studies reported that PAH and nitro-derivatives contributed to the carcinogenic impact of diesel exhaust condensates evaluated by implantation into the lungs of rats (Grimmer et al., 1987).

Biodiesel fuel derived from soybean oil was used in two 1998 Cummins diesel engines operated by the US EPA heavy-duty engine dynamometer schedule. This biodiesel exposure to F344 rats (30/exposure group) was to sub-chronic inhalation exposure levels of 0.04, 0.2, and 0.5 mg particles/m^3. Significant exposure-related effects were limited to the lung and were greater in female rats than in males and the effects were primarily found in the highest exposure (0.5 mg particles/m^3equal to 50 ppm). Among the high-level (50 ppm) females, the lung weight/body weight ratio was increased and multifocal bronchiolar metaplasia of alveolar ducts was reported in 4 of 30 rats. There were no other significant exposure-related effects on survival, clinical signs, or toxicology evaluations (Finch et al., 2002).

Mechanisms of carcinogenicity

Since the 1960s, evidence has increasingly supported the theory that chemical carcinogens (e.g., polycyclic aromatic hydrocarbons (PAH) and nitro- polycyclic aromatic hydrocarbons (nitro-PAH) are metabolized via oxidative pathways to produce electrophilic reactive products (e.g., epoxides) that react covalently with DNA and possibly with other nucleophiles (e.g., diesel particles and other combustion particles). Bioassay-directed chemical analysis of the constituents of complex combustion emissions has facilitated the identification of mutagenic and carcinogenic constituents of these complex mixtures (Schuetzle and Lewtas, 1986) (Lewtas, 1988). In 1986, el-Bayoumy and Hecht reported the mutagenicity of several K-region lactone derivatives of 1-nitropyrene that were highly mutagenic and ten years later 3-nitrobenzanthrone was isolated from both diesel and air particles (Enya et al., 1997). Diesel and other soot particles have also been reported to generate free radicals that lead to biologically damaging hydroxyl radicals. The formation of DNA adducts by nitro-PAH and PAH in animal and cellular studies of diesel particles is very well documented in a series of

studies reviewed in Mutation Research Reviews (Lewtas, 2007). This review also compares a wide range of combustion emissions, including diesel emissions and the causative agents and mechanisms associated with cancer, reproductive, and cardiovascular effects that have been reported (Lewtas, 2007).

Research needs and recommendations

Possible future epidemiologic studies:

Epidemiologic evidence to date suggests that the relation between DE exposure and lung cancer risk may be causal. To establish causality will require well-designed epidemiologic studies of large cohorts of DE-exposed workers with (a) quantitative estimates of DE exposure for study subjects, (b) with adequate latent period for the development of lung cancer, and (c) with information on smoking and other potential confounders (e.g., employment in other high-risk occupations for lung cancer). Both heavily exposed workers (i.e., nonmetal miners) and light-to-moderately exposed workers (i.e., truck drivers) are currently being studied to estimate risk for a wide range of DE exposure. The study of US nonmetal miners will be particularly informative because of several unique features. First, based on a cohort of 12,400 workers who have exposures many times higher than that observed in other DE-exposed occupations, adequate information is available to quantify historical exposures to DE for all cohort members. The historical assessment is strengthened by the availability of industrial hygiene data from NIOSH surveys carried out at study mines in 1976 and again in the late 1990s. Second, the follow-up period for the cohort ranges up to 50 years, which should provide a sufficient latent period to detect an elevation in lung cancer mortality. Lastly, information on cigarette smoking and other potential confounders was obtained from interviews with next of kin. This study is close to completion and results are expected to be published soon. In ongoing and future studies, it will also be important to evaluate any potential interaction between cigarette smoking and DE exposure. If ongoing epidemiologic studies of nonmetal miners and/or truck drivers yield consistent significant, positive exposure-response relationships, it will be important to conduct research into the underlying mechanisms of DE-induced carcinogenesis. Cross-sectional molecular epidemiological studies in DE-exposed human populations will be needed to evaluate the relationship between DE exposure and biomarkers of inflammation, genotoxicity, and other relevant early biological effects, and to study potential sources of genetic susceptibility. In addition, such studies may help us identify the components of DE that are most biologically active in humans, to the extent that these components are not highly correlated. In the long-term, the design and implementation of technologies for population surveillance of DE exposure coupled with biomarkers of effect merit consideration.

Impact of biodiesel fuels on the emissions, mutagenicity, and carcinogenicity of diesel emissions:

Biodiesel fuels (e.g., rapeseed oil, rapeseed oil methyl ester, soybean oil methyl ester) and blends of biodiesel fuel with petroleum diesel fuel (e.g., a biodiesel blend with petroleum diesel designated as B35 is 35% biodiesel and 65% petroleum diesel) are now being investigated as well as natural gas-derived synthetic fuels (gas-to-liquid). Vegetable oils have been used as fuels for diesel engines as early as the late 1800's by Rudolf Diesel, who used peanut oil in a diesel engine, and recent studies are investigating renewable biological sources for fuels such as vegetable oils or animal fats. Heavy duty diesel trucks performed well with

35% biodiesel and 65% petroleum diesel blend designated B35 and B20 (20% biodiesel) (Wang et al., 2000). A series of publications by Bunger et al., 2006 and 2007 report on the influence of fuel properties, nitrogen oxides (NOx), and exhaust treatment by oxidation catalytic converters that increased the mutagenicity of the diesel engine emissions. The fuels included common fossil diesel fuel (DF), low-sulfur DF (LSDF), rapeseed oil (RSO), rapeseed oil methyl ester (RME) biodiesel, and soybean oil methyl ester (SME). The strong increase in mutagenicity (~10 to 60 fold) when using RSO or RME as diesel fuels needs to be considered before the rapeseed-based fuels are used to replace established diesel fuels (Bunger et al., 2007).

With the increased use of biodiesel in recent years, the potential carcinogenicity of biodiesel warrants future evaluation. Although several biodiesel fuels derived from rapeseed oil or rapeseed methyl ester have been found to be highly mutagenic (Bunger et al., 2007), the soy-oil-based biodiesel emissions are less mutagenic. It is premature to conduct epidemiologic studies of biodiesel because the latent period for the development of solid tumors is currently inadequate. However, experimental laboratory studies of biodiesel should be a priority in view of the increasing prevalence of use of biodiesel in the US and European populations.

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