

µm in diameter) are more strongly associated than "coarse" respirable particulates (i.e., particles greater than 2.5 µm but less than 10 µm in diameter) with the adverse health effects observed (EPA, 1996).

MSHA recognizes that there are two difficulties involved in utilizing the evidence from such studies in assessing risks to miners from occupational dpm exposures. First, although dpm is a fine particulate, ambient air also contains fine particulates other than dpm. Therefore, health effects associated with exposures to fine particulate matter in air pollution studies are not associated specifically with exposures to dpm or any other one kind of fine particulate matter. Second, observations of adverse health effects in segments of the general population do not necessarily apply to the population of miners. Since, due to age and selection factors, the health of miners differs from that of the public as a whole, it is possible that fine particles might not affect miners, as a group, to the same degree as the general population.

Some commenters reiterated these two points, recognized by MSHA in the proposal, without addressing MSHA's stated reasons for including health effects associated with fine particulates in this risk assessment. There are compelling reasons why MSHA considered this body of evidence in this rulemaking.

Since dpm is a type of respirable particle, information about health effects associated with exposures to respirable particles, and especially to fine particulate matter, is certainly relevant, even if difficult to apply directly to dpm exposures. Adverse health effects in the general population have been observed at ambient atmospheric particulate concentrations well below the dpm concentrations studied in occupational settings. The potency of dpm differs from the total fine particulate found in ambient air. This makes it difficult to establish a specific exposure-response relationship for dpm that is based on fine particle results. However, this does not mean that these results should be ignored in a dpm risk assessment. The available evidence of adverse health effects associated with fine particulates is still highly relevant for dpm hazard identification. Furthermore, as shown in Subsection 3.c.ii of this risk assessment, the fine particle research findings can be used to construct a rough exposure-response relationship for dpm, showing significantly increased risks of material impairment among exposed miners. MSHA's estimates are based on the best available epidemiologic evidence and

show risks high enough to warrant regulatory action.

Moreover, extensive scientific literature shows that occupational dust exposures contribute to the development of Chronic Obstructive Pulmonary Diseases (COPD), thereby compromising the pulmonary reserve of some miners. Miners experience COPD at a significantly higher rate than the general population (Becklake 1989, 1992; Oxman 1993; NIOSH 1995). In addition, many miners also smoke tobacco. This places affected miners in subpopulations specifically identified as susceptible to the adverse health effects of respirable particle pollution (EPA, 1996). Some commenters (e.g., MARG) repeated MSHA's observation that the population of miners differs from the general population but failed to address MSHA's concern for miners' increased susceptibility due to COPD incidence and/or smoking habits. The Mine Act requires that standards " * * * most adequately assure on the basis of the best available evidence that no miner suffer material impairment of health or functional capacity * * *" (Section 101(a)(6), emphasis added). This most certainly authorizes MSHA to protect miners who have COPD and/or smoke tobacco.

MARG also submitted the opinion that if " * * * regulation of fine particulate matter is necessary, it [MSHA] should propose a rule dealing specifically with the issue of concern, rather than a rule that limits total airborne carbon or arbitrarily singles out diesel exhaust * * *." MSHA's concern is not with "total airborne carbon" but with dpm, which consists mostly of submicrometer airborne carbon. At issue here, however, are the adverse health effects associated with dpm exposure. Dpm is a type of fine particulate, and there is no evidence to suggest that the dpm fraction contributes less than other fine particulates to adverse health effects linked to exposures in ambient air.

For this reason, and because miners may be especially susceptible to fine particle effects, MSHA has concluded, after considering the public comments, that the body of evidence from air pollution studies is highly relevant to this risk assessment. The Agency is, therefore, taking the evidence fully into account.

b. Acute Health Effects

Information pertaining to the acute health effects of dpm includes anecdotal reports of symptoms experienced by exposed miners, studies based on exposures to diesel emissions, and studies based on exposures to

particulate matter in the ambient air. These will be discussed in turn.

Subsection 2.a.iii of this risk assessment addressed the relevance to dpm of studies based on exposures to particulate matter in the ambient air.

Only the evidence from human studies will be addressed in this section. Data from genotoxicity studies and studies on laboratory animals will be discussed later, in Subsection 2.d on mechanisms of toxicity. Section 3.a and 3.b contain MSHA's interpretation of the evidence relating dpm exposures to acute health hazards.

i. Symptoms Reported by Exposed Miners

Miners working in mines with diesel equipment have long reported adverse effects after exposure to diesel exhaust. For example, at the dpm workshops conducted in 1995, a miner reported headaches and nausea experienced by several operators after short periods of exposure (dpm Workshop; Mt. Vernon, IL, 1995). Another miner reported that smoke from poorly maintained equipment, or from improper fuel use, irritates the eyes, nose, and throat. "We've had people sick time and time again * * * at times we've had to use oxygen for people to get them to come back around to where they can feel normal again." (dpm Workshop; Beckley, WV, 1995). Other miners (dpm Workshops; Beckley, WV, 1995; Salt Lake City, UT, 1995), reported similar symptoms in the various mines where they worked.

At the 1998 public hearings on MSHA's proposed dpm rule for coal mines, one miner, with work experience in a coal mine utilizing diesel haulage equipment at the face, testified that

* * * unlike many, I have not experienced the headaches, the watering of the eyes, the cold-like symptoms and walking around in this cloud of smoke. Maybe it's because of the maintenance programs. Maybe it's because of complying with ventilation. * * * after 25 years, I have not shown any effects. [SLC, 1998]

Other miners working at dieselized coal mines testified at those hearings that they had personally experienced eye irritation and/or respiratory ailments immediately after exposure to diesel exhaust, and they attributed these ailments to their exposure. For example, one miner attributed a case of pneumonia to a specific episode of unusually high exposure. (Birm., 1998) The safety and training manager of the mining company involved noted that "there had been a problem recognized in review with that exhaust system on that particular piece of equipment" and that the pneumonia may have

developed due to "idiosyncrasy of his lungs that respond to any type of a respiratory irritant." The manager suggested that this incident should not be generalized to other situations but provided no evidence that the miner's lungs were unusually susceptible to irritation.²¹

Another miner, who had worked at the same underground mine before and after diesel haulage equipment was introduced, indicated that he and his co-workers began experiencing acute symptoms after the diesel equipment was introduced. This miner suggested that these effects were linked to exposure, and referring to a co-worker stated:

* * * had respiratory problems, after * * * diesel equipment was brought into that mine—he can take off for two weeks vacation, come back—after that two weeks, he felt pretty good, his respiratory problems would straighten up, but at the very instant that he gets back in the face of diesel-powered equipment, it starts up again, his respiratory problems will flare up again, coughing, sore throat, numerous problems in his chest. (Birm., 1998).

Several other underground miners asserted there was a correlation between diesel exposure levels and the frequency and/or intensity of respiratory symptoms, eye irritations, and chest ailments. One miner, for example, stated:

I've experienced [these symptoms] myself. * * * other miners experience the same kind of distresses * * * Some of the stresses you actually can feel—you don't need a gauge to measure this—your burning eyes, nose, throat, your chest irritation. The more you're exposed to, the higher this goes. This includes headaches and nausea and some lasting congestion, depending on how long you've been exposed per shift or per week.

The men I represent have experienced more cold-like symptoms, especially over the past, I would say, eight to ten years, when diesel has really peaked and we no longer really use much of anything else. [SLC, 1998]

Kahn *et al.* (1988) conducted a study of the prevalence and seriousness of such complaints, based on United Mine Workers of America records and subsequent interviews with the miners involved. The review involved reports at five underground coal mines in Utah and Colorado between 1974 and 1985. Of the 13 miners reporting symptoms: 12 reported mucous membrane irritation, headache and light-headedness; eight reported nausea; four reported heartburn; three reported vomiting and weakness, numbness, and tingling in

²¹ MSHA realizes the incidents related in this subsection are anecdotal and draws no statistical conclusions from them. Since they pertain to specific experiences, however, they can be useful in identifying a potential hazard.

extremities; two reported chest tightness; and two reported wheezing (although one of these complained of recurrent wheezing without exposure). All of these incidents were severe enough to result in lost work time due to the symptoms (which subsided within 24 to 48 hours).

In comments submitted for this rulemaking, the NMA pointed out, as has MSHA, that the evidence presented in this subsection is anecdotal. The NMA, further, suggested that the cited article by Kahn *et al.* typified this kind of evidence in that it was "totally devoid of any correlation to actual exposure levels." A lack of concurrent exposure measurements is, unfortunately, not restricted to anecdotal evidence; and MSHA must base its evaluation on the available evidence. MSHA recognizes the scientific limitations of anecdotal evidence and has, therefore, compiled and considered it separately from more formal evidence. MSHA nevertheless considers such evidence potentially valuable for identifying acute health hazards, with the understanding that confirmation requires more rigorous investigation.²²

With respect to the same article (Kahn *et al.*, 1988), and notwithstanding the NMA's claim that the article was totally devoid of any correlation to exposure levels, the NMA also stated that MSHA:

* * * neglects to include in the preamble the article's description of the conditions under which the "overexposures" occurred, *e.g.*, "poor engine maintenance, poor maintenance of emission controls, prolonged idling of machinery, engines pulling heavy loads, use of equipment during times when ventilation was disrupted (such as during a move of longwall machinery), use of several pieces of equipment exhausting into the fresh-air intake, and use of poor quality fuel. The NMA asserted that these conditions, cited in the article, "have been addressed by MSHA's final standards for diesel equipment in underground coal mines issued October 25, 1996."²³ Furthermore, despite its reservations about anecdotal evidence:

NMA is mindful of the testimony of several miners in the coal proceeding who complained of transient irritation owing to exposure to diesel exhaust. * * * the October 1996 regulations together with the phased-in introduction of catalytic converters on all outby equipment and the introduction of such devices on permissible equipment

²² MSHA sees potential value in anecdotal evidence when it relates to immediate experiences. MSHA regards anecdotal evidence to be less appropriate for identifying chronic health effects, since chronic effects cannot readily be linked to specific experiences. Accordingly, this risk assessment places little weight on anecdotal evidence for the chronic health hazards considered.

²³ The 1996 regulations to which the NMA was referring do not apply to M/NM mines.

when such technology becomes available will address the complaints raised by the miners.

The NMA provided no evidence, however, that elimination of the conditions described by Kahn *et al.*, or implementation of the 1996 diesel regulations for coal mines, would reduce dpm levels sufficiently to prevent the sensory irritations and respiratory symptoms described. MSHA completed an analysis of the impact of the 1996 diesel regulations for underground coal mines (See Part II, Section 7). We do expect that the concentrations of diesel emissions at the section loading point and during longwall moves will be reduced as these provisions are fully implemented. These dpm levels, though reduced, are still above the exposures expected to cause sensory irritations and respiratory symptoms (See Section 3(d)(5)). MSHA did not explicitly consider the risks to miners of a working lifetime of dpm exposure at very high levels, nor the actions that could be taken to specifically reduce dpm exposure levels in underground coal mines when developing the 1996 underground coal diesel regulations. It was understood that the agency would be taking a separate look at the health risks of dpm exposure. In addition, the NMA did not provide evidence that these are the only conditions under which complaints of sensory irritations and respiratory symptoms occur, or explain why eliminating them would reduce the need to prevent excessive exposures under other conditions.

In the proposal for the present rule, MSHA requested additional information about such effects from medical personnel who have treated miners. IMC Global submitted letters from four healthcare practitioners in Carlsbad, NM, including three physicians. None of these practitioners attributed any cases of respiratory problems or other acute symptoms to dpm exposure. Three of the four practitioners noted that they had observed respiratory symptoms among exposed miners but attributed these symptoms to chronic lung conditions, smoking, or other factors. One physician stated that "[IMC Global], which has used diesel equipment in its mining operations for over 20 years, has never experienced a single case of injury or illness caused by exposures to diesel particulates."

ii. Studies Based on Exposures to Diesel Emissions

Several experimental and statistical studies have been conducted to investigate acute effects of exposure to

diesel emissions. These more formal studies provide data that are more scientifically rigorous than the anecdotal evidence presented in the preceding subsection. Unless otherwise indicated, diesel exhaust exposures were determined qualitatively.

In a clinical study (Battigelli, 1965), volunteers were exposed to three concentrations of diluted diesel exhaust and then evaluated to determine the effects of exposure on pulmonary resistance and the degree of eye irritation. The investigators stated that "levels utilized for these controlled exposures are comparable to realistic values such as those found in railroad shops." No statistically significant change in pulmonary function was detected, but exposure for ten minutes to diesel exhaust diluted to the middle level produced "intolerable" irritation in some subjects while the average irritation score was midway between "some" irritation and a "conspicuous but tolerable" irritation level. Diluting the concentration by 50% substantially reduced the irritation. At the highest exposure level, more than 50 percent of the volunteers discontinued the experiment before 10 minutes because of "intolerable" eye irritation.

A study of underground iron ore miners exposed to diesel emissions found no difference in spirometry measurements taken before and after a work shift (Jørgensen and Svensson 1970). Similarly, another study of coal miners exposed to diesel emissions detected no statistically significant relationship between exposure and changes in pulmonary function (Ames *et al.* 1982). However, the authors noted that the lack of a statistically significant result might be due to the low concentrations of diesel emissions involved.

Gamble *et al.* (1978) observed decreases in pulmonary function over a single shift in salt miners exposed to diesel emissions. Pulmonary function appeared to deteriorate in relation to the concentration of diesel exhaust, as indicated by NO₂; but this effect was confounded by the presence of NO₂ due to the use of explosives.

Gamble *et al.* (1987a) assessed response to diesel exposure among 232 bus garage workers by means of a questionnaire and before- and after-shift spirometry. No significant relationship was detected between diesel exposure and change in pulmonary function. However, after adjusting for age and smoking status, a significantly elevated prevalence of reported symptoms was found in the high-exposure group. The strongest associations with exposure were found for eye irritation, labored

breathing, chest tightness, and wheeze. The questionnaire was also used to compare various acute symptoms reported by the garage workers and a similar population of workers at a lead acid battery plant who were not exposed to diesel fumes. The prevalence of work-related eye irritations, headaches, difficult or labored breathing, nausea, and wheeze was significantly higher in the diesel bus garage workers, but the prevalence of work-related sneezing was significantly lower.

Ulfvarson *et al.* (1987) studied effects over a single shift on 47 stevedores exposed to dpm at particle concentrations ranging from 130 μm^3 to 1000 μm^3 . Diesel particulate concentrations were determined by collecting particles on glass fiber filters of unspecified efficiency. A statistically significant loss of pulmonary function was observed, with recovery after 3 days of no occupational exposure.

To investigate whether removal of the particles from diesel exhaust might reduce the "acute irritative effect on the lungs" observed in their earlier study, Ulfvarson and Alexandersson (1990) compared pulmonary effects in a group of 24 stevedores exposed to unfiltered diesel exhaust to a group of 18 stevedores exposed to filtered exhaust, and to a control group of 17 occupationally unexposed workers. The filters used were specially constructed from 144 layers of glass fiber with "99.97% degrees of retention of dioctylphthalate mist with particle size 0.3 μm ." Workers in all three groups were nonsmokers and had normal spirometry values, adjusted for sex, age, and height, prior to the experimental workshift.

In addition to confirming the earlier observation of significantly reduced pulmonary function after a single shift of occupational exposure, the study found that the stevedores in the group exposed only to filtered exhaust had 50–60% less of a decline in forced vital capacity (FVC) than did those stevedores who worked with unfiltered equipment. Similar results were observed for a subgroup of six stevedores who were exposed to filtered exhaust on one shift and unfiltered exhaust on another. No loss of pulmonary function was observed for the unexposed control group. The authors suggested that these results "support the idea that the irritative effect of diesel exhausts [sic] to the lungs is the result of an interaction between particles and gaseous components and not of the gaseous components alone." They concluded that " * * * it should be a useful practice to filter off particles from diesel

exhausts in work places even if potentially irritant gases remain in the emissions" and that "removal of the particulate fraction by filtering is an important factor in reducing the adverse effect of diesel exhaust on pulmonary function."

Rudell *et al.* (1996) carried out a series of double-blind experiments on 12 healthy, non-smoking subjects to investigate whether a particle trap on the tailpipe of an idling diesel engine would reduce acute effects of diesel exhaust, compared with exposure to unfiltered exhaust. Symptoms associated with exposure included headache, dizziness, nausea, tiredness, tightness of chest, coughing, and difficulty in breathing. The most prominent symptoms were found to be irritation of the eyes and nose, and a sensation of unpleasant smell. Among the various pulmonary function tests performed, exposure was found to result in significant changes only as measured by increased airway resistance and specific airway resistance. The ceramic wall flow particle trap reduced the number of particles by 46 percent, but resulted in no significant attenuation of symptoms or lung function effects. The authors concluded that diluted diesel exhaust caused increased irritant symptoms of the eyes and nose, unpleasant smell, and bronchoconstriction, but that the 46-percent reduction in median particle number concentration observed was not sufficient to protect against these effects in the populations studied.

Wade and Newman (1993) documented three cases in which railroad workers developed persistent asthma following exposure to diesel emissions while riding immediately behind the lead engines of trains having no caboose. None of these workers were smokers or had any prior history of asthma or other respiratory disease. Asthma diagnosis was based on symptoms, pulmonary function tests, and measurement of airway hyperreactivity to methacholine or exercise.

Although MSHA is not aware of any other published report directly relating diesel emissions exposures to the development of asthma, there have been a number of recent studies indicating that dpm exposure can induce bronchial inflammation and respiratory immunological allergic responses in humans. Studies published through 1997 are reviewed in Peterson and Saxon (1996) and Diaz-Sanchez (1997).

Diaz-Sanchez *et al.* (1994) challenged healthy human volunteers by spraying

300 µg dpm into their nostrils.²⁴ Immunoglobulin E (IgE) binds to mast cells where it binds antigen leading to secretion of biologically active amines (e.g., histamine) causing dilation and increased permeability of blood vessels. These amines are largely responsible for clinical manifestations of such allergic reactions as hay fever, asthma, and hives. Enhanced IgE levels were found in nasal washes in as little as 24 hours, with peak production observed 4 days after the dpm was administered.²⁵ No effect was observed on the levels of other immunoglobulin proteins. The selective enhancement of local IgE production was demonstrated by a dramatic increase in IgE-secreting cells. The authors suggested that dpm may augment human allergic disease responses by enhancing the production of IgE antibodies. Building on these results, Diaz-Sanchez *et al.* (1996) measured cytokine production in nasal lavage cells from healthy human volunteers challenged with 150 µg dpm sprayed into each nostril. Based on the responses observed, including a broad increase in cytokine production, along with the results of the 1994 paper, the authors concluded that dpm exposure contributes to enhanced local IgE production and thus plays a role in allergic airway disease.

Salvi *et al.* (1999) exposed healthy human volunteers to diluted diesel exhaust at a dpm concentration of 300 µg/m³ for one hour with intermittent exercise. Although there were no changes in pulmonary function, there were significant increases in various markers of allergic response in airway lavage fluid. Bronchial biopsies obtained six hours after exposure also showed significant increases in markers of immunologic response in the bronchial tissue. Significant increases in other markers of immunologic response

²⁴ Assuming that a working miner inhales approximately 1.25 m³ of air per hour, this dose corresponds to a 1-hour exposure at a dpm concentration of 240 µg/m³.

²⁵ IgE is one of five types of immunoglobulin, which are proteins produced in response to allergens. Cytokine (mentioned later) is a substance involved in regulating IgE production.

were also observed in peripheral blood following exposure. A marked cellular inflammatory response in the airways was reported. The authors concluded that “at high ambient concentrations, acute short-term DE [diesel exhaust] exposure produces a well-defined and marked systemic and pulmonary inflammatory response in healthy human volunteers, which is underestimated by standard lung function measurements.”

iii. Studies Based on Exposures to Particulate Matter in Ambient Air

Due to an incident in Belgium's industrial Meuse Valley, it was known as early as the 1930s that large increases in particulate air pollution, created by winter weather inversions, could be associated with large simultaneous increases in mortality and morbidity. More than 60 persons died from this incident, and several hundred suffered respiratory problems. The mortality rate during the episode was more than ten times higher than normal, and it was estimated that over 3,000 sudden deaths would occur if a similar incident occurred in London. Although no measurements of pollutants in the ambient air during the episode are available, high PM levels were obviously present (EPA, 1996).

A significant elevation in particulate matter (along with SO₂ and its oxidation products) was measured during a 1948 incident in Donora, PA. Of the Donora population, 42.7 percent experienced some acute adverse health effect, mainly due to irritation of the respiratory tract. Twelve percent of the population reported difficulty in breathing, with a steep rise in frequency as age progressed to 55 years (Schrenk, 1949).

Approximately as projected by Firket (1931), an estimated 4,000 deaths occurred in response to a 1952 episode of extreme air pollution in London. The nature of these deaths is unknown, but there is clear evidence that bronchial irritation, dyspnea, bronchospasm, and, in some cases, cyanosis occurred with unusual prevalence (Martin, 1964).

These three episodes “left little doubt about causality in regard to the

induction of serious health effects by very high concentrations of particle-laden air pollutant mixtures” and stimulated additional research to characterize exposure-response relationships (EPA, 1996). Based on several analyses of the 1952 London data, along with several additional acute exposure mortality analyses of London data covering later time periods, the U.S. Environmental Protection Agency (EPA) concluded that increased risk of mortality is associated with exposure to combined particulate and SO₂ levels in the range of 500–1000 µg/m³. The EPA also concluded that relatively small, but statistically significant increases in mortality risk exist at particulate (but not SO₂) levels below 500 µg/m³, with no indications of a specific threshold level yet indicated at lower concentrations (EPA, 1986).

Subsequently, between 1986 and 1996, increasingly sophisticated techniques of particulate measurement and statistical analysis have enabled investigators to address these questions more quantitatively. The studies on acute effects carried out since 1986 are reviewed in the 1996 EPA Air Quality Criteria for Particulate Matter, which forms the basis for the discussion below (EPA, 1996).

At least 21 studies have been conducted that evaluate associations between acute mortality and morbidity effects and various measures of fine particulate levels in the ambient air. These studies are identified in Tables III–2 and III–3. Table III–2 lists 11 studies that measured primarily fine particulate matter using filter-based optical techniques and, therefore, provide mainly qualitative support for associating observed effects with fine particles. Table III–3 lists quantitative results from 10 studies that reported gravimetric measurements of either the fine particulate fraction or of components, such as sulfates, that serve as indicators or surrogates of fine particulate exposures.

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Table III-2. — Studies of acute health effects using filter based optical indicators of fine particles in the ambient air.

City	Study Years	Indicator*	Reference†
Acute Mortality			
London	1963-1972 (winters)	BS	Thurston et al., 1989
	1965-1972 (winters)		Ito et al., 1993
Athens	1975-1987	BS	Katsouyanni et al., 1990
	July, 1987		Katsouyanni et al., 1993
	1984-1988		Touloumi et al., 1994
Los Angeles	1970-1979	KM	Shumway et al., 1988
	1970-1979		Kinney and Ozkaynak, 1991
Santa Clara	1980-1986 (winters)	COH	Fairley, 1990
Increased Hospitalization			
Barcelona	1985-1989	BS	Sunyer et al., 1993
Acute Change in Pulmonary Function			
Wageningen, Netherlands		BS	Hoek and Brunkreef, 1993
Netherlands		BS	Roemer et al., 1993

† All references are from EPA, 1996

*BS (black smoke), KM (carbonaceous material), and COH (coefficient of haze) are optical measurements that are most directly related to elemental carbon concentrations, but only indirectly to mass. Site specific calibrations and/or comparisons of such optical measurements with gravimetric mass measurements in the same time and city are needed to make inferences about particle mass. However, all three of these indicators preferentially measure carbon particles found in the fine fraction of total airborne particulate matter. (EPA, 1996).

Table III-3. — Studies of acute health effects using gravimetric indicators of fine particles in the ambient air.

Study	Indicator	RR per 25 $\mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ Increase (95% Confidence Interval)	Mean $\text{PM}_{2.5}$ Levels (Min/Max) [†]
Acute Mortality			
Six Cities ^A (overall)	$\text{PM}_{2.5}$	1.038 (1.026, 1.055)	
Portage, WI	$\text{PM}_{2.5}$	1.030 (0.993, 1.071)	11.2 (± 7.8)
Topeka, KS	$\text{PM}_{2.5}$	1.020 (0.951, 1.092)	12.2 (± 7.4)
Boston, MA	$\text{PM}_{2.5}$	1.056 (1.038, 1.071)	15.7 (± 9.2)
St. Louis, MO	$\text{PM}_{2.5}$	1.028 (1.010, 1.043)	18.7 (± 10.5)
Kingston/Knoxville, TN	$\text{PM}_{2.5}$	1.035 (1.005, 1.066)	20.8 (± 9.6)
Steubenville, OH	$\text{PM}_{2.5}$	1.025 (0.998, 1.053)	29.6 (± 21.9)
Increased Hospitalization			
Ontario, CAN ^B	SO_4^-	1.03 (1.02, 1.04)	Min/Max = 3.1 - 8.2
Ontario, CAN ^C	SO_4^- O_3	1.03 (1.02, 1.04) 1.03 (1.02, 1.05)	Min/Max = 2.0 - 7.7
NYC/Buffalo, NY ^D	SO_4^-	1.05 (1.01, 1.10)	NR
Toronto, CAN ^D	H^+ (Nmol/m ³) SO_4^- $\text{PM}_{2.5}$	1.16 (1.03, 1.30)* 1.12 (1.00, 1.24) 1.15 (1.02, 1.78)	28.8 (NR, 391) 7.6 (NR, 48.7) 18.6 (NR, 66.0)
Increased Respiratory Symptoms			
Southern California ^F	SO_4^-	1.48 (1.14, 1.91)	R = 2 - 37
Six Cities ^G (Cough)	$\text{PM}_{2.5}$ $\text{PM}_{2.5}$ Sulfur H^+	1.19 (1.01, 1.42)** 1.23 (0.95, 1.59)** 1.06 (0.87, 1.29)**	18.0 (7.2, 37)*** 2.5 (3.1, 61)*** 18.1 (0.8, 5.9)***
Six Cities ^G (Lower Resp. Symp.)	$\text{PM}_{2.5}$ $\text{PM}_{2.5}$ Sulfur H^+	1.44 (1.15 - 1.82)** 1.82 (1.28 - 2.59)** 1.05 (0.25 - 1.30)**	18.0 (7.2, 37)*** 2.5 (0.8, 5.9)*** 18.1 (3.1, 61)***
Denver, CO ^P (Cough, adult asthmatics)	$\text{PM}_{2.5}$ SO_4^- H^+	0.0012 (0.0043)**** 0.0042 (0.00035)**** 0.0076 (0.0038)****	0.41 - 73 0.12 - 12 2.0 - 41
Decreased Lung Function			
Uniontown, PA ^E	$\text{PM}_{2.5}$	PEFR 23.1 (-0.3, 36.9) (per 25 $\mu\text{g}/\text{m}^3$)	25/88 (NR/88)
Seattle, WA ^Q (Asthmatics)	b _{ext.} calibrated by $\text{PM}_{2.5}$	FEV1 42 ml (12,73) FVC 45 ml (20,70)	5/45

References from EPA, 1996, Staff Report

^A Schwartz et al. (1996a)

^B Burnett et al. (1994)

^C Burnett et al. (1995) O_3

^D Thurston et al. (1992, 1994)

^E Neas et al. (1995)

^F Ostro et al. (1993)

^G Schwartz et al. (1994)

^P Ostro et al. (1991)

^Q Koenig et al. (1993)

[†] Min/Max 24-hr PM indicator level shown in parentheses unless otherwise noted as (\pm S.D.), 10 and 90 percentile (10,90).

* Change per 100 nmoles/m³.

** Change per 20 $\mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$; per 5 $\mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$ sulfur; per 25 nmoles/m³ for H^+ .

*** 50th percentile value (10,90 percentile).

**** Coefficient and SE in parenthesis.

A total of 38 studies examining relationships between short-term particulate levels and increased mortality, including nine with fine particulate measurements, were published between 1988 and 1996 (EPA, 1996). Most of these found statistically significant positive associations. Daily or several-day elevations of particulate concentrations, at average levels as low as 18–58 $\mu\text{g}/\text{m}^3$, were associated with increased mortality, with stronger relationships observed in those with preexisting respiratory and cardiovascular disease. Overall, these studies suggest that an increase of 50 $\mu\text{g}/\text{m}^3$ in the 24-hour average of PM_{10} is associated with a 2.5 to 5-percent increase in the risk of mortality in the general population, excluding accidents, suicides, and homicides. Based on Schwartz *et al.* (1996), the relative risk of mortality in the general population increases by about 2.6 to 5.5 percent per 25 $\mu\text{g}/\text{m}^3$ of fine particulate ($\text{PM}_{2.5}$) (EPA, 1996). More specifically, Schwartz *et al.* (1996) reported significantly elevated risks of mortality due to pneumonia, chronic obstructive pulmonary disease (COPD), and ischemic heart disease (IHD). For these three causes of death, the estimated increases in risk per incremental increase of 10 $\mu\text{g}/\text{m}^3$ in the concentration of $\text{PM}_{2.5}$ were 4.0 percent, 3.3 percent, and 2.1 percent, respectively. Each of these three results was statistically significant at a 95-percent confidence level.

A total of 22 studies were published on associations between short-term particulate levels and hospital admissions, outpatient visits, and emergency room visits for respiratory disease, Chronic Obstructive Pulmonary Disease (COPD), pneumonia, and heart disease (EPA, 1996). Fifteen of these studies were focused on the elderly. Of the seven that dealt with all ages (or in one case, persons less than 65 years old), all showed positive results. All of the five studies relating fine particulate measurements to increased hospitalization, listed in Tables III–2 and III–3, dealt with general age populations and showed statistically significant associations. The estimated increase in risk ranges from 3 to 16 percent per 25 $\mu\text{g}/\text{m}^3$ of fine particulate. Overall, these studies are indicative of acute morbidity effects being related to fine particulate matter and support the mortality findings.

Most of the 14 published quantitative studies on ambient particulate exposures and acute respiratory diseases were restricted to children (EPA, 1996, Table 12–12). Although they generally showed positive associations, and may

be of considerable biological relevance, evidence of toxicity in children is not necessarily applicable to adults. The few studies on adults have not produced statistically significant evidence of a relationship.

Thirteen studies since 1982 have investigated associations between ambient particulate levels and loss of pulmonary function (EPA, 1996, Table 12–13). In general, these studies suggest a short term effect, especially in symptomatic groups such as asthmatics, but most were carried out on children only. In a study of adults with mild COPD, Pope and Kanner (1993) found a 29 ± 10 ml decrease in 1-second Forced Expiratory Volume (FEV_1) per 50 $\mu\text{g}/\text{m}^3$ increase in PM_{10} , which is similar in magnitude to the change generally observed in the studies on children. In another study of adults, with PM_{10} ranging from 4 to 137 $\mu\text{g}/\text{m}^3$, Dusseldorp *et al.* (1995) found 45 and 77 ml/sec decreases, respectively, for evening and morning Peak Expiratory Flow Rate (PEFR) per 50 $\mu\text{g}/\text{m}^3$ increase in PM_{10} (EPA, 1996). In the only study carried out on adults that specifically measured fine particulate ($\text{PM}_{2.5}$), Perry *et al.* (1983) did not detect any association of exposure with loss of pulmonary function. This study, however, was conducted on only 24 adults (all asthmatics) exposed at relatively low concentrations of $\text{PM}_{2.5}$ and, therefore, had very little power to detect any such association.

c. Chronic Health Effects

During the 1995 dpm workshops, miners reported observable adverse health effects among those who have worked a long time in dieselized mines. For example, a miner (dpm Workshop; Salt Lake City, UT, 1995), stated that miners who work with diesel “have spit up black stuff every night, big black—what they call black (expletive) * * * [they] have the congestion every night * * * the 60-year-old man working there 40 years.” Similarly, in comments submitted in response to MSHA’s proposed dpm regulations, several miners reported cancers and chronic respiratory ailments they attributed to dpm exposure.

Scientific investigation of the chronic health effects of dpm exposure includes studies based specifically on exposures to diesel emissions and studies based more generally on exposures to fine particulate matter in the ambient air. Only the evidence from human studies will be addressed in this section of the risk assessment. Data from genotoxicity studies and studies on laboratory animals will be discussed later, in Subsection 2.d on mechanisms of

toxicity. Subsection 3.a(iii) contains MSHA’s interpretation of the evidence relating dpm exposures to one chronic health hazard: lung cancer.

i. Studies Based on Exposures to Diesel Emissions

The discussion will (1) summarize the epidemiologic literature on chronic effects other than cancer, and then (2) concentrate on the epidemiology of cancer in workers exposed to dpm.

(1) Chronic Effects Other Than Cancer

A number of epidemiologic studies have investigated relationships between diesel exposure and the risk of developing persistent respiratory symptoms (*i.e.*, chronic cough, chronic phlegm, and breathlessness) or measurable loss in lung function. Three studies involved coal miners (Reger *et al.*, 1982; Ames *et al.*, 1984; Jacobsen *et al.*, 1988); four studies involved metal and nonmetal miners (Jørgenson & Svensson, 1970; Attfield, 1979; Attfield *et al.*, 1982; Gamble *et al.*, 1983). Three studies involved other groups of workers—railroad workers (Battigelli *et al.*, 1964), bus garage workers (Gamble *et al.*, 1987), and stevedores (Purdham *et al.*, 1987).

Reger *et al.* (1982) examined the prevalence of respiratory symptoms and the level of pulmonary function among more than 1,600 underground and surface U.S. coal miners, comparing results for workers (matched for smoking status, age, height, and years worked underground) at diesel and non-diesel mines. Those working at underground dieselized mines showed some increased respiratory symptoms and reduced lung function, but a similar pattern was found in surface miners who presumably would have experienced less diesel exposure. Miners in the dieselized mines, however, had worked underground for less than 5 years on average.

In a study of 1,118 U.S. coal miners, Ames *et al.* (1984) did not detect any pattern of chronic respiratory effects associated with exposure to diesel emissions. The analysis, however, took no account of baseline differences in lung function or symptom prevalence, and the authors noted a low level of exposure to diesel-exhaust contaminants in the exposed population.

In a cohort of 19,901 British coal miners investigated over a 5-year period, Jacobsen *et al.* (1988) found increased work absence due to self-reported chest illness in underground workers exposed to diesel exhaust, as compared to surface workers, but found

no correlation with their estimated level of exposure.

Jörgenson & Svensson (1970) found higher rates of chronic productive bronchitis, for both smokers and nonsmokers, among Swedish underground iron ore miners exposed to diesel exhaust as compared to surface workers at the same mine. No significant difference was found in spirometry results.

Using questionnaires collected from 4,924 miners at 21 U.S. metal and nonmetal mines, Attfield (1979) evaluated the effects of exposure to silica dust and diesel exhaust and obtained inconclusive results with respect to diesel exposure. For both smokers and non-smokers, miners occupationally exposed to diesel for five or more years showed an elevated prevalence of persistent cough, persistent phlegm, and shortness of breath, as compared to miners exposed for less than five years, but the differences were not statistically significant. Four quantitative indicators of diesel use failed to show consistent trends with symptoms and lung function.

Attfield et al. (1982) reported on a medical surveillance study of 630 white male miners at 6 U.S. potash mines. No relationships were found between measures of diesel use or exposure and various health indices, based on self-reported respiratory symptoms, chest radiographs, and spirometry.

In a study of U.S. salt miners, Gamble and Jones (1983) observed some elevation in cough, phlegm, and dyspnea associated with mines ranked according to level of diesel exhaust exposure. No association between respiratory symptoms and estimated cumulative diesel exposure was found after adjusting for differences among mines. However, since the mines varied widely with respect to diesel exposure levels, this adjustment may have masked a relationship.

Battigelli et al. (1964) compared pulmonary function and complaints of respiratory symptoms in 210 U.S. railroad repair shop employees, exposed to diesel for an average of 10 years, to a control group of 154 unexposed railroad workers. Respiratory symptoms were less prevalent in the exposed group, and there was no difference in pulmonary function; but no adjustment was made for differences in smoking habits.

In a study of workers at four diesel bus garages in two U.S. cities, Gamble et al. (1987b) investigated relationships between job tenure (as a surrogate for cumulative exposure) and respiratory symptoms, chest radiographs, and

pulmonary function. The study population was also compared to an unexposed control group of workers with similar socioeconomic background. After indirect adjustment for age, race, and smoking, the exposed workers showed an increased prevalence of cough, phlegm, and wheezing, but no association was found with job tenure. Age- and height-adjusted pulmonary function was found to decline with duration of exposure, but was elevated on average, as compared to the control group. The number of positive radiographs was too small to support any conclusions. The authors concluded that the exposed workers may have experienced some chronic respiratory effects.

Purdham et al. (1987) compared baseline pulmonary function and respiratory symptoms in 17 exposed Canadian stevedores to a control group of 11 port office workers. After adjustment for smoking, there was no statistically significant difference in self-reported respiratory symptoms between the two groups. However, after adjustment for smoking, age, and height, exposed workers showed lower baseline pulmonary function, consistent with an obstructive ventilatory defect, as compared to both the control group and the general metropolitan population.

In a review of these studies, Cohen and Higgins (1995) concluded that they did not provide strong or consistent evidence for chronic, nonmalignant respiratory effects associated with occupational exposure to diesel exhaust. These reviewers stated, however, that "several studies are suggestive of such effects * * * particularly when viewed in the context of possible biases in study design and analysis." Glenn et al (1983) noted that the studies of chronic respiratory effects carried out by NIOSH researchers in coal, salt, potash, and trona mines all "revealed an excess of cough and phlegm in the diesel exposed group." IPCS (1996) noted that "[a]lthough excess respiratory symptoms and reduced pulmonary function have been reported in some studies, it is not clear whether these are long-term effects of exposure." Similarly, Morgan et al. (1997) concluded that while there is "some evidence that the chronic inhalation of diesel fumes leads to the development of cough and sputum, that is chronic bronchitis, it is usually impossible to show a cause and effect relationship * * *." MSHA agrees that these dpm studies are not conclusive but considers them to be suggestive of adverse chronic, non-cancerous respiratory effects.

(2) Cancer

Because diesel exhaust has long been known to contain carcinogenic compounds (*e.g.*, benzene in the gaseous fraction and benzopyrene and nitropyrene in the dpm fraction), a great deal of research has been conducted to determine if occupational exposure to diesel exhaust actually results in an increased risk of cancer. Evidence that exposure to dpm increases the risk of developing cancer comes from three kinds of studies: human studies, genotoxicity studies, and animal studies. In this risk assessment, MSHA has placed the most weight on evidence from the human epidemiologic studies and views the genotoxicity and animal studies as lending support to the epidemiologic evidence.

In the epidemiologic studies, it is generally impossible to disassociate exposure to dpm from exposure to the gasses and vapors that form the remainder of whole diesel exhaust. However, the animal evidence shows no significant increase in the risk of lung cancer from exposure to the gaseous fraction alone (Heinrich et al., 1986, 1995; Iwai et al., 1986; Brightwell et al., 1986). Therefore, dpm, rather than the gaseous fraction of diesel exhaust, is usually assumed to be the agent associated with any excess prevalence of lung cancer observed in the epidemiologic studies. Subsection 2.d of this risk assessment contains a summary of evidence supporting this assumption.

(a) Lung Cancer

MSHA evaluated 47 epidemiologic studies examining the prevalence of lung cancer within groups of workers occupationally exposed to dpm. This includes four studies not included in MSHA's risk assessment as originally proposed.²⁶ The earliest of these studies was published in 1957 and the latest in 1999. The most recent published reviews of these studies are by Mauderly (1992), Cohen and Higgins (1995), Muscat and Wynder (1995), IPCS (1996), Stöber and Abel (1996), Cox (1997), Morgan et al. (1997), Cal-EPA (1998), ACGIH (1998), and U.S. EPA (1999). In response to both the ANPRM and the 1998 proposals, several commenters also provided MSHA with

²⁶ One of these studies (Christie et al., 1995) was cited in the discussion on mechanisms of toxicity but not considered in connection with studies involving dpm exposures. Several commenters advocated that it be considered. The other three were published in 1997 or later. Johnston et al. (1997) was introduced to these proceedings in 64 FR 7144. Säverin et al. (1999) is the published English version of a Germany study submitted as part of the public comments by NIOSH on May 27, 1999. The remaining study is Brüske-Hohlfeld et al. (1999).

their own reviews of many of these studies. In arriving at its conclusions, MSHA considered all of these reviews, including those of the commenters, as well as the 47 source studies available to MSHA.

In addition, MSHA relied on two comprehensive statistical "meta-analyses"²⁷ of the epidemiologic literature: Lipsett and Campleman (1999) thru²⁸ and Bhatia et al. (1998).²⁹ These meta-analyses, which weight, combine, and analyze data from the various epidemiologic studies, were themselves the subject of considerable public comment and are discussed primarily in Subsection 3.a.iii of this risk assessment. The present section tabulates results of the studies and addresses their individual strengths and weaknesses. Interpretation and evaluation of the collective evidence,

²⁷ MSHA restricts the term "meta-analysis" to formal, statistical analyses of the pooled data taken from several studies. Some commenters (and Cox in the article itself) referred to the review by Cox (op.cit.) as a meta-analysis. Although this article seeks to identify characteristics of the individual studies that might account for the general pattern of results, it performs no statistical analysis on the pooled epidemiologic data. For this reason, MSHA does not regard the Cox article as a meta-analysis in the same sense as the two studies so identified. MSHA does, however, recognize that the Cox article evaluates and rejects the collective evidence for causality, based on the common characteristics identified. In that context, Cox's arguments and conclusions are addressed in Subsection 3.a.iii. Cox also presents a statistical analysis of data from one of the studies, and that portion of the article is considered here, along with his observations about other individual studies.

²⁸ MSHA's risk assessment as originally proposed cited an unpublished version, attributed to Lipsett and Alexeff (1998), of essentially the same meta-analysis. Both the 1999 and 1998 versions are now in the public record.

²⁹ Silverman (1998) reviewed the meta-analysis by Bhatia et al. (op.cit.) and discussed, in general terms, the body of available epidemiologic evidence on which it is based. Some commenters stated that MSHA had not sufficiently considered Silverman's views on the limitations of this evidence. MSHA has thoroughly considered these views and addresses them in Subsection 3.a.(iii).

including discussion of potential publication bias or any other systematic biases, is deferred to Subsection 3.a.iii.

Tables III-4 (27 cohort studies) and III-5 (20 case-control studies) identify all 47 known epidemiologic studies that MSHA considers relevant to an assessment of lung cancer risk associated with dpm exposure.³⁰ These tables include, for each of the 47 studies listed, a brief description of the study and its findings, the method of exposure assessment, and comments on potential biases or other limitations. Presence or absence of an adjustment for smoking habits is highlighted, and adjustments for other potentially confounding factors are indicated when applicable. Although MSHA constructed these tables based primarily on its own reading of the 48 source publications, the tables also incorporate strengths and weaknesses noted in the literature reviews and/or in the public comments submitted.

Some degree of association between occupational dpm exposure and an excess prevalence of lung cancer was reported in 41 of the 47 studies reviewed by MSHA: 22 of the 27 cohort studies and 19 of the 20 case-control studies. Despite some commenters' use of conflicting terminology, which will be addressed below, MSHA refers to these 41 studies as "positive." The 22 positive cohort studies in Table III-4 are identified as those reporting a relative risk (RR) or standardized mortality ratio (SMR) exceeding 1.0. The 19 positive case-control studies in Table III-5 are identified as those reporting an RR or odds ratio (OR) exceeding 1.0. A study does not need to be statistically

³⁰ For simplicity, the epidemiologic studies considered here are placed into two broad categories. A *cohort study* compares the health of persons having different exposures, diets, etc. A *case-control study* starts with two defined groups known to differ in health and compares their exposure characteristics.

significant (at the 0.05 level) or meet all criteria described, in order to be considered a "positive" study. The six remaining studies were entirely negative: they reported a deficit in the prevalence of lung cancer among exposed workers, relative to whatever population was used in the study as a basis for comparison. These six negative studies are identified as those reporting no relative risk (RR), standard mortality ratio (SMR), or odds ratio (OR) greater than 1.0.³¹

MSHA recognizes that these 47 studies are not of equal importance for determining whether dpm exposure leads to an increased risk of lung cancer. Some of the studies provide much better evidence than others. Furthermore, since no epidemiologic study can be perfectly controlled, the studies exhibit various strengths and weaknesses, as described by both this risk assessment and a number of commenters. Several commenters, and some of the reviewers cited above, focused on the weaknesses and argued that none of the existing studies is conclusive. MSHA, in accordance with other reviewers and commenters, maintains: (1) That the weaknesses identified in both negative and positive studies mainly cause underestimation of risks associated with high occupational dpm exposure; (2) that it is legitimate to base conclusions on the combined weight of all available evidence and that, therefore, it is not necessary for any individual study to be conclusive; and (3) that even though the 41 positive studies vary a great deal in strength, nearly all of them contribute something to the weight of positive evidence.

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³¹ The six entirely negative studies are: Kaplan (1959); DeCoulle et al. (1977); Waller (1981); Edling et al. (1987); Bender et al. (1989); Christie et al. (1995).

Table III-4. — Summary of information from 27 cohort studies on lung cancer and occupational exposure to diesel exhaust.

Study	Occupation	No. of Subjects	Follow-up period	Exposure Assessment	Smk. Adj.	Findings ^a	Stat. Sig. ^b	Comments
Ahlberg et al. (1981)	Male truck drivers	35,883	1961-73	Occupation only		RR = 1.33 for drivers of "ordinary" trucks.	*	Risk relative to males employed in trades thought to have no exposure to "petroleum products or other chemicals." Comparison controlled for age and province of residence (Sweden). Based on comparison of smoking habits between truck drivers and general Stockholm population, authors concluded that excess rate of lung cancer could not be entirely attributed to smoking.
Ahlman et al. (1991)	Underground sulfide ore miners	597	1968-86	Job histories from personnel records. Measurements of alpha energy concentration from radon daughters at each mine worked.		RR = 1.45 overall. RR = 2.9 for 45-64 age group. (calculated by MSHA)		Age-adjusted relative risk compared to males living in same area of Finland. No excess observed among 338 surface workers at same mines, with similar smoking and alcohol consumption, based on questionnaire. Based on calculation of expected lung cancers due to radon, excess risk attributed by author partly to radon exposure and partly to diesel exhaust & silica exposure.
Balarajan & McDowall (1988)	Professional drivers	3,392	1950-84	Occupation only		SMR = 0.86 for taxi drivers. SMR = 1.42 for bus drivers. SMR = 1.59 for truck drivers.	*	Possibly higher rates of smoking among bus and truck drivers than among taxi drivers.
Bender et al. (1989)	Highway maintenance workers	4,849	1945-84	Occupation only		SMR = 0.69		No adjustment for healthy worker effect.
Boffetta et al. (1988)	Railroad worker	2,973	1982-84	Occupation and diesel exposure by questionnaire	✓	RR = 1.24 for truck drivers.	*	Risk relative to workers reporting that they never worked in these four occupations and were never occupationally exposed to diesel exhaust. Adjusted for age and smoking only.
	Truck drivers	16,208				RR = 1.59 for railroad workers.		
Christie et al. (1994, 1995)	Heavy Eq. Op's.	855	1973-92	Occupation only		RR = 2.60 for heavy Eq. Op's.		Based on self-reported exposure, relative to unexposed workers. Adjusted for occupational exposures to asbestos, coal and stone dusts, coal tar & pitch, and gasoline exhaust (in addition to age and smoking). Possible biases due to volunteered participation and elevated lung cancer rate among 98,026 subjects with unknown dpm exposure.
	Miners	2,034				RR = 2.67 for miners.		
	All workers	476,648				RR = 1.05 for 1-15 years. RR = 1.21 for 16+ years.		No adjustment for healthy worker effect. Cohort includes workers who entered workforce up through 1992. SMR reported to be greater than for occupationally unexposed petroleum workers.

Dubrow & Wegman (1984)	Truck & tractor drivers	not reported	1971-73	Occupation only		SMOR = 1.73 based on 176 deaths.	*	Excess cancers observed over the entire respiratory system and upper alimentary tract.
Edling et al. (1987)	Bus workers	694	1951-83	Occupation only		SMR = 0.7 for overall cohort		Small size of cohort lacks statistical power to detect excess risk of lung cancer. No adjustment for healthy worker effect.
Garshick et al. (1988, 1991)	Railroad workers	55,395 (1991 report)	1959-80	Job in 1959 & years of diesel exposure since 1959		RR = 1.31 for 1-4 years.	*	Adjusted for attained age (1991 report). Cumulative diesel exposure-years lagged by 5 years. Subjects with likely asbestos exposure excluded from cohort. Statistically significant results corroborated if 12,872 shopworkers and hostlers possibly exposed to asbestos are also excluded. Missing 12% of death certificates. Cigarette smoking judged to be uncorrelated with diesel exposure within cohort. Higher RR for each exposure group if shopworkers and hostlers are excluded.
						RR = 1.28 for 5-9 years.	*	
RR = 1.19 for 10-14 years.	*							
RR = 1.40 for 15 or more years.	*							
Guberman et al. (1992)	Professional drivers	1,726	1961-86	Occupation only		SMR = 1.50	*	Approximately 1/3 to 1/4 of cohort reported to be long-haul truck drivers. SMR based on regional lung cancer mortality rate.
Gustafsson et al. (1986)	Dock workers	6,071	1961-80	Occupation only		SMR = 1.32 (mortality).	*	No adjustment for healthy worker effect.
						SMR = 1.68 (morbidity).	*	
Gustafsson et al. (1990)	Bus garage workers	708	1952-86	Semi-quantitative, based on job history & exposure intensity estimated for each job.		SMR = 1.22 for overall cohort.		Lack of statistical significance may be attributed to small size of cohort.
						SMR = 1.27 for highest-exposed subgroup.		
Hansen (1993)	Truck drivers	14,225	1970-80	Occupation only		SMR = 1.60 for overall cohort.	*	Compared to unexposed control group of 38,301 laborers considered to "resemble the group of truck drivers in terms of work-related demands on physical strength and fitness, educational background, social class, and life style." Correction for estimated differences in smoking habits between cohort and control group reduces SMR from 1.60 to 1.52. Results judged "unlikely *** [to] have been seriously confounded by smoking habit differences."
						Some indication of increasing SMR with age (i.e., greater cumulative exposure).		

Howe et al. (1983)	Railroad workers	43,826	1965-77	Jobs classified by diesel exposure		RR = 1.20 for "possibly exposed." RR = 1.35 for "probably exposed."	*	Risk is relative to unexposed subgroup of cohort. Similar results obtained for coal dust exposure. Possible confounding with asbestos and coal dust.
Johnston et al. (1997)	Underground coal miners	18,166	1950-85	Quantitative, based on detailed job history & surrogate dpm measurements	✓	mine-adjusted model: RR = 1.156 per g-hr/m ³ mine-unadjusted model: RR = 1.227 per g-hr/m ³		Risk is relative to unexposed workers in cohort. Adjusted for age, smoking habit & intensity, mine site, and cohort entry date. Mine site highly correlated with dpm exposure. Both models lag exposure by 15 years.
Kaplan (1959)	Railroad workers	Approx. 32000	1953-58	Jobs classified by diesel exposure		SMR=0.88 for operationally exposed. SMR = 0.72 for somewhat exposed. SMR = 0.80 for rarely exposed.		No adjustment for healthy worker effect. Clerks (in rarely exposed group) found more likely to have had urban residence than occupationally exposed workers. No attempt to distinguish between diesel and coal-fired locomotives. Results may be attributable to short duration of exposure and/or inadequate follow-up time.
Leupker & Smith (1978)	Truck drivers	183,791	May-July, 1976	Occupation only		SMR = 1.21		Lack of statistical significance may be due to inadequate follow-up period. Retirees excluded from cohort, so lung cancers occurring after retirement were not included.
Lindsay et al. (1993)	Truck drivers	not reported	1965-79	Occupation only		SMR = 1.15	*	
Menck & Henderson (1976)	Truck drivers	34,800 estimated	1968-73	Occupation only		SMR = 1.65	*	Number of subjects in cohort estimated from census data.
Raffle (1957)	Transport engineers	2,666 estimated from many years at risk	1950-55	Occupation only		SMR = 1.42		SMR calculated by combining data presented for four quadrants of London. Excluded most retirees and lung cancers occurring after retirement.
Rafnsson & Gunnarsdottir (1991)	Truck drivers	868	1951-88	Occupation only		SMR = 2.14	*	No trend of increasing risk with increased duration of employment or increased follow-up time. Based on survey of smoking habits in cohort compared to general male population, and fact that there were fewer than expected deaths from respiratory disease, authors concluded that differences in smoking habits were unlikely to be enough to explain excess rate of lung cancer. However, not all trucks were diesel prior to 1951, and there is possible confounding by asbestos exposure.

Rushton et al. (1983)	Bus maintenance workers	8,480	5.9 yrs (mean)	Occupation only	SMR = 1.01 for overall cohort. SMR = 1.33 for "general hand" subgroup.	*	Short follow-up period. SMR based on comparison to national rates, with no adjustment for regional or socioeconomic differences, which could account for excess lung cancers observed among general hands. No adjustment for healthy worker effect.
Saverin et al. (1999)	Underground potash miners	5,536	1970-94	Quantitative, based on TC measurements & detailed job history	RR = 2.17 for highest compared to least exposed categories. RR=1.03 to 1.225 per mg-yr/m ³ , depending on statistical model & inclusion criteria.		Based on routine measurements, miners determined to have had no occupational exposure to radon progeny. Authors judged asbestos exposure minor, with negligible effects. Cigarette smoking determined to be uncorrelated with cumulative TC exposure within cohort.
Schenker et al. (1984)	Railroad workers	2,519	1967-79	Job histories, with exposure classified as unexposed, high, low, or undefined.	RR = 1.50 for low exposure subgroup. RR = 2.77 for high exposure subgroup.		Risk relative to unexposed subgroup. Jobs considered to have similar socioeconomic status. Differences in smoking calculated to be insufficient to explain findings. Possible confounding by asbestos exposure.
Waller (1981)	Bus workers	16,828 Est. from many years at risk	1950-74	Occupation only	SMR = 0.79 for overall cohort.		Lung cancers occurring after retirement or resignation from London Transport Authority were not counted. No adjustment for healthy worker effect.
Waxweiler et al. (1973)	Potash miners	3,886	1941-67	Miners classified as underground or surface	SMR = 1.1 for both underground and surface miners.		No adjustment for healthy worker effect. SMR based on national lung cancer mortality, which is about 1/3 higher than lung cancer mortality rate in New Mexico, where miners resided. Authors judged this to be balanced by smoking among miners. A substantial percentage of the underground subgroup may have had little or no occupational exposure to diesel exhaust.
Wong et al. (1985)	Heavy equipment operators	34,156	1964-78	Job histories, latency, & years of union membership	SMR = 0.99 for overall cohort. SMR = 1.07 for ≥20 yr member. SMR = 1.12 for ≥20 yr. latency. SMR = 1.30 for 4,075 "normal" retirees. SMR = 3.43 for "high exposure" dozer operators with 15-19 yr union membership & ≥20 yr latency.	* *	Increasing trend in SMR with latency and (up to 15 yr) with duration of union membership. No adjustment for healthy worker effect.

^a RR = Relative Risk; SMR = Standardized Mortality Ratio. Values greater than 1.0 indicate excess prevalence of lung cancer associated with diesel exposure.

^b An asterisk (*) indicates statistical significance based on 2-tailed test at confidence level of at least 95%.

Table III-5. — Summary of published information from 20 case-control studies on lung cancer and exposure to diesel exhaust.

Study	Cases	Controls	No. of Cases	No. of Controls	Exposure Assessment	Matching		Findings ^a	Stat. Sig. ^b	Comments
						Smk.	Additional			
Benhamou et al. (1988)	Historically confirmed lung cancers	Non-tobacco related diseases	1,625	3,091	Occupational history by questionnaire.	✓	Sex, age at diagnosis, hospital, interviewer.	RR = 2.14 for miners RR = 1.42 for professional drivers.	*	Mine type not reported. No evidence of an increase in risk with duration of exposure
Boffetta et al. (1990)	Hospitalized males with histologically confirmed lung cancer	Hospitalized males with no tobacco related disease	2,584	5,099	Occupation classified by probability of diesel exposure		Sex, age within 2 yr, hospital, year of interview.	OR = 0.95 for 13 jobs with probable exposure. OR = 1.49 for more than 30 yr in "probable" jobs.		Adjusted for race, asbestos exposure, education, & number of cigarettes per day.
			477	846	Occupational history & duration of diesel exposure by interview	✓		OR = 1.21 for any self-reported diesel exposure. OR = 2.39 for more than 30 yr of self-reported diesel exposure.		
Bruske-Hohlfeld et al. (1999)	Cytologically and/or histologically confirmed lung cancers	Randomly selected from compulsory registries of residents.	3,498	3,541	Occupational history by interview; total duration of diesel exposure compiled from individual job episodes.	✓	Sex, age, region of residence.	OR = 1.43 for any occupational diesel exposure during lifetime. OR = 1.56 for West German professional drivers post-1955. OR = 2.88 for > 20 yr in "traffic-related" jobs other than driving. OR = 6.81 for > 30 yr as full-time driver of farm tractors. OR = 4.30 for > 20 yr as heavy equipment operator.	*	Adjusted for cumulative smoking & asbestos exposure. All interviews conducted directly with cases and controls. Lack of elevated risk for East German professional drivers attributed to relatively low traffic density & low proportion of vehicles with diesel engines in East Germany. Non-driving "traffic-related jobs" include switchmen & operators of diesel locomotives & forklifts.
				892	Occupational history from interview	✓	Sex, age, admission date.	OR = 1.8 for taxi drivers.		Adjusted for current and past smoking patterns and for asbestos exposure.

Coggon et al. (1984)	Lung cancer deaths of males under 40	Deaths from other causes in males under 40	598	1,180	Occupation from death certificate, classified as high, low, or no diesel exposure		Sex, death year, region, and birth year (approx.)	RR = 1.3 for all jobs with diesel exposure. RR = 1.1 for jobs classified as high exposure.	* Only most recent full-time occupation recorded on death certificate.
Damber & Larsson (1985)	Male patients with lung cancer	One living and one deceased without lung cancer	604	1,071	Job, with tenure, from mailed questionnaire	✓	Sex, death year, age, municipality	RR = 1.9 for non-smoking truck drivers aged <70 yr. RR = 4.5 for non-smoking truck drivers aged ≥70 yr.	Ex-smokers who did not smoke for at least last 10 years included with non-smokers.
DeCoulfe et al. (1977)	Male patients with lung cancer	Non-neoplastic disease patients	6,434	Not reported	Occupation only, from questionnaire	✓	Unmatched	RR = 0.92 for bus, taxi, and truck drivers. RR = 0.94 for locomotive engineers.	Selected occupation compared to clerical workers. Positive associations found before smoking adjustment.
Emmelin et al. (1993)	Deaths from primary lung cancer among dock workers	Dock workers without lung cancer	50	154	Semi-quantitative from work history & records of diesel fuel usage	✓	Date of birth, port, and survival to within 2 years of case's diagnosis of lung cancer	RR = 1.6 for "medium" duration of exposure. RR = 2.9 for "high" duration of exposure.	Increasing relative risk also observed using exposure estimates based on machine usage & diesel fuel consumption. Confounding from asbestos may be significant.
Garshick et al. (1987)	Deaths with primary lung cancer among railroad workers	Deaths from other than cancer, suicide, accidents, or unknown causes	1,256	2,385	Job history and tenure combined with current exposure levels measured for each job	✓	Date of birth and death	RR = 1.41 for 20+ diesel-years in workers aged ≤ 64 yr. RR = 0.91 for 20+ diesel-years in workers aged ≥ 65 yr.	Adjusted for asbestos exposure. Older workers had relatively short diesel exposure, or none.
Gustavsson et al. (1990)	Deaths from lung cancer among bus garage workers	Non-cases within cohort mortality study	20	120	Semi-quantitative based on job, tenure, & exposure class for each job		Born within two years of case.	RR = 1.34, 1.81, and 2.43 for increasing cumulative diesel exposure categories, relative to lowest exposure category.	Authors judged smoking habits to be similar for different exposure categories. RR did not increase with increasing asbestos exposure
Hall & Wynder (1984)	Hospitalized males with lung cancer	Hospitalized males with no tobacco-related diseases	502	502	Usual occupation by interview	✓	Age, race, hospital, and hospital room status	RR = 1.4 for jobs with diesel exposure. RR = 1.9 for heavy equipment operators & repairmen.	Confounding with other occupational exposures possible.

Hayes et al. (1989)	Lung cancer deaths pooled from 3 studies	Various -- lung disease excluded	2,291	2,570	Occupational history by interview	✓	Sex, age, and either race or area of residence	OR = 1.5 for ≥ 10 yr truck driving. OR = 2.1 for ≥ 10 yr operating heavy equipment. OR = 1.7 for ≥ 10 yr bus driving.	*	OR adjusted for birth-year cohort and state of residence (FL, NJ, or LA), in addition to average cigarette use. Smaller OR for <10 yr in these jobs.
Lerchen et al. (1987)	New Mexico residents with lung cancer	Medicare recipients	506	771	Occupational history, industry, & self-reported exposure, by interview	✓	Sex, age, ethnicity	OR = 0.6 for ≥ 1 yr occupational exposure to diesel exhaust. OR = 2.1 for underground non-uranium mining.		Small number of cases and controls in diesel-exposed jobs. Possibly insufficient exposure duration. Not matched on date of birth or death.
Milne et al. (1983)	Lung cancer deaths	Deaths from any other cancer	925	6,565	Occupation from death certificate		None	OR = 3.5 for bus drivers. OR = 1.6 for truck drivers.	*	Inadequate latency allowance.
Morabia et al. (1992)	Male lung cancer patients	Patients without lung cancer or other tobacco-related condition	1,793	3,228	Job, with coal and asbestos exposure durations, by interview	✓	Race, age, hospital, and smoking history	OR = 2.3 for miners. OR = 1.1 for bus drivers. OR = 1.0 for truck or tractor drivers.		Mine type not specified. Potential confounding by other occupational exposures for miners.
Pfluger and Minder (1994)	Professional drivers	Workers in occupational categories with no known excess lung cancer risk.	284	1,301	Occupation only, from death certificate.		None.	OR = 1.48 for professional drivers.	*	Stratified by age. Indirectly adjusted for smoking, based on smoking-rate for occupation.
Siemiatycki et al. (1988)	Squamous cell lung cancer patients by type of lung cancer	Other cancer patients	359	1,523	Semi-quantitative, from occupational history by interview, & exposure class for each job	✓	None	OR = 1.2 for diesel exposure; OR = 2.8 for mining.		Stratified by age, socioeconomic status, ethnicity, and blue- vs. white-collar job history. Examination of files indicated that most miners "were exposed to diesel exhaust for short periods of time." Mining included quarrying, so result is likely to be confounded by silica exposure.

Steenland et al. (1990, 1992, 1998)	Deaths from lung CA among Teamsters	996	1,085	Occupational history and tenure from next-of-kin, supplemented by IH data	✓	Time of death within 2 years	OR = 1.27 for diesel truck drivers with 1-24 yr tenure. OR = 1.26 for diesel truck drivers with 25-34 yr tenure. OR = 1.89 for diesel truck drivers with ≥35 yr tenure. OR = 1.50 for truck mechanics with ≥18 yr tenure after 1959.	Years of tenure not necessarily all at main job (i.e., diesel truck driver). OR adjusted for asbestos exposure.
Swanson et al. (1993) See also Burns & Swanson (1991)	Deaths other than lung or bladder cancer or motor vehicle accidents	3,792 males 5,935 total	1,966 males 3,956 total	Occupational history from interview	✓	None	OR = 1.4 for heavy truck drivers with 1-9 yr tenure. OR = 1.6 for heavy truck drivers with 10-19 yr tenure. OR = 2.5 for heavy truck drivers with ≥20 yr tenure. OR = 1.2 for railroad workers with 1-9 yr tenure. OR = 2.5 for railroad workers with ≥10 yr tenure. OR = 2.98 for mining industry workers. OR = 5.03 for mining machinery operators.	OR for truck drivers & RR workers is for white males, relative to corresponding group with <1 yr tenure, adjusted for age at diagnosis. Pattern of increasing risk with duration of employment also reported for black male railroad workers, based on fewer cases. (1993 report) OR for mining machinery operators and mining is for all males, adjusted for race and age at diagnosis. Type of mining not reported. Potential confounding by other occupational exposures. (1991 report)
Williams et al. (1977)	Deaths from lung cancer patients	432	2,817	Main lifetime occupation from interview	✓	Sex	OR = 1.52 for male truck drivers.	Controlled for age, race, alcohol use, and socioeconomic status. Unexplained discrepancies in reported number of controls.

* RR = Relative Risk; OR = Odds Ratio. Values greater than 1.0 indicate excess prevalence of lung cancer associated with diesel exposure.

^b An asterisk (*) indicates statistical significance based on 2-tailed test at confidence level of at least 95%.

(i) Evaluation Criteria

Several commenters contended that MSHA paid more attention to positive studies than to negative ones and indicated that MSHA had not sufficiently explained its reasons for discounting studies they regarded as providing negative evidence. MSHA used five principal criteria to evaluate the strengths and weaknesses of the individual studies:

- (1) power of the study to detect an exposure effect;
- (2) composition of comparison groups;
- (3) exposure assessment;
- (4) statistical significance; and
- (5) potential confounders.

These criteria are consistent with those proposed by the HEI Diesel Epidemiology Expert Panel (HEI, 1999). To help explain MSHA's reasons for valuing some studies over others, these five criteria will now be discussed in turn.

Power of the Study

There are several factors that contribute to a study's power, or ability to detect an increased risk of lung cancer in an exposed population. First is the study's size—i.e., the number of subjects in a cohort or the number of lung cancer cases in a case-control study. If few subjects or cases are included, then any statistical relationships are likely to go undetected. Second is the duration and intensity of exposure among members of the exposed group. The greater the exposure, the more likely it is that the study will detect an effect if it exists. Conversely, a study in which few members of the exposed group experienced cumulative exposures significantly greater than the background level is unlikely to detect an exposure effect. Third is the length of time the study allows for lung cancer to exhibit a statistical impact after exposure begins. This involves a latency period, which is the time required for lung cancer to develop in affected individuals, or (mainly pertaining to cohort studies) a follow-up period, which is the time allotted, including latency, for lung cancers in affected individuals to show up in the study. It is generally acknowledged that lung cancer studies should, at the very minimum, allow for a latency period of at least 10 years from the time exposure begins and that it is preferable to allow for latency periods of at least 20 years. The shorter the latency allowance, the less power the study has to detect any increased risk of lung cancer that may be associated with exposure.

As stated above, six of the 47 studies did not show positive results: One of these studies (Edling et al.) was based on a small cohort of 694 bus workers, thus having little statistical power. Three other of these studies (DeCoufle, Kaplan, and Christie) included exposed workers for whom there was an inadequate latency allowance (i.e., less than 10 years). The entire period of follow-up in the Kaplan study was 1953–1958. The Christie study was designed in such a way as to provide for neither a minimum period of exposure nor a minimum period of latency: the report covers lung cancers diagnosed only through 1992, but the “exposed” cohort includes workers who may have entered the work force (and thus begun their exposure) as late as Dec. 31, 1992. Such workers would not be expected to develop lung cancer during the study period. The remaining two negative studies (Bender, 1989 and Waller, 1981) appear to have included a reasonably adequate number of exposed workers and to have allowed for an adequate latency period.

Some of the 41 positive studies also had little power, either because they included relatively few exposed workers (e.g., Lerchen et al., 1987; Ahlman et al., 1991; Gustavsson et al., 1990) or an inadequate latency allowance or follow-up period (e.g., Leupker and Smith (1978); Milne, 1983; Rushton et al., 1983). In those based on few exposed workers, there is a strong possibility that the positive association arose merely by chance.³² The other studies, however, found increased prevalence of lung cancer despite the relatively short periods of latency and follow-up time involved. It should be noted that, for reasons other than lack of power, MSHA places very little weight on the Milne and Rushton studies. As mentioned in Table III–4, the Rushton study compared the cohort to the national population, with no adjustment for regional or socioeconomic differences. This may account for the excess rate of lung cancers reported for the exposed “general hand” job category. The Milne study did not control for potentially important “confounding” variables, as explained below in MSHA's discussion of that criterion.

³² As noted in Table III–4, the underground sulfide ore miners studied by Ahlman et al. (1991) were exposed to radon in addition to diesel emissions. The total number of lung cancers observed, however, was greater than what was attributable to the radon exposure, based on a calculation by the authors. Therefore, the authors attributed a portion of the excess risk to diesel exposure.

Composition of Comparison Groups

This criterion addresses the question of how equitable is the comparison between the exposed and unexposed populations in a cohort study, or between the subjects with lung cancer (i.e., the “cases”) and the subjects without lung cancer (i.e., the “controls”) in a case-control study. MSHA includes bias due to confounding variables under this criterion if the groups differ systematically with respect to such factors as age or exposure to non-diesel carcinogens. For example, unless adequate adjustments are made, comparisons of underground miners to the general population may be systematically biased by the miners' greater exposure to radon gas. Confounding not built into a study's design or otherwise documented is considered potential rather than systematic and is considered under a separate criterion below. Other factors included under the present criterion are systematic (i.e., “differential”) misclassification of those placed into the “exposed” and “unexposed” groups, selection bias, and bias due to the “healthy worker effect.”

In several of the studies, a group identified with diesel exposure may have systematically included workers who, in fact, received little or no occupational diesel exposure. For example, a substantial percentage of the “underground miner” subgroup in Waxweiler et al. (1973) worked in underground mines with no diesel equipment. This would have diluted any effect of dpm exposure on the group of underground miners as a whole.³³ Similarly, the groups classified as miners in Benhamou et al. (1988), Boffetta et al. (1988), and Swanson et al. (1993) included substantial percentages of miners who were probably not occupationally exposed to diesel emissions. Potential effects of exposure misclassification are discussed further under the criterion of “Exposure Assessment” below.

Selection bias refers to systematic differences in characteristics of the comparison groups due to the criteria and/or methods used to select those included in the study. For example, three of the cohort studies (Raffle, 1957; Leupker and Smith, 1976; Waller, 1981) systematically excluded retirees from the cohort of exposed workers—but not

³³ Furthermore, as pointed out in comments submitted by Dr. Peter Valberg through the NMA, the subgroup of underground miners working at mines with diesel engines was small, and the exposure duration in one of the mines with diesel engines was only ten years. Therefore, the power of the study was inadequate to detect an excess risk of lung cancer for that subgroup by itself.

from the population used for comparison. Therefore, cases of lung cancer that developed after retirement were counted against the comparison population but not against the cohort. This artificially reduced the SMR calculated for the exposed cohort in these three studies.

Another type of selection bias may occur when members of the control group in a case-control study are non-randomly selected. This happens when cases and controls are selected from the same larger population of patients or death certificates, and the controls are simply selected (prior to case matching) from the group remaining after those with lung cancer are removed. Such selection can lead to a control group that is biased with respect to occupation and smoking habits. Specifically, " * * * a severely distorted estimate of the association between exposure to diesel exhaust and lung cancer, and a severely distorted picture of the direction and degree of confounding by cigarette smoking, can come from case-control studies in which the controls are a collection of 'other deaths'" when the cause of most "other deaths" is itself correlated with smoking or occupational choice (HEI, 1999). This selection bias can distort results in either direction.

MSHA judged that seven of the 20 available case-control studies were susceptible to this type of selection bias because controls were drawn from a population of "other deaths" or "other patients."³⁴ These control groups were likely to have over-represented cases of cardiovascular disease, which is known to be highly correlated with smoking and is possibly also correlated with occupation. The only case-control study not reporting a positive result (DeCoulfle et al., 1977) fell into this group of seven. The remaining 13 case-control studies all reported positive results.

It is "well established that persons in the work force tend to be 'healthier' than persons not employed, and therefore healthier than the general population. Worker mortality tends to be below average for all major causes of death." (HEI, 1999) Because workers tend to be healthier than non-workers, the prevalence of disease found among workers exposed to a toxic substance may be lower than the rate prevailing in the general population, but higher than the rate occurring in an unexposed population of similar workers. This phenomenon is called the "healthy worker effect."

³⁴ These were: Buiatti et al. (1985), Coggan et al. (1984), DeCoulfle et al. (1977), Garshick et al. (1987), Hayes et al. (1989), Lerchen et al. (1987), and Steenland et al. (1990).

All five cohort studies reporting entirely negative results drew comparisons against the general population and made no adjustments to take the healthy worker effect into account. (Kaplan, 1959; Waller (1981); Edling et al. (1987); Bender et al. (1989); Christie et al. (1995)). The sixth negative study (DeCoulfle, 1977) was a case-control study in which vehicle drivers and locomotive engineers were compared to clerical workers. As mentioned earlier, this study did not meet the criterion for a minimum 10-year latency period. All other studies in which exposed workers were compared against similar but unexposed workers reported some degree of elevated lung cancer risk for exposed workers.

Many of the 41 positive studies also drew comparisons against the general population with no compensating adjustment for the healthy worker effect. But the healthy worker effect can influence results even when the age-adjusted mortality or morbidity rate observed among exposed workers is greater than that found in the general population. In such studies, comparison with the general population tends to reduce the excess risk attributable to the substance being investigated. For example, Gustafsson et al. (1986), Rushton et al. (1983), and Wong et al. (1985) each reported an unadjusted SMR exceeding 1.0 for lung cancer in exposed workers and an SMR significantly less than 1.0 for all causes of death combined. Since the SMR for all causes is less than 1.0, there is evidence of a healthy worker effect. Therefore, the SMR reported for lung cancer was probably lower than if the comparison had been made against a more similar population of unexposed workers. Bhatia et al. (1998) constructed a simple estimate of the healthy worker effect evident in these studies, based on the SMR for all causes of death except lung cancer. This estimate was then used to adjust the SMR reported for lung cancer. For the three positive studies mentioned, the adjustment raised the SMR from 1.29 to 1.48, from 1.01 to 1.23, and from 1.07 to 1.34, respectively.³⁵

Exposure Assessment

Many commenters suggested that a lack of concurrent exposure measurements in available studies

³⁵ A similar adjustment was applied to the SMR for lung cancer reported in one of the negative studies (Edling et al., 1987). This raised the SMR from 0.67 to 0.80. Because of insufficient data, Bhatia et al. did not carry out the adjustment for the three other studies they considered with potentially important healthy worker effects. (Bhatia et al., 1998)

limits their utility for quantitative risk assessment (QRA). MSHA is fully aware of these limitations but also recognizes that less desirable surrogates of exposure must frequently be employed out of practical necessity. As stated by HEI's expert panel on diesel epidemiology:

Quantitative measures of exposures are important in any epidemiologic study used for QRA. The greater the detail regarding specific exposure, including how much, for how long, and at what concentration, the more useful the study is for this purpose. Frequently, however, individual measurements are not available, and surrogate measures or markers are used. For example, the most general surrogate measures of exposure in occupational epidemiologic studies are job classification and work location. (HEI, 1999)

It is important to distinguish, moreover, between studies used to identify a hazard (i.e., to establish that dpm exposure is associated with an excess risk of lung cancer) and studies used for QRA (i.e., to quantify the amount of excess risk corresponding to a given level of exposure). Although detailed exposure measurements are desirable in any epidemiologic study, they are more important for QRA than for identifying and characterizing a hazard. Conversely, epidemiologic studies can be highly useful for purposes of hazard identification and characterization even if a lack of personal exposure measurements renders them less than ideal for QRA.

Still, MSHA agrees that the quality of exposure assessment affects the value of a study for even hazard identification. Accordingly, MSHA has divided the 47 studies into four categories, depending on the degree to which exposures were quantified for the specific workers included. This ranking refers only to exposure assessment and does not necessarily correspond to the overall weight MSHA places on any of the studies.

The highest rank, with respect to this criterion, is reserved for studies having quantitative, concurrent exposure measurements for specific workers or for specific jobs coupled with detailed work histories. Only two studies (Johnston et al., 1997 and Säverin et al., 1999) fall into this category.³⁶ Both of these recent cohort studies took smoking habits into account. These

³⁶ The study of German potash miners by Säverin et al. was introduced by NIOSH at the Knoxville public hearing prior to publication. The study, as cited, was later published in English. Although the dpm measurements (total carbon) were all made in one year, the authors provide a justification for assuming that the mining technology and type of machinery used did not change substantially during the period miners were exposed (ibid., p.420).

studies both reported an excess risk of lung cancer associated with dpm exposure.

The second rank is defined by semi-quantitative exposure assessments, based on job history and an estimated exposure level for each job. The exposure estimates in these studies are crude, compared to those in the first rank, and they are subject to many more kinds of error. This severely restricts the utility of these studies for QRA (i.e., for quantifying the change in risk associated with various specified exposure levels). For purposes of hazard identification and characterization, however, crude exposure estimates are better than no exposure estimates at all. MSHA places two cohort studies and five case-control studies into this category.³⁷ All seven of these studies reported an excess risk of lung cancer risk associated with diesel exposure. Thus, results were positive in all nine studies with quantitative or semi-quantitative exposure assessments.

The next rank belongs to those studies with only enough information on individual workers to construct estimates of exposure duration. Although these studies present no data relating excess risk to specific exposure levels, they do provide excess risk estimates for those working a specified minimum number of years in a job associated with diesel exposure. One cohort study and five case-control studies fall into this category, and all six of them reported an excess risk of lung cancer.³⁸ With one exception (Benhamou et al. 1988), these studies also presented evidence of increased age-adjusted risk for workers with longer exposures and/or latency periods.

The bottom rank, with respect to exposure assessment, consists of studies in which no exposure information was collected for individual workers. These studies used only job title to distinguish between exposed and unexposed workers. The remaining five of the six with entirely negative results, fall into this category.

Studies basing exposure assessments on only a current job title (or even a history of job titles) are susceptible to significant misclassification of exposed and unexposed workers. Unless the

study is poorly designed, this misclassification is "nondifferential" i.e., those who are misclassified are no more and no less likely to develop lung cancer (or to have been exposed to carcinogens such as tobacco smoke) than those who are correctly classified. If workers are sometimes misclassified nondifferentially, then this will tend to mask or dilute any excess risk attributable to exposure. Furthermore, differential misclassification in these studies usually consists of systematically including workers with little or no diesel exposure in a job category identified as "exposed." This too would generally mask or dilute any excess risk attributable to exposure. Therefore, MSHA assumes that in most of these studies, more rigorous and detailed exposure assessments would have resulted in somewhat higher estimates of excess risk.

IMC Global, MARG, and some other commenters expressed special concern about potential exposure misclassification and suggested that such misclassification might be partly responsible for results showing excess risk. IMC Global, for example, quoted a textbook observation that, contrary to popular misconceptions, nondifferential exposure misclassification can sometimes bias results away from the null. MSHA recognizes that this can happen under certain special conditions. However, there is an important distinction between "can sometimes" and "can frequently." There is an even more important distinction between "can sometimes" and "in this case does." As noted by the HEI Expert Panel on Diesel Epidemiology (HEI, 1999, p.48), " * * * nondifferential misclassification most often leads to an overall underestimation of effect." Similarly, Silverman (1998) noted, specifically with respect to the diesel studies, that " * * * this [exposure misclassification] bias is most likely to be nondifferential, and the effect would probably have been to bias point estimates [of excess risk] toward the null value."

Statistical Significance

A "statistically significant" finding is a finding unlikely to have arisen by chance in the particular group, or statistical sample, of persons being studied. An association arising by chance would have no predictive value for exposed workers outside the sample. However, a specific epidemiologic study may fail to achieve statistical significance for two very different reasons: (1) there may be no real difference in risk between the two groups being compared, or (2) the study

may lack the power needed to detect whatever difference actually exists. As described earlier, a lack of sufficient power comes largely from limitations such as a small number of subjects in the sample, low exposure and/or duration of exposure, or too short a period of latency or follow-up time. Therefore, a lack of statistical significance in an individual study does not demonstrate that the results of that study were due merely to chance—only that the study (viewed in isolation) is statistically inconclusive.

As explained earlier, MSHA classifies a reported RR, SMR, or OR (i.e., the point estimate of relative risk) as "positive" if it exceeds 1.0 and "negative" if it is less than or equal to 1.0. By common convention, a positive result is considered statistically significant if its 95-percent confidence interval does not overlap 1.0. If all other relevant factors are equal, then a statistically significant positive result provides stronger evidence of an underlying relationship than one that is not statistically significant. On the other hand, a study must meet two requirements in order to provide statistically significant evidence of no positive relationship: (1) the upper limit of its 95-percent confidence interval must not exceed 1.0 by an appreciable amount³⁹ and (2) it must have allowed for sufficient exposure, latency, and follow-up time to have detected an existing relationship.

As shown in Tables III-4 and III-5, statistically significant positive results were reported in 25 of the 47 studies: 11 of the 19 positive case-control studies and 14 of the 22 positive cohort studies. In 16 of the 41 studies showing a positive association, the association observed was not statistically significant. Results in five of the six negative studies were not statistically significant. One of the six negative studies (Christie et al., 1995, in full version), reported a statistically significant deficit in lung cancer for miners. This study, however, provided for no minimum period of exposure or latency and, therefore, lacked the power necessary to provide statistically significant evidence.⁴⁰

Whether or not a study provides statistically significant evidence is dependent upon many variables, such as study size, adequate follow-up time (to account for enough exposure and latency), and adequate case ascertainment. In the ideal world, a

³⁷ The cohort studies are Garshick et al. (1988) and Gustavsson et al. (1990). The case-control studies are Emmelin et al. (1993), Garshick et al. (1997), Gustavsson et al. (1990), Siemiatycki et al. (1988), and Steenland et al. (1990, 1992).

³⁸ The cohort study is Wong et al. (1985). The case-control studies are Brüske-Hohlfeld et al. (1999), Benhamou et al. (1988), Boffetta et al. (1990), Hayes et al. (1989), and Swanson et al. (1993).

³⁹ As a matter of practicality, MSHA places the threshold at 1.05.

⁴⁰ More detailed discussion of this study appears later in this subsection.

sufficiently powerful study that failed to demonstrate a statistically significant positive relationship would, by its very failure, provide statistically significant evidence that an underlying relationship between an exposure and a specific disease was unlikely. It is important to note that MSHA regards a real 10-percent increase in the risk of lung cancer (i.e., a relative risk of 1.1) as constituting a clearly significant health hazard. Therefore, "sufficiently powerful" in this context means that the study would have to be of such scale and quality as to detect a 10-percent increase in risk if it existed. The outcome of such a study could plausibly be called "negative" even if the estimated RR slightly exceeded 1.0—so long as the lower confidence limit did not exceed 1.0 and the upper confidence limit did not exceed 1.05. Rarely does an epidemiological study fall into this "ideal" study category. MSHA reviewed the dpm epidemiologic studies to determine which of them could plausibly be considered to be negative.

For example, one study (Waxweiler et al., 1973) reported positive but statistically non-significant results corresponding to an RR of about 1.1. Among the studies MSHA counts as positive, this is the one that is numerically closest to being "negative". This study, however, relied on a relatively small cohort containing an indeterminate but probably substantial percentage of occupationally unexposed workers. Furthermore, there was no minimum latency allowance for the exposed workers. Therefore, even if MSHA were to use 1.1 rather than 1.05 as a threshold for significant relative risk, the study had insufficient statistical power to merit "negative" status.

One commenter (Dr. James Weeks, representing the UMWA) argued that "MSHA's reliance on * * * statistical significance is somewhat misplaced. Results that are not significant statistically * * * can nevertheless indicate that the exposure in question caused the outcome." MSHA agrees that an otherwise sound study may yield positive (or negative) results that provide valuable evidence for (or against) an underlying relationship but fail, because of an insufficient number of exposed study subjects, to achieve statistical significance. In the absence of other evidence to the contrary, a single positive but not statistically significant result could even show that a causal relationship is more likely than not. By definition, however, such a result would not be conclusive at a high level of confidence. A finding of even very high excess risk in a single, well-designed

study would be far from conclusive if based on a very small number of observed lung cancer cases or if it were in conflict with evidence from toxicity studies.

MSHA agrees that evidence should not be ignored simply because it is not conclusive at a conventional but arbitrary 95-percent confidence level. Lower confidence levels may represent weaker but still important evidence. Nevertheless, to rule out chance effects, the statistical significance of individual studies merits serious consideration when only a few studies are available. That is not the case, however, for the epidemiology literature relating lung cancer to diesel exposure. Since many studies contribute to the overall weight of evidence, the statistical significance of individual studies is far less important than the statistical significance of all findings combined. Statistical significance of the combined findings is addressed in Subsection 3.a.iii of this risk assessment.

Potential Confounders

There are many variables, both known and unknown, that can potentially distort the results of an epidemiologic study. In studies involving lung cancer, the most important example is tobacco smoking. Smoking is highly correlated with the development of lung cancer. If the exposed workers in a study tend to smoke more (or less) than the population to which they are being compared, then smoking becomes what is called a "confounding variable" or "confounder" for the study. In general, any variable affecting the risk of lung cancer potentially confounds observed relationships between lung cancer and diesel exposure. Conspicuous examples are age, smoking habits, and exposure to airborne carcinogens such as asbestos or radon progeny. Diet and other lifestyle factors may also be potential confounders, but these are probably less important for lung cancer than for other forms of cancer, such as bladder cancer.

There are two ways to avoid distortion of study results by a potential confounder: (1) Design the study so that the populations being compared are essentially equivalent with respect to the potentially confounding variable; or (2) allow the confounding to take place, but adjust the results to compensate for its effects. Obviously, the second approach can be applied only to known confounders. Since no adjustment can be made for unknown confounders, it is important to minimize their effects by designing the comparison groups to be as similar as possible.

The first approach requires a high degree of control over the two groups

being compared (exposed and unexposed in a cohort study; with and without lung cancer in a case-control study). For example, the effects of age in a case-control study can be controlled by matching each case of lung cancer with one or more controls having the same year of birth and age in year of diagnosis or death. Matching on age is never perfect, because it is generally not feasible to match within a day or even a month. Similarly, the effects of smoking in a case-control study can be imperfectly controlled by matching on smoking habits to the maximum extent possible.⁴¹ In a cohort study, there is no confounding unless the exposed cohort and the comparison group differ with respect to a potential confounder. For example, if both groups consist entirely of never-smokers, then smoking is not a confounder in the study. If both groups contain the same percentage of smokers, then smoking is still an important confounder to the extent that smoking intensity and history differ between the two groups. In an attempt to minimize such differences (along with potentially important differences in diet and lifestyle) some studies restrict comparisons to workers of similar socioeconomic status and area of residence. Studies may also explicitly investigate smoking habits and histories and forego any adjustment of results if these factors are found to be homogeneously distributed across comparison groups. In that case, smoking would not actually appear to function as a confounder, and a smoking adjustment might not be required or even desirable. Nevertheless, a certain amount of smoking data is still necessary in order to check or verify homogeneity. The study's credibility may also be an important consideration. Therefore, MSHA agrees with the HEI's expert panel that even when smoking appears not to be a confounder,

* * * a study is open to criticism if no smoking data are collected and the association between exposure and outcome is weak. * * * When the magnitude of the association of interest is weak, uncontrolled confounding, particularly from a strong confounder such as cigarette smoking, can have a major impact on the study's results and on the credibility of their use. [HEI, 1999]

However, this does not mean that a study cannot, by means of an efficient study design and/or statistical verification of homogeneity,

⁴¹ If cases and controls cannot be closely matched on smoking or other potentially important confounder, then a hybrid approach is often taken. Cases and controls are matched as closely as possible, differences are quantified, and the study results are adjusted to account for the differences.

demonstrate adequate control for smoking without applying a smoking adjustment.

The second approach to dealing with a confounder requires knowledge or estimation both of the differences in group composition with respect to the confounder and of the effect that the confounder has on lung cancer. Ideally, this would entail specific, quantitative knowledge of how the variable affects lung cancer risk for each member of both groups being compared. For example, a standardized mortality ratio (SMR) can be used to adjust for age differences when a cohort of exposed workers with known birth dates is compared to an unexposed reference population with known, age-dependent lung cancer rates.⁴² In practice, it is not usually possible to obtain detailed information, and the effects of smoking and other known confounders cannot be precisely quantified.

Stoäber and Abel (1996) argue, along with Morgan *et al.* (1997) and some commenters, that even in those epidemiologic studies that are adjusted for smoking and show a statistically significant association, the magnitude of relative or excess risk observed is too small to demonstrate any causal link between dpm exposure and cancer. Their reasoning is that in these studies, errors in the collection or interpretation of smoking data can create a bias in the results larger than any potential contribution attributable to diesel particulate. They propose that studies failing to account for smoking habits should be disqualified from consideration, and that evidence of an association from the remaining, smoking-adjusted studies should be discounted because of potential confounding due to erroneous, incomplete, or otherwise inadequate characterization of smoking histories.

It should be noted, first of all, that five of the six negative studies neither matched nor adjusted for smoking.⁴³ But more importantly, MSHA concurs with IARC (1989), Cohen and Higgins (1995), IPCS (1996), CAL-EPA (1998), ACGIH (1998), Bhatia *et al.* (1998), and Lipsett and Campleman (1999) in not accepting

the view that studies should automatically be disqualified from consideration because of potential confounders. MSHA recognizes that unknown exposures to tobacco smoke or other human carcinogens can distort the results of some lung cancer studies. MSHA also recognizes, however, that it is not possible to design a human epidemiologic study that perfectly controls for all potential confounders. It is also important to note that a confounding variable does not necessarily inflate an observed association. For example, if the exposed members of a cohort smoke less than the reference group to which they are compared, then this will tend to reduce the apparent effects of exposure on lung cancer development. In the absence of evidence to the contrary, it is reasonable to assume that a confounder is equally likely to inflate or to deflate the results.

As shown in Tables III-4 and III-5, 18 of the published epidemiologic studies involving lung cancer did, in fact, control or adjust for exposure to tobacco smoke, and five of these 18 also controlled or adjusted for exposure to asbestos and other carcinogenic substances (Garshick *et al.*, 1987; Boffetta *et al.*, 1988; Steenland *et al.*, 1990; Morabia *et al.*, 1992; Brüske-Hohlfeld *et al.*, 1999). These results are less likely to be confounded than results from most of the studies with no adjustment. All but one of these 18 studies reported some degree of excess risk associated with occupational exposure to diesel particulate, with statistically significant results reported in eight.

In addition, several of the studies with no smoking adjustment took the first approach described above for preventing or substantially mitigating potential confounding by smoking habits: they drew comparisons against internal control groups or other control groups likely to have similar smoking habits as the exposed groups (*e.g.*, Garshick *et al.*, 1988; Gustavsson *et al.*, 1990; Hansen, 1993; and Säverin *et al.*, 1999). Therefore, MSHA places more weight on these studies than on studies drawing comparisons against dissimilar groups with no smoking controls or adjustments. This emphasis is in accordance with the conclusion by Bhatia *et al.* (1998) that smoking homogeneity typically exists within cohorts and is associated with a uniform lifestyle and social class. Although it was not yet available at the time Bhatia *et al.* performed their analysis, an analysis of smoking patterns by Säverin *et al.* (*op cit.*) within the cohort they studied also supports this conclusion.

IMC Global and MARG objected to MSHA's position on potential confounders and submitted comments in general agreement with the views of Morgan *et al.* (*op cit.*) and Stöbel and Abel (*op cit.*). Specifically, they suggested that studies reporting relative risks solely between 1.0 and 2.0 should be discounted because of potential confounders. Of the 41 positive studies considered by MSHA, 22 fall into this category (16 cohort and 6 case-control). In support of their suggestion, IMC Global quoted Speizer (1986), Muscat and Wynder (1995), Lee (1989), WHO (1980), and NCI (1994). These authorities all urged great caution when interpreting the results of such studies, because of potential confounders. MSHA agrees that none of these studies, considered individually, is conclusive and that each result must be considered with due caution. None of the quoted authorities, however, proposed that such studies should automatically be counted as "negative" or that they could not add incrementally to an aggregate body of positive evidence.

IMC Global also submitted the following reference to two Federal Court decisions pertaining to estimated relative risks less than 2.0:

The Ninth Circuit concluded in *Daubert v. Merrell Dow Pharmaceuticals* that "for an epidemiologic study to show causation * * * the relative risk * * * arising from the epidemiologic data will, at a minimum, have to exceed 2." Similarly, a District Court stated in *Hall v. Baxter Healthcare Corp.*⁴⁹: The threshold for concluding that an agent was more likely the cause of the disease than not is relative risk greater than 2.0. Recall that a relative risk of 1.0 means that the agent has no effect on the incidence of disease. When the relative risk reaches 2.0, the agent is responsible for an equal number of cases of disease as all other background causes. Thus a relative risk of 2.0 implies a 50% likelihood that an exposed individual's disease was caused by the agent. [IMC Global]

In contrast with the two cases cited, the purpose of this risk assessment is not to establish civil liabilities for personal injury. MSHA's concern is with reducing the risk of lung cancer, not with establishing the specific cause of lung cancer for an individual miner. The excess risk of an outcome, given an excessive exposure, is not the same thing as the likelihood that an excessive exposure caused the outcome in a given case. To understand the difference, it may be helpful to consider two analogies: (1) The likelihood that a given death was caused by a lightning strike is relatively low, yet exposure to lightning is rather hazardous; (2) a specific smoker may not be able to prove that his or her lung cancer was

⁴² Since these rates may vary by race, geographic region, or other factors, the validity of this adjustment depends heavily on choice of an appropriate reference population. For example, Waxweiler *et al.* (1973) based SMRs for a New Mexico cohort on national lung cancer mortality rates. Since the national age-adjusted rate of lung cancer is about 1/3 higher than the New Mexico rate, the reported SMRs were roughly 3/4 of what they would have been if based on rates specific to New Mexico.

⁴³ The exception is DeCoufle *et al.* (1977), a case-control study that apparently did not match or otherwise adjust for age.

“more likely than not” caused by radon exposure, yet radon exposure significantly increases the risk—especially for smokers. Lung cancer has a variety of alternative causes, but this fact does not reduce the risk associated with any one of them.

Furthermore, there is ample precedent for utilizing epidemiologic studies reporting relative risks less than 2.0 in making clinical and public policy decisions. For example, the following table contains the RR for death from cardiovascular disease associated with cigarette smoking reported in several prospective epidemiologic studies:

Study on cigarette smoking	Estimate of RR of death from cardiovascular disease
British doctors	1.6
Males in 25 states:	
Ages 45–64	2.08
Ages 65–79	1.36
U.S. Veterans	1.74
Japanese study	1.96
Canadian veterans	1.6
Males in nine states	1.70
Swedish males	1.7
Swedish females	1.3
California occupations	2.0

Source: U.S. Department of Health and Human Services (1989).

By IMC Global’s rule of thumb, all but one or two of these studies would be discounted as evidence of increased risk attributable to smoking. These studies, however, have not been widely discounted by scientific authorities. To the contrary, they have been instrumental in establishing that cigarette smoking is a principal cause of heart disease.

A second example is provided by the increased risk of lung cancer found to be caused by residential exposure to radon progeny. As in the case of dpm, tobacco smoking has been an important potential confounder in epidemiological studies used to investigate whether exposures to radon concentrations at residential levels can cause lung cancer. Yet, in the eight largest residential epidemiological studies used to help establish the reality of this now widely accepted risk, the reported relative risks were all less than 2.0. Based on a meta-analysis of these eight studies, the combined relative risk of lung cancer attributable to residential radon exposure was 1.14. This elevation in the risk of lung cancer, though smaller than that reported in most studies of dpm effects, was found to be statistically significant at a 95-percent confidence level (National Research Council, 1999, Table G–25).

(ii) Studies Involving Miners

In the proposed risk assessment, MSHA identified seven epidemiologic studies reporting an excess risk of lung cancer among miners thought to have been exposed occupationally to diesel exhaust. As stated in the proposal, two of these studies specifically investigated miners, and the other five treated miners as a subgroup within a larger population of workers.⁴⁴ MSHA placed two additional studies specific to exposed coal miners (Christie et al., 1995; Johnston et al., 1997) into the public record with its Feb. 12, 1999 **Federal Register** notice. Another study,⁴⁵ investigating lung cancer in exposed potash miners, was introduced by NIOSH at the Knoxville public hearing on May 27, 1999 and later

⁴⁴ In the proposed risk assessment, the studies identified as specifically investigating miners were Waxweiler et al. (1973) and Ahlman et al. (1991). At the Albuquerque public hearing, Mr. Bruce Watzman, representing the NMA, asked a member of the MSHA panel (Mr. Jon Kogut) to list six studies involving miners that he had cited earlier in the hearing and to identify those that were specific to miners. In both his response to Mr. Watzman, and in his earlier remarks, Mr. Kogut noted that the studies involving miners were listed in Tables III–4 and III–5. However, he inadvertently neglected to mention Ahlman et al. (op cit.) and Morabia et al. (1992). (The latter study addressed miners as a subgroup of a larger population.)

In his response to Mr. Watzman, Mr. Kogut cited Swanson et al. (1993) but not Burns and Swanson (1991), which he had mentioned earlier in the hearing in connection with the same study. These two reports are listed under a single entry in Table III–5 (Swanson et al.) because they both report findings based on the same body of data. Therefore, MSHA considers them to be two parts of the same study. The 5.03 odds ratio for mining machine operators mentioned by Mr. Kogut during the hearing was reported in Burns and Swanson (1991).

Only the six studies specified by Mr. Kogut in his response to Mr. Watzman were included in separate critiques by Dr. Peter Valberg and Dr. Jonathan Borak later submitted by the NMA and by MARG, respectively. Dr. Valberg did not address Burns and Swanson (1991), and he addressed a different report by Siemietycki than the one listed in Table III–5 and cited during the hearing (i.e., Siemietycki et al., 1988). Neither Dr. Valberg nor Dr. Borak addressed Ahlman et al. (op cit.) or Morabia et al. (op cit.). Also excluded were two additional miner-specific studies placed into the record on Feb. 12, 1999 (Fed Reg. 64:29 at 59258). Mr. Kogut did not include them in his response to Mr. Watzman, or in his prior remarks, because he was referring only to studies listed in Tables III–4 and III–5 of the published proposals. Mr. Kogut also did not include a study specific to German potash miners submitted by NIOSH at a subsequent public hearing, and this too was left out of both critiques. A published version of the study (Säverin et al., 1999) was placed into the record on June 30, 2000. All of the studies involving miners are in the public record and have been available for comment by interested parties throughout the posthearing comment periods.

⁴⁵ Some commenters suggested that MSHA “overlooked” a recently published study on NSW miners, Brown et al., 1997. This study evaluated the occurrence of forms of cancer other than lung cancer in the same cohort studied by Christie et al. (1995).

published as Säverin et al., 1999. Finally, one study reporting an excess risk of lung cancer for presumably exposed miners was listed in Table III–5 as originally published, and considered by MSHA in its overall assessment, but inadvertently left out of the discussion on studies involving miners in the previous version of this risk assessment.⁴⁶ There are, therefore, available to MSHA a total of 11 epidemiologic studies addressing the risk of lung cancer for miners, and five of these studies are specific to miners.

Five cohort studies (Waxweiler et al., 1973; Ahlman et al., 1991; Christie et al., 1996; Johnston et al., 1997; Säverin et al., 1999) were performed specifically on groups of miners, and one (Boffetta et al., 1988) addressed miners as a subgroup of a larger population. Except for the study by Christie et al., the cohort studies all showed elevated lung cancer rates for miners in general or for the most highly exposed miners within a cohort. In addition, all five case-control studies reported elevated rates of lung cancer for miners (Benhamou et al., 1988; Lerchen et al., 1987; Siemietycki et al., 1988; Morabia et al., 1992; Burns and Swanson, 1991).

Despite the risk assessment’s emphasis on human studies, some members of the mining community apparently believed that the risk assessment relied primarily on animal studies and that this was because studies on miners were unavailable. Canyon Fuels, for example, expressed concerns about relying on animal studies instead of studies on western diesel-exposed miners:

Since there are over a thousand miners here in the West that have fifteen or more years of exposure to diesel exhaust, why has there been no study of the health status of those miners? Why must we rely on animal studies that are questionable and inconclusive?

Actually, western miners were involved in several studies of health effects other than cancer, as described earlier in this risk assessment. With respect to lung cancer, there are many reasons why workers from a particular group of mines might not be selected for study. Lung cancer often takes considerably more than 15 years to develop, and a valid study must allow not only for adequate duration of exposure but also for an adequate period of latency following exposure. Furthermore, many mines contain radioactive gases and/or

⁴⁶ This study was published in two separate reports on the same body of data: Burns and Swanson (1991) and Swanson et al. (1993). Both published reports are listed in Table III–5 under the entry for Swanson et al.

respirable silica dust, making it difficult to isolate the effects of a potential carcinogen.

Similarly, at the public hearing in Albuquerque on May 13, 1999, a representative of Getchell Gold stated that he thought comparing miners to rats was irrational and that "there has not been a study on these miners as to what the effects are." To correct the impression that MSHA was basing its risk assessment primarily on laboratory animal studies, an MSHA panelist pointed out Tables III-4 and III-5 of the proposed preamble and identified six studies pertaining to miners that were listed in those tables. However, he placed no special weight on these studies and cited them only to illustrate the existence of epidemiologic studies reporting an elevated risk of lung cancer among miners.

With their post-hearing comments, the NMA and MARG submitted critiques by Dr. Peter Valberg and Dr. Jonathan Borak of six reports involving miners (see Footnote 42). Drs. Valberg and Borak both noted that the six studies reviewed lacked information on diesel exposure and were vulnerable to confounders and exposure misclassification. For these reasons, Dr. Valberg judged them "particularly poor in identifying what specific role, if any, diesel exhaust plays in lung cancer for miners." He concluded that they do not "implicate diesel exposure per se as strongly associated with lung cancer risk in miners." Similarly, Dr. Borak suggested that, since they do not relate adverse health effects in miners to any particular industrial exposure, "the strongest conclusion that can be drawn from these six studies is that the miners in the studies had an increased risk of lung cancer."

MSHA agrees with Drs. Valberg and Borak that none of the studies they reviewed provides direct evidence of a link between dpm exposure and the excess risk of lung cancer reported for miners. (A few disagreements on details of the individual studies will be discussed below). As MSHA said at the Albuquerque hearing, the lack of exposure information on miners in these studies led MSHA to rely more heavily on associations reported for other occupations. MSHA also noted the limitations of these studies in the proposed risk assessment. MSHA explicitly stated that other epidemiologic studies exist which, though not pertaining specifically to mining environments, contain better diesel exposure information and are less susceptible to confounding by extraneous risk factors.

Inconclusive as they may be on their own, however, even studies involving miners with only presumed or sporadic occupational diesel exposure can contribute something to the weight of evidence. They can do this by corroborating evidence of increased lung cancer risk for other occupations with likely diesel exposures and by providing results that are at least consistent with an increased risk of lung cancer among miners exposed to dpm. Moreover, two newer studies pertaining specifically to miners do contain dpm exposure assessments based on concurrent exposure measurements (Johnston *et al.*, op cit.; Säverin *et al.*, op cit.). The major limitations pointed out by Drs. Valberg and Borak with respect to other studies involving miners do not apply to these two studies.

Case-Control Studies

Five case-control studies, all of which adjusted for smoking, found elevated rates of lung cancer for miners, as shown in Table III-5. The results for miners in three of these studies (Benhamou *et al.*, 1988; Morabia *et al.*, 1992; Siemiatycki *et al.*, 1988) are given little weight, partly because of possible confounding by occupational exposure to radioactive gasses, asbestos, and silica dust. Also, Benhamou and Morabia did not verify occupational diesel exposure status for the miners. Siemiatycki performed a large number of multiple comparisons and reported that most of the miners "were exposed to diesel exhaust for short periods of time," Lerchen *et al.* (1987) showed a marginally significant result for underground non-uranium miners, but cases and controls were not matched on date of birth or death, and the frequency of diesel exposure and exposure to known occupational carcinogens among these miners was not reported.

Burns and Swanson (1991)⁴⁷ reported elevated lung cancer risk for miners and especially mining machine operators, which the authors attributed to diesel exposure. Potential confounding by other carcinogens associated with mining make the results inconclusive, but the statistically significant odds ratio of 5.0 reported for mining machine operators is high enough to cause concern with respect to diesel exposures, especially in view of the significantly elevated risks reported in the same study for other diesel-exposed occupations. The authors noted that the "occupation most likely to have high levels of continuous exposure to diesel

exhaust and to experience that exposure in a confined area has the highest elevated risks: mining machine operators."

Cohort Studies

As shown in Table III-4, MSHA identified six cohort studies reporting results for miners likely to have been exposed to dpm. An elevated risk of lung cancer was reported in five of these six studies. These results will be discussed chronologically.

Waxweiller (1973) investigated a cohort of underground and surface potash miners. The authors noted that potash ore "is not embedded in siliceous rock" and that the "radon level in the air of potash mines is not significantly higher than in ambient air." Contrary to Dr. Valberg's review of this study, the number of lung cancer cases was reported to be slightly higher than expected, for both underground and surface miners, based on lung cancer rates in the general U.S. population (after adjustment for age, sex, race, and date of death). Although the excess was not statistically significant, the authors noted that lung cancer rates in the general population of New Mexico were about 25 percent lower than in the general U.S. population. They also noted that a higher than average percentage of the miners smoked and that this would "tend to counterbalance" the adjustment needed for geographic location. The authors did not, however, consider two other factors that would tend to obscure or deflate an excess risk of lung cancer, if it existed: (1) A healthy worker effect and (2) the absence of any occupational diesel exposure for a substantial percentage of the underground miners.

MSHA agrees with Dr. Valberg's conclusion that "low statistical power and indeterminate diesel-exhaust exposure render this study inadequate for assessing the effect of diesel exhaust on lung-cancer risk in miners." However, given the lack of any adjustment for a healthy worker effect, and the likelihood that many of the underground miners were occupationally unexposed, MSHA views the slightly elevated risk reported in this study as consistent with other studies showing significantly greater increases in risk for exposed workers.

Boffetta *et al.* (1988) investigated mortality in a cohort of male volunteers who enrolled in a prospective study conducted by the American Cancer Society. Lung cancer mortality was analyzed in relation to self-reported diesel exhaust exposure and to employment in various occupations

⁴⁷ This report is listed in Table III-5 under Swanson *et al.* (1993), which provides further analysis of the same body of data.

identified with diesel exhaust exposure, including mining. After adjusting for smoking patterns,⁴⁸ there was a statistically significant excess of 167 percent (RR = 2.67) in lung cancers among 2034 workers ever employed as miners, compared to workers never employed in occupations associated with diesel exposure. No analysis by type of mining was reported. Other findings reported from this study are discussed in the next subsection.

Although an adjustment was made for smoking patterns, the relative risk reported for mining did not control for exposures to radioactive gasses, silica dust, and asbestos. These lung carcinogens are probably present to a greater extent in mining environments than in most of the occupational environments used for comparison. Self-reported exposures to asbestos and stone dusts were taken into account in other parts of the study, but not in the calculation of excess lung cancer risks associated with specific occupations, including mining.

Several commenters reiterated two caveats expressed by the study's authors and noted in Table III-4. These are (1) that the study is susceptible to selection biases because participants volunteered and because the age-adjusted mortality rates differed between those who provided exposure information and those who did not; and (2) that all exposure information was self-reported with no quantitative measurements. Since these caveats are not specific to mining and pertain to most of the study's findings, they will be addressed when this study's overall results are described in the next subsection.

One commenter, however (Mr. Mark Kaszniak of IMC Global), argued that selection bias due to unknown diesel exposure status played an especially important role in the RR calculated for miners. About 21 percent of all participants provided no diesel exposure information. Mr. Kaszniak noted that diesel exposure status was unknown for an even larger percentage of miners and suggested that the RR calculated for miners was, therefore, inflated. He presented the following argument:

In the miner category, this [unknown diesel exposure status] accounted for 44.2% of the study participants, higher than any

other occupation studied. This is important as this group experienced a higher mortality for all causes as well as lung cancer than the analyzed remainder of the cohort. If these persons had been included in the "no exposure to diesel exhaust group," their inclusion would have lowered any risk estimates from diesel exposure because of their higher lung cancer rates. [IMC Global post-hearing comments]

This argument, which was endorsed by MARG, was apparently based on a misunderstanding of how the comparison groups used to generate the RR for mining were defined.⁴⁹ Actually, persons with unknown diesel exposure status were included among the miners, but excluded from the reference population. Including sometime miners with unknown diesel exposure status in the "miners" category would tend to mask or reduce any strong association that might exist between highly exposed miners and an increased risk of lung cancer. Excluding persons with unknown exposure status from the reference population had an opposing effect, since they happened to experience a higher rate of lung cancer than cohort members who said they were unexposed. Therefore, removing "unknowns" from the "miner" group and adding them to the reference group could conceivably shift the calculated RR for miners in either direction. However, the RR reported for persons with unknown diesel exposure status, compared to unexposed persons, was 1.4 (*ibid.*, p. 412)—which is smaller than the 2.67 reported for miners. Therefore, it appears more likely that the RR for mining was deflated than inflated on account of persons with unknown exposure status.

Although confounders and selection effects may have contributed to the 2.67 RR reported for mining, MSHA believes this result was high enough to support

⁴⁹During the public hearing on May 25, 1999, Mr. Kaszniak stated his belief that, for miners, the "relative risk calculation excluded that 44% of folks who did not respond to the questionnaire with regards to diesel exposure." Contrary to Mr. Kaszniak's belief, however, the "miners" on which the 2.67 RR was based included all 2034 cohort members who had ever been a miner, regardless of whether they had provided diesel exposure information (see Boffetta et al., 1988, p. 409).

Furthermore, the 44.2-percent nonrespondent figure is not pertinent to potential selection bias in the RR calculation reported for miners. The group of 2034 "sometime" miners used in that calculation was 65 percent larger than the group of 1233 "mainly" miners to which the 44-percent nonrespondent rate applies. The reference group used for comparison in the calculation consisted of all cohort members "with occupation different from those listed [i.e., railroad workers, truck drivers, heavy equipment operators, and miners] and not exposed [to diesel exhaust]." The overall nonrespondent rate for occupations in the reference group was about 21 percent (calculated by MSHA from Table VII of Boffetta et al., 1988).

a dpm effect, especially since elevated lung cancer rates were also reported for the three other occupations associated with diesel exhaust exposure. Dr. Borak stated without justification that "[the] association between dpm and lung cancer was confounded by age, smoking, and other occupational exposures * * *." He ignored the well-documented adjustments for age and smoking. Although it does not provide strong or direct evidence that dpm exposure was responsible for any of the increased risk of lung cancer observed among miners, the RR for miners is consistent with evidence provided by the rest of the study results.

Ahlman et al. (1991) studied cohorts of 597 surface miners and 338 surface workers employed at two sulfide ore mines using diesel powered front-end loaders and haulage equipment. Both of these mines (one copper and one zinc) were regularly monitored for alpha energy concentrations (i.e., due to radon progeny), which were at or below the Finish limit of 0.3 WL throughout the study period. The ore in both mines contained arsenic only as a trace element (less than 0.005 percent). Lung cancer rates in the two cohorts were compared to rates for males in the same province of Finland. Age-adjusted excess mortality was reported for both lung cancer and cardiovascular disease among the underground miners, but not among the surface workers. None of the underground miners who developed lung cancer had been occupationally exposed to asbestos, metal work, paper pulp, or organic dusts. Based on the alpha energy concentration measurements made for the two mines, the authors calculated that not all of the excess lung cancer for the underground miners was attributable to radon exposure. Based on a questionnaire, the authors found similar underground and surface age-specific smoking habits and alcohol consumption and determined that "smoking alone cannot explain the difference in lung cancer mortality between the [underground] miners and surface workers. Due to the small size of the cohort, the excess lung cancer mortality for the underground miners was not statistically significant. However, the authors concluded that the portion of excess lung cancer not attributable to radon exposure could be explained by the combined effects of diesel exhaust and silica exposure. Three of the ten lung cancers reported for underground miners were experienced by conductors of diesel-powered ore trains.

Christie et al. (1994, 1995) studied mortality in a cohort of 23,630 male Australian (New South Wales, NSW)

⁴⁸During the public hearing on May 25, 1999, Mr. Mark Kaszniak of IMC Global incorrectly asserted that "smoking was treated in a simplistic way in this study by using three categories: smokers, ex-smokers, and non-smokers." The study actually used five categories, dividing smokers into separate categories for 1-20 cigarettes per day, 21 or more cigarettes per day, and exclusively pipe and/or cigar smoking.

coal mine workers who entered the industry after 1972. Although the majority of these workers were underground miners, most of whom were presumably exposed to diesel emissions, the cohort included office workers and surface ("open cut") miners. The cohort was followed up through 1992. After adjusting for age, death rates were lower than those in the general male population for all major causes except accidents. This included the mortality rate for all cancers as a group (Christie et al., 1995, Table 1). Lower-than-normal incidence rates were also reported for cancers as a group and for lung cancer specifically (Christie et al., 1994, Table 10).

The investigators noted that the workers included in the cohort were all subject to pre-employment physical examinations. They concluded that "it is likely that the well known 'healthy worker' effect * * * was operating" and that, instead of comparing to a general population, "a more appropriate comparison group is Australian petroleum industry workers." (Christie et al., 1995) In contrast to the comparison with the population of NSW, the all-cause standardized mortality ratio (SMR) for the cohort of coal miners was greater than for petroleum workers by a factor of over 20 percent—i.e., 0.76 vs. 0.63 (ibid., p. 20). However, the investigators did not compare the cohort to petroleum workers specifically with respect to lung cancer or other causes of death. Nor did they adjust for a healthy worker effect or make any attempt to compare mortality or lung cancer rates among workers with varying degrees of diesel exposure within the cohort.

Despite the elevated SMR relative to petroleum workers, several commenters cited this study as evidence that exposure to diesel emissions was not causally associated with an increased risk of lung cancer (or with adverse health effects associated with fine particulates). These commenters apparently ignored the investigators' explanation that the low SMRs they reported were likely due to a healthy worker effect. Furthermore, since the cohort exhibited lower-than-normal mortality rates due to heart disease and non-cancerous respiratory disease, as well as to cancer, there may well have been less tobacco smoking in the cohort than in the general population. Therefore, it is reasonably likely that the age-adjusted lung cancer rate would have been elevated, if it had been adjusted for smoking and for a healthy worker effect based on mortality from causes other than accidents or respiratory disease. In addition, the

cohort SMR for accidents (other than motor vehicle accidents) was significantly above that of the general population. Since the coal miners experienced an elevated rate of accidental death, they had a lower-than-normal chance to die from other causes or to develop lung cancer. The investigators made no attempt to adjust for the competing, elevated risk of death due to occupational accidents.

Given the lack of any adjustment for smoking, healthy worker effect, or the competing risk of accidental death, the utility of this study in evaluating health consequences of Dpm exposure is severely limited by its lack of any internal comparisons or comparisons to a comparable group of unexposed workers. Furthermore, even if such adjustments or comparisons were made, several other attributes of this study limit its usefulness for evaluating whether exposure to diesel emissions is associated with an increased risk of lung cancer. First, the study was designed in such a way as to allow inadequate latency for a substantial portion of the cohort. Although the cohort was followed up only through 1992, it includes workers who entered the workforce at the end of 1992. Therefore, there is no minimum duration of occupational exposure for members of the cohort. Approximately 30 percent of the cohort was employed in the industry for less than 10 years, and the maximum duration of employment and latency combined was 20 years. Second, average age for members of the cohort was only 40 to 50 years (Christie et al., p. 7), and the rate of lung cancer was based on only 29 cases. The investigators acknowledged that "it is a relatively young cohort" and that "this means a small number of cancers available for analysis, because cancer is more common with advancing age * * *." They further noted that "* * * the number of cancers available for analysis is increasing very rapidly. As a consequence, every year that passes makes the cancer experience of the cohort more meaningful in statistical terms." (ibid., p. 27) Third, miners' work history was not tracked in detail, beyond identifying the first mine in which a worker was employed. Some of these workers may have been employed, for various lengths of time, in both underground and surface operations at very different levels of diesel exposure. Without detailed work histories, it is not possible to construct even semi-quantitative measures of diesel exposure for making internal comparisons within the cohort.

One commenter (MARG) claimed that this (NSW) study "* * * reflects the

latest and best scientific evidence, current technology, and the current health of miners" and that it "is not rational to predicate regulations for the year 2000 and beyond upon older scientific studies * * *." For the reasons stated above, MSHA believes, to the contrary, that the NSW study contributes little or no information on the potential health effects of long-term dpm exposures and that whatever information it does contribute does not extend to effects, such as cancer, expected in later life.

Furthermore, three even more recent studies are available that MSHA regards as far more informative for the purposes of the present risk assessment. Unlike the NSW study, these directly address Dpm exposure and the risk of lung cancer. Two of these studies (Johnston et al., 1997; Säverin et al., 1999), both incorporating a quantitative Dpm exposure assessment, were carried out specifically on mining cohorts and will be discussed next. The third (Brüske-Hohlfeld et al., 1999) is a case-control study not restricted to miners and will be discussed in the following subsection. In accordance with MARG's emphasis on the timeliness of scientific studies, MSHA places considerable weight on the fact that all three—the most recent epidemiologic studies available—reported an association between diesel exposure and an increased risk of lung cancer.

Johnston et al. (1997) studied a cohort of 18,166 coal miners employed in ten British coal mines over a 30-year period. Six of these coal mines used diesel locomotives, and the other four were used for comparison. Historical NO_x and respirable dust concentration measurements were available, having routinely been collected for monitoring purposes. Two separate approaches were taken to estimate dpm exposures, leading to two different sets of estimates. The first approach was based on NO_x measurements, combined with estimated ratios between dpm and NO_x. The second approach was based on complex calculations involving measurements of total respirable dust, ash content, and the ratio of quartz to dust for diesel locomotive drivers compared to the ratio for face workers (ibid., Figure 4.1 and pp 25–46). These calculations were used to estimate dpm exposure concentrations for the drivers, and the estimates were then combined with traveling times and dispersion rates to form estimates of dpm concentration levels for other occupational groups. In four of the six dieselized mines, the NO_x-based and dust-based estimates of dpm were in generally good agreement, and they

were combined to form time-independent estimates of shift average dpm concentration for individual seams and occupational groups within each mine. In the fifth mine, the PFR measurements were judged unreliable for reasons extensively discussed in the report, so the NO_x-based estimates were used. There was no NO_x exposure data for the sixth mine, so they used dust-based estimates of dpm exposure.

Final estimates of shift-average dpm concentrations ranged from 44 µg/m³ to 370 µg/m³ for locomotive drivers and from 1.6 µg/m³ to 40 µg/m³ for non-drivers at various mines and work locations (*ibid.*, Tables 8.3 and 8.6, respectively). These were combined with detailed work histories, obtained from employment records, to provide an individual estimate of cumulative dpm exposure for each miner in the cohort. Although most cohort members (including non-drivers) had estimated cumulative exposures less than 1 g-hr/m³, some members had cumulative exposures that ranged as high as 11.6 g-hr/m³ (*ibid.*, Figure 9.1 and Table 9.1).

A statistical analysis (time-dependent proportional hazards regression) was performed to examine the relationship between lung cancer risk and each miner's estimated cumulative dpm exposure (unlagged and lagged by 15 years), attained age, smoking habit, mine, and cohort entry date. Smoking habit was represented by non-smoker, ex-smoker, and smoker categories, along with the average number of cigarettes smoked per day for the smokers. Pipe tobacco consumption was expressed by an equivalent number of cigarettes per day.

In their written comments, MARG and the NMA both mischaracterized the results of this study, apparently confusing it with a preliminary analysis of the same cohort. The preliminary analysis (one part of what Johnston et al. refer to as the "wider mortality study") was summarized in Section 1.2 (pp 3–5) of the 105-page report at issue, which may account for the confusion by MARG and the NMA.⁵⁰

⁵⁰ Since MARG and the NMA both stressed the importance of a quantitative exposure assessment, it is puzzling that they focused on a crude SMR from the preliminary analysis and ignored the quantitative results from the subsequent analysis. Johnston et al. noted that SMRs from the preliminary analysis were consistent "with other studies of occupational cohorts where a healthy worker effect is apparent." But even the preliminary analysis explored a possible surrogate exposure-response relationship, rather than simply relying on SMRs. Unlike the analysis by Johnston et al., the preliminary analysis used travel time as a surrogate measure of dpm exposure and made no attempt to further quantify dpm exposure concentrations. (*ibid.*, p.5)

Contrary to the MARG and NMA characterization, Johnston et al. found a positive, quantitative relationship between cumulative dpm exposure (lagged by 15 years) and an excess risk of lung cancer, after controlling for age, smoking habit, and cohort entry date. For each incremental g-hr/m³ of cumulative occupational dpm exposure, the relative risk of lung cancer was estimated to increase by a factor of 22.7 percent. Adjusting for mine-to-mine differences that may account for a portion of the elevated risk reduced the estimated RR factor to 15.6 percent. Therefore, with the mine-specific adjustment, the estimated RR was 1.156 per g-hr/m³ of cumulative dpm exposure. It follows that, based on the mine-adjusted model, the estimated RR for a specified cumulative exposure is 1.156 raised to a power equal to that exposure. For example, RR = (1.156)^{3.84} = 1.74 for a cumulative dpm exposure of 3.84 g-hr/m³, and RR = (1.156)^{7.68} = 3.04 for a cumulative dpm exposure of 7.68 g-hr/m³.⁵¹ Estimates of RR based on the mine-unadjusted model would substitute 1.227 for 1.156 in these calculations.

Two limitations of this study weaken the evidence it presents of an increasing exposure-response relationship. First, although the exposure assessment is quantitative and carefully done, it is indirect and depends heavily on assumptions linking surrogate measurements to dpm exposure levels. The authors, however, analyzed sources of inaccuracy in the exposure assessment and concluded that "the similarity between the estimated * * * [dpm] exposure concentrations derived by the two different methods give some degree of confidence in the accuracy of the final values * * *." (*ibid.*, pp. 71–75) Second, the highest estimated cumulative dpm exposures were clustered at a single coal mine, where the SMR was elevated relative to the regional norm. Therefore, as the authors pointed out, this one mine greatly influences the results and is a possible confounder in the study. The investigators also noted that this mine was " * * * found to have generally the higher exposures to respirable quartz and low level radiation." Nevertheless, MSHA regards it likely that the relatively high dpm exposures at this mine were responsible for at least some of the excess mortality. There is no apparent way, however, to ascertain just how much of the excess mortality

⁵¹ Assuming an average dpm concentration of 200 µg/m³ and 1920 work hours per year, 3.84 g-hr/m³ and 7.68 g-hr/m³ correspond to 10 and 20 years of occupational exposure, respectively.

(including lung cancer) at this coal mine should be attributed to high occupational dpm exposures and how much to confounding factors distinguishing it (and the employees working there) from other mines in the study.

The RR estimates based on the mine-unadjusted model assume that the excess lung cancer observed in the cohort is entirely attributable to dpm exposures, smoking habits, and age distribution. If some of the excess lung cancer is attributed to other differences between mines, then the dpm effect is estimated by the lower RR based on the mine-adjusted model.

For purposes of comparison with the findings of Säverin et al. (1999), it will be useful to calculate the RR for a cumulative dpm exposure of 11.7 g-hr/m³ (i.e., the approximate equivalent of 4.9 mg-yr/m³ TC).⁵² At this exposure level, the mine-unadjusted model produces an estimated RR = (1.227)^{11.7} = 11, and the mine-adjusted model produces an estimated RR = (1.156)^{11.7} = 5.5.

Säverin et al. (1999) studied a cohort of male potash miners in Germany who had worked underground for at least one year after 1969, when the mines involved began converting to diesel powered vehicles and loading equipment. Members of the cohort were selected based on company medical records, which also provided bi-annual information on work location for each miner and, routinely after 1982, the miner's smoking habits. After excluding miners whose workplace histories could not be reconstructed from the medical records (5.5 percent) and miners lost to follow-up (1.9 percent), 5,536 miners remained in the cohort. Within this full cohort, the authors defined a sub-cohort consisting of 3,258 miners who had "worked underground for at least ten years, held one single job during at least 80% of their underground time, and held not more than three underground jobs in total."

The authors divided workplaces into high, medium, and low diesel exposure categories, respectively corresponding

⁵² This value represents 20 years of cumulative exposure for the most highly exposed category of workers in the cohort studied by Säverin et al.

As explained elsewhere in this preamble, TC constitutes approximately 80 percent of total dpm. Therefore, the TC value of 4.9 mg-yr/m³ presented by Säverin et al. must first be divided by 0.8 to produce a corresponding dpm value of 6.12 mg-yr/m³. To convert this result to the units used by Johnston et al., it is then multiplied by 1920 work hours per year and divided by 1000 mg/g to yield 11.7 g-hr/m³. This is nearly identical to the maximum cumulative dpm exposure estimated for locomotive drivers in the study by Johnston et al. (See Johnston et al., *op cit.*, Table 9.1.)

to production, maintenance, and workshop areas of the mine. Each of these three categories was assigned a representative respirable TC concentration, based on an average of measurements made in 1992. These averages were 390 µg/m³ for production, 230 µg/m³ for maintenance, and 120 µg/m³ for workshop. Some commenters expressed concern about using average exposures from 1992 to represent exposure throughout the study. The authors justified using these measurement averages to represent exposure levels throughout the study period because "the mining technology and the type of machinery used did not change substantially after 1970." This assumption was based on interviews with local engineers and industrial hygienists.

Thirty-one percent of the cohort consented to be interviewed, and information from these interviews was used to validate the work history and smoking data reconstructed from the medical records. The TC concentration assigned to each work location was combined with each miner's individual work history to form an estimate of cumulative exposure for each member of the cohort. Mean duration of exposure was 15 years. As of the end of follow-up in 1994, average age was 49 years, average time since first exposure was 19 years, and average cumulative exposure was 2.70 mg-y/m³.

The authors performed an analysis (within each TC exposure category) of smoking patterns compared with cumulative TC exposure. They also analyzed smoking misclassification as estimated by comparing information from the interviews with medical records. From these analyses, the authors determined that the cohort was homogeneous with respect to smoking and that a smoking adjustment was neither necessary nor desirable for internal comparisons. However, they did not entirely rule out the possibility that smoking effects may have biased the results to some extent. On the other hand, the authors concluded that asbestos exposure was minor and restricted to jobs in the workshop category, with negligible effects. The miners were not occupationally exposed to radon progeny, as documented by routine measurement records.

As compared to the general male population of East Germany, the cohort SMR for all causes combined was less than 0.6 at a 95-percent confidence level. The authors interpreted this as demonstrating a healthy worker effect, noting that "underground workers are heavily selected for health and sturdiness, making any surface control

group incomparable." Accordingly, they performed internal comparisons within the cohort of underground miners. The RR reported for lung cancer among miners in the high-exposure production category, compared to those in the low-exposure workshop category, was 2.17. The corresponding RR was not elevated for other cancers or for diseases of the circulatory system.

Two statistical methods were used to investigate the relationship between lung cancer RR and each miner's age and cumulative TC exposure: Poisson regression and time-dependent proportional hazards regression. These two statistical methods were applied to both the full cohort and the subcohort, yielding four different estimates characterizing the exposure-response relationship. Although a high confidence level was not achieved, all four of these results indicated that the RR increased with increasing cumulative TC exposure. For each incremental mg-yr/m³ of occupational TC exposure, the relative risk of lung cancer was estimated to increase by the following multiplicative factor:⁵³

Method	RR per mg-yr/m ³	
	Full cohort	Sub-cohort
Poisson	1.030	1.139
Proportional Hazards	1.112	1.225

Based on these estimates, the RR for a specified cumulative TC exposure (X) can be calculated by raising the tabled value to a power equal to X. For example, using the proportional hazards analysis of the subcohort, the RR for X = 3.5 mg-yr/m³ is (1.225)^{3.5} = 2.03.⁵⁴ The authors calculated the RR expected for a cumulative TC exposure of 4.9 mg-yr/m³, which corresponds to 20 years of occupational exposure for miners in the production category of the cohort. These miners were exposed for five hours per 8-hour shift at an average TC concentration of 390 µg/m³. The resulting RR values were reported as follows:

Method	RR for 4.9 mg-yr/m ³	
	Full cohort	Sub-cohort
Poisson	1.16	1.89
Proportional Hazards	1.68	2.70

This study has two important limitations that weaken the evidence it presents of a positive correlation between cumulative TC exposure and the risk of lung cancer. These are (1) potential confounding due to tobacco smoking and (2) a significant probability (i.e., greater than 10 percent) that a correlation of the magnitude found could have arisen simply by chance, given that it were based on a relatively small number of lung cancer cases.

Although data on smoking habits were compiled from medical records for approximately 80 percent of the cohort, these data were not incorporated into the statistical regression models. The authors justified their exclusion of smoking from these models by showing that the likelihood of smoking was essentially unrelated to the cumulative TC exposure for cohort members. Based on the portion of the cohort that was interviewed, they also determined that the average number of cigarettes smoked per day was the same for smokers in the high and low TC exposure categories (production and workshop, respectively). However, these same interviews led them to question the accuracy of the smoking data that had been compiled from medical records. Despite the cohort's apparent homogeneity with respect to smoking, the authors noted that smoking was potentially such a strong confounder that "even small inaccuracies in smoking data could cause effects comparable in size to the weak carcinogenic effect of diesel exhaust." Therefore, they excluded the smoking data from the analysis and stated they could not entirely rule out the possibility of a smoking bias. MSHA agrees with the authors of this report and the HEI Expert Panel (op cit.) that even a high degree of cohort homogeneity does not rule out the possibility of a spurious correlation due to residual smoking effects. Nevertheless, because of the cohort's homogeneity, the authors concluded that "the results are unlikely to be substantially biased by confounding," and MSHA accepts this conclusion.

The second limitation of this study is related to the fact that the results are based on a total of only 38 cases of lung cancer for the full cohort and 21 cases for the subcohort. In their description of this study at the May 27, 1999, public

⁵³ MSHA determined these values by calculating the antilog, to the base e, of each corresponding estimate of α reported by Säverin et al. (op cit.) in their Tables III and IV. The cumulative exposure unit of mg-yr/m³ refers to the average TC concentration experienced over a year's worth of 8-hour shifts.

⁵⁴ This is the estimated risk relative not to miners in the workshop category but to a theoretical age-adjusted baseline risk for cohort members accumulating zero occupational TC exposure.

hearing, NIOSH noted that the “lack of [statistical] significance may be a result of the study having a small cohort (approximately 5,500 workers), a limited time from first exposure (average of 19 years), and a young population (average age of 49 years at the end of follow-up).” More cases of lung cancer may be expected to occur within the cohort as its members grow older. The authors of the study addressed statistical significance as follows:

* * * the small number of lung cancer cases produced wide confidence intervals for all measures of effect and substantially limited the study power. We intend to extend the follow-up period in order to improve the statistical precision of the exposure-response relationship. [Säverin et al., op cit.]

Some commenters stated that due to these limitations, data from the Säverin et al. study should not be the basis of this rule. On the other hand, NIOSH commented that “[d]espite the limitations discussed * * * the findings from the Säverin et al. (1999) study should be used as an alternative source of data for quantifying the possible lung cancer risks associated with Dpm exposures.” As stated earlier, MSHA is not relying on any single study but, instead, basing its evaluation on the weight of evidence from all available data.

(iii) Best Available Epidemiologic Evidence

Based on the evaluation criteria described earlier, and after considering

all the public comment that was submitted, MSHA has identified four cohort studies (including two from U.S.) and four case-control studies (including three from U.S.) that provide the best currently available epidemiologic evidence relating dpm exposure to an increased risk of lung cancer. Three of the 11 studies involving miners fall into this select group. MSHA considers the statistical significance of the combined evidence far more important than confidence levels for individual studies. Therefore, in choosing the eight most informative studies, MSHA placed less weight on statistical significance than on the other criteria. The basis for MSHA’s selection of these eight studies is summarized as follows:

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STUDY	STATISTICAL SIGNIFICANCE (at 95% Conf.)	COMPARISON GROUPS	EXPOSURE ASSESSMENT	CONTROLS ON POTENTIAL CONFOUNDING
Boffetta et al. 1988 (cohort)	YES	Internal Comparison	Job history and self-reported duration of occupational diesel exposure.	Adjustments for age, smoking, and, in some analyses, for occupational exposures to asbestos, coal & stone dusts, coal tar & pitch, and gasoline exhaust.
Boffetta et al. 1990 (case-control)	NO	Matched within hospital on smoking, age, year of interview.	Job history and self-reported duration of occupational diesel exposure.	Adjustments for age, smoking habit and intensity, asbestos exposure, race, and education.
Brüske-Hohlfeld et al. 1999 (case-control)	YES	Matched on sex, age, and region of residence.	Total duration of occupational diesel exposure based on detailed job history.	Adjustments for current and past smoking patterns, cumulative amount smoked (packyears), and asbestos exposure.
Garshick et al. 1987 (case-control)	YES	Matched within cohort on dates of birth and death.	Semi-quantitative, based on job history and tenure combined with exposure status established later for each job.	Adjustments for lifetime smoking and asbestos exposure.
Garshick et al. 1988, 1991 (cohort)	YES	Internal Comparison	Semi-quantitative, based on job history and tenure combined with exposure status established later for each job.	Subjects with likely or possible asbestos exposure excluded from cohort. Cigarette smoking determined to be uncorrelated with diesel exposure within cohort.
Johnston et al. 1997 (cohort)	NO (marginal)	Internal Comparison	Quantitative, based on surrogate exposure measurements and detailed employment records.	Adjustments for age, smoking habit & intensity, mine site, and cohort entry date.
Säverin et al. 1999 (cohort)	NO	Internal Comparison	Quantitative, based on TC exposure measurements and detailed employment records.	Adjustment for age. Cigarette smoking determined to be uncorrelated with cumulative TC exposure within cohort.
Steenland et al. 1990, 1992, 1998 (case-control)	YES	Matched within cohort on date of death within 2 years.	Semi-quantitative, based on job history and subsequent EC measurements.	Adjustments for age, smoking, and asbestos exposure. Dietary covariates were tested and found not to confound the analysis.

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Six entirely negative studies were identified earlier in this risk assessment. Several commenters objected to MSHA's treatment of the negative studies, indicating that they had been discounted without sufficient

justification. To put this in proper perspective, the six negative studies should be compared to those MSHA has identified as the best available epidemiologic evidence, with respect to the same evaluation criteria. (It should be noted that the statistical significance

of a negative study is best represented by its power.) In accordance with those criteria, MSHA discounts the evidentiary significance of these six studies for the following reasons:

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STUDY	POWER	COMPARISON GROUPS	EXPOSURE ASSESSMENT	CONTROLS ON POTENTIAL CONFOUNDING
Bender et al. 1989 (cohort)	Relatively small cohort (N = 4849)	External comparison; No adjustment for healthy worker effect.	Job only: highway maintenance workers.	Disparate comparison groups with no smoking adjustment.
Christie et al. 1996 (cohort)	Inadequate latency allowance.	External comparison; No adjustment for healthy worker effect.	Industry only: combined all underground and surface workers at coal mines.	Disparate comparison groups with no smoking adjustment
DeCoufle et al. 1977 (case-control)	Inadequate latency allowance.	Cases not matched with controls.	Job only: (1) Combined bus, taxi, and truck drivers; (2) locomotive engineers.	Age differences not taken into account.
Edling et al. 1987 (cohort)	Small cohort (N = 694)	External comparison; No adjustment for healthy worker effect.	Job only: bus workers.	Disparate comparison groups with no smoking adjustment
Kaplan 1959 (cohort)	Inadequate latency allowance.	External comparison; No adjustment for healthy worker effect.	Jobs classified by diesel exposure. No attempt to differentiate between diesel and coal-fired locomotives.	Disparate comparison groups with no smoking adjustment
Waller 1981 (cohort)	Acceptable.	External comparison; No adjustment for healthy worker effect; Selection bias due to excluding retirees from cohort.	Job only: bus workers.	Disparate comparison groups with no smoking adjustment

Other studies proposed as counter-evidence by some commenters will be addressed in the next subsection of this risk assessment.

The eight studies MSHA identified as representing the best available epidemiologic evidence all reported an elevated risk of lung cancer associated with diesel exposure. The results from these studies will now be reviewed, along with MSHA's response to public comments as appropriate.

Boffetta et al., 1988

The structure of this cohort study was summarized in the preceding subsection of this risk assessment. The following table contains the main results. The relative risks listed for duration of exposure were calculated with reference to all members of the cohort reporting no diesel exposure, regardless of occupation, and adjusted for age, smoking pattern, and other occupational exposures (asbestos, coal and stone dusts, coal tar and pitch, and gasoline exhausts). The relative risks listed for

occupations were calculated for cohort members that ever worked in the occupation, compared to cohort members never working in any of the four occupations listed and reporting no diesel exposure. These four relative risks were adjusted for age and smoking pattern only. Smoking pattern was coded by 5 categories: never smoker; current 1–20 cigarettes per day; current 21 or more cigarettes per day; ex-smoker of cigarettes; current or past pipe and/or cigar smoker.

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Main results from Boffetta et al., 1988

(RRs by duration adjusted for age, smoking, and other occupational exposures;

Occupational RRs adjusted for age and smoking only)

Self-Reported Duration of Exposure to Diesel Exhaust (years)	Lung Cancer RR	95-Percent Confidence Interval
1 to 15	1.05	0.80 - 1.39
16 or more	1.21	0.94 - 1.56
Occupation		
Truck Drivers	1.24	0.93 - 1.66
Railroad Workers	1.59	0.94 - 2.69
Heavy Equipment Operators	2.60	1.12 - 6.06
Miners	2.67	1.63 - 4.37

In addition to comments (addressed earlier) on the RR for miners in this study, IMC Global submitted several comments pertaining to the RR calculated for persons who explicitly stated that they had been occupationally exposed to diesel emissions. This RR was 1.18 for persons reporting any exposure (regardless of duration) compared to all subjects reporting no exposure. MSHA considers the most important issue raised by IMC Global to be that 20.6 percent of all cohort members did not answer the question about occupational diesel exhaust exposure during their lifetimes, and these subjects experienced a higher age-adjusted mortality rate than the others. As the authors of this study acknowledged, this "could introduce a substantial bias in the estimate of the association." (Boffetta et al., 1988, p.412).

To show that the impact of this bias could indeed be substantial, the authors of the study addressed one extreme possibility, in which all "unknowns" were actually unexposed. Under this scenario, excluding the "unknowns" would have biased the calculated RR upward by a sufficient amount to explain the entire 18-percent excess in RR. This would not, however, explain the higher RR for persons reporting more than 16 years exposure, compared to the RR for persons reporting 1 to 15 years. Moreover, the authors did not discuss the opposite extreme: if all or most of the "unknowns" who experienced lung cancer were actually exposed, then excluding them would have biased the calculated RR downward. There is little basis for favoring one of these extremes over the other.

Another objection to this study raised by IMC Global was:

All exposure information in the study was self-reported and not validated. The authors of the study have no quantitative data or measurements of actual diesel exhaust exposures.

MSHA agrees with IMC Global and other commenters that a lack of quantitative exposure measurements limits the strength of the evidence this study presents. MSHA believes, however, that the evidence presented is nevertheless substantial. The possibility of random classification errors due to self-reporting of exposures does not explain why persons reporting 16 or more years of exposure would experience a higher relative risk of lung cancer than persons reporting 1 to 15 years of exposure. This difference is not statistically significant, but random exposure misclassification would tend

to make the effects of exposure less conspicuous. Nor can self-reporting explain why an elevated risk of lung cancer would be observed for four occupations commonly associated with diesel exposure.

Furthermore, the study's authors did perform a rough check on the accuracy of the cohort's exposure information. First, they confirmed that, after controlling for age, smoking, and other occupational exposures, a statistically significant relationship was found between excess lung cancer and the cohort's self-reported exposures to asbestos. Second they found no such association for self-reported exposure to pesticides and herbicides, which they considered unrelated to lung cancer (*ibid.*, pp. 410–411).

IMC Global also commented that the " * * * study may suffer from volunteer bias in that the cohort was healthier and less likely to be exposed to important risk factors, such as smoking or alcohol." They noted that this possibility "is supported by the U.S. EPA in their draft Health Assessment Document for Diesel Emissions."

The study's authors noted that enrollment in the cohort was nonrandom and that participants tended to be healthier and less exposed to various risk factors than the general population. These differences, however, would tend to reduce any relative risk for the cohort calculated in comparison to the external, general population. The authors pointed out that external comparisons were, therefore, inappropriate; but "the internal comparisons upon which the foregoing analyses are based are not affected strongly by selection biases." (*ibid.*)

Although the 1999 EPA draft notes potential volunteer bias, it concludes: "Given the fact that all diesel exhaust exposure occupations * * * showed elevated lung cancer risk, this study is suggestive of a causal association."⁵⁵ (EPA, 1999, p. 7–13) No objection to this conclusion was raised in the most

⁵⁵ In his review of this study for the NMA, Dr. Peter Valberg stated: "This last sentence reveals EPA's bias; the RRs for truck drivers and railroad workers were not statistically elevated." Contrary to Dr. Valberg's statement, the RRs were greater than 1.0 and, therefore, were "statistically elevated." Although the elevation for these two occupations was not statistically significant at a 95-percent confidence level, the EPA made no claim that it was. Under a null hypothesis of no real association, the probability should be 1/2 that the RR would exceed 1.0 for an occupation associated with diesel exposure. Therefore, under the null hypothesis, the probability that the RR would exceed 1.0 for all four such occupations is $(1/2)^4 = 0.06$. This corresponds to a 94-percent confidence level for rejecting the null hypothesis.

recent CASAC review of the EPA draft (CASAC, 2000).

Boffetta et al., 1990

This case-control study was based on 2,584 male hospital patients with histologically confirmed lung cancer, matched with 5099 male patients with no tobacco-related diseases. Cases and controls were matched within each of 18 hospitals by age (within two years) and year of interview. Information on each patient, including medical and smoking history, occupation, and alcohol and coffee consumption, was obtained at the time of diagnosis in the hospital, using a structured questionnaire. For smokers, smoking data included the number of cigarettes per day. Prior to 1985, only the patient's usual job was recorded. In 1985, the questionnaire was expanded to include up to five other jobs and the length of time worked in each job. After 1985, information was also obtained on dietary habits, vitamin consumption, and exposure to 45 groups of chemicals, including diesel exhaust.

The authors categorized all occupations into three groups, representing low, possible, and probable diesel exhaust exposure. The "low exposure" group was used as the reference category for calculating odds ratios for the "possible" and "probable" job groups. These occupational comparisons were based on the full cohort of patients, enrolled both before and after 1985. A total of 35 cases and 49 controls (all enrolled after the questionnaire was expanded in 1985) reported a history of diesel exposure. The reference category for self-reported diesel exposure consisted of a corresponding subset of 442 cases and 897 controls reporting no diesel exposure on the expanded questionnaire. The authors made three comparisons to rule out bias due to self-reporting of exposure: (1) No difference was found between the average number of jobs reported by cases and controls; (2) the association between self-reported asbestos exposure was in agreement with previously published estimates; and (3) no association was found for two exposures (pesticides and fuel pumping) considered unrelated to lung cancer (*ibid.*, p. 584).

Stöber and Abel (1996) identified this study as being "of eminent importance owing to the care taken in including the most influential confounding factors and analyses of dose-effect relationships." The main findings are presented in the following table. All of these results were obtained using logistic regression, factoring in the estimated effects of age, race, years of

education, number of cigarettes per day, and asbestos exposure (yes or no). An elevated risk of lung cancer was reported for workers with more than 30

years of either self-reported or "probable" diesel exposure. The authors repeated the occupational analysis using "ever" rather than "usual" employment

in jobs classified as "probable" exposure, with "remarkably similar" results (*ibid.*, p. 584).

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Main results from Boffetta et al., 1990

(adjusted for age, race, education, smoking, and asbestos exposure)

Self-Reported Duration of Exposure to Diesel Exhaust (years)	Lung Cancer Odds Ratio	95-Percent Confidence Interval
1 to 15	0.90	0.40 - 1.99
16 to 30	1.04	0.44 - 2.48
31 or more	2.39	0.87 - 6.57
Likelihood of Exposure		
19 jobs with "possible" exposure	0.92	0.76 - 1.10
13 jobs with "probable" exposure	0.95	0.78 - 1.16
1 to 15 years in "probable" jobs	0.52	0.15 - 1.86
16 to 30 years in "probable" jobs	0.70	0.34 - 1.44
31 or more years in "probable" jobs	1.49	0.72 - 3.11

BILLING CODE 4510-43-C

The study's authors noted that most U.S. trucks did not have diesel engines until the late 1950s or early 1960s and that many smaller trucks are still powered by gasoline engines. Therefore, they performed a separate analysis of truck drivers cross-classified by self-reported diesel exposure "to compare presumptive diesel truck drivers with nondiesel drivers." After adjusting for smoking, the resulting OR for diesel drivers was 1.25, with a 95-percent confidence interval of 0.85 to 2.76 (*ibid.*, p. 585).

Bröske-Hohlfeld et al., 1999

This was a pooled analysis of two case-control studies on lung cancer in Germany. The data pool consisted of 3,498 male cases with histologically or cytologically confirmed lung cancer and 3,541 male controls randomly drawn from the general population. Cases and controls were matched for age and

region of residence. For the pooled analysis, information on demographic characteristics, smoking, and detailed job and job-task history was collected by personal interviews with the cases and controls, using a standardized questionnaire.

Over their occupational lifetimes, cases and controls were employed in an average of 2.9 and 2.7 different jobs, respectively. Jobs considered to have had potential exposure to diesel exhaust were divided into four groups: Professional drivers (including trucks, buses, and taxis), other "traffic-related" jobs (including switchmen and operators of diesel locomotives or diesel forklift trucks), full-time drivers of farm tractors, and heavy equipment operators. Within these four groups, each episode of work in a particular job was classified as being exposed or not exposed to diesel exhaust, based on the written description of job tasks obtained during the interview. This exposure

assessment was done without knowledge of the subject's case or control status. Each subject's lifetime duration of occupational exposure was compiled using only the jobs determined to have been diesel-exposed. There were 264 cases and 138 controls who accumulated diesel exposure exceeding 20 years, with 116 cases and 64 controls accumulating more than 30 years of occupational exposure.

For each case and control, detailed smoking histories from the questionnaire were used to establish smoking habit, including consumption of other tobacco products, cumulative smoking exposure (expressed as pack-years), and years since quitting smoking. Cumulative asbestos exposure (expressed as the number of exposed working days) was assessed based on 17 job-specific questionnaires that supplemented the main questionnaire.

The main findings of this study, all adjusted for cumulative smoking and asbestos exposure, are presented in the following table. Although the odds ratio for West German professional drivers was a statistically significant 1.44, as shown, the odds ratio for East German

professional drivers was not elevated. As a possible explanation, the authors noted that after 1960, the number of vehicles (cars, busses, and trucks) with diesel engines per unit area was about five times higher in West Germany than in East Germany. Also, the higher OR

shown for professional drivers first exposed after 1955, compared to earlier years of first exposure, may have resulted from the higher density of diesel traffic in later years.

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Main results from Brüske-Hohlfeld et al., 1999

(controlled for age; adjusted for smoking and asbestos exposure)

Occupational Exposure to Diesel Exhaust	Lung Cancer Odds Ratio	95-Percent Confidence Interval
Any During Lifetime	1.43	1.23 - 1.67
<i>West German Professional Drivers</i>	1.44	1.18 - 1.76
First exposed before 1946	1.32	0.68 - 2.07
First exposed 1946 - 1955	1.49	0.96 - 1.88
First exposed after 1955	1.56	1.21 - 2.03
<i>"Traffic-Related" Jobs other than Driving</i>	1.53	1.04-2.24
4 to 10 years	1.18	0.6 - 2.4 [†]
11 to 20 years	2.49	1.1 - 5.6 [†]
More than 20 years	2.88	1.1 - 7.2 [†]
<i>Full-Time Drivers of Farm Tractors</i>	1.29	0.78 - 2.14
11 to 20 years	1.51	0.4 - 3.8 [‡]
21 to 30 years	3.67	1.0 - 13 [‡]
More than 30 years	6.81	1.1 - 40 [‡]
<i>Heavy Equipment Operators</i>	2.31	1.44 - 3.70
More than 20 years	4.30	statistically significant (interval not reported)
[†] Confidence limits estimated from Fig. 1 of Brüske-Hohlfeld et al. (1999). [‡] Confidence limits estimated from Fig. 2 of Brüske-Hohlfeld et al. (1999).		

As the authors noted, a strength of this study is the good statistical power resulting from having a significant number of workers exposed to diesel emissions for more than 30 years. Another strength is the statistical treatment of potential confounders, using quantitative measures of cumulative smoking and asbestos exposures.

Although they did not rely solely on job title, and differentiated between diesel-exposed and unexposed work periods, the authors identified limitations in the assessment of diesel exposure, "under these circumstances leading to an odds ratio that is biased towards one and an underestimation of the true [relative] risk of lung cancer." A more quantitative assessment of diesel exposure would tend to remove this bias, thereby further elevating the relative risks. Therefore, the authors concluded that their study "showed a statistically significant increase in lung cancer risk for workers occupationally exposed to [diesel exhaust] in Germany with the exception of professional drivers in East Germany."

Garshick et al., 1987

This case-control study was based on 1,256 primary lung cancer deaths and 2,385 controls whose cause of death was not cancer, suicide, accident, or unknown. Cases and controls were drawn from records of the U.S. Railroad Retirement Board (RRB) and matched within 2.5 years of birth date and 31 days of death date. Selected jobs, with and without regular diesel exposure,

were identified by a review of job titles and duties and classified as "exposed" or "unexposed" to diesel exhaust. For 39 jobs, this exposure classification was confirmed by personal sampling of current respirable dust concentrations, adjusted for cigarette smoke, at four different railroads. Jobs for which no personal sampling was available were classified based on similarities in location and activity to sampled jobs.

A detailed work history for each case and control was obtained from an annual report filed with the RRB. This was combined with the exposure classification for each job to estimate the lifetime total diesel exposure (expressed as "diesel-years") for each subject. Years spent not working for a railroad, or for which a job was not recorded, were considered to be unexposed. This amounted to 2.4% of the total worker-years from 1959 to death or retirement.

Because of the transition from steam to diesel locomotives in the 1950s, occupational lifetime exposures were accumulated beginning in 1959. Since many of the older workers retired not long after 1959 and received little or no diesel exposure, separate analyses were carried out for subjects above and below the age of 65 years at death. The group of younger workers was considered to be less susceptible to exposure misclassification.

Detailed smoking histories, including years smoked, cigarettes per day, and years between quitting and death, were obtained from next of kin. Based on job history, each case and control was also classified as having had regular,

intermittent, or no occupational asbestos exposure.

The main results of this study, adjusted for smoking and asbestos exposure, are presented in the following table for workers aged less than 65 years at the time of their death. All of these results were obtained using logistic regression, conditioned on dates of birth and death. The odds ratio presented in the shaded cell for 20 years of unlagged exposure was derived from an analysis that modeled diesel-years as a continuous variable. All of the other odds ratios in the table were derived from analyses that modeled cumulative exposure categorically, using workers with less than five diesel-years of exposure as the reference group. Statistically significant elevations of lung cancer risk were reported for the younger workers with at least 20 diesel-years of exposure or at least 15 years accumulated five years prior to death. No elevated risk of lung cancer was observed for the older workers, who were 65 or more years old at the time of their death. The authors attributed this to the fact, mentioned above, that many of these older workers retired shortly after the transition to diesel-powered locomotives and, therefore, experienced little or no occupational diesel exposure. Based on the results for younger workers, they concluded that "this study supports the hypothesis that occupational exposure to diesel exhaust increases lung cancer risk."

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Main results from Garshick et al., 1987, for workers aged less than 65 years at death

(controlled for dates of birth and death; adjusted for cigarette smoking and asbestos exposure).

Diesel Exposure (no lag)	Lung Cancer Odds Ratio	95-Percent Confidence Interval
0 - 4 diesel-years	1	N/A (reference group)
5 - 19 diesel-years	1.02	0.72 - 1.45
20 diesel-years (diesel exposure modeled as continuous variable)	1.41	1.06 - 1.88
20 or more diesel-years	1.64	1.18 - 2.29
Diesel Exposure (accumulated at least 5 years before death)		
0 - 4 diesel-years	1	N/A (reference group)
5 - 14 diesel-years	1.07	0.69 - 1.66
15 or more diesel-years	1.43	1.06 - 1.94

BILLING CODE 4510-43-C

In its 1999 draft Health Assessment Document for Diesel Emissions, the U.S. EPA noted various limitations of this study but concluded that "compared with previous studies [i.e., prior to 1987] * * *, [it] provides the most valid evidence that occupational diesel exhaust emission exposure increases the risk of lung cancer." (EPA, 1999, p. 7-33) No objection to this conclusion was raised in the most recent CASAC review of the EPA draft (CASAC, 2000).

The EMA objected to this study's determination of smoking frequency based on interviews with next of kin, stating that such determination "generally results in an underestimate, as it has been shown that cigarette companies manufacture 60% more product than public surveys indicate are being smoked."

A tendency to mischaracterize smoking frequency would have biased the study's reported results if the degree of under- or over-estimation varied systematically with diesel exposure. The EMA, however, submitted no evidence that the smoking underestimate, if it existed at all, was in any

way correlated with cumulative duration of diesel exposure. In the absence of such evidence, MSHA finds no reason to assume differential misreporting of smoking frequency.

Even more importantly, the EMA failed to distinguish between "public surveys" of the smokers themselves (who may be inclined to understate their habit) and interviews with next of kin. The investigators specifically addressed the accuracy of smoking data obtained from next of kin, citing two studies on the subject. Both studies reported a tendency for surrogate respondents to overestimate, rather than underestimate, cigarette consumption. The authors concluded that "this could exaggerate the contribution of cigarette smoking to lung cancer risk if the next of kin of subjects dying of lung cancer were more likely to report smoking histories than were those of controls." (ibid, p.1246)

IMC Global, along with Cox (1997) objected to several methodological features of this study. MSHA's response to each of these criticisms appears immediately following a summary

quotation from IMC Global's written comments:

(A) The regression models used to analyze the data assumed without justification that an excess risk at any exposure level implied an excess risk at all exposure levels.

The investigators did not extrapolate their regression models outside the range supported by the data. Furthermore, MSHA is using this study only for purposes of hazard identification at exposure levels at least as high as those experienced by workers in the study. Therefore, the possibility of a threshold effect at much lower levels is irrelevant.

(B) The regression model used did not specify that the exposure estimates were imperfect surrogates for true exposures. As a result, the regression coefficients do not bear any necessary relationship to the effects that they try to measure.

As noted by Cox (op cit.), random measurement errors for exposures in an univariate regression model will tend to bias results in the direction of no apparent association, thereby masking or reducing any apparent effects of exposure. The crux of Cox's criticism, however, is that, for statistical analysis

of the type employed in this study, random errors in a multivariate exposure (such as an interdependent combination of smoking, asbestos, and diesel exposure) can potentially bias results in either direction. This objection fails to consider the fact that a nearly identical regression result was obtained for the effect of diesel exposure when smoking and asbestos exposure were removed from the model: OR = 1.39 instead of 1.41. Furthermore, even with a multivariate exposure, measurement errors in the exposure being evaluated typically bias the estimate of relative risk downward toward a null result. Relative risk is biased upwards only when the various exposures are interrelated in a special way. No evidence was presented that the data of this study met the special conditions necessary for upward bias or that any such bias would be large enough to be of any practical significance.

C) The * * * analysis used regression models without presenting diagnostics to show whether the models were appropriate for the data.

MSHA agrees that regression diagnostics are a valuable tool in assuring the validity of a statistical regression analysis. There is nothing at all unusual, however, about their not having been mentioned in the published report of this study. Regression diagnostics are rarely, if ever, published in epidemiologic studies making use of regression analysis. This does not imply that such diagnostics were not considered in the course of identifying an appropriate model or checking how well the data conform to a given model's underlying assumptions. Evaluation of the validity of any statistical analysis is (or should be) part of the peer-review process prior to publication.

D) The * * * risk models assumed that 1959 was the effective year when DE exposure started for each worker. Thus, the analysis ignored the potentially large differences in pre-1959 exposures among workers. This modeling assumption makes it impossible to interpret the results of the study with confidence.

MSHA agrees that the lack of diesel exposure information on individual workers prior to 1959 represents an important limitation of this study. This limitation, along with a lack of quantitative exposure data even after 1959, may preclude using it to determine, with reasonable confidence, the shape or slope of a quantitative exposure-response relationship. Neither of these limitations, however, invalidates the study's finding of an elevated lung cancer risk for exposed

workers. MSHA is not basing any quantitative risk assessment on this study and is relying on it, in conjunction with other evidence, only for purposes of hazard identification.

E) The risk regression models * * * assume, without apparent justification, that all exposed individuals have identical dose-response model parameters (despite the potentially large differences in their pre-1959 exposure histories). This assumption was not tested against reasonable alternatives, *e.g.*, that individuals born in different years have different susceptibilities * * *

Cases and controls were matched on date of birth to within 2.5 years, and separate analyses were carried out for the two groups of younger and older workers. Furthermore, it is not true that the investigators performed no tests of reasonable alternatives even to the assumption that younger workers shared the same model parameters. They explored and tested potential interactions between smoking intensity and diesel exposure, with negative results. The presence of such interactions would have meant that the response to diesel exposure differed among individuals, depending on their smoking intensity.

One other objection that Cox (*op. cit.*) raised specifically in connection with this study was apparently overlooked by IMC Global. To illustrate what he considered to be an improper evaluation of statistical significance when more than one hypothesis is tested in a study, Cox noted the finding that for workers aged less than 65 years at time of death, the odds ratio for lung cancer was significantly elevated at 20 diesel-years of exposure. He then asserted that this finding was merely

* * * an instance of a whole family of statements of the form "Workers who were A years or younger at the time of death and who were exposed to diesel exhaust for Y years had a significantly increased relative odds ratios for lung cancer. The probability of at least one false positive occurring among the multiple hypotheses in this family corresponding to different combinations of A (*e.g.*, no more than 54, 59, 64, 69, 74, 79, etc. years old at death) and durations of exposure (*e.g.*, Y = 5, 10, 15, 20, 25, etc. years) is not limited to 5% when each combination of A and Y values is tested at a $p = 5\%$ significance level. For example, if 30 different (A, Y) combinations are considered, each independently having a 5% probability of a false positive (*i.e.*, a reported 5% significance level), then the probability of at least one false positive occurring in the study as a whole is $p = 1 - (1 - 0.05)^{30} = 78\%$. This p-value for the whole study is more than 15 times greater than the reported significance level of 5%.

MSHA is evaluating the cumulative weight of evidence from many studies

and is not relying on the level of statistical significance attached to any single finding or study viewed in isolation. Furthermore, Cox's analysis of the statistical impact of multiple comparisons or hypothesis tests is flawed on several counts, especially with regard to this study in particular. First, the analysis relies on a highly unrealistic assumption that when several hypotheses are tested within the same study, the probabilities of false positives are statistically independent. Second, Cox fails to distinguish between those hypotheses or comparisons suggested by exploration of the data and those motivated by prior considerations. Third, Cox ignores the fact that the result in question was based on a statistical regression analysis in which diesel exposure duration was modeled as a single continuous variable. Therefore, this particular result does not depend on multiple hypothesis-testing with respect to exposure duration. Fourth, and most importantly, Cox assumes that age and exposure duration were randomly picked for tested from a pool of interchangeable possibilities and that the only thing distinguishing the combination of "65 years of age" and "20 diesel-years of exposure" from other random combinations was that it happened to yield an apparently significant result. This is clearly not the case. The investigators divided workers into only two age groups and explained that this division was based on the history of dieselization in the railroad industry—not on the results of their data analysis. Similarly, the result for 20 diesel-years of exposure was not favored over shorter exposure times simply because 20 years yielded a significant result and the shorter times did not. Lengthy exposure and latency periods are required for the expression of increased lung cancer risks, and this justifies a focus on the longest exposure periods for which sufficient data are available.

Garshick et al., 1988; Garshick, 1991

In this study, the investigators assessed the risk of lung cancer in a cohort of 55,407 white male railroad workers, aged 40 to 64 years in 1959, who had begun railroad work between 1939 and 1949 and were employed in one of 39 jobs later surveyed for exposure. Workers whose job history indicated likely occupational exposure to asbestos were excluded. Based on the subsequent exposure survey, each of the 39 jobs represented in the cohort was classified as either exposed or unexposed to diesel emissions. The cohort was followed through 1980, and

1,694 cases of death due to lung cancer were identified.

As in the 1987 study by the same investigators, detailed railroad job histories from 1959 to date of death or retirement were obtained from RRB records and combined with the exposure classification for each job to provide the years of diesel exposure accumulated since 1959 for each worker in the cohort. Using workers classified as "unexposed" within the cohort to establish a baseline, time-dependent proportional hazards regression models were employed to evaluate the relative risk of lung cancer for exposed workers. Although the investigators believed they had excluded most workers with significant past asbestos exposures from the cohort, based on job codes, they considered it possible that some workers classified as hostlers or shop

workers may have been included in the cohort even if occupationally exposed to asbestos. Therefore, they carried out statistical analyses with and without shop workers and hostlers included.

The main results of this study are presented in the following table. Statistically significant elevations of lung cancer risk were found regardless of whether or not shop workers and hostlers were included. The 1988 analysis adjusted for age in 1959, and the 1991 analysis adjusted, instead, for age at death or end of follow-up (i.e., end of 1980).⁵⁶ In the 1988 analysis, any work during a year counted as a diesel-year if the work was in a diesel-exposed job category, and the results from the 1991 analysis presented here are based on this same method of compiling exposure durations. Exposure durations excluded the year of death and the four

prior years, thereby allowing for some latency in exposure effects. Results for the analysis excluding shop workers and hostlers were not presented in the 1991 report, but the report stated that "similar results were obtained." Using either method of age adjustment, a statistically significant elevation of lung cancer risk was associated with each exposure duration category. Using "attained age," however, there was no strong indication that risk increased with increasing exposure duration. The 1991 report concluded that "there appears to be an effect of diesel exposure on lung cancer mortality" but that "because of weaknesses in exposure ascertainment * * *, the nature of the exposure-response relationship could not be found in this study."

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Main results from Garshick et al., 1988 and Garshick, 1991.

Exposure Duration (diesel-years, last 5 years excluded)	Full Cohort		Shopworkers & Hostlers Excluded	
	Relative Risk	95% Conf. Int.	Relative Risk	95% Conf. Int.
1 - 4	1.20	1.01 - 1.44	1.34	1.08 - 1.65
	1.31	1.09 - 1.57	N.R.	N.R.
5 - 9	1.24	1.06 - 1.44	1.33	1.12 - 1.58
	1.28	1.09 - 1.49	N.R.	N.R.
10 - 14	1.32	1.13 - 1.56	1.33	1.10 - 1.60
	1.19	1.002 - 1.41	N.R.	N.R.
15 or more	1.72	1.27 - 2.33	1.82	1.30 - 2.55
	1.40	1.03 - 1.90	N.R.	N.R.

Top entry within each cell is from 1988 analysis, adjusted for age in 1959. Bottom entry is from 1991 analysis, adjusted for age at death or end of follow-up ("attained age"). N.R. means "not reported."

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Some commenters noted that removing the shop workers and hostlers from the analysis increased the relative risk estimates. Dr. Peter Valberg found

this "paradoxical," since workers in these categories had later been found to experience higher average levels of diesel exposure than other railroad workers.

This so-called paradox is likely to have resulted simply from exposure misclassification for a significant portion of the shop workers. The effect was explained by Garshick (1991) as follows:

¹ Also, the 1991 analysis excluded 12 members of the cohort due to discrepancies between work

history and reported year of death, leaving 55,395 railroad workers included in the analysis.

* * * shop workers who worked in the diesel repair shops shared job codes with workers in non-diesel shops where there was no diesel exhaust * * *. Apparent exposure as a shop worker based on the job code was then diluted with workers with the same job code but without true exposure, making it less likely to see an effect in the shop worker group. In addition, workers in the shop worker group of job codes tended to have less stable career paths * * * compared to the other diesel exposure categories.

So although many of the shopworkers may have been exposed to relatively high dpm concentrations, many others were among the lowest-exposed workers or were even unexposed because they spent their entire occupational lifetimes in unexposed locations. This could readily account for the increase in relative risks calculated when shop workers were excluded from the analysis.

Dr. Valberg also noted that, according to Crump (1999), mortality rates for cirrhosis of the liver and heart disease were significantly elevated for "train riders," who were exposed to diesel emissions, as compared to other members of the cohort, who were less likely to be exposed. It is also the train riders who account, primarily, for the elevated risk of lung cancer associated with diesel exposure in the overall cohort. Dr. Valberg interpreted this as suggesting that "lifestyle" factors such as diet or smoking habits, rather than diesel exposure, were responsible for the increased risk of lung cancer observed among the diesel-exposed workers.

Dr. Valberg presented no evidence that, apart from diesel exposure, the train riders differed systematically from the other workers in their smoking habits or in other ways that would be expected to affect their risk of lung cancer. Therefore, MSHA views the suggestion of such a bias as speculative. Even if lifestyle factors associated with train ridership were responsible for an increased risk of cirrhosis of the liver or heart disease, this would not necessarily mean that the same factors were also responsible for the increased risk of lung cancer. Still, it is hypothetically possible that systematic differences, other than diesel exposure, between train riders and other railroad workers could account for some or even all of the increased lung cancer risk. That is why MSHA does not rely on this, or any other, single study in isolation.

Some commenters, including the NMA, objected to this study on grounds that it failed to control for potentially confounding factors, principally smoking. The NMA stated that this "has rendered its utility questionable at

best." As explained earlier, there is more than one way in which a study can control for smoking or other potential confounders. One of the ways is to make sure that groups being compared do not differ with respect to the potential confounder. In this study, workers with likely asbestos exposure were excluded from the cohort, stability of workers within job categories was well documented, and similar results were reported when job categories subject to asbestos exposure misclassification were excluded. In their 1988 report, the investigators provided the following reasons to believe that smoking did not seriously affect their findings:

* * * the cohort was selected to include only blue-collar workers of similar socioeconomic class, a known correlate of cigarette smoking * * *, in our case-control study [Garshick et al., 1987], when cigarette smoking was considered, there was little difference in the crude or adjusted estimates of diesel exhaust effects. Finally, in the group of 517 current railroad workers surveyed by us in 1982 * * *, we found no difference in cigarette smoking prevalence between workers with and without potential diesel exhaust exposure. [Garshick et al., 1988]

Since relative risks were based on internal comparisons, and the cohort appears to have been fairly homogeneous, MSHA regards it as unlikely that the association of lung cancer with diesel exposure in this study resulted entirely from uncontrolled asbestos or smoking effects. Nevertheless, MSHA recognizes that differential smoking patterns may have affected, in either direction, the degree of association reported in each of the exposure duration categories.

Cox (1997) re-analyzed the data of this study using exploratory, nonparametric statistical techniques. As quoted by IMC Global, Cox concluded that "these methods show that DE [i.e., dpm] concentration has no positive causal association with lung cancer mortality risk." MSHA believes this quotation (taken from the abstract of Cox's article) overstates the findings of his analysis. At most, Cox confirmed the conclusion by Garshick (1991) that these data do not support a positive exposure-response relationship. Specifically, Cox determined that inter-relationships among cumulative diesel exposure, age in 1959, and retirement year make it "impossible to prove causation by eliminating plausible rival hypotheses based on this dataset." (Cox, 1997; p.826) Even if Cox's analysis were correct, it would not follow that there is no underlying causal connection between dpm exposure and lung cancer. It would merely mean that the data do not contain internal evidence

implicating dpm exposure as the cause, rather than one or more of the variables with which exposure is correlated. Cox presented no evidence that any "rival hypotheses" were more plausible than causation by dpm exposure. Furthermore, it may simply be, as Garshick suggested, that an underlying exposure-response relationship is not evident "because of weaknesses in exposure ascertainment." (Garshick, 1991, op cit.) None of this negates the fact that, after adjusting for either age in 1959 or "attained" age, lung cancer was significantly more prevalent among the exposed workers.

Along similar lines, many commenters pointed out that an HEI expert panel examined the data of this study (HEI, 1999) and found that it had very limited use for quantitative risk assessment (QRA). Several of these commenters mischaracterized the panel's findings. The NMA, for example, drew the following unjustified conclusion from the panel's report: "In short, * * * the correct interpretation of the Garshick study is that any occupational increase in lung cancer among train workers was not due to diesel exposures."

Contrary to the NMA's characterization, the HEI Expert Panel's report stated that the data are

* * * consistent with findings of a weak association between death from lung cancer and occupational exposure to diesel exhaust. Although the secondary exposure-response analyses * * * are conflicting, the overall risk of lung cancer was elevated among diesel-exposed workers. [ibid., p.25]

The panel agreed with Garshick (1991) and Cox (1997) that the data of this study do not support a positive exposure-response relationship. Like Garshick and unlike Cox, however, the panel explicitly recognized that problems with the data could mask such a relationship and that this does not negate the statistically significant finding of elevated risk among exposed workers. Indeed, the panel even identified several factors, in addition to weak exposure assessment as suggested by Garshick, that could mask a positive relationship: unmeasured confounding variables such as cigarette smoking, previous occupational exposures, or other sources of pollution; a "healthy worker survivor effect"; and differential misclassification or incomplete ascertainment of lung cancer deaths. (HEI, 1999; p.32)

Positive exposure-response relationships based on these data were reported by the California EPA (OEHHA, 1998). MSHA recognizes that those findings were sensitive to various assumptions and that other investigators

have obtained contrary results. The West Virginia Coal Association, paraphrasing Dr. Peter Valberg, concluded that although the two studies by Garshick et al. “ * * * may represent the best in the field, they fail to firmly support the proposition that lung cancer risk in workers derives from exposure to dpm.” At least one commenter (IMC Global) apparently reached a considerably stronger conclusion that they were of no value whatsoever, and urged MSHA to “discount their results and not consider them in this rulemaking.” On the other hand, in response to the ANPRM, a consultant to the National Coal Association who was critical of all other studies available at the time acknowledged that these two:

* * * have successfully controlled for severally [sic] potentially important confounding factors * * * Smoking represents so strong a potential confounding variable that its control must be nearly perfect if an observed association between cancer and diesel exhaust is * * * [inferred to be causal]. In this regard, two observations

are relevant. First, both case-control [Garshick et al., 1987] and cohort [Garshick et al., 1988] study designs revealed consistent results. Second, an examination of smoking related causes of death other than lung cancer seemed to account for only a fraction of the association observed between diesel exposure and lung cancer. A high degree of success was apparently achieved in controlling for smoking as a potentially confounding variable. [Robert A. Michaels, RAM TRAC Corporation, submitted by National Coal Association].

To a limited extent, MSHA agrees with Dr. Valberg and the West Virginia Coal Association: these two studies—like every real-life epidemiologic study—are not “firmly” conclusive when viewed in isolation. Nevertheless, MSHA believes that they provide important contributions to the overall body of evidence. Whether or not they can be used to quantify an exposure-response relationship, these studies—among the most comprehensive and carefully controlled currently available—do show statistically

significant increases in the risk of lung cancer among diesel-exposed workers.

Johnston et al. (1997)

Since it focused on miners, this study has already been summarized and discussed in the previous subsection of this risk assessment. The main results are presented in the following table. The tabled relative risk estimates presented for cumulative exposures greater than 1000 mg-hr/m³ (i.e., 1 g-hr/m³) were calculated by MSHA based on the regression coefficients reported by the authors. The conversion from mg-hr/m³ to mg-yr/m³ assumes 1,920 occupational exposure hours per year. Although 6.1 mg-yr/m³ Dpm roughly equals the cumulative exposure estimated for the most highly exposed locomotive drivers in the study, the relative risk associated with this exposure level is presented primarily for purposes of comparison with findings of Säverin et al. (1999).

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Main results from Johnston et al., 1997.

Cumulative dpm exposure	Mine-adjusted Model (15-yr lag)		Mine-unadjusted Model (15-yr lag)	
	Relative Risk	95% Conf. Interval	Relative Risk	95% Conf. Interval
1000 mg-hr/m ³ (≈ 0.521 mg-yr/m ³)	1.156	0.90 - 1.49	1.227	1.00 - 1.50
1920 mg-hr/m ³ (≈ 1 mg-yr/m ³)	1.321	Not Reported	1.479	Not Reported
11,700 mg-hr/m ³ (≈ 6.1 mg-yr/m ³)	5.5	Not Reported	11.0	Not Reported

BILLING CODE 4510-43-C

In its post-hearing comments, MARG acknowledged that this study “found a ‘weak association’ between lung cancer and respiratory diesel particulate exposure” but failed to note that the estimated relative risk increased with increasing exposure. MARG also stated that the association was “deemed non-significant by the researchers” and that “no association was found among men with different exposures working in the same mines.” Although the mine-adjusted model did not support 95-percent confidence for an increasing

exposure-response relationship, the mine-unadjusted model yielded a statistically significant positive slope at this confidence level. Furthermore, since the mine-adjusted model adjusts for differences in lung cancer rates between mines, the fact that relative risk increased with increasing exposure under this model indicates (though not at a 95-percent confidence level) that the risk of lung cancer increased with exposure among men with different exposures working in the same mines.

Säverin et al. (1999)

Since this study, like the one by Johnston et al., was carried out on a cohort of miners, it too was summarized and discussed in the previous subsection of this risk assessment. The main results are presented in the following table. The relative risk estimates and confidence intervals at the mean exposure level of 2.7 mg-yr/m³ TC (total carbon) were calculated by MSHA, based on values of α and corresponding confidence intervals presented in Tables III and IV of the

published report (ibid., p.420). The approximate equivalency between 4.9 mg-yr/m³ TC and 6.1 mg-yr/m³ dpm

assumes that, on average, TC comprises 80 percent of dpm.

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Main results from Säverin et al., 1999.

	Relative Risk	95% Confidence Interval
Highest Compared to Least Exposed Worker Category	2.17	0.79 - 5.99

Cumulative Total Carbon Exposure	Proportional Hazards (Cox) Model*		Poisson Model*	
	Relative Risk	95% Conf. Interval	Relative Risk	95% Conf. Interval
2.7 mg-yr/m ³ TC (i.e., cohort mean)	1.33	0.67 - 2.64	1.08	0.59 - 1.99
	1.73	0.70 - 4.30	1.42	0.65 - 3.92
4.9 mg-yr/m ³ TC (≈ 6.1 mg-yr/m ³ Dpm)	1.68	0.49 - 5.8	1.16	0.38 - 3.3
	2.70	0.52 - 14.1	1.89	0.46 - 11.9

* Top entry in each cell is based on full cohort; bottom entry is based on subcohort, which was restricted to miners who worked underground at least ten years, with at least 80 percent of employment in same job, etc.

BILLING CODE 4510-43-C

These results are not statistically significant at the conventional 95-percent confidence level. However, the authors noted that the relative risk calculated for the subcohort was consistently higher than that calculated for the full cohort. They also considered the subcohort to have a superior exposure assessment and a better latency allowance than the full cohort. According to the authors, these factors provide "some assurance that the observed risk elevation was not entirely due to chance since improving the exposure assessment and allowing for latency effects should, in general, enhance exposure effects."

Steenland et al., (1990, 1992, 1998)

The basis for the analyses in this series was a case-control study comparing the risk of lung cancer for diesel-exposed and unexposed workers who had belonged to the Teamsters Union for at least twenty years (Steenland et al., 1990). Drawing from union records, 996 cases of lung cancer were identified among more than 10,000 deaths in 1982 and 1983. For comparison to these cases, a total of 1,085 controls was selected (presumably at random) from the remaining deaths, restricted to those who died from causes other than lung cancer, bladder cancer,

or motor vehicle accident. Information on work history, duration and intensity of cigarette smoking, diet, and asbestos exposure was obtained from next of kin. Detailed work histories were also obtained from pension applications on file with the Teamsters Union.

Both data sources were used to classify cases and controls according to a job category in which they had worked the longest. Based on the data obtained from next of kin, the job categories were diesel truck drivers, gasoline truck drivers, drivers of both truck types, truck mechanics, and dock workers. Based on the pension applications, the principal job categories were long-haul drivers, short-haul or city drivers, truck mechanics, and dock workers. Of the workers identified by next of kin as primarily diesel truck drivers, 90 percent were classified as long-haul drivers according to the Teamster data. The corresponding proportions were 82 percent for mechanics and 81 percent for dock workers. According to the investigators, most Teamsters had worked in only one exposed job category. However, because of the differences in job category definitions, and also because the next of kin data covered lifetimes whereas the pension applications covered only time in the Teamsters Union, the investigators found it problematic to fully evaluate

the concordance between the two data sources.

In the 1990 report, separate analyses were conducted for each source of data used to compile work histories. The investigators noted that "many trucking companies (where most study subjects worked) had completed most of the dieselization of their fleets by 1960, while independent drivers and nontrucking firms may have obtained diesel trucks later. * * *" Therefore, they specifically checked for associations between increased risk of lung cancer and occupational exposure after 1959 and, separately, after 1964. In the 1992 report, the investigators presented, for the Union's occupational categories used in the study, dpm exposure estimates based on subsequent measurements of submicrometer elemental carbon (EC) as reported by Zaebs et al. (1991). In the 1998 report, cumulative dpm exposure estimates for individual workers were compiled by combining the individual work histories obtained from the Union's records with the subsequently measured occupational exposure levels, along with an evaluation of historical changes in diesel engine emissions and patterns of diesel usage. Three alternative sets of cumulative exposure estimates were considered, based on alternative assumptions about the extent of

improvement in diesel engine emissions between 1970 and 1990. A variety of statistical models and techniques were then employed to investigate the relationship between estimated cumulative dpm exposure (expressed as EC) and the risk of lung cancer. The authors pointed out that the results of these statistical analyses depended heavily on "very broad assumptions" used to generate the estimates of cumulative dpm exposure. While acknowledging this limitation, however, they also evaluated the sensitivity of their results to various changes in their assumptions and found these changes to have little impact on the results.

The investigators also identified and addressed several other limitations of this study as follows:

(1) possible misclassification smoking habits by next of kin, (2) misclassification of exposure by next of kin, (3) a relatively small non-exposed group (n = 120) which by chance may have had a low lung cancer risk,

and (4) lack of sufficient latency (time since first exposure) to observe a lung cancer excess. On the other hand, next-of-kin data on smoking have been shown to be reasonably accurate, non-differential misclassification of exposure * * * would only bias our findings toward * * * no association, and the trends of increased risk with increased duration of employment in certain jobs would persist even if the non-exposed group had a higher lung cancer risk. Finally, the lack of potential latency would only make any positive results more striking. (Steenland et al., 1990)

The main results from the three reports covering this study are summarized in the following table. All of the analyses were controlled for age, race, smoking (five categories), diet, and asbestos exposure as reported by next of kin. Odds ratios for the occupations listed were calculated relative to the odds of lung cancer for occupations other than truck driver (all types), mechanic, dock worker, or other potentially diesel exposed jobs

(Steenland et al., 1990, Appendix A). The exposure-response analyses were carried out using logistic regression. Although the investigators performed analyses under three different assumptions for the rate of engine emissions (gm/mile) in 1970, they considered the intermediate value of 4.5 gm/mile to be their best estimate, and this is the value on which the results shown here are based. Under this assumption, cumulative occupational EC exposure for all workers in the study was estimated to range from 0.45 to 2,440 $\mu\text{g}\text{-yr}/\text{m}^3$, with a median value of 373 $\mu\text{g}\text{-yr}/\text{m}^3$. The estimates of relative risk (expressed as odds ratios) presented for EC exposures of 373 $\mu\text{g}\text{-yr}/\text{m}^3$, 1000 $\mu\text{g}\text{-yr}/\text{m}^3$, and 2450 $\mu\text{g}\text{-yr}/\text{m}^3$ were calculated by MSHA based on the regression coefficients reported by the authors for five-year lagged exposures (Steenland et al. 1998, Table II).

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Main results from Steenland et al., (1990, 1992, 1998)

Principal Occupation	Mean 1990 EC Concentration ($\mu\text{g}/\text{m}^3$)	Duration of Employment	Lung Cancer Odds Ratio	95-percent Conf. Interval
Diesel truck driver	N.A.	35 or more years*	1.89	1.04 - 3.42
Short-haul driver	5.4	18 or more years after 1959	1.79	0.94 - 3.42
Long-haul driver	5.1	18 or more years after 1959	1.55	0.97 - 2.47
		13 or more years after 1964	1.64	1.05 - 2.57
Truck mechanic	26.6	18 or more years after 1959	1.50	0.59 - 3.40
Cumulative Occupational Exposure ($\mu\text{g}\text{-yr}/\text{m}^3$, lagged 5 years)**			Lung Cancer Odds Ratio	95-percent Conf. Interval
EC	TC \approx 2•EC	Dpm \approx TC/0.8 \approx 2.5•EC		
0 - 169	0 - 338	0 - 422	1.08	0.72 - 1.63
169 - 257	338 - 514	422 - 642	1.10	0.74 - 1.65
257 - 331	514 - 662	642 - 827	1.36	0.90 - 2.04
more than 331	more than 662	more than 827	1.64	1.09 - 2.49
Logistic regression model \rightarrow			Lung Cancer Odds Ratio [†]	
			Simple Cum. Exposure	Log of Cum. Exposure
373	746	932	1.16	1.41
1,000	2,000	2,500	1.48	1.66
2,450	4,900	6,100	2.59	1.93

*Although primary occupation was driving diesel trucks, employment duration includes years driving any type of truck.

**Conversions between EC, TC, and Dpm assume that, on average, TC \approx 2•EC and TC \approx 0.8•DPM.

[†] Calculated by MSHA from regression coefficients presented by Steenland et al. (1990), Table II. Statistically significant regression coefficients reported for both models (95% Conf. level). Tabled results for Log(Cum. exposure) model have been adjusted for lifetime background exposure of $65 \mu\text{g}\text{-yr}/\text{m}^3$ assumed in regression analysis.

Under the assumption of a 4.5 gm/mile emissions rate in 1970, the cumulative EC exposure of 2450 $\mu\text{g}\text{-yr}/\text{m}^3$ ($\approx 6.1 \text{ mg}\text{-yr}/\text{m}^3 \text{ Dpm}$) shown in the table closely corresponds to the upper limit of the range of data on which the regression analyses were based (Steenland et al., 1998, p. 224). However, the relative risks (i.e., odds ratios) calculated for this level of occupational exposure are presented primarily for purposes of comparison with the findings of Johnston et al. (1997) and Säverin et al. (1999). At a cumulative Dpm exposure of approximately $6.1 \text{ mg}\text{-yr}/\text{m}^3$, it is evident that the Johnston models predict a far greater elevation in lung cancer risk than either the Säverin or Steenland models. A possible explanation for this is that the Johnston data included exposures of up to 30 years in duration, and the statistical models showing an exposure-response relationship allowed for a 15-year lag in exposure effects. The other two studies were based on generally shorter diesel exposures and allowed less time for latent effects. In Subsection 3.b.ii(3) of this risk assessment, the quantitative results of these three studies will be further compared with respect to exposure levels found in underground mines.

Several commenters noted that the HEI Expert Panel (HEI, 1999) had identified uncertainties in the diesel exposure assessment as an important limitation of the exposure-response analyses by Steenland et al. (1998) and had recommended further investigation before the quantitative results of this study were accepted as conclusive. In addition, Navistar International Transportation (NITC) raised a number of objections to the methods by which diesel exposures were estimated for the period between 1949 and 1990 (NITC, 1999). In general, the thrust of these objections was that exposures to diesel engine emissions had been overestimated, while potentially relevant exposures to gasoline engine emissions had been underestimated and/or unduly discounted.⁵⁷

⁵⁷ Many of the issues NITC raised in its critique of this study depend on a peculiar identification of Dpm exclusively with elemental carbon. For example, NITC argued that "more than 65 percent of the total carbon to which road drivers (and mechanics) were exposed consisted of organic (i.e., non-diesel) carbon, further suggesting that some other etiology caused or contributed to excess lung cancer mortality in these workers." (NITC, 1999, p. 16) Such lines of argument, which depend on identifying organic carbon as "non-diesel," ignore the fact that Dpm contains a large measure of organic carbon compounds (and also some sulfates), as well as elemental carbon. Any adverse health effects due to the organic carbon or sulfate

As mentioned above, the investigators recognized that these analyses rely on "broad assumptions rather than actual [concurrent] measurements," and they proposed that the "results should be regarded with appropriate caution." While agreeing with both the investigators and the HEI Expert Panel that these results should be interpreted with appropriate caution, MSHA also agrees with the Panel " * * * that regulatory decisions need to be made in spite of the limitations and uncertainties of the few studies with quantitative data currently available." (HEI, 1999, p. 39) In this context, MSHA considers it appropriate to regard the 1998 exposure-response analyses as contributing to the weight of evidence that dpm exposure increases the risk of lung cancer, even if the results are not conclusive when viewed in isolation.

Some commenters also noted that the HEI Expert Panel raised the possibility that the method for selecting controls in this study could potentially have biased the results in an unpredictable direction. Such bias could have occurred because deaths among some of the controls were likely due to diseases (such as cardiovascular disease) that shared some of the same risk factors (such as tobacco smoking) with lung cancer. The Panel presented hypothetical examples of how this might bias results in either direction. Although the possibility of such bias further demonstrates why the results of this study should be regarded with "appropriate caution," it is important to distinguish between the mere possibility of a control-selection bias, evidence that such a bias actually exists in this particular study, and the further evidence required to show that such bias not only exists but is of sufficient magnitude to have produced seriously misleading results. Unlike the commenters who cited the HEI Expert Panel on this issue, the Panel itself clearly drew this distinction, stating that "no direct evidence of such bias is apparent" and emphasizing that "even though these examples [presented in HEI (1999), Appendix D] could produce misleading results, it is important to note that they are only hypothetical examples. Whether or not such bias is present will require further examination." (HEI, 1999, pp. 37–38) As the HEI showed in its examples, such bias (if it exists) could lead to underestimating the association between lung cancer and dpm exposure, as well as to overestimating it. Therefore, in the absence of evidence

constituents of Dpm would nonetheless be due to Dpm exposures.

that control-selection bias actually distorted the results of this study one way or the other, MSHA considers it prudent to accept the study's finding of an association at face value.

One commenter (MARG) noted that information on cigarette smoking, asbestos exposure, and diet in the trucking industry study was obtained from next of kin and stated that such information was "likely to be unreliable." By increasing random variability in the data, such errors could widen the confidence intervals around an estimated odds ratio or reduce the confidence level at which a positive exposure-response relationship might be established. However, unless such errors were correlated with diesel exposure or lung cancer in such a way as to bias the results, they would not, on average, inflate the estimated degree of association between diesel exposure and an increased risk of lung cancer. The commenter provided no reason to suspect that errors with respect to these factors were in any way correlated with diesel exposure or with the development of lung cancer.

Some commenters pointed out that EC concentrations measured in 1990 for truck mechanics were higher, on average, than for truck drivers, but the mechanics, unlike the drivers, showed no evidence of increasing lung cancer risk with increasing duration of employment. NITC referred to this as a "discrepancy" in the data, assuming that "cumulative exposure increases with duration of employment such that mechanics who have been employed for 18 or more years would have greater cumulative exposure than workers who have been employed for 1–11 years." (NITC, 1999)

Mechanics were included in the logistic regression analyses (Steenland et al., 1998) showing an increase in lung cancer risk with increasing cumulative exposure. These analyses pooled the data for all occupations by estimating exposure for each worker based on the worker's occupation and the particular years in which the worker was employed. There are at least three reasons why, for mechanics viewed as a separate group, an increase in lung cancer risk with increasing dpm exposure may not have been reflected by increasing duration of employment.

First, relatively few truck mechanics were available for analyzing the relationship between length of employment and the risk of lung cancer. Based on the union records, 50 cases and 37 controls were so classified; based on the next-of-kin data, 43 cases and 41 controls were more specifically classified as diesel truck mechanics

(Steenland et al., 1990). In contrast, 609 cases and 604 controls were classified as long-haul drivers (union records). This was both the largest occupational category and the only one showing statistically significant evidence of increasing risk with increasing employment duration. The number of mechanics included in the study population may simply not have been sufficient to detect a pattern of increasing risk with increasing length of employment, even if such a pattern existed.

The second part of the explanation as to why mechanics did not exhibit a pattern similar to truck drivers could be that the data on mechanics were more subject to confounding. After noting that "the risk for mechanics did not appear to increase consistently with duration of employment," Steenland et al. (1990) further noted that the mechanics may have been exposed to asbestos when working on brakes. The data used to adjust for asbestos exposure may have been inadequate to control for variability in asbestos exposure among the mechanics.

Third, as noted by NITC, the lung cancer risk for mechanics (adjusted for age, race, tobacco smoking, asbestos exposure, and diet) would be expected to increase with increasing duration of employment only if the mechanics' cumulative dpm exposure corresponded to the length of their employment. None of the commenters raising this issue, however, provided any support for this assumption, which fails to consider the particular calendar years in which mechanics included in the study were employed. In compiling cumulative exposure for an individual worker, the investigators took into account historical changes in both diesel emissions and the proportion of trucks with diesel engines—so the exposure level assigned to each occupational category was not the same in each year. In general, workers included in the study neither began nor ended their employment in the same year. Consequently, workers with the same duration of employment in the same occupational category could be assigned different cumulative exposures, depending on when they were employed. Similarly, workers in the same occupational category who were assigned the same cumulative exposure may not have worked the same length of time in that occupation. Therefore, it should not be assumed that duration of employment corresponds very well to the cumulative exposure estimated for workers within any of the occupational categories. Furthermore, in the case of mechanics, there is an additional

historical variable that is especially relevant to actual cumulative exposure but was not considered in formulating exposure estimates: the degree of ventilation or other means of protection within repair shops. Historical changes in shop design and work practices, as well as differences between shops, may have caused more exposure misclassification among mechanics than among long-haul or diesel truck drivers. Such misclassification would tend to further obscure any relationship between mechanics' risk of lung cancer and either duration of employment or cumulative exposure.

(iv) Counter-Evidence

Several commenters stated that, in the proposal, MSHA had dismissed or not adequately addressed epidemiology studies showing no association between lung cancer and exposures to diesel exhaust. For example, the EMA wrote:

MSHA's discussion of the negative studies generally consists of arguments to explain why those studies should be dismissed. For example, MSHA states that, "All of the studies showing negative or statistically insignificant positive associations * * * lacked good information about dpm exposure * * *" or showed similar shortcomings. 63 Fed. Reg. at 17533. The statement about exposure information is only partially true, for, in fact, very few of any of the cited studies (the "positive" studies as well) included any exposure measurements, and none included concurrent exposures.

It should, first of all, be noted that the statement in question on dpm exposure referred to the issue of any diesel exposure—not to quantitative exposure measurements, which MSHA acknowledges are lacking in most of the available studies. In the absence of quantitative measurements, however, studies comparing workers known to have been occupationally exposed to unexposed workers are preferable to studies not containing such comparisons. Furthermore, two of the studies now available (and discussed above) utilize essentially concurrent exposure measurements, and both show a positive association (Johnston et al., 1997; Säverin et al., 1999).

MSHA did not entirely "dismiss" the negative studies. They were included in both MSHA's tabulation (see Tables III-4 and III-5) and (if they met the inclusion criteria) in the two meta-analyses cited both here and in the proposal (Lipsett and Campleman, 1999, and Bhatia et al., 1998). As noted by the commenter, MSHA presented reasons (such as an inadequate latency allowance) for why negative studies may have failed to detect an association. Similarly MSHA gave reasons for giving

less weight to some of the positive studies, such as Benhamou et al. (1988), Morabia et al. (1992), and Siemiatycki et al., 1988. Additional reasons for giving less weight to the six entirely negative studies have been tabulated above, under the heading of "Best Available Epidemiologic Evidence." The most recent of these negative studies (Christie et al., 1994, 1995) is discussed in detail under the heading of "Studies Involving Miners."

One commenter (IMC Global) listed the following studies (all of which MSHA had considered in the proposed risk assessment) as "examples of studies that reported negative associations between [dpm] exposure and lung cancer risk":

- Waller (1981). This is one of the six negative studies discussed earlier. Results were likely to have been biased by excluding lung cancers occurring after retirement or resignation from employment with the London Transit Authority. Comparison was to a general population, and there was no adjustment for a healthy worker effect. Comparison groups were disparate, and there was no adjustment for possible differences in smoking frequency or intensity.

- Howe et al. (1983). Contrary to the commenter's characterization of this study, the investigators reported statistically significant elevations of lung cancer risk for workers classified as "possibly exposed" or "probably exposed" to diesel exhaust. MSHA recognizes that these results may have been confounded by asbestos and coal dust exposures.

- Wong et al. (1985). The investigators reported a statistically insignificant deficit for lung cancer in the entire cohort and a statistically significant deficit for lung cancer in the less than 5-year duration group. However, since comparisons were to a general population, these deficits may be the result of a healthy worker effect, for which there was no adjustment. Because of the latency required for development of lung cancer, the result for "less than 5-year duration" is far less informative than the results for longer durations of employment and greater latency allowances. Contrary to the commenter's characterization of this study, the investigators reported statistically significant elevations of lung cancer risks for "normal" retirees (SMR = 1.30) and for "high exposure" dozer operators with 15–19 years of union membership and a latency allowance of at least 20 years (SMR = 3.43).

- Edling et al. (1987). This is one of the six negative studies discussed

earlier. The cohort consisted of only 694 bus workers and, therefore, lacked statistical power. Furthermore, comparison was to a general, external population with no adjustment for a healthy worker effect.

- Garshick (1988). The reason the commenter (IMC Global) gave for characterizing this study as negative was: "That the sign of the association in this data set changes based on the models used suggests that the effect is not robust. It apparently reflects modeling assumptions more than data." Contrary to the commenter's characterization, however, the finding of increased lung cancer risk for workers classified as diesel-exposed did not change when different methods were used to analyze the data. What changed, depending on modeling assumptions, was the shape and direction of the exposure-response relationship among exposed workers (Cal-EPA, 1998; Stayner et al., 1998; Crump, 1999; HEI, 1999). MSHA agrees that the various exposure-response relationships that have been derived from this study are highly sensitive to data modeling assumptions. This includes assumptions about historical patterns of exposure, as well as assumptions related to technical aspects of the statistical analysis. However, as noted by the HEI Expert Panel, the study provides evidence of a positive association between exposure and lung cancer despite the conflicting exposure-response analyses. Even though different assumptions and methods of analysis have led to different conclusions about the utility of this study for quantifying an exposure-response relationship, "the overall risk of lung cancer was elevated among diesel-exposed workers" (HEI, 1999, p. 25).

Another commenter (MARG) cited a number of studies (all of which had already been placed in the public record by MSHA) that, according to the commenter, "reflect either negative health effects trends among miners or else failed to demonstrate a statistically significant positive trend correlated with dpm exposure." It should be noted that, as explained earlier, failure of an individual study to achieve statistical significance (i.e., a high confidence level for its results) does not necessarily prevent a study from contributing important information to a larger body of evidence. An epidemiologic study may fail to achieve statistical significance simply because it did not involve a sufficient number of subjects or because it did not allow for an adequate latency period. In addition to this general point, the following

responses apply to the specific studies cited by the commenter.

- Ahlman et al. (1991). This study is discussed above, under the heading of "Studies Involving Miners." MSHA agrees with the commenter that this study did not "establish" a relationship between diesel exposure and the excess risk of lung cancer reported among the miners involved. Contrary to the commenter's characterization, however, the evidence presented by this study does incrementally point in the direction of such a relationship. As mentioned earlier, none of the underground miners who developed lung cancer had been occupationally exposed to asbestos, metal work, paper pulp, or organic dusts. Based on measurements of the alpha energy concentration at the mines, and a comparison of smoking habits between underground and surface miners, the authors concluded that not all of the excess lung cancer for the underground miners was attributable to radon daughter exposures and/or smoking. A stronger conclusion may have been possible if the cohort had been larger.

- Ames et al. (1984). MSHA has taken account of this study, which made no attempt to evaluate cancer effects, under the heading of "Chronic Effects other than Cancer." The commenter repeated MSHA's statement (in the proposed risk assessment) that the investigators had not detected any association of chronic respiratory effects with diesel exposure, but ignored MSHA's observation that the analysis had failed to consider baseline differences in lung function or symptom prevalence. Furthermore, as acknowledged by the investigators, diesel exposure levels in the study population were low.

- Ames et al. (1983). As discussed later in this risk assessment, under the heading of "Mechanisms of Toxicity," this study was among nine (out of 17) that did not find evidence of a relationship between exposure to respirable coal mine dust and an increased risk of lung cancer. Unlike the Australian mines studied by Christie et al. (1995), the coal mines included in this study were not extensively dieselized, and the investigators did not relate their findings to diesel exposures.

- Ames et al. (1982). As noted earlier under the heading of "Acute Health Effects," this study, which did not attempt to evaluate cancer or other chronic health effects, detected no statistically significant relationship between diesel exposure and pulmonary function. However, the authors noted that this might have been due to the low concentrations of diesel emissions involved.

- Armstrong et al. (1979). As discussed later in this risk assessment, this study was among nine (out of 17) that did not find evidence of a relationship between exposure to respirable coal mine dust and an increased risk of lung cancer. As pointed out by the commenter, comparisons were to a general population. Therefore, they were subject to a healthy worker effect for which no adjustment was made. The commenter further stated that "diesel emissions were not found to be related to increased health risks." However, diesel emissions were not mentioned in the report, and the investigators did not attempt to compare lung cancer rates in exposed and unexposed miners.

- Attfield et al. (1982). MSHA has taken the results of this study into account, under the heading of "Chronic Effects other than Cancer."

- Attfield (1979). MSHA has taken account of this study, which did not attempt to evaluate cancer effects, under the heading of "Chronic Effects other than Cancer." Although the results were not conclusive at a high confidence level, miners occupationally exposed to diesel exhaust for five or more years exhibited an increase in various respiratory symptoms, as compared to miners exposed for less than five years.

- Boffetta et al. (1988). This study is discussed in two places above, under the headings "Studies Involving Miners" and "Best Available Epidemiologic Evidence." The commenter stated that "the study obviously does not demonstrate risks from dpm exposure." If the word "demonstrate" is taken to mean "conclusively prove," then MSHA would agree that the study, viewed in isolation, does not do this. As explained in the earlier discussion, however, MSHA considers this study to contribute to the weight of evidence that dpm exposure increases the risk of lung cancer.

- Costello *et al.* (1974). As discussed later in this risk assessment, this study was among nine (out of 17) that did not find evidence of a relationship between exposure to respirable coal mine dust and an increased risk of lung cancer. Since comparisons were to a general population, they were subject to a healthy worker effect for which no adjustment was made. Diesel emissions were not mentioned in the report.

- Gamble and Jones (1983). MSHA has taken account of this study, which did not attempt to evaluate cancer effects, under the heading of "Chronic Effects other than Cancer." The commenter did not address MSHA's observation that the method of

statistical analysis used by the investigators may have masked an association of respiratory symptoms with diesel exposure.

- Glenn *et al.* (1983). As summarized by the commenter, this report reviewed NIOSH medical surveillance on miners exposed to dpm and found that “* * * neither consistent nor obvious trends implicating diesel exhaust in the mining atmosphere were revealed.” The authors noted that “results were rather mixed,” but also noted that “levels of diesel exhaust contaminants were generally low,” and that “overall tenure in these diesel equipped mines was fairly short.” MSHA acknowledges the commenter’s emphasis on the report’s 1983 conclusion: “further research on this subject is needed.” However, the authors also pointed out that “all four of the chronic effects analyses revealed an excess of cough and phlegm among the diesel exposed group. In the potash, salt and trona groups, these excesses were substantial.” The miners included in the studies summarized by this report would not have been exposed to Dpm for sufficient time to exhibit a possible increase in the risk of lung cancer.

- Johnston *et al.* (1997). This study is discussed in two places above, under the headings “Studies Involving Miners” and “Best Available Epidemiologic Evidence.” MSHA disagrees with the commenter’s assertion that “the study does not support a health risk from dpm.” This was not the conclusion drawn by the authors of the study. As explained in the earlier discussion, this study, one of the few containing quantitative estimates of cumulative dpm exposures, provides evidence of increasing lung cancer risk with increasing exposure.

- Jörgenson and Svensson (1970). MSHA discussed this study, which did not attempt to evaluate cancer effects, under the heading of “Chronic Effects other than Cancer.” Contrary to the commenter’s characterization, the investigators reported higher rates of chronic productive bronchitis, for both smokers and nonsmokers, among the underground iron ore miners exposed to diesel exhaust as compared to surface workers at the same mine.

- Kuempel (1995); Lidell (1973); Miller and Jacobsen (1985). As discussed later in this risk assessment, under the heading of “Mechanisms of Toxicity,” these three studies were among the nine (out of 17) that did not find evidence of a relationship between exposure to respirable coal mine dust and an increased risk of lung cancer. The extent, if any, to which workers involved in these studies were occupationally exposed to diesel

emissions was not documented, and diesel emissions were not mentioned in any of these reports.

- Morfeld *et al.* (1997). The commenter’s summary of this study distorted the investigators’ conclusions. Contrary to the commenter’s characterization, this is one of eight studies that showed an increased risk of lung cancer for coal miners, as discussed later in this risk assessment under the heading of “Mechanisms of Toxicity.” For lung cancer, the relative SMR, which adjusts for the healthy worker effect, was 1.11. (The value of 0.70 cited by the commenter was the unadjusted SMR.) The authors acknowledged that the relative SMR obtained by the “standard analysis” (*i.e.*, 1.11) was not statistically significant. However, the main object of the report was to demonstrate that the “standard analysis” is insufficient. The investigators presented evidence that the 1.11 value was biased downward by a “healthy-worker-survivor-effect,” thereby masking the actual exposure effects in these workers. They found that “all the evidence points to the conclusion that a standard analysis suffers from a severe underestimate of the exposure effect on overall mortality, cancer mortality and lung cancer mortality.” (Morfeld *et al.*, 1997, p. 350)

- Reger (1982). MSHA has taken account of this study, which made no attempt to evaluate cancer effects, under the heading of “Chronic Effects other than Cancer.” As summarized by the commenter, “diesel-exposed miners were found to have more cough and phlegm, and lower pulmonary function,” but the author found that “the evidence would not allow for the rejection of the hypothesis of health equality between exposed and non-exposed miners.” The commenter failed to note, however, that miners in the dieselized mines, had worked underground for less than 5 years on average.

- Rockette (1977). This is one of eight studies, discussed under “Mechanisms of Toxicity,” showing an increased risk of lung cancer for coal miners. As described by the commenter, the author reported SMRs of 1.12 for respiratory cancers and 1.40 for stomach cancer. MSHA agrees with the commenter that “the study does not establish a dpm-related health risk,” but notes that dpm effects were not under investigation. Diesel emissions were not mentioned in the report, and, given the study period, the miners involved may not have been occupationally exposed to diesel exhaust.

- Waxweiler (1972). MSHA’s discussion of this study appears earlier

in this risk assessment, under “Studies Involving Miners.” As noted by the commenter, the slight excess in lung cancer, relative to the general population of New Mexico, was not statistically significant. The commenter failed to note, however, that no adjustment was made for a healthy worker effect and that a substantial percentage of the underground miners were not occupationally exposed to diesel emissions.

(v) Summation

Limitations identified in both positive and negative studies include: lack of sufficient power, inappropriate comparison groups, exposure misclassification, statistically insignificant results, and potential confounders. As explained earlier, under “Evaluation Criteria,” weaknesses of the first three of these types can reasonably be expected, for the most part, to artificially decrease the apparent strength of any observed association between diesel exposure and increased risk of lung cancer. Statistical insignificance and potential confounders may, in the absence of evidence to the contrary, be regarded as neutral on average. The weaknesses that have been identified in these studies are not unique to epidemiologic studies involving lung cancer and diesel exhaust. They are sources of uncertainty in virtually all epidemiologic research.

Even when there is a strong possibility that the results of a study have been affected by confounding variables, it does not follow that the effect has been to inflate rather than deflate the results or that the study cannot contribute to the weight of evidence supporting a putative association. As cogently stated by Stöber and Abel (*op cit.*, p. 4), “* * * associations found in epidemiologic studies can always be, at least in part, attributed to confounding.” Therefore, an objection grounded on potential confounding can always be raised against any epidemiologic study. It is well known that this same objection was, in the past, raised against epidemiologic studies linking lung cancer and radon exposure, lung cancer and asbestos dust exposure, and even lung cancer and tobacco smoking.

Some commenters have now proposed that virtually every existing epidemiologic study relating lung cancer to dpm exposure be summarily discredited because of susceptibility to confounding or other perceived weaknesses. Given the practical difficulties of designing and executing an epidemiologic study, this is not so much an objection to any specific study