EPA'S ASSESSMENT OF HUMAN HEALTH RISK FROM EXPOSURE TO DIESEL ENGINE EMISSIONS

W.E. Pepelko
U.S. Environmental Protection Agency

INTRODUCTION

EPA's concerns regarding the possible health effects of diesel engine emissions arose in the mid to late 1970s as a result of the energy crisis and the accompanying belief that the number of diesel equipped passenger automobiles would increase greatly with accompanying increases in particulate matter pollution. This concern was enhanced by the possibility that diesel exhaust may be carcinogenic. Although the ability of diesel particle extracts to induce skin cancer had been reported in an early study by Kotin et al. (1955), the carcinogenic potential of diesel exhaust received little notice until publication of a report by Huisingh et al. (1978). This report indicated that organic extracts of diesel particulate matter are mutagenic. Furthering this interest was the knowledge that organic extracts of diesel particles contain compounds such as benzo(*a*)-pyrene, albeit at very low concentrations, that are well known for their ability to cause cancer.

The increase in diesel engine equipped automobiles did not occur due to the initial low quality of diesel engines available for passenger cars; decreasing fuel costs with the passing of the energy crisis; and the fact that diesel engines lacked wide appeal because of noisiness, greater purchase costs, slow acceleration, and unpleasant odors. While the number of diesel engine equipped automobiles has remained low, however, diesel engine usage has steadily increased in trucks, construction and mining equipment, locomotives, and ships. The potential threat to human health due to increased diesel usage is at least partially offset by improved engine design resulting in increased engine efficiency and decreased emissions. Nevertheless, because chronic exposure to diesel exhaust (DE) has been shown to induce adverse health effects, interest in further evaluation of the nature as well as the degree of human susceptibility to these effects has remained high.

EVALUATION OF NONCANCER HEALTH EFFECTS

Acute toxicity The most readily identified acute effects of diesel exhaust in humans are subjective complaints of eye, throat, and bronchial irritation and neuropsychological symptoms such as headache, lightheadedness, nausea, vomiting, numbness, and tingling of extremities. Diesel odors are also considered to be noxious. Over the course of workshifts in studies of underground miners, bus garage workers, dock workers, and locomotive repairmen, decrements in lung function occasionally have been reported (Cohen and Higgins, 1995). The only evidence of permanent harm from acute exposure, however, is an unpublished case report (private communication from EPA Office of Mobile Sources) of a mechanic suffering from severe and disabling lung damage following a brief exposure to a very high concentration of diesel exhaust.

Exposures of 5 hours duration to pure diesel exhaust from an engine running under a heavy load resulted in 100% mortality in guinea pigs, rabbits and mice. Lighter loads resulted in progressively lower mortality rates (Pattle et al., 1957). Exposure of laboratory animals for several days to diesel particle concentrations of up to about 6 mg/m^3 induced an inflammatory response as indicated by alveolar macrophage (AM) aggregation near the terminal bronchioles, Type II cell proliferation, and the thickening of alveolar walls adjacent to AM aggregations. Lung function decrements, however, were generally minimal and overall impairment of health was not reported (Watson

and Green, 1995).

Dose-response for acute exposure. Lung pathology was the primary effect reported in experimental animals acutely exposed to concentrations of several mg/m^3. Adverse clinical effects in humans, on the other hand, noxious odor, headache, and mucous membrane irritation occurred at considerably lower concentrations. In clinical trials a threshold for odor detection of diesel exhaust diluted as much as 475-fold with clean air (i.e. estimated to equal a particle concentration of about about 200 *u*g/m^3) was reported (Linnell and Scott, 1962). Although a formal determination of safe acute exposure levels have not been determined, concentrations greater than 200 *u*g/m^3 may be noxious and even lower concentrations may induce adverse effects in sensitive individuals.

Chronic toxicity. Epidemiologic evidence from chronic exposure to Diesel exhaust is conflicting. Although effects in occupationally exposed workers have generally been quite limited, indications of obstructive or restrictive lung disease have occasionally been reported. Many of these studies are difficult to interpret because they suffer from methodological problems including incomplete information on DE concentrations, the presence of confounding variables such as smoking or concomitant exposure to other toxic substances, as well as short duration and low intensity of exposure. Moreover, definitive data regarding possible pathologicial effects from autopsies or lung biopsies are generally unavailable (Cohen and Higgins, 1995). Information regarding effects in other organ systems are limited

An extensive database on animal studies (rats, mice, hamsters, cats, and monkeys) is available. The study results are consistent among all species in that the critical target site is the deep lung. Long-term exposure to a DE particulate matter concentration of 2 mg/m^3 and above have typically resulted in restrictive lung disease. Histopathological findings included alveolar histiocytosis, macrophage aggregation, tissue inflammation, increases in polymorphonuclear leukocytes, hyperplasia of bronchiolar and alveolar Type II cells, thickened alveolar septa, edema, fibrosis, and emphysema. The severity of these inflammatory responses were directly related to exposure levels. Decreased rates of particle clearance were noted at exposure concentrations greater than 1 mg/m^3. Behavioral effects were also reported in rats exposed from birth to 28 days of age These included a decrease in spontaneous locomotor activity and a detrimental effect on learning during adulthood. These studies, however, were only conducted at exposure concentrations of several mg/m^3. For further details regarding noncancer health effects see Watson and Green (1995).

Dose-response for chronic toxicity. The determination of safe levels for chronic noncancer effects was carried out by the development of a reference concentration (RfC). An RfC is defined as an estimate (with uncertainty spanning perhaps an order of magnitude of a continuous inhalation exposure to the human population, including sensitive subgroups) that is likely to be without appreciable risks of deleterious effects during a lifetime. Two studies of rats exposed for 2 years or longer to particle concentrations ranging from 0.11 to 7.1 mg/m^3, and having measurements of a large number of endpoints, were used for the development of the RfC (Ishinishi et al., 1986; Mauderly et al., 1987).

An RfC is derived from the highest no-observable-effect-level (NOAEL). Based on the Ishinish et al. (1986) study, the NOAEL was determined to be 460 *u*g per m^3 with lung pathology the critical endpoint. Since the animals were exposed 16 hours/day, 6 days/-week, an adjustment to continuous exposure of 0.57 (16/24 x 6/7) was made. A dosimetry model developed by Yu et al. (1991) was used to extrapolate concentration from animals to humans. According to this model, which accounted for rat to human differences in respiratory exchange rates, particle deposition efficiency, particle clearance rates, and transport of particles from lung associated lymph nodes, an adjustment of 0.57 is appropriate. After these adjustments and division by an uncertainty factor of 30, 10 for varia-

tions in human sensitivity and 3 for possible differences in sensitivity of rats and humans, an RfC of 5 ug/m^3 was derived.

The RfC is considered to be sufficiently protective even for sensitive populations. Lower thresholds for adverse health effects have not been noted in a variety of other species tested. Effects from DE exposure were only noted in occupationally exposed humans at concentrations considerably greater than the RfC. Although sensitive humans are unlikely to be found among this group, addition of a 30-fold uncertainty factor should protect sensitive individuals.

EVALUATION OF CARCINOGENICITY

Qualitative assessment of carcinogenicity. The possible carcinogenic effects of DE in humans have been reviewed by Cohen and Higgins (1995). The studies suggest that exposure to diesel exhaust in a variety of occupational circumstances is associated with small to moderate increases in relative risk of lung cancer mortality. These elevations do not appear to be fully explicable by confounding due to cigarette smoking or other sources of bias. DE exposure, therefore, provides the most reasonable explanation for these elevations. Cohen and Higgins (1995), however, have cautioned that risk elevations of the magnitude reported (20%-40%) should not be overinterpreted. For example, inaccuracies of exposure measurement could either spuriously elevate or underestimate risk.

Animal carcinogenicity studies have been reviewed by Busby and Newberne (1995) and Mauderly (1992). The carcinogenicity of DE has been confirmed in two strains of rats in at least five different laboratories. The data for mice are equivocal. Lung cancer studies were generally negative in common laboratory strains of mice. However, increases were noted on the Sencar strain which is very sensitive to cancer induction in epithelial tissue (Pepelko and Peirano, 1983). Syrian hamsters have not developed lung tumors in any of the studies reported thus far.

Under EPA's 1986 Cancer Risk Assessment Guidelines (U.S. EPA, 1986), DE is tentatively considered to be a probable human carcinogen. According to EPA's Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996), diesel exhaust is considered "highly likely" to be carcinogenic in humans by the inhalation route of exposure. These classifications are based primarily on reported increases in lung cancer mortality in a number of occupational exposure studies. The conclusion that DE is a "probable" or a "highly likely" rather than a "known" carcinogen is due to lack of specific DE exposure data in human studies. The exposure data limitations include an inability to completely eliminate confounding factors such as exposure to other pollutants, especially tobacco smoke. Strong support for the conclusion that DE is "highly likely" to be a human carcinogen is provided by positive cancer data in bioassays with rats, positive genotoxicity data, and the knowledge that diesel exhaust contains carcinogenic compounds.

Dose response assessment. Cancer potency estimates for inhaled agents are published as unit risks. The unit risk for DE is defined as the estimated 95% upper bound of the lifetime risk of cancer from continuous lifetime exposure to 1 ug/m^3 of diesel particulate matter. Estimates are based upon particle concentration because few effects have been noted following exposure to the vapor phase of DE, intratracheal instillation of DE particles is capable of inducing lung cancer, and particle concentration is the most practicle dosimeter. A variety of approaches for estimating cancer potency have been attempted for DE utilizing data from epidemiology studies, laboratory animal bioassays, and in vitro studies.

The earliest attempts to determine the carcinogenic potency of DE were based upon the so called "comparative potency" method. This method was developed because of a lack of either human cancer epidemiology studies or animal cancer bioassays for DE exposure. It is based upon the belief that the carcinogenic effects are due to the organic constituents of the particles and that these constituents in various combustion products acted by similar

mechanisms. In this approach, the potency of DE particle extracts were compared in a variety of short-term tests such as skin painting, mutagenicity, sister chromatid exchange, etc. to related combustion or pyrolysis products, roofing tar, cigarette smoke condensate, and coke oven emissions. The ratio of the potency of DE paarticle extracts to each of these pollutants was then multiplied by the epidemiology based unit risk estimate for each of these agents. Using this method, Albert et al. (1983) derived unit risk estimates for DE averaging near 3×10^{-5} per ug/m^3.

Pike and Henderson (1981) found good agreement between lung cancer risk and concentration of benzo(*a*)pyrene [B(*a*)P] in the inspired air of smokers, British gas workers, U.S. coke oven workers, U.S. hot pitch workers, and when comparing residents of rural and urban locations. Based upon an estimated lung cancer risk of 1/1500 per ng/m^3 B(*a*)P and B(*a*)P concentration in particles from a Volkswagen engine (Heinrich et al.,1995), a unit risk estimate of about 1×10^{-5} per ug/m^3 particulate matter can be derived. Which is essentiall equivalent to Albert et al. (1983).

During the mid to late 1980s, several long-term animal cancer bioassays including those by Brightwell et al. (1989), Ishinishi et al. (1986), and Mauderly et al. (1987) were published. As a result, a number of cancer risk estimates based upon experimental tumor data in rats were derived (Albert and Chen, 1986; Pott and Heinrich, 1987; McClellan et al., 1989; Smith and Stayner, 1990; Pepelko and Chen, 1993; and Chen and Oberdoerster, 1996). A variety of low-dose extrapolation models were used, although none departed significantly from linearity. The more recent ones, such as those derived by Pepelko and Chen (1993) used a detailed dosimetry model to more accurately extrapolate dose from animals to humans. These unit risk estimates ranged from about 1.6×10^{-5} to 1.2×10^{-4} per ug/m^3.

During this period, a number of epidemiologic studies were also reported. A case-control study of railroad workers published by Garshick et al. (1987) was the most useful for quantitating cancer risk. Using this study McClellan et al. (1989) estimated the annual number of lung cancer deaths due to DE exposure in the United States. From these mortality estimates and assuming a mean exposure concentration of 500 ug/m^3, a unit risk estimate of 6×10^{-4} per ug/m^3 could be derived.

Each of these approaches has strengths as well as uncertainties. Well controlled epidemiology studies are preferable for assessing human risk. Human data eliminates uncertainties due to dose extrapolation and possible differences in sensitivity between experimental animals and humans. Human exposures also are usually at lower concentrations than those used in animal bioassays and thus require a shorter extrapolation to ambient levels. The greatest uncertainty in use of human data is accurate determination of exposure levels. Although recent measurements for occupationally exposed groups are generally available, historic exposure measurements are very limited. Because of the long induction time for carcinogenesis, lack of accurate historic exposure data increases uncertainty considerably. Also, there is a chance for error due to small increases in relative risk coupled with an inability to completely eliminate confounding variables such as smoking and exposure to other chemicals.

In the comparative potency method it is assumed that carcinogenic effects are due to the organic matter constituents of diesel particles. Laboratory studies, however, show that carbon black, which is similar to the carbon core of diesel particles, is capable of inducing lung cancer in experimental animals (Heinrich et al., 1995). Failure to account for particle effects increases the uncertainty of using this approach. This approach, however, still deserves consideration since lung cancer induction at low doses is more likely to be induced by the organic fraction.

A strength of the biomarker approach is the fact that the risk estimates for a variety of the related pollutants compared are derived from human data. On the other hand, particles from

other combustion and pyrolysis products consist of, to a large extent, organic compounds, with little or no elemental, insoluble carbon core. Differences in the composition of the particle core increases uncertainty since particle effects may be minimal with soluble particles.

In estimating risk based upon chronic animal bioassays, actual tumor counts are available and exposure conditions are usually quite well defined. Some uncertainty occurs in extrapolating dose from animals to humans, but this can usually be minimized by the use of a suitable dosimetry model. Greater uncertainty occurs during low-dose extrapolation. There is at least some evidence suggesting that the mode of action of lung tumor induction in rats exposed at high doses may be related to lung pathology associated lung particle overload. If so, the dose response curve may be nonlinear. Another source of uncertainty is the suitability of the rat model for assessing human risk from exposure to particulate matter (Mauderly, 1996).

Each of the above approaches for estimating human lung cancer risk from DE exposure has uncertainties of sufficient magnitude to preclude selecting one as the "most scientifically valid." As a result, a single point estimate of risk, at least tentatively, is not proposed. Collectively, however, the various estimates are considered to be adequate for bounding risk. The estimate of 6×10^{-4} per ug/m^3 derived from the Garshick et al. (1987) case-control study of railroad workers provides a reasonable upper bound. Because few of the the relative risk ratios reported in other studies exceeded that reported by Garshick et al. and because exposure estimates were quite conservative, risk is unlikely to be underestimated. Risk estimates using the comparative potency or B(*a*)P method were lower, ranging from as little as 1×10^{-5} per *u*g/m^3. Since they are based primarily upon the organic fraction of DE, risk is unlikely to be underestimated because of the possibility that particles also may play a role in tumor induction. Risk estimates derived from animal bioassays also fall within this range. For these reasons upper confidences limits of lung cancer risk are considered to be bounded by a range of 1×10^{-5} to 6×10^{-4} per *u*g/m^3 of diesel particulate matter. It should be noted, however, that this recommendation has not been approved as official EPA policy and is subject to revision. No endorsement by EPA is intended.

SUMMARY

DE is considered to be a probable human carcinogen under EPA's 1986 cancer risk assessment guidelines and highly likely to be carcinogenic under EPA's 1996 proposed guidelines for cancer risk assessment. The 95% upper confidence limit for cancer potency is tentatively determined to be bounded by a range of 6×10^{-4} to 1×10^{-5} per *u*g/m^3. The critical target organ for noncancer health effects is the lung. An RfC of 5 *u*g/m^3 is recommended.

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