Department of Ecology Air Quality Program

Concerns about Adverse Health Effects of Diesel Engine Emissions White Paper

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Introduction

Beginning in the 1950s, the adverse health effects of diesel exhaust particles have received increasing public and scientific attention. Many published scientific studies show that diesel exhaust significantly affects public health. Diesel exhaust particles may affect the health of all who breathe them. However, they are especially problematic for people with heart or circulatory problems and people with lung disease. Exposure to diesel exhaust can result in both immediate and long-term health effects. These effects range from cardiopulmonary, immune, endocrine, and developmental and reproductive impairments to lung- and certain other types of cancer.

Because the Department of Ecology is tasked with developing policies related to diesel sources, the Air Quality Program has developed this document to summarize our position on the current regulatory guidelines available for diesel. This paper gives an overview of the health concerns about diesel emissions by exploring diesel exhaust's:

- Composition
- Human exposure
- Adverse health effects
- Health-protective exposure guidelines

A list of publications cited in this report begins on page 16.

This paper also explains our rationale for selection of the California Environmental Protection Agency Office of Environmental Health Hazard Assessment cancer potency estimate to evaluate the carcinogenic risk associated with ambient concentrations of diesel exhaust particles, and for our selection of the United States Environmental Protection Agency (USEPA) reference concentration and equivalent California Environmental Protection Agency-Office of Environmental Health Hazard Assessment reference exposure level to evaluate the non-carcinogenic effects.

Composition of diesel exhaust

The characteristics of exhaust emitted from the combustion of diesel fuel vary according to the combustion conditions. Diesel exhaust is a complex mixture composed of particulate and gaseous components. Important gaseous components include carbon dioxide (because of its 'greenhouse' effect), carbon monoxide, sulfur oxides, nitrogen oxides, and 18,000 identified volatile and semivolatile hydrocarbon compounds. Carbon

particles adsorb the majority of these compounds, which may enhance their ability to become lodged in lung tissues. Over 98% of the particles are less than 2.5 microns in diameter, and approximately 94% of those particles are less than 1 micron in diameter (California Air Resources Board, 1998). The hydrocarbon compounds adhere to these minute carbon particles during the combustion process.

The diesel exhaust particles component consists mainly of elemental carbon particles with large surface area, which adsorb numerous hydrocarbons. These hydrocarbons include carcinogenic polycyclic aromatic hydrocarbons, aldehydes, and other chemical agents. Diesel exhaust particles can also undergo atmospheric transformation after they have been emitted. For example, polycyclic aromatic hydrocarbons adhered to carbon particles may react with hydroxyl radicals in the air, and create highly mutagenic and carcinogenic nitro-polycyclic aromatic hydrocarbons (Cohen and Nikula, 1999).

The amount and composition of diesel exhaust also varies depending on the kind of engine, its mode of operation, its degree of wear, maintenance, load, and the type and the sulfur content of the fuel among other factors. The amount of sulfur in diesel fuel is one of the most critical components in determining the amount of particles in the exhaust. Sulfur in fuel combusts to sulfur dioxide, which combines with the water of combustion to form sulfurous and sulfuric acid droplets. Much of the ultrafine particles measured in the PM2.5 fraction are formed after exhaust leaves the tailpipe, and condenses around such sulfate cores (Kittelson and Abdul-Khalek, 1999). Use of low sulfur or ultra-low sulfur fuel decreases fine particle emissions considerably. Kittleson and Abdul-Khalek estimate that total particle emissions can be reduced by about half with the removal of sulfur from fuels.

Exposure

Determining people's exposure to air pollution is the most challenging task in assessing risk. This is due to the vagaries of air movement, differences in contribution of sources, and effects of topography, as well as human activity patterns and proximity to sources. However, scientists began to develop methods for discriminating diesel particles from other kinds of smoke in the early 1980s, and they have continued to improve and expand these methods ever since, resulting in better estimates of diesel exhaust exposure.

Some people have greater exposure to diesel exhaust than others mainly due to closer proximity to sources. Those near major roadways (within 300 meters) are especially exposed. This is of obvious importance to schools, day-care centers and hospitals close to major roadways because children and the sick are more vulnerable than average persons.

Health data are available from studies of workers in various industries, such as railroad, tunnel, heavy equipment and trucking. Exposure in working conditions studies varies by job category. This allows investigators to classify exposures as high, medium, or low or no exposures. They can then examine these exposure classifications to determine their

relationship to the number of lung cancer cases in each job category. Since these studies were mostly retrospective, investigators did not measure actual exposure concentrations but estimated exposure concentrations after the fact.

Adverse health effects

In this section, we give a technical overview of the range and scope of adverse effects associated with diesel exhaust exposure along with examples from scientific literature. This is not an exhaustive review. Readers seeking more information should refer to recent systematic reviews such as the USEPA Office of Research and Development *Health Assessment Document for Diesel Engine Exhaust*, published in 2002, and to other publications discussed in the following section.

Diesel exhaust exposure appears to cause respiratory system and circulatory system health impairments. The associations between diesel exhaust exposure and respiratory health impairment endpoints are stronger than for circulatory system impairments. However, because more people suffer from cardiovascular diseases than respiratory diseases, the population-level public health impact is greater for cardiac and circulatory problems. Likewise, research shows an association between diesel exhaust exposure and lung cancer, but the greater prevalence of both cardiovascular and respiratory diseases related to diesel exposures may be more important from a population-wide public health viewpoint. This is because these disease conditions result in illness and death for a larger portion of the population than lung cancer.

People may be more susceptible to diesel exhaust based on their age and their state of health. Many Washingtonians are members of a sensitive age group or have one or more medical conditions aggravated by air pollution. The Washington State Department of Health's Health of Washington State report informs that about 9.1% of Washington's adult residents had asthma , and there were 3117 deaths from lung cancer in Washington State in 2005 (WDOH 2007). Also, in 2006, 7734 Washingtonians died of coronary heart disease (WDOH, 2007).

Diesel exhaust particles irritate respiratory membranes and causes inflammation, allergic reactions, and worsening of allergic reactions to other allergens such as pollen or dust mites. Inhalation of diesel particles enhance the effect of allergens inhaled with or shortly after breathing in the particles (Kobayashi 2000; Steerenberg et al. 1999; Ichinose et al. 2004), and elicits allergic responses to diesel particles themselves (Walters et al., 2001; Hao et al. 2003). Animals exposed in their mother's womb to diesel particles and extracts from them show increased tendency towards allergic reaction (Watanabe and Ohsawa, 2002).

Human reactions to airborne allergens are similar to those observed in animals. Diesel exhaust particles enhance reactions to airborne allergens (Bartra et al., 2007; Dávila et al., 2007). Studies of humans exposed to diesel particles for short periods of time have shown increased airway responsiveness (Nordenhäll et al. 2001), respiratory symptoms (Rudell

et al., 1996), biochemical markers of allergic response (Wichmann, 2007), and markers of inflammation (Nordenhäll et al., 2000; Salvi et al., 1999; Salvi et al., 2000). Researchers have also observed an association between exposure and inflammation of the airways (Nightingale et al., 2000), enhancement of allergic response to other allergens such as dust mite and pollen (Fujieda et al., 1998; Svartengren et al., 2000; Fahy et al., 2000) and worsening of asthma (Pandya et al., 2002).

People with lung disease such as asthma, chronic bronchitis, or emphysema who are exposed to diesel may experience a worsening of their symptoms. People with asthma may have an immediate reaction such as an asthma attack. Over time, exposure may lead to more severe disease, with permanent airway changes, more severe asthma attacks, and symptoms requiring more medical intervention. Children who develop asthma as a result of exposure to air pollutants are more susceptible to developing serious chronic obstructive lung disease like emphysema or chronic bronchitis in later life. Animal data show that inhalation of diesel particles increases airway responsiveness (Ishihara and Kagawa, 2003), causes inflammation and increases markers for inflammation (Fujimaki et al., 2001). Asthma attacks are more frequent and more severe and the disease progresses towards greater remodeling of the airways with increased exposure to diesel exhaust (Finkelman et al., 2004; Chalupa et al., 2004; Zmirou et al., 2004; Nicolai et al., 2003; Sénéchal et al., 2003).

Diesel exhaust contains chemicals that react with ultraviolet light in sunlight to form ozone, which has also been shown to decrease lung growth and function in children, initiate asthma, and make asthma worse (Peters et al., 2004). Epidemiological studies have found associations with respiratory effects and lung function decrements in children living near roadways. The California Children's Health Study has found occurrence of new asthma cases, not only exacerbation of asthma in children exposed to particulate air pollution including diesel particulates (Peters et al. 2004; Gauderman et al. 2004). Exposure to ozone formed from the action of UV light on hydrocarbons (in part from diesel engine emissions) and nitrates formed in high temperature combustion, including that which occurs in diesel engines, also decrease lung function (Lewis et al., 2005; Peters et al., 2004).

Diesel exhaust affects the immune system by lowering resistance to infectious organisms like viruses and bacteria. It also inhibits the cells that cleanse the airways, allowing pathogenic organisms more chances to get established and cause infections. When people are exposed to diesel exhaust and infectious organisms at the same time, they are more likely to get pneumonia, influenza, or other respiratory infections. Inhalation of diesel particles inhibits respiratory defenses against infectious organisms (Castranova et al., 2001; Yang et al, 2001; Harrod et al., 2003), changes lung function (Dai et al., 2003), alters pulmonary immunity against infectious organisms (Yin et al., 2002; Yang et al, 2001), and inhalation of diesel particles increases susceptibility to infectious agents (Yang et al. 2001).

People with heart or circulatory problems who are exposed to diesel may be more likely to suffer a heart attack or stroke; or to have symptoms like chest pain, fatigue, or extreme

weakness related to impending cardiovascular events. Controlled exposures of animals to diesel exhaust and road aerosols containing diesel exhaust indicate it affects the cardiovascular system. For instance, diesel exhaust particles worsened cardiac arrhythmias induced by short period ischemia/ reperfusion in rats (Yokota et al., 2004). Spontaneously hypertensive rats responded to inhaled diesel exhaust at realistic exposure concentrations with prolonged elevated heart rate and prolonged PQ interval (assessed by electrocardiography), an index of atrio-ventricular node sensitivity in a concentration-dependent manner, indicating that the pacemaker function of the heart was affected (Campen et al., 2003).

Diesel exhaust exposure has been implicated in diminished reproductive performance. Epidemiological studies have noted reduced sperm quality in men with exposure to air pollution, primarily diesel exhaust. One of these studies investigated semen quality in men employed at highway tollgates. While sperm count, and serum levels of follicle stimulating hormone and testosterone were within normal limits in exposed men compared to an age-matched unexposed group, sperm function (total motility, forward progression and other sperm kinetics) were significantly lower in the exposed men (DeRosa et al., 2003). Other studies have found that episodes of air pollution, including diesel exhaust, were associated with decreased sperm quality in exposed young men in the Czech Republic, compared to a matched, unexposed control group (Selevan et al., 2000; Rubes et al., 2005).

Diesel exhaust exposure has been implicated in disruption of normal sexual differentiation during fetal development. For example, one study found the odds of baby boys having cryptorchidism *i.e.*, undescended testes (one of the most common congenital malformations in males) are 2. 42 higher (95% confidence interval = 1.06-5.55) among babies of fathers exposed to diesel exhaust before conception than among babies of fathers without preconception diesel exhaust exposure (Kurahashi et al., 2005). A number of studies in rats and mice have shown that diesel exhaust disrupts endocrine function, affecting reproduction and development. Male animals exposed in the womb during critical windows of development seem to be more sensitive to diesel exhaust than females (Tsukue et al. 2004). While female mice do have reduction of an essential protein related to oöcyte development (Tsukue et al. 2004), male pups whose mothers were exposed had a decreased ability to produce proteins essential to development of testes and other male reproductive structures (Yoshida et al. 2002). Mothers exposed to both filtered or to total exhaust had higher levels of testosterone and lower levels of progesterone in contrast to the normal increase in both hormones during pregnancy, indicating that both gaseous exhaust and particles could be involved. In pups exposed in the wombs of these dams, differentiation of the ovaries, testes and thymus were delayed and disrupted (Watanabe and Kurita, 2001).

Epidemiological studies of truck drivers, railroad employees, heavy equipment operators and other types of workers with chronic exposure to diesel exhaust particles, and of members of the public, have found associations with chronic diseases, including lung cancer (Boffetta et al., 2001; Dawson and Alexeeff 2001; Larkin et al., 2000; Nyberg et al., 2000; Saverin et al., 1999; Bruske-Hohlfeld et al., 2000; Steenland et al., 1998;

Stayner et al., 1998; Bhatia et al., 1998; Lippsett and Campleman, 1999), bladder, and soft tissue cancers (Lee et al., 2003; Crosignani et al. 2004; Nyberg et al., 2000; Seidler et al., 1998; Zeegers et al., 2001),

Studies show an association between exposure to diesel exhaust and lung cancer, as well as cancers of the bladder and soft tissues (Guo et al., 2004). The immune suppressing effects of diesel exhaust can also increase the susceptibility to cancer among those exposed. Several extensive and detailed reviews have been conducted on the body of literature relating long-term exposure to diesel exhaust particles and lung cancer (California EPA, 1998; USEPA, 2002; Cohen and Nikula, 1999). In addition, over 40 studies conducted among those populations exposed to diesel exhaust have found increased rates of lung cancer associated with diesel exhaust particles exposure (Cohen and Nikula, 1999). Occupational studies conducted in railroad workers and truck drivers have consistently found increased lung cancer risk, even after adjusted for smoking. Similar studies conducted among bus garage workers and dock workers also demonstrate increased lung cancer risks, although these findings are not as consistent as the railroad workers and truck drivers (Cohen and Nikula, 1999).

Recent studies further support associations between occupational exposure to diesel exhaust particles and increased risk of lung cancer (Boffeta et al., 2001; Larkin et al., 2000). Other studies also show diesel exhaust can be responsible for lung cancer, as well as cancers of the bladder and soft tissues (Sydbom et al. 2001; International Agency for Research on Cancer, 1989; World Health Organization International Programme on Chemical Safety, 1996; USEPA, 2002).

The review conducted by Boffetta and Silverman (2001) examined the human epidemiological literature regarding bladder cancer and occupational exposures to diesel exhaust. These authors evaluated 35 studies, and performed a meta-analysis of 12 of these studies. The ratio of the risk of disease or death among the exposed to the risk among the unexposed, known as the relative risk, ranged from 1.1 to 1.3, suggesting a 10 to 30% increase in potential risk for developing bladder cancer in some occupationally exposed people (Boffetta and Silverman, 2001).

Experimental animal studies have been done to determine how diesel exhaust affects systems that are shared across animal species; since deliberate exposure of human subjects to concentrations of substances that can do permanent harm is unethical. Studies with animals have involved inhalation exposure to known amounts of diesel exhaust particles or whole diesel exhaust. These studies indicated a proportional relationship between the amount of exposure and adverse effects (dose-response) in tissues, organs and multi-organ systems. Such controlled studies on animals have also been used to investigate the mechanisms by which diesel exhaust causes injury. The animals used in these experiments have been generally healthy, raised in optimum conditions, and not exposed to other toxic agents. Therefore, the effects can be attributed to the experimental exposure itself. Since there is less incidence of measurable changes in the healthy homogeneous populations of animals than would be expected in a heterogeneous population of humans (that varies in susceptibilities by age, gender, genetic background and state of health), the exposure (dose) in animal studies is set considerably higher than

typical human exposure in order to create a discernable effect. Conversely, human populations in epidemiological studies are often large and varied in their susceptibilities, so effects, possibly related to diesel exhaust exposure, have been be detected at far lower levels of exposure than those in the animal studies. In addition, dose-response relationships determined from animal studies have been interpolated to lower levels to give additional information on biological effects in the range of doses experienced by humans.

The carcinogenic effects of diesel exhaust in the lung have been extensively studied and in laboratory animals, using a range of different species, exposure periods, and exposure pathways. The California Environmental Protection Agency Office of Environmental Health Hazard Assessment and the USEPA have reviewed a large number of animal studies, including ones with mice, rats, monkeys, and hamsters. These studies have covered a range of exposures and observation periods from a few hours to greater than two years (or the life expectancy) of the animals. For example, rats and hamsters exposed to diesel soot for two years developed lung tumors (Brightwell et al. 1989). Hyperplastic foci (precursors to neoplastic or carcinogenic changes) resulting from DNA damage became prominent in the lungs of rats exposed to diesel exhaust, increasing over a twelve-month exposure. Persistent oxidative stress and inflammation seem to play an important role in carcinogenesis that occurs after a long latent period (Iwai et al. 2000). Short-term exposure to mouse lung changed the expression of certain genes related to defenses against oxidative stress (Risom et al., 2003). Chronic inhalation rat studies have consistently shown increases in lung tumors associated with exposure to diesel exhaust particles at levels equal to or greater than 2.2-mg/m^3. Significant associations between lower diesel exhaust particles exposure levels (0.35 to 2.2-mg/m^3) and lung tumors in rats were not consistently observed. Gender differences in rat tumor rates could not be definitively established. Diesel exhaust particle exposure has not been shown to increase lung tumors in either monkeys or hamsters.

Summary of adverse effects

In summary, exposure to diesel exhaust is associated with increased incidence and prevalence of respiratory and cardiovascular diseases as well as lung cancer and possibly other types of cancers such as cancers of the bladder and soft tissues. The immune suppressing effects of diesel exhaust can also increase the susceptibility to cancer among those exposed. Some people with asthma, allergic rhinitis, and certain acute and chronic respiratory and cardiovascular disorders are prone to increased effects of these conditions secondary to elevation of diesel exhaust exposure. Diesel exhaust exposure heightens susceptibility to respiratory infections, and is associated with hormonal imbalances, reproductive impairments and developmental abnormalities.

As stated above, although cancer risk is of great concern to the public, cardiac and respiratory effects of diesel exposure have a larger public health impact because they cause death and illness for a greater number of people.

Health protective exposure guidelines

In this section, we briefly summarize the conclusions of systematic literature reviews of diesel-effects toxicology and epidemiology studies conducted by six different organizations. In 1989, the International Agency for Research on Cancer, and in 1996 the World Health Organization's International Programme on Chemical Safety reached the same conclusion that diesel engine exhaust is "probably carcinogenic to humans." Fifteen of the substances in diesel exhaust particles are listed by the International Agency for Research on Cancer as carcinogenic to humans, or as probable or possible human carcinogens. In 1988, the National Institute for Occupational Safety and Health concluded that diesel exhaust particulate matter is a "potential occupational carcinogen." In 1998, the State of California also concluded a likely "causal association of diesel exhaust exposure with lung cancer" in humans; and in 2000, the National Toxicology Program concluded diesel exhaust particulate matter is "reasonably anticipated to be a carcinogen." Currently, the USEPA Integrated Risk Information System database states that diesel exhaust is "likely to be carcinogenic to humans." Although USEPA has not yet adopted a cancer unit risk factor for diesel exhaust particles, it is clear that exposure to diesel exhaust particles is associated with carcinogenesis in both humans and animals.

The International Agency for Research on Cancer review of diesel exhaust evaluated animal and human studies pertaining to lung cancer and found that rat and mice studies showed increased incidence in lung tumors related to exposure concentrations. The International Agency for Research on Cancer also concluded that studies conducted in hamsters and monkeys did not show increases in lung tumor incidence associated with exposure, although study design issues precluded firm conclusions. Similar to the USEPA and California EPA, the International Agency for Research on Cancer found that the human epidemiological data provided limited evidence regarding the association between diesel exhaust particles exposure and lung cancer. They concluded that the laboratory animal evidence was sufficient to conclude diesel exhaust particulate matter is carcinogenic in experimental animals. Overall, the International Agency for Research on Cancer judged diesel exhaust to be a probable human carcinogen in Group 2A (IARC, 1989).

In 1996, the International Programme on Chemical Safety stated that diesel exhaust was a probable human carcinogen and developed a unit risk factor of 3.4×10^{-5} $(\mu g/m^3)^{-1}$. This factor is the upper 95% confidence interval limit of cancer risk apparently associated with lifelong continuous exposure to 1-$\mu g/m^3$ of diesel particulate matter.

In 2002, the USEPA Office of Research and Development published their *Health Assessment Document for Diesel Engine Exhaust*. It states that diesel exhaust is "likely to be carcinogenic to humans by inhalation at any exposure condition. This characterization is based on the totality of evidence from human, animal, and other supporting studies." The USEPA reviewed numerous epidemiologic studies and concluded that many have shown increased lung cancer risks among workers in certain occupations. The relative risks or odds ratios in this systematic review ranged from 1.2 to 2.6. The *Health Assessment Document for Diesel Engine Exhaust* (USEPA ORD,

2002) also noted that two independent meta-analyses show smoking-adjusted relative risk increases of 1.35 and 1.47. Taking this information together, the USEPA analysts selected a relative risk of 1.4 as a reasonable estimate of risk in these diesel exhaust-exposed workers, which is equivalent to an additional lifetime lung cancer risk of 2% more than the average risk in the whole U.S population. The *Health Assessment Document* gives a possible range of upper-bound risk of 1×10^{-3} $(\mu g/m^3)^{-1}$ to 1×10^{-5} $(\mu g/m^3)^{-1}$ for lifetime diesel exhaust exposure; however, to date the USEPA has not promulgated a specific point unit risk factor. To provide a perspective of the potential significance of the lung cancer hazard, the *Health Assessment Document* summarized the estimated possible unit risk factor ranges (10^{-5} to 10^{-3} per $\mu g/m^3$ "as well as lower and zero risk"). It clarified this by stating:

> *"Lower risks are possible and one cannot rule out zero risk. The risks could be zero because (a) some individuals within the population may have a high tolerance to exposure from [diesel exhaust] and therefore not be susceptible to the cancer risk from environmental exposure, and (b) although evidence of this has not been seen, there could be a threshold of exposure below which there is no cancer risk."*

The California Environmental Protection Agency Office of Environmental Health Hazard Assessment completed a comprehensive health assessment of diesel exhaust in 1998 that formed the basis for a decision by the California Air Resources Board to identify particles in diesel exhaust as a toxic air contaminant that may pose a threat to human health. The assessment included review of in vitro, animal experiments and more than 30 epidemiology studies, and performed an epidemiological meta-analysis of these studies to assess potential and actual human health effects from exposure to diesel exhaust.

The California Environmental Protection Agency Office of Environmental Health Hazard Assessment and USEPA also systematically reviewed studies of diesel exhaust-adverse health effects, and, although both the California Environmental Protection Agency and USEPA concluded that diesel exhaust is a carcinogen, only the California Environmental Protection Agency developed a quantitative estimate of risk. The California EPA evaluated several options for developing a quantitative risk estimate, and considered both human and animal studies as the basis for the final value.

The California Environmental Protection Agency concluded that the human epidemiological data provided a more solid basis for deriving a unit risk factor for two main reasons. First, the uncertainties associated with extrapolating the laboratory rat data to humans are relatively large. Factors such as differing particle clearance mechanisms, the presence or absence of an effect threshold, and the likely presence of multiple carcinogenic agents or possible multiple mechanisms can potentially influence toxic outcomes and the exposure-response relationship. Second, a number of human epidemiological studies have been conducted and provide sufficient information on potential dose-response relationships.

The California Environmental Protection Agency focused on two studies as being especially useful for developing a range of unit risk factors for lung cancer. These are the nationwide studies of lung cancer risks for U.S. railroad workers. A case control study (Garshick et al., 1987) was used to determine the coefficient of the logistic relationship of the odds of lung cancer for the duration of the worker's exposure to diesel exhaust. The other Garshick study (1988), a cohort study, was used to calculate a relative hazard of lung cancer for increasing duration of worker exposure, using a proportional hazards model. The case-control study had information on smoking rates, while the cohort study has a smaller confidence interval for the risk estimates. Larkin and others (Larkin et al., 2000) examined the extent to which smoking may have confounded the risk of the cohort study by developing adjustment factors based on the distribution of job-specific smoking rates. After considering differences in smoking rates between workers exposed and unexposed to diesel exhaust, the authors concluded that there were still elevated lung cancer risks attributable to diesel exposure among these workers.

Subsequently, Garshick and others (2004) concluded that because shop workers who had no exposure were included in the cohort, their presence in the study diluted the effect of diesel exhaust. The California Environmental Protection Agency therefore excluded them from their analysis. Exposures of other workers, specifically train workers, were sufficiently low that their lung burden was assumed to be proportional to atmospheric exposures. Data from these studies were supplemented with more refined exposure profiles for US railroad workers collected by Woskie et al. (1988 a, b) and combined with different assumptions regarding exposure concentrations and the effect of exposure time and worker age. Exposure measures for 1982-83 (Woskie et al., 1988 a,b) showed that the train workers considered in the analysis all experienced approximately the same average concentration of 50-$\mu g/m^3$, (rounded) which could be used for determining the cancer unit risk factor.

The California Environmental Protection Agency Office of Environmental Health Hazard Assessment calculated several cancer unit risk factor values based on these studies and different dose-response models and model assumptions. They determined that the model using linear and quadratic continuous covariates, age and calendar year was most satisfactory for calculating slope for relative risk per year of exposure. This slope of 0.015 yr^{-1} (95% confidence interval: 0.0086-0.022), when divided by the intermittency correction (0.033) and the assumed constant concentration (e.g. 50-$\mu g/m^3$ for 29 years) and multiplied by attained age provided the excess relative hazard to determine the increase of lung cancer rates for the life table calculation of a cancer unit risk factor. Because the populations studied were healthy male workers, it was not possible to quantify the risk to women, children or other more susceptible individuals. Therefore, the California EPA used the 95% upper confidence interval limit on the slope of the dose-response curve in male workers.

These studies were conducted nationally among U.S. railroad workers. Garshick and others (1988) conducted a case-control study that obtained death certificates for over 15,000 railroad workers who died in 1981. From this group, 1256 individuals who died of lung cancer were matched with individuals of the same age but who died of natural

causes. Results from a multivariate analysis found a relative risk of 1.55 (95% confidence interval = 1.09, 2.22) for workers with over 20 years of exposure to diesel exhaust. Garshick and other's (1988) study was one involving a cohort of approximately 55,000 railroad workers who were between the ages of 40 and 62 in 1959. Approximately 25% of this cohort included "unexposed" individuals who worked as clerks or signal tenders during the study period (1959 to 1980).

The Scientific Review Panel (California Air Resources Board, 1998) recommended the final unit risk factor (3.0×10^{-4} $(\mu g/m^3)^{-1}$) selected by the California Environmental Protection Agency Office of Environmental Health Hazard Assessment. In their report, the Panel considered the California EPA findings in light of several other quantitative cancer analyses.

When considering causality inference based on epidemiological studies, it is essential to know that these studies seek to find a real association between incidence of a disease or harmful endpoint and exposure to an agent, such as a toxic substance. While such studies can be carefully designed to address if an association is linked to the exposure being observed, and not some other event or concurring exposure, they can still only assure that the association is real. A single study cannot determine whether the exposure observed causes the effect observed. To infer a causal relationship between exposure and effect, scientists use certain guidelines sometimes referred to as the Hill criteria after Sir Austin Bradford Hill, who wrote about factors that contribute to the judgment that a specific exposure causes a specific harmful endpoint (Hill 1965). While not every one of the Hill criteria need to be fulfilled to infer a causal relationship between an exposure and a disease, the presence of multiple criteria strengthens the judgment of causality, as in the case of the available evidence on diesel exhaust. Both the Office of Environmental Health Hazard Assessment and the USEPA evaluated the human lung cancer-diesel exhaust particles exposure association using modified Hill criteria (Hill, 1965; Rothman, 1986):

- *Temporal relationship (the exposure occurs before the effect is observed)* – The Office of Environmental Health Hazard Assessment stated that the diesel lung cancer studies clearly meet this criterion since all of the subjects were exposed prior to contracting cancer. USEPA also stated clearly that this criterion has been met, however, they noted that a latency analysis had not been conducted on many of the studies reviewed in the *Health Assessment Document for Diesel Engine Exhaust* (USEPA ORD 2002);

- *Strength of the association (magnitude of the relative risk or odds ratio)* – USEPA concluded that the relative risks from the lung cancer studies – ranging between 1.2 to 2.6 – are weak to moderate. Nonetheless, USEPA stated that although more confidence can be given to relative risks that are stronger, the low values observed between diesel and lung cancer should not be constituted to rule out the causal link. Similarly, the California Environmental Protection Agency Office of Environmental Health Hazard Assessment found that although the relative risk of diesel exhaust particles-associated lung cancer was low, it was

similar in range to other significant health outcomes such as environmental tobacco smoke-associated cardiovascular disease (relative risk ranges from 1.3 to 2.08) and environmental tobacco smoke-associated lung cancer (relative risk range from 1.2 to 1.9);

- *Exposure-response relationship (the association of exposure concentrations to the incidence of an effect); and cessation of exposure (a particular disease outcome should be reduced if exposure to a causative agent ends)* – Since exposure in occupational diesel exposure epidemiology studies has been estimated primarily through job classifications instead of monitored workplace diesel exhaust particles concentrations, it is more difficult to show exposure-response relationships. However, the California Environmental Protection Agency Office of Environmental Health Hazard Assessment pointed to a number of studies where subgroups with the longest durations of exposure experienced the highest risks. USEPA also found that the lack of exposure information in the occupational studies severely limits the confidence in the dose-response relationship. However, they also found that "significant dose-response (using duration of employment as a surrogate) was observed in various studies for railroad workers,… truck drivers… transportation/heavy equipment operators,… and dock workers."

- *Consistency of findings (the effect is seen consistently across studies)* – USEPA found increased lung cancer in a number of human studies conducted among diesel exhaust particles exposed populations. They stated that findings from two recent meta-analyses demonstrated a consistent, positive relationship between diesel exposure and lung cancer, even though the original data reflected significant heterogeneity. The California Environmental Protection Agency Office of Environmental Health Hazard Assessment also conducted a meta-analysis that found a consistent positive association between occupational exposures and lung cancer. They noted a large degree of consistency among the worker studies such as truck drivers, railroad workers, equipment operators, although the results are not always statistically significant;

- *Biological plausibility (the effect is coherent with current biological knowledge of the effects of the exposure agent)* – Both USEPA and the California Environmental Protection Agency Office of Environmental Health Hazard Assessment summarized evidence supporting biological plausibility as:
  a) Evidence that diesel exhaust particles cause lung cancer in laboratory animal studies,
  b) Evidence that diesel exhaust particles contain mutagenic and carcinogenic substances such as polycyclic aromatic hydrocarbons and nitrosamines,

  Additional evidence cited by the California EPA included the fact that diesel exhaust particles contain compounds that occur in other carcinogenic mixtures such as cigarette smoke and coke oven emissions. Similarly, USEPA cited evidence of tumorigenicity associated with the organic components of diesel

exhaust particles, as well as DNA adducts found in blood samples of occupationally exposed workers;

- *Consideration of alternate explanations (ruling out confounders)*
  a) *The possibility that the association is due to bias* – the California Environmental Protection Agency Office of Environmental Health Hazard Assessment considered the effect of confounding factors (e.g., smoking), recall bias, and selection bias. In brief, they concluded erroneous conclusions resulting from factors like smoking and asbestos exposure were unlikely since the association between diesel exhaust particles and lung cancer is actually strengthened in studies that control for exposures to these substances. The California EPA also stated that exposure misclassification probably occurs in these studies, but would result in a bias toward the null. Exposure was determined through job classifications obtained from unions or facility records. Relatives or others were not asked directly if the subjects were "exposed to diesel," and were therefore unlikely to bias cancer victim exposure towards diesel. Selection bias was also a possibility, since the healthy worker effect is likely to influence the results. However, the California EPA found that this type of selection bias would also result in a bias towards the null, and was not sufficient to explain the increase lung cancer rates observed in the studies.
  b) *The likelihood that the findings are due to chance* – the California EPA noted that the majority of the occupational studies resulted in positive findings and that if the association was due to chance, the findings would represent a more even "distribution of risks above and below unity." In addition, other reviews have also demonstrated the consistency in positive results among the range of human epidemiological studies conducted in diesel exhaust exposed populations (Cohen and Nikula, 1999); and

- *Specificity of association (implying that a specific agent is associated with only one disease).* When specificity of an association is found, it provides more support for a causal relationship. However, absence of specificity in no way negates a causal relationship because toxic outcomes often have multiple factors influencing them: Future research will not find a one-to-one relationship between exposure to each component of diesel exhaust and any single type of toxic effect.

In summary, the California Environmental Protection Agency Office of Environmental Health Hazard Assessment identified statistically significant increases in lung cancer from case-control studies in truck drivers, railroad workers, heavy equipment operators and self-reported diesel exhaust exposure. Other more recent studies have supported the association between occupational exposures to diesel exhaust particles and lung cancer (Boffetta et al., 2001).

The 1998 the California Environmental Protection Agency Office of Environmental Health Hazard Assessment health assessment of diesel exhaust established a chronic reference exposure level of 5-$\mu g/m^3$ for chronic non-cancer health effects, and proposed a

range of values for the upper confidence interval limit of the unit risk factor to be used for risk assessment. The *Health Assessment Document for Diesel Engine Exhaust* (USEPA ORD 2002) report also established a chronic non-cancer health effects exposure guidance, the reference concentration of 5-$\mu g/m^3$ based on human epidemiological studies and animal bioassays.

Recommended risk-based diesel exhaust particles concentration levels

Although the cancer unit risk factor values presented by several agencies and researchers reflect some uncertainty, the estimated unit risk factors range from 1.4×10^{-2} to 3.9×10^{-4} per $\mu g/m^3$. This indicates some consistency among the estimates relative to many unit risk factor estimates for other chemicals. The authors base their recommendations primarily on reviews conducted by other agencies, particularly the USEPA and the California Environmental Protection Agency Office of Environmental Health Hazard Assessment. The Department of Ecology will apply the cancer unit risk factor developed by the Office of Environmental Health Hazard Assessment, 3.0×10^{-4} $(\mu g/m^3)^{-1}$ (an excess of three cancer cases in an exposed population of 10,000 per 1-$\mu g/m^3$ of diesel particles breathed) in diesel particle risk assessments. Accordingly, the Department will use the California Environmental Protection Agency inhalation slope factor of 1.1-mg/kg-day to evaluate the potential carcinogenic risk associated with diesel exhaust particles. This is consistent also with the California Air Resources Board Scientific Review Panel's unit risk factor "reasonable estimate" of 3.0×10^{-4} $(\mu g/m^3)^{-1}$. The unit risk factor is the upper-bound additional lifetime cancer risk (in addition to those risks already existing without exposure to the carcinogen in question) estimated to result from continuous life-long exposure to an agent at a concentration of 1-$\mu g/m^3$ air. The California Air Resources Board Scientific Review Panel's unit risk factor "reasonable estimate" of 3.0×10^{-4} is equivalent to a negligible risk (risk *de minimis*) concentration of 0.003-$\mu g/m^3$. Risks that are negligible and too small to be of societal concern are usually assumed to have probabilities less than 10^{-6}.

Even the least exposed Washingtonians are likely to be exposed to higher diesel particulate contrarians than 0.003-$\mu g/m^3$, but overall most Washingtonians' average daily exposures to diesel exhaust particles are probably less than 5-$\mu g/m^3$ – the non-cancer respiratory effects guideline concentration. Some evidence for this is provided in the USEPA's 2002 National-Scale Air Toxics Assessment data tables. The tables contain USEPA's concentration estimates of diesel particulate matter arising from on-road sources and non-road sources in each of Washington's census tracts. The overall median concentrations of diesel particulate matter estimated to arise from on-road sources was 0.355-$\mu g/m^3$, and from non-road sources was 0.601-$\mu g/m^3$. These sum to a total concentration of 0.956-$\mu g/m^3$. USEPA used an exposure model to develop estimates of how much diesel particulate matter people are actually exposed to. Their estimate of median exposure in Washington was 0.249-$\mu g/m^3$.

USEPA' estimate of median diesel exposure concentration in Washington corresponds to an apparently non-negligible upper-bound additional lifetime cancer risk of 75 per million (using the California Environmental Protection Agency inhalation unit risk factor), but an evidently safe non-cancer respiratory hazard (Hazard quotient = 0.109, using 5-$\mu g/m^3$ as a 24-hour time-weighted average to evaluate the non-carcinogenic effects. A hazard quotient lower than one is below the level of concern). Referring to the National-Scale Air Toxics Assessment data tables, the census tract USEPA found to have Washington's highest exposure to diesel exhaust would have a corresponding upper-bound additional lifetime cancer risk of 1226 per million, but a hazard quotient of just 0.817. The census tract USEPA estimated to have the lowest diesel exposure would have a corresponding upper-bound additional lifetime cancer risk of 7 per million and a hazard quotient of 0.005.

The models USEPA used in the National-Scale Air Toxics Assessment may not be able to discern risks to people located next to high-traffic roadways, truck stops, rail yards or other areas where higher diesel exhaust particles concentrations occur, despite the fact that some people live, work, attend school, or other sustained activities, near such sources. In fact, some people are routinely exposed to diesel exhaust particles levels exceeding the 5-$\mu g/m^3$ guideline. For example, the average diesel exhaust particles concentrations have been estimated to be around 10-$\mu g/m^3$ in the maximally impacted, high-traffic area of the Duwamish valley in south Seattle (US Department of Health and Human Services, 2008), but this area is smaller than individual census tracts in the same area.

Consistent with both USEPA and the California Environmental Protection Agency Office of Environmental Health Hazard Assessment, Ecology will use a reference concentration of 5-$\mu g/m^3$ as a 24-hour time-weighted average concentration to evaluate the non-carcinogenic effects associated with diesel exhaust particles. As mentioned above, the Department will use the California Environmental Protection Agency inhalation unit risk factor of 3×10^{-4} $(\mu g/m^3)^{-1}$ and slope factor of 1.1-mg/kg-day to evaluate the potential carcinogenic risk from diesel exhaust particles.

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