

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.

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Under the assumption of a 4.5 gm/mile emissions rate in 1970, the cumulative EC exposure of $2450 \mu\text{g}\text{-yr}/\text{m}^3$ ($\approx 6.1 \text{ mg}\text{-yr}/\text{m}^3$ 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.⁵⁵

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 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

⁵⁵ 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 constituents of dpm would nonetheless be due to dpm exposures.

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" (HEL, 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.

- Jørgenson 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.

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 as it is an attack on applied epidemiology in general. Indeed, in their review of these studies, Stöber and Abel (1996) conclude that

In this field * * * epidemiology faces its limits (Taubes, 1995). * * * Many of these studies were doomed to failure from the very beginning.

For important ethical reasons, however, tightly controlled lung cancer experiments cannot be performed on humans. Therefore, despite their inherent limitations, MSHA must rely on the weight of evidence from epidemiologic studies, placing greatest weight on the most carefully designed and executed studies available.

(b) Bladder Cancer

With respect to cancers other than lung cancer, MSHA's review of the literature identified only bladder cancer as a possible candidate for a causal link to dpm. Cohen and Higgins (1995) identified and reviewed 14 epidemiologic case-control studies containing information related to dpm exposure and bladder cancer. All but one of these studies found elevated risks of bladder cancer among workers in jobs frequently associated with dpm exposure. Findings were statistically significant in at least four of the studies (statistical significance was not evaluated in three).

These studies point quite consistently toward an excess risk of bladder cancer among truck or bus drivers, railroad workers, and vehicle mechanics. However, the four available cohort studies do not support a conclusion that exposure to dpm is responsible for the excess risk of bladder cancer associated with these occupations. Furthermore, most of the case-control studies did not distinguish between exposure to diesel-powered equipment and exposure to gasoline-powered equipment for workers having the same occupation. When such a distinction was drawn, there was no evidence that the prevalence of bladder cancer was higher for workers exposed to the diesel-powered equipment.

This, along with the lack of corroboration from existing cohort studies, suggests that the excessive rates of bladder cancer observed may be a consequence of factors other than dpm exposure that are also associated with these occupations. For example, truck and bus drivers are subjected to vibrations while driving and may tend to have different dietary and sleeping habits than the general population. For these reasons, MSHA does not find that convincing evidence currently exists for a causal relationship between dpm exposure and bladder cancer. MSHA received no public comments objecting to this conclusion.

ii. Studies Based on Exposures to PM_{2.5} in Ambient Air. Prior to 1990, the relationship between mortality and long-term exposure to particulate matter was generally investigated by means of cross-sectional studies, but unaddressed spatial confounders and other methodological problems inherent in such studies limited their usefulness (EPA, 1996).⁵⁶ Two more recent prospective cohort studies provide better evidence of a link between excess mortality rates and exposure to fine particulate, although some of the uncertainties here are greater than with the short-term studies conducted in single communities. The two studies are the "Six Cities" study (Dockery et al., 1993), and the American Cancer Society (ACS) study (Pope et al., 1995).⁵⁷ The first study followed about 8,000 adults in six U.S. cities over 14 years; the second looked at survival data for half

⁵⁶ Unlike *longitudinal studies*, which examine responses at given locations to changes in conditions over time, *cross-sectional studies* compare results from locations with different conditions at a given point in time.

⁵⁷ A third such study, the California Seventh Day Adventist study (Abbey et al., 1991), investigated only TSP, rather than fine particulate. It did not find significant excess mortality associated with chronic TSP exposures.

a million adults in 151 U.S. cities for 7 years. After adjusting for potential confounders, including smoking habits, the studies considered differences in mortality rates between the most polluted and least polluted cities.

Both the Six Cities study and the ACS study found a significant association between chronically higher concentrations of PM_{2.5} (which includes dpm) and age-adjusted total mortality.⁵⁸ The authors of the Six Cities Study concluded that the results suggest that exposures to fine particulate air pollution "contributes to excess mortality in certain U.S. cities." The ACS study, which not only controlled for smoking habits and various occupational exposures, but also, to some extent, for passive exposure to tobacco smoke, found results qualitatively consistent with those of the Six Cities Study.⁵⁹ In the ACS study, however, the estimated increase in mortality associated with a given increase in fine particulate exposure was lower, though still statistically significant. In both studies, the largest increase observed was for cardiopulmonary mortality.

Both studies also showed an increased risk of lung cancer associated with increased exposure to fine particulate. Although the lung cancer results were not statistically significant, they are consistent with reports of an increased risk of lung cancer among workers occupationally exposed to diesel emissions (discussed above).

The few studies on associations between chronic PM_{2.5} exposure and morbidity in adults show effects that are difficult to separate from measures of PM₁₀ and measures of acid aerosols. The available studies, however, show positive associations between particulate air pollution and adverse health effects for those with pre-existing respiratory or cardiovascular disease. This is significant for miners occupationally exposed to fine particulates such as dpm because, as mentioned earlier, there is a large body of evidence showing that respiratory diseases classified as COPD are

⁵⁸ The Six Cities study also found such relationships at elevated levels of PM₁₀ and sulfates. The ACS study was designed to follow up on the fine particle results of the Six Cities Study, and also investigated sulfates separately. As explained earlier in this preamble, sulfates may be a significant constituent of dpm, depending on the type of diesel fuel used.

⁵⁹ The Six Cities study did not find a statistically significant increase in risk among non-smokers, suggesting that non-smokers might be less sensitive than smokers to adverse health effects from fine particulate exposures; however, the ACS study, with more statistical power, did find significantly increased risk even for non-smokers.

significantly more prevalent among miners than in the general population. It also appears that PM exposure may exacerbate existing respiratory infections and asthma, increasing the risk of severe outcomes in individuals who have such conditions (EPA, 1996).

d. Mechanisms of Toxicity

Four topics will be addressed in this section of the risk assessment: (i) the agent of toxicity, (ii) clearance and deposition of dpm, (iii) effects other than cancer, and (iv) lung cancer. The section on lung cancer will include discussions of the evidence from (1) genotoxicity studies (including bioavailability of genotoxins) and (2) animal studies.

i. Agent of Toxicity. As described in Part II of this preamble, the particulate fraction of diesel exhaust is made up of aggregated soot particles, vapor phase hydrocarbons, and sulfates. Each soot particle consists of an insoluble, elemental carbon core and an adsorbed, surface coating of relatively soluble organic compounds, such as polycyclic aromatic hydrocarbons (PAHs). Many of these organic carbon compounds are suspected or known mutagens and/or carcinogens. For example, nitrated PAHs, which are present in dpm, are potent mutagens in microbial and human cell systems, and some are known to be carcinogenic to animals (IPCS, 1996, pp. 100–105).

When released into an atmosphere, the soot particles formed during combustion tend to aggregate into larger particles. The total organic and elemental carbon in these soot particles accounts for approximately 80 percent of the dpm mass. The remaining 20 percent consists mainly of sulfates, such as H₂SO₄ (sulfuric acid).

Several laboratory animal studies have been performed to ascertain whether the effects of diesel exhaust are attributable specifically to the particulate fraction. (Heinrich et al., 1986, 1995; Iwai et al., 1986; Brightwell et al., 1986). These studies compare the effects of chronic exposure to whole diesel exhaust with the effects of filtered exhaust containing no particles. The studies demonstrate that when the exhaust is sufficiently diluted to nullify the effects of gaseous irritants (NO₂ and SO₂), irritant vapors (aldehydes), CO, and other systemic toxicants, diesel particles are the prime etiologic agents of noncancer health effects. Exposure to dpm produced changes in the lung that were much more prominent than those evoked by the gaseous fraction alone. Marked differences in the effects of whole and filtered diesel exhaust were also evident from general toxicological

indices, such as body weight, lung weight, and pulmonary histopathology.

These studies show that, when the exhaust is sufficiently diluted, it is the particles that are primarily responsible for the toxicity observed. However, the available studies do not completely settle the question of whether the particles might act additively or synergistically with the gases in diesel exhaust. Possible additivity or interaction effects with the gaseous portion of diesel exhaust cannot be completely ruled out.

One commenter (MARG) raised an issue with regard to the agent of toxicity in diesel exhaust as follows:

MSHA has not attempted to regulate exposure to suspected carcinogens contained in dpm, but has opted instead, in metal/non-metal mines, to regulate total carbon ("TC") as a surrogate for diesel exhaust, without any evidence of adverse health effects from TC exposure. * * * Nor does the mere presence of suspected carcinogens, in minute quantities, in diesel exhaust require a 95 percent reduction of total diesel exhaust [sic] in coal mines. If there are small amounts of carcinogenic substances of concern in diesel exhaust, those substances, not TC, should be regulated directly on the basis of the risks (if any) posed by those substances in the quantities actually present in underground mines. [MARG]

First, it should be noted that the "suspected carcinogens" in diesel exhaust to which the commenter referred are part of the organic fraction of the total carbon. Therefore, limiting the concentration of airborne total carbon attributable to dpm, or removing the soot particles from the diesel exhaust by filtration, are both ways of effectively limiting exposures to these suspected carcinogens. Second, the commenter seems to have assumed that cancer is the only adverse health effect of concern and that the only agents in dpm that could cause cancer are the "suspected carcinogens" in the organic fraction. This not only ignores non-cancer health effects associated with exposures to dpm and other fine particles, but also the possibility (discussed below) that, with sufficient deposition and retention, soot particles themselves could promote or otherwise increase the risk of lung cancer—either directly or by stimulating the body's natural defenses against foreign substances.

The same commenter [MARG] also stated that "* * * airborne carbon has not been shown to be harmful at levels currently established in MSHA's dust rules. If the problem is dpm, as MSHA asserts, then it is not rationally addressed by regulating airborne carbon." MSHA's intent is to limit dpm exposures in M/NM mines by regulating

the submicrometer carbon from diesel emissions—not any and all airborne carbon. MSHA considers its approach a rational means of limiting dpm exposures because most of the dpm consists of carbon (approximately 80 percent by weight), and because using low sulfur diesel fuel will effectively reduce the sulfates comprising most of the remaining portion. The commenter offered no practical suggestion of a more direct, effective, and rational way of limiting airborne dpm concentrations in M/NM mines. Furthermore, direct evidence exists that the risk of lung cancer increases with increasing cumulative occupational exposure to dpm as measured by total carbon (Säverin *et al.*, 1999, discussed earlier in this risk assessment).

ii. Deposition, Clearance, and Retention. As suggested by Figure II–1 of this preamble, most of the aggregated particles making up dpm are no larger than one micrometer in diameter. Particles this small are able to penetrate into the deepest regions of the lungs, called *alveoli*. In the *alveoli*, the particles can mix with and be dispersed by a substance called *surfactant*, which is secreted by cells lining the alveolar surfaces.

The literature on deposition of fine particles in the respiratory tract was reviewed in Green and Watson (1995) and U.S. EPA (1996). The mechanisms responsible for the broad range of potential particle-related health effects varies depending on the site of deposition. Once deposited, the particles may be cleared from the lung, translocated into the interstitium, sequestered in the lymph nodes, metabolized, or be otherwise chemically or physically changed by various mechanisms. Clearance of dpm from the *alveoli* is important in the long-term effects of the particles on cells, since it may be more than two orders of magnitude slower than mucociliary clearance (IPCS, 1996).

IARC (1989) and IPCS (1996) reviewed factors affecting the deposition and clearance of dpm in the respiratory tracts of experimental animals. Inhaled PAHs adhering to the carbon core of dpm are cleared from the lung at a significantly slower rate than unattached PAHs. Furthermore, there is evidence that inhalation of whole dpm may increase the retention of subsequently inhaled PAHs. IARC (*op cit.*) suggested that this can happen when newly introduced PAHs bind to dpm particles that have been retained in the lung.

The evidence points to significant differences in deposition and clearance for different animal species (IPCS,

1996). Under equivalent exposure regimens, hamsters exhibited lower levels of retained dpm in their lungs than rats or mice and consequently less pulmonary function impairment and pulmonary pathology. These differences may result from a lower intake rate of dpm, lower deposition rate and/or more rapid clearance rate, or lung tissue that is less susceptible to the cytotoxicity of dpm. Observations of a decreased respiration in hamsters when exposed by inhalation favor lower intake and deposition rates.

Retardation of lung clearance, called "overload" is not specific to dpm and may be caused by inhaling, at a sufficiently high rate, dpm in combination with other respirable particles, such as mineral dusts typical of mining environments. The effect is characterized by (1) an overwhelming of normal clearance processes, (2) disproportionately high retention and loading of the lung with particles, compared to what occurs at lower particle inhalation rates, (3) various pathological responses; generally including chronic inflammation, epithelial hyperplasia and metaplasia, and pulmonary fibrosis; and sometimes including lung tumors.

In the proposed risk assessment, MSHA requested additional information, not already covered in the sources cited above, on fine particle deposition in the respiratory tract, especially as it might pertain to lung loading in miners exposed to a combination of diesel particulate and other dusts. In response to this request, NIOSH submitted a study that investigated rat lung responses to chronic inhalation of a combination of coal dust and diesel exhaust, compared to coal dust or dpm alone (Castranova *et al.*, 1985). Although this report did not directly address deposition or clearance, the investigators reported that another phase of the study had shown that "particulate clearance, as determined by particulate accumulation in the lung, is inhibited after two years of exposure to diesel exhaust but is not inhibited by exposure to coal dust."

iii. Effects other than Cancer. A number of controlled animal studies have been undertaken to ascertain the toxic effects of exposure to diesel exhaust and its components. Watson and Green (1995) reviewed approximately 50 reports describing noncancerous effects in animals resulting from the inhalation of diesel exhaust. While most of the studies were conducted with rats or hamsters, some information was also available from studies conducted using cats, guinea pigs, and monkeys. The authors also

correlated reported effects with different descriptors of dose, including both gravimetric and non-gravimetric (*e.g.*, particle surface area or volume) measures. From their review of these studies, Watson and Green concluded that:

(a) Animals exposed to diesel exhaust exhibit a number of noncancerous pulmonary effects, including chronic inflammation, epithelial cell hyperplasia, metaplasia, alterations in connective tissue, pulmonary fibrosis, and compromised pulmonary function.

(b) Cumulative weekly exposure to diesel exhaust of 70 to 80 mg• hr/m³ or greater are associated with the presence of chronic inflammation, epithelial cell proliferation, and depressed alveolar clearance in chronically exposed rats.

(c) The extrapolation of responses in animals to noncancer endpoints in

humans is uncertain. Rats were the most sensitive animal species studied.

Subsequent to the review by Watson and Green, there have been a number of animal studies on allergic immune responses to dpm. Takano et al. (1997) investigated the effects of dpm injected into mice through an intratracheal tube and found manifestations of allergic asthma, including enhanced antigen-induced airway inflammation, increased local expression of cytokine proteins, and increased production of antigen-specific immunoglobulins. The authors concluded that the study demonstrated dpm's enhancing effects on allergic asthma and that the results suggest that dpm is "implicated in the increasing prevalence of allergic asthma in recent years." Similarly, Ichinose et al. (1997a) found that five different strains of mice injected intratracheally with dpm

exhibited manifestations of allergic asthma, as expressed by enhanced airway inflammation, which were correlated with an increased production of antigen-specific immunoglobulin due to the dpm. The authors concluded that dpm enhances manifestations of allergic airway inflammation and that " * * * the cause of individual differences in humans at the onset of allergic asthma may be related to differences in antigen-induced immune responses * * *."

The mechanisms that may lead to adverse health effects in humans from inhaling fine particulates are not fully understood, but potential mechanisms that have been hypothesized for non-cancerous outcomes are summarized in Table III-6. A comprehensive review of the toxicity literature is provided in U.S. EPA (1996).

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Table III-6. — Hypothesized mechanisms of particulate toxicity[†]

Response	Description
Increased Airflow Obstruction	<p>PM exposure may aggravate existing respiratory symptoms which feature airway obstruction. PM-induced airway narrowing or airway obstruction from increased mucous secretion may increase abnormal ventilation/perfusion ratios in the lung and create hypoxia. Hypoxia may lead to cardiac arrhythmias and other cardiac electrophysiologic responses that in turn may lead to ventricular fibrillation and ultimately cardiac arrest. For those experiencing airflow obstruction, increased airflow into non-obstructed areas of the lung may lead to increased particle deposition and subsequent deleterious effects on remaining lung tissue, further exacerbating existing disease processes. More frequent and severe symptoms may be present or more rapid loss of function.</p>
Impaired Clearance	<p>PM exposure may impair clearance by promoting hypersecretion of mucus which in turn results in plugging of airways. Alterations in clearance may also extend the time that particles or potentially harmful biogenic aerosols reside in the tracheobronchial region of the lung. Consequently alterations in clearance from either disturbance of the mucociliary escalator or of macrophage function may increase susceptibility to infection, produce an inflammatory response, or amplify the response to increased burdens of PM. Acid aerosols impair mucociliary clearance.</p>
Altered Host Defense	<p>Responses to an immunological challenge (e.g., infection), may enhance the subsequent response to inhalation of nonspecific material (e.g., PM). PM exposure may also act directly on macrophage function which may not only affect clearance of particles but also increase susceptibility and severity of infection by altering their immunological function. Therefore, depression or over-activation of the immune system, caused by exposure to PM, may be involved in the pathogenesis of lung disease. Decreased respiratory defense may result in increased risk of mortality from pneumonia and increased morbidity (e.g., infection).</p>

Cardiovascular Perturbation	Pulmonary responses to PM exposure may include hypoxia, bronchoconstriction, apnea, impaired diffusion, and production of inflammatory mediators that can contribute to cardiovascular perturbation. Inhaled particles could act at the level of the pulmonary vasculature by increasing pulmonary vascular resistance and further increase ventilation/perfusion abnormalities and hypoxia. Generalized hypoxia could result in pulmonary hypertension and interstitial edema that would impose further workload on the heart. In addition, mediators released during an inflammatory response could cause release of factors in the clotting cascade that may lead to increased risk of thrombus formation in the vascular system. Finally, direct stimulation by PM of respiratory receptors found throughout the respiratory tract may have direct cardiovascular effects (e.g., bradycardia, hypertension, arrhythmia, apnea and cardiac arrest).
Epithelial Lining Changes	PM or its pathophysiological reaction products may act at the alveolar capillary membrane by increasing the diffusion distances across the respiratory membrane (by increasing its thickness) and causing abnormal ventilation/perfusion ratios. Inflammation caused by PM may increase "leakiness" in pulmonary capillaries leading eventually to increased fluid transudation and possibly to interstitial edema in susceptible individuals. PM induced changes in the surfactant layer leading to increased surface tension would have the same effect.
Inflammatory Response	Diseases which increase susceptibility to PM toxicity involve inflammatory response (e.g., asthma, COPD, and infection). PM may induce or enhance inflammatory responses in the lung which may lead to increased permeability, diffusion abnormality, or increased risk of thrombus formation in vascular system. Inflammation from PM exposure may also decrease phagocytosis by alveolar macrophages and therefore reduce particle clearance. (See discussions above for other inflammatory effects from PM exposure.)

[†] This table was derived from information in EPA (1996) 11:179-185; 13:67-72; and Appendix D of EPA staff report.

Deposition of particulates in the human respiratory tract may initiate events leading to increased airflow obstruction, impaired clearance, impaired host defenses, or increased epithelial permeability. Airflow obstruction can result from laryngeal constriction or bronchoconstriction secondary to stimulation of receptors in extrathoracic or intrathoracic airways. In addition to reflex airway narrowing, reflex or local stimulation of mucus secretion can lead to mucus hypersecretion and, eventually, to mucus plugging in small airways.

Pulmonary changes that contribute to cardiovascular responses include a variety of mechanisms that can lead to hypoxemia, including bronchoconstriction, apnea, impaired diffusion, and production of inflammatory mediators. Hypoxia can lead to cardiac arrhythmias and other cardiac electrophysiologic responses that, in turn, may lead to ventricular fibrillation and ultimately cardiac arrest. Furthermore, many respiratory receptors have direct cardiovascular effects. For example, stimulation of C-fibers leads to bradycardia and hypertension, and stimulation of laryngeal receptors can result in hypertension, cardiac arrhythmia, bradycardia, apnea, and even cardiac arrest. Nasal receptor or pulmonary J-receptor stimulation can lead to vagally-mediated bradycardia and hypertension (Widdicombe, 1988).

Some commenters mistakenly attributed the sensory irritant effects of diesel exhaust entirely to its gaseous components. The mechanism by which constituents of dpm can cause sensory irritations in humans is much better understood than the mechanisms for other adverse health effects due to fine particulates. In essence, sensory irritants are "scrubbed" from air entering the upper respiratory tract, thereby preventing a portion from penetrating more deeply into the lower respiratory tract. However, the sensory irritants stimulate trigeminal nerve endings, which are located very close to the oronasal mucosa and also to the watery surfaces of the eye (cornea). This produces a burning, painful sensation. The intensity of the sensory irritant response is related to the irritant concentration and duration of exposure. Differences in relative potency are observed with different sensory irritants. Acrolein and formaldehyde are examples of highly potent sensory irritants which, along with others having low molecular weights (acids, aldehydes), are often found in the organic fraction of dpm (Nauss et al., 1995). They may be adsorbed onto the carbon-based core or released in a vapor

phase. Thus, mixtures of sensory irritants in dpm may impinge upon the eyes and respiratory tract of miners and produce adverse health effects.

It is also important to note that mixtures of sensory irritants in dpm may produce responses that are not predicted solely on the basis of the individual chemical constituents. Instead, these irritants may interact at receptor sites to produce additive, synergistic, or antagonistic effects. For example, because of synergism, dpm containing a mixture of sensory irritants at relatively low concentrations may produce intense sensory responses (*i.e.*, responses far above those expected for the individual irritants). Therefore, the irritant effects of whole dpm cannot properly be evaluated by simply adding together the known effects of its individual components.

As part of its public comments on the proposed preamble, NIOSH submitted a study (Hahon et al., 1985) on the effects of diesel emissions on mice infected with influenza virus. The object of this study was to determine if exposure to diesel emissions (either alone or in combination with coal dust) could affect resistance to pulmonary infections. The investigators exposed groups of mice to either coal dust, diesel emissions, a combination of both, or filtered air (control group) for various durations, after which they were infected with influenza. Although not reflected by excess mortality, the severity of influenza infection was found to be more pronounced in mice previously exposed to diesel emissions than in control animals. The effect was not intensified by inhalation of coal dust in combination with those emissions.

In addition to possible acute toxicity of particles in the respiratory tract, chronic exposure to particles that deposit in the lung may induce inflammation. Inflammatory responses can lead to increased permeability and possibly diffusion abnormality. Furthermore, mediators released during an inflammatory response could cause release of factors in the clotting cascade that may lead to an increased risk of thrombus formation in the vascular system (Seaton, 1995). Persistent inflammation, or repeated cycles of acute lung injury and healing, can induce chronic lung injury. Retention of the particles may be associated with the initiation and/or progression of COPD.

Takenaka et al. (1995) investigated mechanisms by which dpm may act to cause allergenic effects in human cell cultures. The investigators reported that application of organic dpm extracts over a period of 10 to 14 days increased IgE production from the cells by a factor of

up to 360 percent. They concluded that enhanced IgE production in the human airway resulting from the organic fraction of dpm may be an important factor in the increasing incidence of allergic airway disease. Similarly, Tsien et al. (1997) investigated the effects of the organic fraction of dpm on IgE production in human cell cultures and found that application of the organic extract doubled IgE production after three days in cells already producing IgE.

Sagai et al. (1996) investigated the potential role of dpm-induced oxygen radicals in causing pulmonary injuries. Repeated intratracheal instillation of dpm in mice caused marked infiltration of inflammatory cells, proliferation of goblet cells, increased mucus secretion, respiratory resistance, and airway constriction. The results indicated that oxygen radicals, induced by intratracheally instilled dpm, can cause responses characteristic of bronchial asthma.

Lovik et al. (1997) investigated inflammatory and systemic IgE responses to dpm, alone and in combination with the model allergen ovalbumin (OA), in mice. To determine whether it was the elemental carbon core or substances in the organic fraction of dpm that were responsible for observed allergenic effects, they compared the effects of whole dpm with those of carbon black (CB) particles of comparable size and specific surface area. Although the effects were slightly greater for dpm, both dpm and CB were found to cause significant, synergistic increases in allergenic responses to the OA, as expressed by inflammatory responses of the local lymph node and OA-specific IgE production. The investigators concluded that both dpm and CB synergistically enhance and prolong inflammatory responses in the lymph nodes that drain the site of allergen deposition. They further concluded that the elemental carbon core contributes substantially to the adjuvant activity of dpm.

Diaz-Sanchez et al. (1994, 1996, 1997) conducted a series of experiments on human subjects to investigate the effects of dpm on allergic inflammation as measured by IgE production. The studies by Takenaka et al. (op cit.) and Tsien et al. (op cit.) were also part of this series but were based on human cell cultures rather than live human volunteers. A principal objective of these experiments was to investigate the pathways and mechanisms by which dpm induces allergic inflammation. The investigators found that the organic fraction of dpm can enhance IgE production, but that the major

polyaromatic hydrocarbon in this fraction (phenanthrene) can enhance IgE without causing inflammation. On the other hand, when human volunteers were sprayed intranasally with carbon particles lacking the organic compounds, the investigators found a large influx of cells in the nasal mucosa but no increase in IgE. These results suggest that while the organic portion of dpm is not necessary for causing irritation and local inflammation, it is the organic compounds that act on the immune system to promote an allergic response.

Salvi et al. (1999) investigated the impact of diesel exhaust on human airways and peripheral blood by exposing healthy volunteers to diesel exhaust at a concentration of 300 $\mu\text{g}/\text{m}^3$ for one hour with intermittent exercise. Following exposure, they found significant evidence of acute inflammatory responses in airway lavage and also in the peripheral blood. Some commenters expressed a belief that the gaseous, rather than particulate, components of diesel exhaust caused these effects. The investigators noted that the inflammatory responses observed could not be attributed to NO_2 in the diesel exhaust because previous studies they had conducted, using a similar experimental protocol, had revealed no such responses in the airway tissues of volunteers exposed to a higher concentration of NO_2 , for a longer duration, in the absence of dpm. They concluded that “[i]t therefore seems more likely that the particulate component of DE is responsible.”

iv. Lung Cancer. (1) *Genotoxicity Studies.* Many studies have shown that diesel soot, or its organic component, can increase the likelihood of genetic mutations during the biological process of cell division and replication. A survey of the applicable scientific literature is provided in Shirnamé-Moré (1995). What makes this body of research relevant to the risk of lung cancer is that mutations in critical genes can sometimes initiate, promote, or advance a process of carcinogenesis.

The determination of genotoxicity has frequently been made by treating diesel soot with organic solvents such as dichloromethane and dimethyl sulfoxide. The solvent removes the organic compounds from the carbon core. After the solvent evaporates, the mutagenic potential of the extracted organic material is tested by applying it to bacterial, mammalian, or human cells propagated in a laboratory culture. In general, the results of these studies have shown that various components of the organic material can induce mutations and chromosomal aberrations.

One commenter (MARG) pointed out that “even assuming diesel exhaust contains particular genotoxic substances, the bioavailability of these genotoxins has been questioned.” As acknowledged in the proposed risk assessment, a critical issue is whether whole diesel particulate is mutagenic when dispersed by substances present in the lung. Since the laboratory procedure for extracting organic material with solvents bears little resemblance to the physiological environment of the lung, it is important to establish whether dpm as a whole is genotoxic, without solvent extraction. Early research indicated that this was not the case and, therefore, that the active genotoxic materials adhering to the carbon core of diesel particles might not be biologically damaging or even available to cells in the lung (Brooks *et al.*, 1980; King *et al.*, 1981; Siak *et al.*, 1981). A number of more recent research papers, however, have shown that dpm, without solvent extraction, can cause DNA damage when the soot is dispersed in the pulmonary surfactant that coats the surface of the alveoli (Wallace *et al.*, 1987; Keane *et al.*, 1991; Gu *et al.*, 1991; Gu *et al.*, 1992). From these studies, NIOSH concluded in 1992 that:

* * * the solvent extract of diesel soot and the surfactant dispersion of diesel soot particles were found to be active in prokaryotic cell and eukaryotic cell *in vitro* genotoxicity assays. The cited data indicate that respired diesel soot particles on the surface of the lung alveoli and respiratory bronchioles can be dispersed in the surfactant-rich aqueous phase lining the surfaces, and that genotoxic material associated with such dispersed soot particles is biologically available and genotoxicity active. Therefore, this research demonstrates the biological availability of active genotoxic materials without organic solvent interaction. [Cover letter to NIOSH response to ANPRM, 1992].

If this conclusion is correct, it follows that dpm itself, and not only its organic extract, can cause genetic mutations when dispersed by a substance present in the lung.

One commenter (IMC Global) noted that Wallace *et al.* (1987) used aged dpm samples from scrapings inside an exhaust pipe and contended that this was not a realistic representation of dpm. The commenter further argued that the two studies cited by Gu *et al.* involved “direct application of an unusually high concentration gradient” that does not replicate normal conditions of dpm exposure.

MSHA agrees with this commenter’s general point that conditions set up in such experiments do not duplicate actual exposure conditions. However, as

a follow-up to the Wallace study, Keane *et al.* (op. cit.) demonstrated similar results with both exhaust pipe soot and particles obtained directly from an exhaust stream. With regard to the two Gu studies, MSHA recognizes that any well-controlled experiment serves only a limited purpose. Despite their limitations, however, these experiments provided valuable information. They avoided solvent extraction. By showing that solvent extraction is not a necessary condition of dpm mutagenicity, these studies provided incremental support to the hypothesis of bioavailability under more realistic conditions. This possibility was subsequently tested by a variety of other experiments, including experiments on live animals and humans.

For example, Sagai *et al.* (1993) showed that whole dpm produced active oxygen radicals in the trachea of live mice, but that dpm stripped of organic compounds did not. Whole dpm caused significant damage to the lungs and also high mortality at low doses. According to the investigators, most of the toxicity observed appeared to be due to the oxygen radicals, which can also have genotoxic effects. Subsequently, Ichinose *et al.* (1997b) examined the relationship between tumor response and the formation of oxygen radicals in the lungs of mice injected with dpm. The mice were treated with sufficiently high doses of dpm to produce tumors after 12 months. As in the earlier study, the investigators found that the dpm generated oxygen radicals, even in the absence of biologically activating systems (such as macrophages), and that these oxygen radicals were implicated in the lung toxicity of the dpm. The authors concluded that “oxidative DNA damage induced by the repeated DEP [*i.e.*, dpm] treatment could be an important factor in enhancing the mutation rate leading to lung cancer.”

The formation of DNA adducts is an important indicator of genotoxicity and potential carcinogenicity. Adduct formation occurs when molecules, such as those in dpm, attach to the cellular DNA. These adducts can negatively affect DNA transcription and/or cellular duplication. If DNA adducts are not repaired, then a mutation or chromosomal aberration can occur during normal mitosis (*i.e.*, cell replication) eventually leading to cancer cell formation. IPCS (1996) contains a survey of animal experiments showing DNA adduct induction in the lungs of experimental animals exposed to diesel

exhaust.⁶⁰ MSHA recognizes that such studies provide limited information regarding the bioavailability of organics, since positive results may well have been related to factors associated with lung particle overload. However, the bioavailability of genotoxic dpm components is also supported by human studies showing genotoxic effects of exposure to whole dpm. DNA adduct formation and/or mutations in blood cells following exposure to dpm, especially at levels insufficient to induce lung overload, can be presumed to result from organics diffusing into the blood.

Hemminki *et al.* (1994) found that DNA adducts were significantly elevated in lymphocytes of nonsmoking bus maintenance and truck terminal workers, as compared to a control group of hospital mechanics, with the highest adduct levels found among garage and forklift workers. Hou *et al.* (1995) reported significantly elevated levels of DNA adducts in lymphocytes of non-smoking diesel bus maintenance workers compared to a control group of unexposed workers. Similarly, Nielsen *et al.* (1996) found that DNA adducts were significantly increased in the blood and urine of bus garage workers and mechanics exposed to dpm as compared to a control group.

One commenter (IMC Global) acknowledged that “the studies conducted by Hemminiki [Hemminiki *et al.*, 1994] showed elevations in lymphocyte DNA adducts in garage workers, bus maintenance workers and diesel forklift drivers” but argued that “these elevations were at the borderline of statistical significance.” Although results at a higher level of confidence would have been more persuasive, this does not negate the value of the evidence as it stands. Furthermore, statistical significance in an individual study becomes less of an issue when, as in this case, the results are corroborated by other studies.

IMC Global also acknowledged that the Nielsen study found significant differences in DNA adduct formation between diesel-exposed workers and controls but argued that “the real source of genotoxins was unclear, and other sources of exposure, such as skin contact with lubricating oils could not be excluded.” As is generally the case with studies involving human subjects, this study did not completely control for potential confounders. For this reason, MSHA considers it important that several human studies—not all subject to confounding by the same variables—

found elevated adduct levels in diesel-exposed workers.

IMC Global cited another human study (Qu *et al.*, 1997) as casting doubt on the genotoxic effects of diesel exposure, even though this study (conducted on Australian coal miners) reported significant increases in DNA adducts immediately after a period of intense diesel exposure during a longwall move. As noted by the commenter, adduct levels of exposed miners and drivers were, prior to the longwall move, approximately 50% higher than for the unexposed control group; but differences by exposure category were not statistically significant. A more informative part of the study, however, consisted of comparing adducts in the same workers before and after a longwall move, which involved “intensive use of heavy equipment, diesel powered in these mines, over a 2–3 week period.” MSHA emphasizes that the comparison was made on the same workers, because doing so largely controlled for potentially confounding variables, such as smoking habits, that may be a factor when making comparisons between different persons. After the period of “intensive” exposure, statistically significant increases were observed in both total and individual adducts.

Contrary to the commenter’s characterization of this study, the investigators stated that their analysis “provides results in which the authors have a high level of confidence.” They concluded that “given the * * * apparent increase in adducts during a period of intense DEE [*i.e.*, diesel exhaust emissions] exposures it would be prudent to pay particular attention to keeping exposures as low as possible, especially during LWCO [*i.e.*, ‘longwall change out’] operations.” Although the commenter submitted this study as counter-evidence, it actually provides significant, positive evidence that high dpm exposures in a mining environment can produce genotoxic effects.

The West Virginia Coal Association submitted an analysis by Dr. Peter Valberg, purporting to show that “* * * the quantity of particle-bound mutagens that could potentially contact lung cells under human exposure scenarios is very small.” According to Dr. Valberg’s calculations, the dose of organic mutagens deposited in the lungs of a worker occupationally exposed (40 hours per week) to 500 $\mu\text{g}/\text{m}^3$ of dpm would be equivalent in potency to smoking about one cigarette per

month.⁶¹ Dr. Valberg indicated that a person smoking at this level would generally be classified a nonsmoker, but he made no attempt to quantify the carcinogenic effects. Nor did he compare this exposure level with levels of exposures to environmental tobacco smoke that have been linked to lung cancer.

Since the commenter did not provide details of Dr. Valberg’s calculation, MSHA was unable to verify its accuracy or evaluate the plausibility of key assumptions. However, even if the equivalence is approximately correct, using it to discount the possibility that dpm increases the risk of lung cancer relies on several questionable assumptions. Although their precise role in the analysis is unclear because it was not presented in detail, these assumptions apparently include:

(1) That there is a good correlation between genotoxicity dose-response and carcinogenicity dose-response. Although genotoxicity data can be very useful for identifying a carcinogenic hazard, carcinogenesis is a highly complex process that may involve the interaction of many mutagenic, physiological, and biochemical responses. Therefore, the shape and slope of a carcinogenic dose-response relationship cannot be readily predicted from a genotoxic dose-response relationship.

(2) That only the organic fraction of dpm contributes to carcinogenesis. This contradicts the findings reported by Ichinose *et al.* (1997b) and does not take into account the contribution that inflammation and active oxygen radicals induced by the inorganic carbon core of dpm may have in promoting lung cancers. Multiple routes of carcinogenesis may operate in human lungs—some requiring only the various organic mutagens in dpm and others involving induction of free radicals by the elemental carbon core, either alone or in combination with the organics.

(3) That the only mutagens in dpm are those that have been identified as mutagenic to bacteria and that the

⁶¹ The only details provided for this calculation pertained to adjusting 8-hour occupational exposures. Dr. Valberg adjusted the 500 $\mu\text{g}/\text{m}^3$ concentration for an 8-hour occupational exposure to a supposedly equivalent 24-hour continuous concentration of 92 $\mu\text{g}/\text{m}^3$. This adjustment ignored differences in breathing rates between periods of sleep, leisure activities, and heavy work. Even under the unrealistic assumption of homogeneous breathing rates, the calculation appears to be erroneous, since $(500 \mu\text{g}/\text{m}^3) \times (40 \text{ hours/week})$ is nearly 30 percent greater than $(92 \mu\text{g}/\text{m}^3) \times (168 \text{ hours/week})$. Also, Dr. Valberg stated that the calculation assumed a deposition fraction of 20 percent for dpm but did not state what deposition fraction was being assumed for the particles in cigarette smoke.

⁶⁰ Some of these studies will be discussed in the next subsection of this risk assessment.

mutagenic constituents of dpm have all been identified. One of the most potent of all known mutagens (3-nitrobenzanthrone) was only recently isolated and identified in dpm (Enya *et al.*, 1997).

(4) That the mutagenic components of dpm have the same combined potency as those in cigarette smoke. This ignores the relative potency and amounts of the various mutagenic constituents. If the calculation did not take into account the relative amounts and potencies of all the individual mutagens in dpm and cigarette smoke, then it oversimplified the task of making such a comparison.

In sum, unlike the experimental findings of dpm genotoxicity discussed above, the analysis by Dr. Valberg is not based on empirical evidence from dpm experiments, and it appears to rely heavily on questionable assumptions. Moreover, the contention that active components of dpm are not available in sufficient quantities to cause significant mutagenic damage in humans appears to be directly contradicted by the empirical evidence of elevated DNA adduct levels in exposed workers (Hemminki *et al.*, 1994; Hou *et al.*, 1995; Nielsen *et al.*, 1996; Qu *et al.*, 1997).

(2) *Animal Inhalation Studies.* When dpm is inhaled, a number of adverse effects that may contribute to carcinogenesis are discernable by microscopic and biochemical analysis. For a comprehensive review of these effects, see Watson and Green (1995). In brief, these effects begin with phagocytosis, which is essentially an attack on the diesel particles by cells called alveolar macrophages. The macrophages engulf and ingest the diesel particles, subjecting them to detoxifying enzymes. Although this is a normal physiological response to the inhalation of foreign substances, the process can produce various chemical byproducts injurious to normal cells. In attacking the diesel particles, the activated macrophages release chemical agents that attract neutrophils (a type of white blood cell that destroys microorganisms) and additional alveolar macrophages. As the lung burden of diesel particles increases, aggregations of particle-laden macrophages form in alveoli adjacent to terminal bronchioles, the number of Type II cells lining particle-laden alveoli increases, and particles lodge within alveolar and peribronchial tissues and associated lymph nodes. The neutrophils and macrophages release mediators of inflammation and oxygen radicals, which have been implicated in causing various forms of chromosomal damage, genetic mutations, and malignant transformation of cells (Weitzman and

Gordon, 1990). Eventually, the particle-laden macrophages are functionally altered, resulting in decreased viability and impaired phagocytosis and clearance of particles. This series of events may result in pulmonary inflammatory, fibrotic, or emphysematous lesions that can ultimately develop into cancerous tumors.

IARC (1989), Mauderly (1992), Busby and Newberne (1995), IPCS (1996), Cal-EPA (1998), and US EPA (1999) reviewed the scientific literature relating to excess lung cancers observed among laboratory animals chronically exposed to filtered and unfiltered diesel exhaust. The experimental data demonstrate that chronic exposure to whole diesel exhaust increases the risk of lung cancer in rats and that dpm is the causative agent. This carcinogenic effect has been confirmed in two strains of rats and in at least five laboratories. Experimental results for animal species other than the rat, however, are either inconclusive or, in the case of Syrian hamsters, suggestive of no carcinogenic effect. In two of three mouse studies reviewed by IARC (1989), lung tumor formation (including adenocarcinomas) was increased in the exposed animals as compared to concurrent controls; in the third study, the total incidence of lung tumors was not elevated compared to historical controls. Two more recent mouse studies (Heinrich *et al.*, 1995; Mauderly *et al.*, 1996) have both reported no statistically significant increase in lung cancer rates among exposed mice, as compared to contemporaneous controls. Monkeys exposed to diesel exhaust for two years did not develop lung tumors, but the short duration of exposure was judged inadequate for evaluating carcinogenicity in primates.

Bond *et al.* (1990a) investigated differences in peripheral lung DNA adduct formation among rats, hamsters, mice, and monkeys exposed to dpm at a concentration of 8100 $\mu\text{g}/\text{m}^3$ for 12 weeks. Mice and hamsters showed no increase of DNA adducts in their peripheral lung tissue, whereas rats and monkeys showed a 60 to 80-percent increase. The increased prevalence of lung DNA adducts in monkeys suggests that, with respect to DNA adduct formation, the human lungs' response to dpm inhalation may more closely resemble that of rats than that of hamsters or mice.

The conflicting carcinogenic effects of chronic dpm inhalation reported in studies of rats, mice, and hamsters may be due to non-equivalent delivered doses or to differences in response among species. Indeed, monkey lungs

have been reported to respond quite differently than rat lungs to both diesel exhaust and coal dust (Nikula, 1997). Therefore, the results from rat experiments do not, by themselves, establish that there is any excess risk due to dpm exposure for humans. However, the human epidemiologic and genotoxicity (DNA adduct) data indicate that humans comprise a species that, like rats, do suffer a carcinogenic response to dpm exposure. This would be consistent with the observation, mentioned above, that lung DNA adduct formation is increased among exposed rats but not among exposed hamsters or mice. Therefore, although MSHA recognizes that there are important differences between rats and humans (as there are also between rats and hamsters or mice), MSHA considers the rat studies relevant to an evaluation of human health risks.

Reactions similar to those observed in rats inhaling dpm have also been observed in rats inhaling fine particles with no organic component (Mauderly *et al.*, 1994; Heinrich *et al.*, 1994, 1995; Nikula *et al.*, 1995). Rats exposed to titanium dioxide (TiO_2) or pure carbon ("carbon black") particles, which are not considered to be genotoxic, exhibited similar pathological responses and developed lung cancers at about the same rate as rats exposed to whole diesel exhaust. Carbon black particles were used in these experiments because they are physically similar to the inorganic carbon core of dpm but have negligible amounts of organic compounds adsorbed to their surface. Therefore, at least in some species, it appears that the lung cancer toxicity of dpm may result largely from a biochemical response to the core particle itself rather than from specific, genotoxic effects of the adsorbed organic compounds.⁶²

One commenter stated that, in the proposed risk assessment, MSHA had neglected three additional studies suggesting that lung cancer risks in animals inhaling diesel exhaust are unrelated to genotoxic mechanisms. One of these studies (Mauderly *et al.*, 1996) did not pertain to questions of

⁶² NIOSH commented as follows: "Data cited by MSHA in support of this statement are not comparable. Rats were exposed to dpm at 4 mg/m^3 for 2 years (Mauderly *et al.* 1987; Brightwell *et al.* 1989), in contrast to rats exposed to TiO_2 at 250 mg/m^3 for two years [reference to article (Lee *et al.* 1985) not cited by MSHA]. It is not apparent that the overload mechanism that is proposed to be responsible for tumors in the TiO_2 exposed rats could also have been responsible for the tumors seen in the dpm exposed rats at 62-fold lower exposure concentrations." In the reports cited by MSHA, levels of TiO_2 and/or carbon black were commensurate with dpm levels.

genotoxicity but has been cited in the discussion of mouse studies above. The other two studies (Randerath et al., 1995 and Belinsky et al., 1995) were conducted as part of the cancer bioassay described in the 1994 article by Mauderly et al. (cited in the preceding paragraph). In the Randerath study, the investigators found that no DNA adducts specific to either diesel exhaust or carbon black were induced in the lungs of rats exposed to the corresponding substance. However, after three months of exposure, the total level of DNA adducts and the levels of some individual adducts were significantly higher in the diesel-exposed rats than in the controls. In contrast, multiple DNA adducts thought to be specific to diesel exhaust formed in the skin and lungs of mice treated topically with organic dpm extract. These results are consistent with the findings of Mauderly et al. (1994, op cit.). They imply that although the organic compounds of diesel exhaust are capable of damaging cellular DNA, they did not inflict such damage under the conditions of the inhalation experiment performed. The report noted that these results do not rule out the possibility of DNA damage by inhaled organics in "other species or * * * [in] exposure situations in which the concentrations of diesel exhaust particles are much lower." In the Belinsky study, the investigators measured mutations in selected genes in the tumors of those rats that had developed lung cancer. This study did not succeed in elucidating the mechanisms by which dpm and carbon black cause lung tumors in rats. The authors concluded that "until some of the genes involved in the carcinogenicity of diesel exhaust and carbon black are identified, a role for the organic compounds in tumor development cannot be excluded."

The carbon-black and TiO₂ studies discussed above indicate that lung cancers in rats exposed to dpm may be induced by a mechanism that does not require the bioavailability of genotoxic organic compounds adsorbed on the elemental carbon particles. Some researchers have interpreted these studies as also suggesting that (1) the carcinogenic mechanism in rats depends on massive overloading of the lung and (2) that this may provide a mechanism of carcinogenesis involving a threshold effect specific to rats, which has not been observed in other rodents or in humans (Oberdörster, 1994; Watson and Valberg, 1996). Some commenters on the ANPRM cited the lack of a link between lung cancer and coal dust or carbon black exposure as

evidence that carbon particles, by themselves, are not carcinogenic in humans. Coal mine dust, however, consists almost entirely of particles larger than those forming the carbon core of dpm or used in the carbon black and TiO₂ rat studies. Furthermore, although there have been nine studies reporting no excess risk of lung cancer among coal miners (Liddell, 1973; Costello et al., 1974; Armstrong et al., 1979; Rooke et al., 1979; Ames et al., 1983; Atuhaire et al., 1985; Miller and Jacobsen, 1985; Kuempel et al., 1995; Christie et al., 1995), eight studies have reported an elevated risk of lung cancer for those exposed to coal dust (Enterline, 1972; Rockette, 1977; Howe et al., 1983; Correa et al., 1984; Levin et al., 1988; Morabia et al., 1992; Swanson et al., 1993; Morfeld et al., 1997). The positive results in five of these studies (Enterline, 1972; Rockette, 1977; Howe et al., 1983; Morabia et al., 1992; Swanson et al., 1993) were statistically significant. Morabia et al. (op cit.) reported increased risk associated with duration of exposure, after adjusting for cigarette smoking, asbestos exposure, and geographic area. Furthermore, excess lung cancers have been reported among carbon black production workers (Hodgson and Jones, 1985; Siemiatycki, 1991; Parent et al., 1996). After a comprehensive evaluation of the available scientific evidence, the World Health Organization's International Agency for Research on Cancer concluded: "Carbon black is possibly carcinogenic to humans (Group 2B)." (IARC, 1996).

The carbon black and TiO₂ animal studies cited above do not prove there is a threshold below which dpm exposure poses no risk of causing lung cancer in humans. They also do not prove that dpm exposure has no incremental, genotoxic effects. Even if the genotoxic organic compounds in dpm were biologically unavailable and played no role in human carcinogenesis, this would not rule out the possibility of a genotoxic route to lung cancer (even for rats) due to the presence of the particles themselves. For example, as a byproduct of the biochemical response to the presence of particles in the alveoli, free oxidant radicals may be released as macrophages attempt to digest the particles. There is evidence that dpm can both induce production of reactive oxygen agents and also depress the activity of naturally occurring antioxidant enzymes (Mori, 1996; Ichinose et al., 1997; Sagai et al., 1993). Oxidants can induce carcinogenesis either by reacting directly with DNA, or by stimulating cell replication, or both

(Weitzman and Gordon, 1990). Salvi et al. (1999) reported acute inflammatory responses in the airways of human exposed to dpm for one hour at a concentration of 300 µg/m³. Such inflammation is associated with the production of free radicals and could provide routes to lung cancer with even when normal lung clearance is occurring. It could also give rise to a "quasi-threshold," or surge in response, corresponding to the exposure level at which the normal clearance rate becomes overwhelmed (lung overload).

Oxidant activity is not the only mechanism by which dpm could exert carcinogenic effects in the absence of mutagenic activity by its organic fraction. In its commentary on the Randerath study discussed above, the HEI's Health Review Committee suggested that dpm could both cause genetic damage by inducing free oxygen radicals and also enhance cell division by inducing cytokines or growth hormones:

It is possible that diesel exhaust exerts its carcinogenic effects through a mechanism that does not involve direct genotoxicity (that is, formation of DNA adducts) but involves proliferative responses such as chronic inflammation and hyperplasia arising from high concentrations of particles deposited in the lungs of the exposed rats. * * * Phagocytes (macrophages and neutrophils) released during inflammatory reactions "produce reactive oxygen species that can damage DNA. * * * Particles (with or without adsorbed PAHs) may thus induce oxidative DNA damage via oxygen free radicals. * * * Alternatively, activated phagocytes may release cytokines or growth factors that are known to increase cell division. Increased cell division has been implicated in cancer causation. * * * Thus, in addition to oxidative DNA damage, increased cell proliferation may be an important mechanism by which diesel exhaust and other insoluble particles induce pulmonary carcinogenesis in the rat. [Randerath et al., 1995, p. 55]

Even if lung overload were the primary or sole route by which dpm induced lung cancer, this would not mean that the high dpm concentrations observed in some mines are without hazard. It is noteworthy, moreover, that dpm exposure levels recorded in some mines have been almost as high as laboratory exposures administered to rats showing a clearly positive response. Intermittent, occupational exposure levels greater than about 500 µg/m³ dpm may overwhelm the human lung clearance mechanism (Nauss et al., 1995). Therefore, concentrations at the even higher levels currently observed in some mines could be expected to cause overload in some humans, possibly inducing lung cancer by a mechanism

similar to what occurs in rats. In addition, a proportion of exposed individuals can always be expected to be more susceptible than normal to clearance impairments and lung overload. Inhalation at even moderate levels may significantly impair clearance, especially in susceptible individuals. Exposures to cigarette smoke and respirable mineral dusts may further depress clearance mechanisms and reduce the threshold for overload. Consequently, even at dpm concentrations far lower than 500 $\mu\text{g}/\text{m}^3$ dpm, impaired clearance due to dpm inhalation may provide an important route to lung cancer in humans, especially if they are also inhaling cigarette smoke and other fine dusts simultaneously. (Hattis and Silver, 1992, Figures 9, 10, 11).

Furthermore, as suggested above, lung overload is not necessarily the only route to carcinogenesis in humans. Therefore, dpm concentrations too low to cause overload still may present a hazard. In humans exposed over a working lifetime to doses insufficient to cause overload, carcinogenic mechanisms unrelated to overload may operate, as indicated by the human epidemiologic studies and the data on human DNA adducts cited in the preceding subsection of this risk assessment. It is possible that overload provides the dominant route to lung cancer at high concentrations of fine particulate, while other mechanisms emerge as more relevant for humans under lower-level exposure conditions.

The NMA noted that, in 1998, the US EPA's Clean Air Scientific Advisory Committee (CASAC) concluded that there is "no evidence that the organic fraction of soot played a role in rat tumorigenesis at any exposure level, and considerable evidence that it did not." According to the NMA, this showed "* * * it is the rat data—not the hamster data—that lacks relevance for human health assessment."

It must first be noted that, in MSHA's view, all of the experimental animal data on health effects has relevance for human health risk assessment—whether the evidence is positive or negative and even if the positive results cannot be used to quantify human risk. The finding that different mammalian species exhibit important differences in response is itself relevant for human risk assessment. Second, the passage quoted from CASAC pertains to the route for tumorigenesis in rats and does not discuss whether this does or does not have relevance to humans exposed at high levels. The context for the CASAC deliberations was ambient exposure conditions in the general

environment, rather than the higher occupational exposures that might impair clearance rates in susceptible individuals. Third, the comment assumes that only a finding of tumorigenesis attributable to the organic portion of dpm would elucidate mechanisms of potential health effects in humans. This ignores the possibility that a mechanism promoting tumors, but not involving the organics, could operate in both rats and humans. Induction of free oxygen radicals is an example. Fourth, although there may be little or no evidence that organics contributed to rat tumorigenesis in the studies performed, there is evidence that the organics contributed to increases in DNA adduct formation. This kind of activity could have tumorigenic consequences in humans who may be exposed for periods far longer than a rat's 3-year lifetime and who, as a consequence, have more time to accumulate genetic damage from a variety of sources.

Bond et al. (1990b) and Wolff et al. (1990) investigated adduct formation in rats exposed to various concentrations of either dpm or carbon black for 12 weeks. At the highest concentration (10 mg/m^3), DNA adduct levels in the lung were increased by exposure to either dpm or carbon black; but levels in the rats exposed to dpm were approximately 30 percent higher. Gallagher et al. (1994) exposed different groups of rats to diesel exhaust, carbon black, or TiO_2 and detected no significant difference in DNA adduct levels in the lung. However, the level of one type of adduct, thought to be derived from a PAH, was elevated in the dpm-exposed rats but not found in the control group or in rats exposed to carbon black or TiO_2 .

These studies indicate that the inorganic carbon core of dpm is not the only possible agent of genetic damage in rats inhaling dpm. After a review of these and other studies involving DNA adducts, IPCS (1996) concluded that "Taken together, the studies of DNA adducts suggest that some organic chemicals in diesel exhaust can form DNA adducts in lung tissue and may play a role in the carcinogenic effects. * * * however, DNA adducts alone cannot explain the carcinogenicity of diesel exhaust, and other factors, such as chronic inflammation and cell proliferation, are also important."

Nauss et al. (1995, pp. 35–38) judged that the results observed in the carbon black and TiO_2 inhalation studies on rats do not preclude the possibility that the organic component of dpm has important genotoxic effects in humans. More generally, they also do not prove

that lung overload is necessary for dpm-induced lung cancer. Because of the relatively high doses administered in some of the rat studies, it is conceivable that an overload phenomenon masked or even inhibited other potential cancer mechanisms. At dpm concentrations insufficient to impair clearance, carcinogenesis may have followed other routes, some possibly involving the organic compounds. At these lower concentrations, or among rats for which overload did not occur, tumor rates for dpm, carbon black, and TiO_2 may all have been too low to make statistically meaningful comparisons.

The NMA argued that "MSHA's contention that lung overload might "mask" tumor production by lower doses of dpm has been convincingly rebutted by recognized experts in the field," but provided no convincing explanation of why such masking could not occur. The NMA went on to say:

The [CASAC] Panel viewed the premises that: a) a small tumor response at low exposure was overlooked due to statistical power; and b) soot-associated organic mutagens had a greater effect at low than at high exposure levels to be without foundation. In the absence of supporting evidence, the Panel did not view derivation of a quantitative estimate of human lung cancer risk from the low-level rat data as appropriate.

MSHA is not attempting to "derive a quantitative estimate of human lung cancer risk from the low-level rat data."

Dr. Peter Valberg, writing for the West Virginia Coal Association, provided the following argument for discounting the possibility of other carcinogenic mechanisms being masked by overload in the rat studies:

Some regulatory agencies express concern about the mutagens bound to dpm. They hypothesize that, at high exposure levels, genotoxic mechanisms are overwhelmed (masked) by particle-overload conditions. However, they argue that at low-exposure concentrations, these organic compounds could represent a lung cancer risk. Tumor induction by mutagenic compounds would be characterized by a linear dose-response and should be detectable, given enough exposed rats. By using a "meta-analysis" type of approach and combining data from eight long-term rat inhalation studies, the lung tumor response can be analyzed. When all dpm-exposed rats from lifetime-exposure studies are combined, a threshold of response (noted above) occurs at approximately 600 $\mu\text{g}/\text{m}^3$ continuous lifetime exposure (approximately 2,500 $\mu\text{g}/\text{m}^3$ of occupational exposure). Additional statistical analysis of only those rats exposed to low concentrations of dpm confirms the absence of a tumorigenic effect below that threshold. Thus, even data in rats (the most sensitive laboratory species) do not support the hypothesis that particle-bound organics cause tumors.

MSHA finds that this analysis relies on several questionable and unsupported assumptions and that, for the following reasons, the possibility remains that organic compounds in inhaled dpm may, under the right exposure conditions, contribute to its carcinogenic effects:

(1) The absence of evidence for an organic carbon effect is not equivalent to evidence of the absence of such an effect. Dr. Valberg did not demonstrate that enough rats were exposed, at levels insufficient to cause overload, to ensure detection of a 30- to 40-percent increase in the risk of lung cancer. Also, the normal lifespan of a rat whose lung is not overloaded with particles may, because of the lower concentrations involved, provide insufficient time for the organic compounds to express carcinogenic effects. Furthermore, low bioavailability of the organics could further reduce the likelihood that a carcinogenic sequence of mutations would occur within a rat's relatively short lifespan (i.e., at particle concentrations too low to cause overload).

(2) If the primary mechanism for carcinogenesis requires a reduced clearance rate (due to overload), then acute exposures are important, and it may not be appropriate to represent equivalent hazards by spreading an 8-hour occupational exposures over a 24-hour period. For example, eight hours at 600 $\mu\text{g}/\text{m}^3$ would have different implications for lung clearance than 24 hours at 200 $\mu\text{g}/\text{m}^3$.

(3) Granting that the rat data cannot be used to extrapolate risk for humans, these data should also not be used to rule out mechanisms of carcinogenesis that may operate in humans but not in rats. Clearance, for example, may operate differently in humans than in rats, and there may be a gradual rather than abrupt change in human overload conditions with increasing exposure. Also, at least some of the organic compounds in dpm may be more biologically available to the human lung than to that of the rat.

(4) For experimental purposes, laboratory rats are deliberately bred to be homogeneous. This is done, in part, to deliberately minimize differences in response between individuals. Therefore, individual differences in the threshold for lung overload would tend to be masked in experiments on laboratory rats. It is likely that human populations would exhibit, to a far greater extent than laboratory rats, a range of susceptibilities to lung overload. Also some humans, unlike the laboratory rats in these experiments,

place additional burdens on their lung clearance by smoking.

One commenter (MARG) concluded that "[t]here is * * * no basis for extrapolating the rat results to human beings; the animal studies, taken together, do not justify MSHA's proposals."

MSHA is neither extrapolating the rat results to make quantitative risk estimates for humans nor using them, in isolation, as a justification for these regulations. MSHA does regard it as significant, however, that the evidence for an increased risk of lung cancer due to chronic dpm inhalation comes from both human and animal studies. MSHA agrees that the quantitative results observed for rats in existing studies should not be extrapolated to humans. Nevertheless, the fact that high dpm exposures for two or three years can induce lung cancer in rats enhances the epidemiologic evidence that much longer exposures to miners, at concentrations of the same order of magnitude, could also induce lung cancers.

3. Characterization of Risk

After reviewing the evidence of adverse health effects associated with exposure to dpm, MSHA evaluated that evidence to ascertain whether exposure levels currently existing in mines warrant regulatory action pursuant to the Mine Act. The criteria for this evaluation are established by the Mine Act and related court decisions. Section 101(a)(6)(A) provides that:

The Secretary, in promulgating mandatory standards dealing with toxic materials or harmful physical agents under this subsection, shall set standards which most adequately assure on the basis of the best available evidence that no miner will suffer material impairment of health or functional capacity even if such miner has regular exposure to the hazards dealt with by such standard for the period of his working life.

Based on court interpretations of similar language under the Occupational Safety and Health Act, there are three questions that need to be addressed: (a) Whether health effects associated with dpm exposure constitute a "material impairment" to miner health or functional capacity; (b) whether exposed miners are at significant excess risk of incurring any of these material impairments; and (c) whether the rule will substantially reduce such risks.

Some commenters argued that the link between dpm exposure and material health impairments is questionable, and that MSHA should wait until additional scientific evidence becomes available before concluding

that there are health risks due to such exposure warranting regulatory action. For example, MARG asserted that "[c]ontrary to the suggestions in the [proposed] preamble, a link between dpm exposure and serious illness has never been established by reliable scientific evidence."⁶³ MARG continued as follows:

Precisely because the scientific evidence * * * is inconclusive at best, NIOSH and NCI are now conducting a * * * [study] to determine whether diesel exhaust is linked to illness, and if so, at what level of exposure. * * * MARG is also funding an independent parallel study.

* * * Until data from the NIOSH/NCI study, and the parallel MARG study, are available, the answers to these important questions will not be known. Without credible answers to these and other questions, MSHA's regulatory proposals * * * are premature * * *."

For reasons explained below, MSHA does not agree that the collective weight of scientific evidence is "inconclusive at best." Furthermore, the criteria for evaluating the health effects evidence do not require scientific certainty. As noted by Justice Stevens in an important case on risk involving the Occupational Safety and Health Administration, the need to evaluate risk does not mean an agency is placed into a "mathematical straitjacket." [*Industrial Union Department, AFL-CIO v. American Petroleum Institute*, 448 U.S. 607, 100 S.Ct. 2844 (1980), hereinafter designated the "Benzene" case]. The Court recognized that regulation may be necessary even when scientific knowledge is not complete; and—

so long as they are supported by a body of reputable scientific thought, the Agency is free to use conservative assumptions in interpreting the data * * * risking error on the side of overprotection rather than underprotection. [Id. at 656].

⁶³ MARG supported this assertion by claiming that "[t]he EPA reports which MSHA references in its preamble were found 'not scientifically adequate for making regulatory decisions concerning the use of diesel-powered engines' by EPA's Clean Air Scientific Advisory Committee. [reference to CASAC (1998)]" Contrary to MARG's claim, CASAC (1998) did not review any of the 20 EPA documents MSHA cited in the proposed preamble. Instead, the document reviewed by CASAC (1998) was an unpublished draft of a health risk assessment on diesel exhaust (EPA, 1998), to which MSHA made no reference. Since MSHA has not relied in any way on this 1998 draft document, its "scientific adequacy" is entirely irrelevant to this rulemaking.

In response to the 1998 CASAC review, EPA modified its draft risk assessment (EPA, 1999), and CASAC subsequently reviewed the 1999 draft (CASAC, 2000). CASAC found the revised draft much improved over the previous version and agreed that even environmental exposure to diesel emissions is likely to increase the risk of lung cancer (CASAC, 2000). CASAC endorsed this conclusion for dpm concentrations in ambient air, which are lower, by a factor of more than 100, than the levels observed in some mines (see Fig. III-4).

Moreover, the statutory criteria for evaluating health effects do not require MSHA to wait for incontrovertible evidence. In fact, MSHA is required to set standards based on the "best available evidence" (emphasis added).

a. Material Impairments to Miners' Health or Functional Capacity

MSHA recognizes that there is considerable disagreement, among knowledgeable parties, in the interpretation of the overall body of scientific research and medical evidence related to human health effects of dpm exposures. One commenter for example, interpreted the collective evidence as follows:

* * * the best available scientific evidence shows that diesel particulate exposure is associated with serious material impairment of health. * * * there is *clear* evidence that diesel particulate exposure can cause lung cancer (as well as other serious non-malignant diseases) among workers in a variety of occupational settings. While no body of scientific evidence is ever completely definitive, the evidence regarding diesel particulate is particularly strong * * *. [Michael Silverstein, MD, State of Washington Dept. of Labor and Industries]

Other commenters, including several national and regional organizations representing the mining industry, sharply disagreed with this interpretation. For example, one commenter stated that "[i]n our opinion, the best available evidence does not provide substantial or credible support for the proposal." Several commenters argued that evidence from within the mining industry itself was especially weak.⁶⁴ A representative of one mining company that had been using diesel equipment for many years commented: "[t]o date, the medical history of our employees does not indicate a single case of lung cancer, chronic illness, or material impairment of health due to exposure to diesel exhaust. This appears to be the established norm throughout the U.S. coal mining industry." This commenter, however, submitted no evidence comparing the rate of lung cancer or other material impairment among exposed miners to the rate for unexposed miners (or comparable

workers) of similar age, smoking habits, and geographic location.

With due consideration to all oral and written testimony, comments, and evidence submitted during the rulemaking proceedings, MSHA conducted a review of the scientific literature cited in Part III.2. Based on the combined weight of the best available evidence, MSHA has concluded that underground miners exposed to current levels of dpm are at excess risk of incurring the following three kinds of material impairment: (i) Sensory irritations and respiratory symptoms (including allergenic responses); (ii) premature death from cardiovascular, cardiopulmonary, or respiratory causes; and (iii) lung cancer. The next three subsections will respectively explain MSHA's basis for linking these effects with dpm exposure.

i. Sensory Irritations and Respiratory Symptoms (including allergenic responses). Kahn et al. (1988), Battigelli (1965), Gamble et al. (1987a), and Rudell et al. (1996) identified a number of debilitating acute responses to diesel exhaust exposure. These responses included irritation of the eyes, nose and throat; headaches, nausea, and vomiting; chest tightness and wheeze. These symptoms were also reported by miners at the 1995 workshops and the public hearings held on these proceedings in 1998. In addition, Ulfvarson et al. (1987, 1990) reported evidence of reduced lung function in workers exposed to dpm for a single shift. The latter study supports attributing a portion of the reduction to the dpm in diesel exhaust. After reviewing this body of literature, Morgan et al. (1997) concluded "it is apparent that exposure to diesel fumes in sufficient concentrations may lead to [transient] eye and nasal irritation" and "a transient decline of ventilatory capacity has been noted following such exposures."

One commenter (Nevada Mining Association) acknowledged there was evidence that miners exposed to diesel exhaust experienced, as a possible consequence of their exposure, "acute, short-term or 'transitory' irritation, such as watering eyes, in susceptible individuals * * *"; but asserted that "[a]ddressing any such transient irritant effects does not require the Agency's sweeping, stringent PEL approach [in M/NM mines]."

Although there is evidence that such symptoms subside within one to three days of no occupational exposure, a miner who must be exposed to dpm day after day in order to earn a living may not have time to recover from such effects. Hence, the opportunity for a so-

called "reversible" health effect to reverse itself may not be present for many miners. Furthermore, effects such as stinging, itching and burning of the eyes, tearing, wheezing, and other types of sensory irritation can cause severe discomfort and can, in some cases, be seriously disabling. Also, workers experiencing sufficiently severe sensory irritations can be incapacitated or distracted as a result of their symptoms, thereby endangering themselves and other workers and increasing the risk of accidents. For these reasons, MSHA considers such irritations to constitute "material impairments" of health or functional capacity within the meaning of the Act, regardless of whether or not they are reversible. Further discussion of why MSHA believes reversible effects can constitute material impairments can be found above, in Subsection 2.a.2 of this risk assessment.

The best available evidence also points to more severe respiratory consequences of exposure to dpm. Significant statistical associations have been detected between acute environmental exposures to fine particulates and debilitating respiratory impairments in adults, as measured by lost work days, hospital admissions, and emergency room visits (see Table III-3). Short-term exposures to fine particulates, or to particulate air pollution in general, have been associated with significant increases in the risk of hospitalization for both pneumonia and COPD (EPA, 1996).

The risk of severe respiratory effects is exemplified by specific cases of persistent asthma linked to diesel exposure (Wade and Newman, 1993). Glenn et al. (1983) summarized results of NIOSH health evaluations among coal, salt, trona, and potash miners and reported that "all four of the chronic effects analyses revealed an excess of cough and phlegm among the diesel exposed group." There is persuasive evidence for a causal connection between dpm exposure and increased manifestations of allergic asthma and other allergic respiratory diseases, coming from recent experiments on animals and human cells (Takenaka et al., 1995; Lovik et al., 1997; Takano et al., 1997; Ichinose et al., 1997a). Based on controlled experiments on healthy human volunteers, Diaz-Sanchez et al. (1994, 1996, 1997), Peterson and Saxon (1996), and Salvi et al. (1999) reported significant increases in various markers of allergic response resulting from exposure to dpm.

Peterson and Saxon (1996) reviewed the scientific literature on the relationship between PAHs and other products of fossil fuel combustion found

⁶⁴ At the public hearing on May 11, 1999, a commenter representing MARG suggested there is evidence that miners exposed to dpm experience adverse health effects at lower-than-normal rates. According to this commenter, "[s]ignificantly, the human studies conducted in the mining industry reveal a negative propensity for diesel particulate matter-related health effects." These studies drew comparisons against an external reference population and failed to adjust for the "healthy worker effect." (See MSHA's discussion of this effect, especially as manifested in the study by Christie et al., 1995, in Subsection 2.c.i(2)(a) of this risk assessment.)

in dpm and trends in allergic respiratory disease. They found that the prevalences of allergic rhinitis ("hay fever") and allergic asthma have significantly increased with the historical increase in fossil fuel combustion and that laboratory data support the hypothesis that certain organic compounds found in dpm " * * * are an important factor in the long-term increases in the prevalence in allergic airway disease." Similarly, much of the research on allergenic responses to dpm was reviewed by Diaz-Sanchez (1997), who concluded that dpm pollution in the ambient environment "may play an important role in the increased incidence of allergic airway disease." Morgan et al. (1997) noted that dpm " * * * may be partly responsible for some of the exacerbations of asthma" and that " * * * it would be wise to err on the side of caution." Such health outcomes are clearly "material impairments" of health or functional capacity within the meaning of the Act.

ii. Premature Death from Cardiovascular, Cardiopulmonary, or Respiratory Causes. The evidence from air pollution studies identifies death, largely from cardiovascular, cardiopulmonary, or respiratory causes, as an endpoint significantly associated with acute exposures to fine particulates (PM_{2.5}—see Table III-3). The weight of epidemiologic evidence indicates that short-term ambient exposure to particulate air pollution contributes to an increased risk of daily mortality (EPA, 1996). Time-series analyses strongly suggest a positive effect on daily mortality across the entire range of ambient particulate pollution levels. Relative risk estimates for daily mortality in relation to daily ambient particulate concentration are consistently positive and statistically significant across a variety of statistical modeling approaches and methods of adjustment for effects of relevant covariates such as season, weather, and co-pollutants. The mortality effects of acute exposures appear to be primarily attributable to combustion-related particles in PM_{2.5} (such as dpm) and are especially pronounced for death due to pneumonia, COPD, and IHD (Schwartz et al., 1996). After thoroughly reviewing this body of evidence, the U.S. Environmental Protection Agency (EPA) concluded:

It is extremely unlikely that study designs not yet employed, covariates not yet identified, or statistical techniques not yet developed could wholly negate the large and consistent body of epidemiologic evidence * * *. [EPA, 1996]

There is also substantial evidence of a relationship between chronic exposure to fine particulates (PM_{2.5}) and an excess (age-adjusted) risk of mortality, especially from cardiopulmonary diseases. The Six Cities and ACS studies of ambient air particulates both found a significant association between chronic exposure to fine particles and excess mortality. In some of the areas studied, PM_{2.5} is composed primarily of dpm; and significant mortality and morbidity effects were also noted in those areas. In both studies, after adjusting for smoking habits, a statistically significant excess risk of cardiopulmonary mortality was found in the city with the highest average concentration of PM_{2.5} as compared to the city with the lowest. Both studies also found excess deaths due to lung cancer in the cities with the higher average level of PM_{2.5}, but these results were not statistically significant (EPA, 1996). The EPA concluded that—

* * * the chronic exposure studies, taken together, suggest there may be increases in mortality in disease categories that are consistent with long-term exposure to airborne particles and that at least some fraction of these deaths reflect cumulative PM impacts above and beyond those exerted by acute exposure events * * *. There tends to be an increasing correlation of long-term mortality with PM indicators as they become more reflective of fine particle levels. [EPA, 1996]

Whether associated with acute or chronic exposures, the excess risk of death that has been linked to pollution of the air with fine particles like dpm is clearly a "material impairment" of health or functional capacity within the meaning of the Act.

In a review, submitted by MARG, of MSHA's proposed risk assessment, Dr. Jonathan Borak asserted that "MSHA appears to regard all particulates smaller than 2.5 µg/m³ as equivalent." He argued that "dpm and other ultra-fine particulates represents only a small proportion of ambient particulate samples," that "chronic cough, chronic phlegm, and chronic wheezing reflect mainly tracheobronchial effects," and that tracheobronchial deposition is highly dependent on particle size distribution.

No part of Dr. Borak's argument is directly relevant to MSHA's identification of the risk of death from cardiovascular, cardiopulmonary, or respiratory causes faced by miners exposed to high concentrations of dpm. First, MSHA does not regard all fine particulates as equivalent. However, dpm is a major constituent of PM_{2.5} in many of the locations where increased mortality has been linked to PM_{2.5} levels. MSHA regards dpm as presenting

a risk by virtue of its comprising a type of PM_{2.5}. Second, the studies MSHA used to support the existence of this risk specifically implicate fine particles (i.e., PM_{2.5}), so the percentage of dpm in "total suspended particulate emissions" (which includes particles even larger than PM₁₀) is not relevant. Third, the chronic respiratory symptoms listed by Dr. Borak are not among the material impairments that MSHA has identified from the PM_{2.5} studies. Much of the evidence pertaining to excess mortality is based on acute—not chronic—ambient exposures of relatively high intensity. In the preceding subsection of this risk assessment, MSHA identified various respiratory symptoms, including allergenic responses, but the evidence for these comes largely from studies on diesel emissions.

As discussed in Section 2.a.iii of this risk assessment, many miners smoke tobacco, and miners experience COPD at a significantly higher rate than the general population. This places many miners in two of the groups that EPA (1996) identified as being at greatest risk of premature mortality due to particulate exposures.

iii. Lung Cancer. It is clear that lung cancer constitutes a "material impairment" of health or functional capacity within the meaning of the Act. Therefore, the issue to be addressed in this section is whether there is sufficient evidence (i.e., enough to warrant regulatory action) that occupational exposure to dpm causes the risk of lung cancer to increase.

In the proposed risk assessment, MSHA noted that various national and international institutions and governmental agencies had already classified diesel exhaust or particulate as a probable human carcinogen. Considerable weight was also placed on two comprehensive meta-analyses of the epidemiologic literature, which had both found that the combined evidence supported a causal link. MSHA also acknowledged, however, that some reviewers of the evidence disagreed with MSHA's conclusion that, collectively, it strongly supports a causal connection. As examples of the opposing viewpoint, MSHA cited Stöber and Abel (1996), Watson and Valberg (1996), Cox (1997), Morgan et al. (1997), and Silverman (1998). As stated in the proposed risk assessment, MSHA considered the opinions of these reviewers and agreed that no individual study was perfect: even the strongest of the studies had limitations when viewed in isolation. MSHA nevertheless concluded (in the proposal) that the best available epidemiologic studies, supported by experimental data

showing toxicity, collectively provide strong evidence that chronic dpm exposure (at occupational levels) actually does increase the risk of lung cancer in humans.

Although miners and labor representatives generally agreed with MSHA's interpretation of the collective evidence, many commenters representing the mining industry strongly objected to MSHA's conclusion. Some of these commenters also expressed dissatisfaction with MSHA's treatment, in the proposed risk assessment, of opposing interpretations of the collective evidence—saying that MSHA had dismissed these opposing views without sufficient explanation. Some commenters also submitted new critiques of the existing evidence and of the meta-analyses on which MSHA had relied. These commenters also emphasized the importance of two reports (CASAC, 1998 and HEI, 1999) that both became available after MSHA completed its proposed risk assessment.

MSHA has re-evaluated the scientific evidence relating lung cancer to diesel emissions in light of the comments, suggestions, and detailed critiques submitted during these proceedings. Although MSHA has not changed its conclusion that occupational dpm exposure increases the risk of lung cancer, MSHA believes that the public comments were extremely helpful in identifying areas of MSHA's discussion of lung cancer needing clarification, amplification, and/or additional supportive evidence.

Accordingly MSHA has re-organized this section of the risk assessment into five subsections. The first of these provides MSHA's summary of the collective epidemiologic evidence. Second is a description of results and conclusions from the only two existing peer-reviewed and published statistical meta-analyses of the epidemiologic studies: Bhatia et al. (1998) and Lipsett and Campleman (1999). The third subsection contains a discussion of potential systematic biases that might tend to shift all study results in the same direction. The fourth evaluates the overall weight of evidence for causality, considering not only the collective epidemiologic evidence but also the results of toxicity experiments. Within each of these first four subsections, MSHA will respond to the relevant issues and criticisms raised by commenters in these proceedings, as well as by other outside reviewers. The final subsection will describe general conclusions reached by other reviewers of this evidence, and present some responses by MSHA about opposing

interpretations of the collective evidence.

(1) *Summary of Collective Epidemiologic Evidence.* As mentioned in Section III.2.c.i(2)(a) and listed in Tables III-4 and III-5, MSHA reviewed a total of 47 epidemiologic studies involving lung cancer and diesel exposure. Some degree of association between occupational dpm exposure and an excess rate of lung cancer was reported in 41 of these studies: 22 of the 27 cohort studies and 19 of the 20 case-control studies. Section III.2.c.1(2)(a) explains MSHA's criteria for evaluating these studies, summarizes those on which MSHA places greatest weight, and explains why MSHA places little weight on the six studies reporting no increased risk of lung cancer for exposed workers. It also contains summaries of the studies involving miners, addresses criticisms of individual studies by commenters and reviewers, and discusses studies that, according to some commenters, suggest that dpm exposure does not increase the risk of lung cancer.

Here, as in the earlier, proposed version of the risk assessment, MSHA was careful to note and consider limitations of the individual studies. Several commenters interpreted this as demonstrating a corresponding weakness in the overall body of epidemiologic evidence. For example, one commenter [Energy West] observed that “* * * by its own admission in the preamble * * * most of the evidence in [the epidemiologic] studies is relatively weak” and argued that MSHA's conclusion was, therefore, unjustified.

It should first be noted that the three most recent epidemiologic studies became available too late for inclusion in the risk assessment as originally written. These three (Johnston et al., 1997; Säverin et al., 1999; Brüske-Hohlfeld, 1999) rank among the strongest eight studies available (see Section III.2.c.1(2)(a)) and do not have the same limitations identified in many of the other studies. Even so, MSHA recognizes that no single one of the existing epidemiologic studies, viewed in isolation, provides conclusive evidence of a causal connection between dpm exposure and an elevated risk of lung cancer in humans. Consistency and coherency of results, however, do provide such evidence. An appropriate analogy for the collective epidemiologic evidence is a braided steel cable, which is far stronger than any of the individual strands of wire making it up. Even the thinnest strands can contribute to the strength of the cable.

(a) Consistency of Epidemiologic Results

Although no epidemiologic study is flawless, studies of both cohort and case-control design have quite consistently shown that chronic exposure to diesel exhaust, in a variety of occupational circumstances, is associated with an increased risk of lung cancer. Furthermore, as explained earlier in this risk assessment, limitations such as small sample size, short latency, and (usually) exposure misclassification reduce the power of a study. These limitations make it more difficult to detect a relationship even when one exists. Therefore, the sheer number of studies showing a positive association readily distinguishes those studies criticized by Taubes (1995), where weak evidence is available from only a single study. With only rare exceptions, involving too few workers and/or observation periods too short to have a good chance of detecting excess cancer risk, the human studies have shown a greater risk of lung cancer among exposed workers than among comparable unexposed workers.

Moreover, the fact that 41 out of 47 studies showed an excess risk of lung cancer for exposed workers may itself be a significant result, even if the evidence in most of those 41 studies is relatively weak. Getting “heads” on a single flip of a coin, or two “heads” out of three flips, does not provide strong evidence that there is anything special about the coin. However, getting 41 “heads” in 47 flips would normally lead one to suspect that the coin was weighted in favor of heads. Similarly, results reported in the epidemiologic literature lead one to suspect that the underlying relationship between diesel exposure and an increased risk of lung cancer is indeed positive.

More formally, as MSHA pointed out in the earlier version of this risk assessment, the high proportion of positive studies is statistically significant according to the 2-tailed sign test. Under the “null hypothesis” that there is no systematic bias in one direction or the other, and assuming that the studies are independent, the probability of 41 or more out of 47 studies being either positive or negative is less than one per ten million. Therefore, the sign test rejects, at a very high confidence level, the null hypothesis that each study is equally likely to be positive or negative. This means that the collective results, showing increased risk for exposed workers, are statistically significant at a very high confidence level—regardless

of the statistical significance of any individual study.

MSHA received no comments directly disputing its attribution of statistical significance to the collective epidemiologic evidence based the sign test. However, several commenters objected to the concept that a number of inconclusive studies can, when viewed collectively, provide stronger evidence than the studies considered in isolation. For example, the Engine Manufacturers Association (EMA) asserted that—

[j]ust because a number of studies reach the same conclusion does not make the collective sum of those studies stronger or more conclusive, particularly where the associations are admittedly weak and scientific difficulties exist in each. [EMA]

Similarly, IMC Global stated that

* * * IMC Global does not consider cancer studies with a relative risk of less than 2.0 as showing evidence of a casual relationship between dpm exposure and lung cancer.
* * * Thus while MSHA states [in the proposed risk assessment; now updated to 41 out of 47] that 38 of 43 epidemiologic studies show some degree of association between occupational dpm exposures and lung cancer and considers that fact significant, IMC Global does not. [IMC Global]

Although MSHA agrees that even statistically significant consistency of epidemiologic results is not sufficient to

establish causality, MSHA believes that consistency is an important part of establishing that a suspected association is causal.⁶⁵ Many of the commenters objecting to MSHA's emphasis on the collective evidence failed to distinguish the strength of evidence in each individual study from the strength of evidence in total.

Furthermore, weak evidence (from just one study) should not be confused with a weak effect. As Dr. James Weeks pointed out at the public hearing on Nov. 19, 1998, a 40-percent increase in lung cancer is a strong effect, even if it may be difficult to detect in an epidemiologic study.

Explicable differences, or heterogeneity, in the magnitudes of relative risk reported from different studies should not be confused with inconsistency of evidence. For example, as described by Silverman (1998), one of the available meta-analyses (Bhatia et al., 1998) "examined the primary sources of heterogeneity among studies and found that a main source of

⁶⁵ With respect to the IMC Global's blanket rejection of studies showing a relative risk less than 2.0, please see also the related discussions in Subsection 2.c.i(2)(a) above, under the heading of "Potential Confounders," and in Subsection 3.a.iii(3) below, entitled "Potential Systemic Biases."

heterogeneity is the variation in diesel exhaust exposure across different occupational groups." Figures III-5 and III-6, taken from Cohen and Higgins (1995), respectively show relative risks reported for the two occupations on which the most studies are available: railroad workers and truck drivers.

Each of these two charts compares results from studies that adjusted for smoking to results from studies that did not make such an adjustment. For each study, the point plotted is the estimated relative risk or odds ratio, and the horizontal line surrounding it represents a 95-percent confidence interval. If the left endpoint of a confidence interval exceeds 1.0, then the corresponding result is statistically significant at a 95-percent confidence level.

The two charts show that the risk of lung cancer has consistently been elevated for exposed workers and that the results are not significantly different within each occupational category. Differences in the magnitude and statistical significance of results within occupation are not surprising, since the groups studied differed in size, average exposure intensity and duration, and the time allotted for latent effects.

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Figure III-5

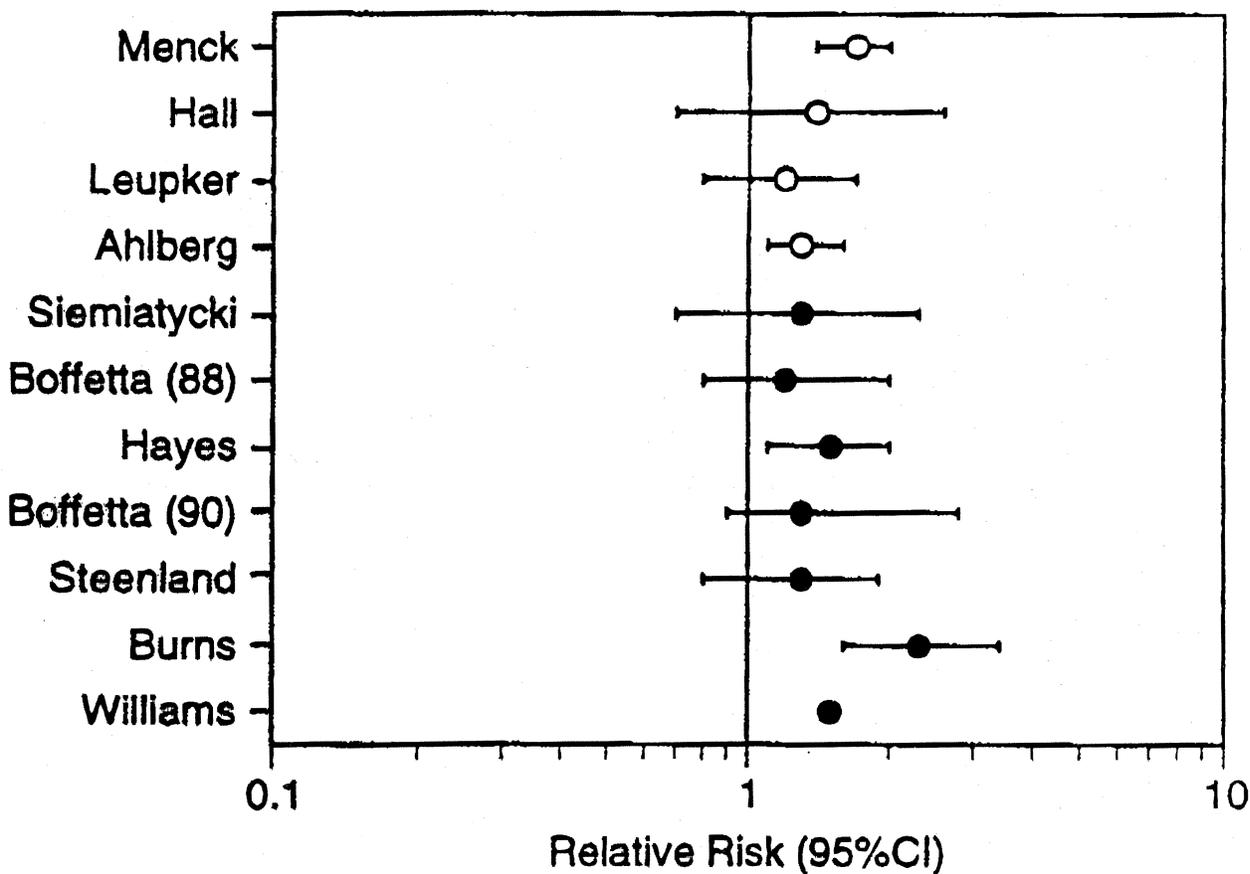


Figure . Lung cancer and exposure to diesel exhaust in truck drivers. ● = RR adjusted for cigarette smoking; ○ = RR not adjusted for cigarette smoking. For the study by Williams, CIs were not reported and could not be calculated. For the Steenland study, the data were gathered from union reports of long-haul truckers; for the Boffetta (1988) study, the data were self-reported by diesel truck drivers; and for the Siemiatycki study, they were self-reported by heavy-duty truck drivers (personal communication).

Figure III-6

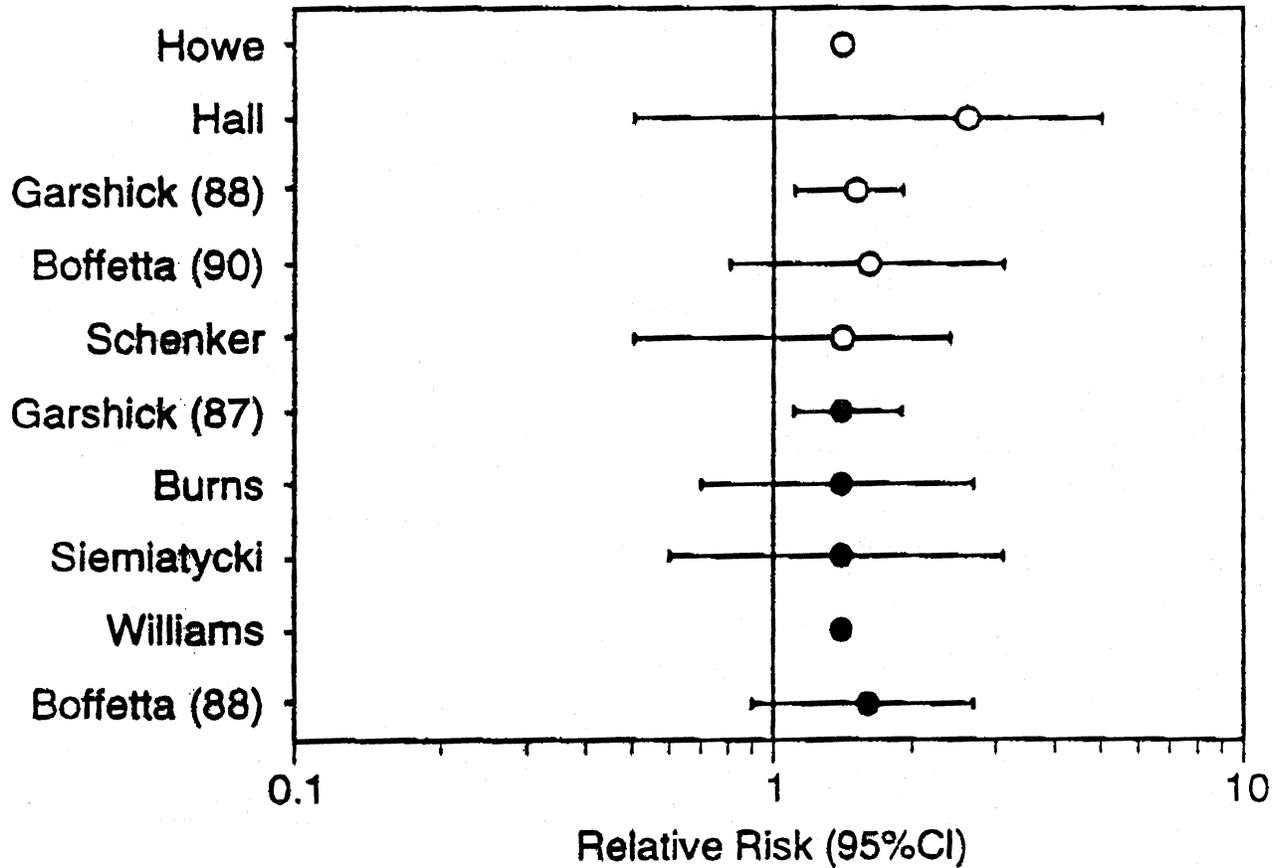


Figure III-6. Lung cancer and exposure to diesel exhaust in railroad workers.
 ● = RR adjusted for cigarette smoking; ○ = RR not adjusted for cigarette smoking. For the two studies by Howe and Williams, CIs were not reported and could not be calculated.

As documented in Subsection 2.c.i(2)(a) of this risk assessment, all of the studies showing negative associations were either based on relatively short observation or follow-up periods, lacked good information about dpm exposure, involved low duration or intensity of dpm exposure, or, because of inadequate sample size or latency allowance, lacked the power to detect effects of the magnitude found in the "positive" studies. Boffetta *et al.* (1988, p. 404) noted that, in addition, studies failing to show a statistically significant association—

* * * often had low power to detect any association, had insufficient latency periods, or compared incidence or mortality rates among workers to national rates only, resulting in possible biases caused by the "healthy worker effect."

Some commenters noted that limitations such as insufficient duration of exposure, inadequate latency allowance, small worker populations, exposure misclassification, and comparison to external populations with no adjustment for a healthy worker effect may explain why not all of the studies showed a statistically significant association between dpm exposure and an increased prevalence of lung cancer. According to these commenters, if an epidemiologic study shows a statistically significant result, this often occurs in spite of methodological weaknesses rather than because of them. MSHA agrees that limitations such as those listed make it more difficult to obtain a statistically significant result when a real relationship exists.

(b) Best Available Epidemiologic Evidence

As explained above, it is statistically significant that 41 of the 47 available epidemiologic studies reported an elevated risk of lung cancer for workers exposed to dpm. MSHA finds it even more informative, however, to examine the collective results of the eight studies identified in Section III.2.c.i(2)(a) as providing the best currently available epidemiologic evidence. These studies, selected using the criteria described earlier, are: Boffetta *et al.* (1988), Boffetta *et al.* (1990), Brüske-Hohlfeld *et al.* (1999), Garshick *et al.* (1987), Garshick *et al.* (1988, 1991), Johnston *et al.* (1997), Steenland *et al.* (90, 92, 98), and Säverin *et al.*, (1999). All eight of these studies reported an increased risk of lung cancer for workers with the longest diesel exposures and for those most likely to have been exposed, compared to unexposed workers. Tables showing the results from each of these

studies are provided in Section III.2.c.1(2)(a).

The sign test of statistical significance can also be applied to the collective results of these eight studies. If there were no underlying association between exposure to diesel exhaust and an increased risk of lung cancer, or anything else systematically favoring a positive result, then there should be equal probabilities (equal to one-half) that any one of these eight studies would turn out positive or negative. Therefore, under the null hypothesis that positive and negative results are equally likely, the probability that all eight studies would show either a positive or a negative association is $(0.5)^8 = 0.0039$, or 0.39 percent. This shows that the collective results of the eight studies comprising the best available epidemiologic evidence are statistically significant at a confidence level exceeding 99 percent (i.e., $100 - 2 \times 0.39$).

When the risk of disease or death increases in response to higher cumulative exposures, this is described by a "positive" exposure-response relationship. Like consistency of results, the existence of a positive exposure-response relationship is important in establishing that the exposures in question actually cause an increase in risk. Among the eight studies MSHA has identified as comprising the best available epidemiologic evidence, there are five that provide evidence of increasing lung cancer risk with increasing cumulative exposure: Boffetta, *et al.* (1990), Brüske-Hohlfeld *et al.* (1999), Johnston *et al.* (1997), Säverin *et al.* (1999), and Steenland *et al.* (1990, 1992, 1998). The results supporting such a relationship are provided in the table accompanying discussion of each of these studies in Section III.2.c.i(2)(a).

Although some have interpreted the results from the two studies by Garshick *et al.* as also providing evidence of a positive exposure-response relationship (e.g., Cal-EPA, 1998), this interpretation is highly sensitive to the statistical models and techniques used to analyze the data (HEI, 1999; Crump 1999). Therefore, for purposes of this risk assessment, MSHA is not relying on Garshick *et al.* (1987) or Garshick *et al.* (1988, 1991) to demonstrate the existence of a positive exposure-response relationship. MSHA used the study for purposes of hazard identification only. The Garshick studies contributed to the weight of evidence favoring a causal interpretation, since they show statistically significant excesses in lung cancer risk for the exposed workers.

The relative importance of the five studies identified in demonstrating the existence of a positive exposure-response relationship varies with the quality of exposure assessment. Boffetta *et al.* (1990) and Brüske-Hohlfeld *et al.* (1999) were able to show such a relationship based on the estimated duration of occupational exposure for exposed workers, but quantitative measures of exposure intensity (i.e., dpm concentration) were unavailable. Although duration of exposure is frequently used as a surrogate of cumulative exposure, it is clearly preferable, as many commenters pointed out, to base estimates of cumulative exposure and exposure-response analyses on quantitative measurements of exposure levels combined with detailed work histories. Positive exposure-response relationships based on such data were reported in all three studies: Johnston *et al.* (1997), Steenland *et al.* (1998), and Säverin *et al.* (1999).

(c) Studies With Quantitative or Semiquantitative Exposure Assessments

Several commenters stressed the fact that most of the available epidemiologic studies contained little or no quantitative information on diesel exposures and that those studies containing such information (such as Steenland *et al.*, 1998) generated it using questionable assumptions. Some commenters also faulted MSHA for insufficiently addressing this issue. For example, one commenter stated:

* * * the Agency fails to highlight the lack of acceptable (or any) exposure measurements concurrent with the 43 epidemiology studies cited in the Proposed Rule. * * * the lack of concurrent exposure data is a significant deficiency of the epidemiology studies at issue and is a major factor that prevents application of those epidemiology results to risk assessment. [EMA]

MSHA agrees that the nature and quality of exposure information should be an important consideration in evaluating the strength of epidemiologic evidence. That is why MSHA included exposure assessment as one of the criteria used to evaluate and rank studies in Section 2.c.1(2)(a) of this risk assessment. Two of the most recent studies, both conducted specifically on miners, utilize concurrent, quantitative exposure data and are included among the eight in MSHA's selection of best available epidemiologic evidence (Johnston *et al.*, 1997 and Säverin *et al.*, 1999). As a practical matter, however, epidemiologic studies rarely have concurrent exposure measurements; and, therefore, the commenter's line of

reasoning would exclude nearly all of the available studies from this risk assessment—including all six of the negative studies. Since Section 101(a)(6) of the Mine Act requires MSHA to consider the “best available evidence” (emphasis added), MSHA has not excluded studies with less-than-ideal exposure assessments, but, instead, has taken the quality of exposure assessment into account when evaluating them. This approach is also consistent with the recognition by the HEI Expert Panel on Diesel Emissions and Lung Cancer 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).

The degree of quantification, however, is not the only relevant consideration in evaluating studies with respect to exposure assessment. MSHA also considered the likely effects of potential exposure misclassification. As expressed by another commenter:

* * * [S]tudies that * * * have poor measures of exposure to diesel exhaust have problems in classification and will have weaker results. In the absence of information that misclassification is systematic or differential, in which case study results would be biased towards either positive or no-effect level, it is reasonable to assume that misclassification is random or nondifferentiated. If so, * * * study results are biased towards a risk ratio of 1.0, a ratio showing no association between diesel exhaust exposure and the occurrence of lung cancer. [Dr. James Weeks, representing UMWA]

In her review of Bhatia *et al.* (1998), Silverman (1998) proposed that “[o]ne approach to assess the impact of misclassification would be to exclude studies without quantitative or semiquantitative exposure data.” According to Dr. Silverman, this would leave only four studies among those considered by Dr. Bhatia: Garshick *et al.* (1988), Gustavsson *et al.* (1990), Steenland *et al.* (1992), and Emmelin *et al.* (1993).⁶⁶ All four of these studies showed higher rates of lung cancer for the workers estimated to have received the greatest cumulative exposure, as compared to workers who had accumulated little or no diesel exposure. Statistically significant results were reported in three of these four studies. Furthermore, the two more recent studies utilizing fully quantitative exposure assessments (Johnston *et al.*, 1997; Säverin *et al.*, 1999) were not evaluated or otherwise considered in the articles by Drs. Bhatia

and Silverman. Like the other four studies, these too reported elevated rates of lung cancer for workers with the highest cumulative exposures. Specific results from all six of these studies are presented in Tables III-4 and III-5.

Once again, the sign test of statistical significance can be applied to the collective results of the four studies identified by Dr. Silverman plus the two more recent studies with quantitative exposure assessments. As before, under the null hypothesis of no underlying effect, the probability would equal one-half that any one of these six studies would turn out positive or negative. The probability that all six studies would show either a positive or a negative association would, under the null hypothesis, be $(0.5)^6 = 0.0156$, or 1.56 percent. This shows that the collective results of these six studies, showing an elevated risk of lung cancer for workers estimated to have the greatest cumulative exposure, are statistically significant at a confidence level exceeding 96 percent (i.e., $100 - 2 \times 1.56$).

As explained in the previous subsection, three studies showing evidence of increased risk with increasing exposure based on quantitative or semi-quantitative exposure assessments are included in MSHA’s selection of best available epidemiologic evidence: Johnston *et al.* (1997), Steenland *et al.* (1998), and Säverin *et al.* (1999). Not only do these studies provide consistent evidence of elevated lung cancer risk for exposed workers, they also each provide evidence of a positive exposure-response relationship—thereby significantly strengthening the case for causality.

(d) Studies Involving Miners

Eleven studies involving miners are summarized and discussed in Section 2.c.i(2)(a) of this risk assessment. Commenters’ observations and criticisms pertaining to the individual studies in this group are also addressed in that section. Three of these studies are among the eight in MSHA’s selection of best available epidemiologic evidence: (Boffetta *et al.*, 1988; Johnston *et al.*, 1997; Säverin *et al.*, 1999). All three of these studies provide evidence of an increased risk of lung cancer for exposed miners. Although MSHA places less weight on the remaining eight studies, seven of them show some evidence of an excess lung cancer risk among the miners involved. The remaining study (Christie *et al.*, 1995) reported a greater all-cause SMR for the coal miners involved than for a comparable population of petroleum workers but did not compare the miners

to a comparable group of workers with respect to lung cancer.

The NMA submitted a review of six of these studies by Dr. Peter Valberg, who concluded that “[t]hese articles do not implicate diesel exhaust, per se, as strongly associated with lung cancer in miners * * * The reviewed studies do not form a consistent and cohesive picture implicating diesel exhaust as a major risk factor for miners.” Similarly, Dr. Jonathan Borak reviewed six of the studies on behalf of MARG and concluded:

[T]he strongest conclusion that can be drawn from these six studies is that the miners in those studies had an increased risk of lung cancer. These studies cannot relate such increased [risk] to any particular industrial exposure, lifestyle or combination of such factors.

Apparently, neither Dr. Valberg nor Dr. Borak disputed MSHA’s observation that the miners involved in the studies they reviewed exhibited, overall, an excess risk of lung cancer. It is possible that any excess risk found in epidemiologic studies may be due to extraneous unknown or uncontrolled risk factors (i.e., confounding variables). However, neither Drs. Valberg or Borak, nor the NMA or MARG, offered evidence, beyond a catalog of speculative possibilities, that the excess lung cancer risk for these miners was due to anything other than dpm exposure.

Nevertheless, MSHA agrees that the studies reviewed by Drs. Valberg and Borak do not, by themselves, conclusively implicate dpm exposure as the causal agent. Miners are frequently exposed to other occupational hazards associated with lung cancer, such as radon progeny, and it is not always possible to distinguish effects due to dpm exposure from effects due to these other occupational hazards. This is part of the reason why MSHA did not restrict its consideration of evidence to epidemiologic studies involving miners. What implicates exposure to diesel exhaust is the fact that diesel-exposed workers in a variety of different occupations, under a variety of different working conditions (including different types of mines), and in a variety of different geographical areas consistently exhibit an increased risk of lung cancer.

Drs. Valberg and Borak did not review the two studies that utilize quantitative dpm exposure assessments: Johnston *et al.* (1997) and Säverin *et al.* (1999). In recently received comments Dr. Valberg, writing for the NMA brought up four issues on the Säverin *et al.* 1999. These issues were potential exposure misclassification, potential flaws in the sampling method, potential smoker

⁶⁶ Emmelin *et al.* (1993) was considered but excluded from the meta-analysis by Bhatia *et al.* (1998) for reasons explained by the authors.

misclassification, and insufficient latency. Two of these issues have already been extensively discussed in section 2.c.i.2.a.ii and therefore will not be repeated here. Dr. Valberg suggested that the potential flaw in the sampling method would tend to over-estimate exposure and that there was insufficient latency. If, in fact, both of these issues are relevant, they would act to UNDERESTIMATE the lung cancer risk in this cohort instead of

OVERESTIMATE it. MSHA regards these, along with Boffetta et al. (1988), Burns and Swanson (1991),⁶⁷ and Lerchen et al. (1987) to be the most informative of the available studies involving miners. Results on miners from these five studies are briefly summarized in the following table, with additional details provided in Section 2.c.1(2)(a) and Tables III-4 and III-5 of

⁶⁷ Listed in Table III-5 under Swanson et al., 1993.

this risk assessment. The cumulative exposures at which relative risks from the Johnston and Säverin studies are presented are equivalent, assuming that TC constitutes 80 percent of total dpm. The cumulative dpm exposure of 6.1 mg-yr/m³ is the multiplicative product of exposure duration and dpm concentration for the most highly exposed workers in each of these two studies.

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Results from best available studies involving miners.

Study	Mine Type	Exposure Assessment	Smoking Adjustm't	Result
Boffetta et al. (1988)	various	Occupational history	yes	RR = 2.67 for miners, compared to workers never employed in diesel -exposed occupations. [†]
Burns and Swanson (1991)	unknown	Occupational history	yes	OR = 5.03 for mining machinery operators. [†]
Johnston et al. (1997)	UG coal	Occupational history & indirect dpm measurements	yes	For cumulative dpm exposure = 6.12 mg-yr/m ³ : RR = 5.5 using mine-adjusted statistical model; RR= 11.0 using mine-unadjusted statistical model.
Lerchen et al. (1987)	various	Occupational history	yes	OR = 2.1 for underground non-uranium mining.
Säverin et al. (1999)	UG potash	Occupational history & TC measurements	smoking uncorrelated with TC within cohort	RR = 2.17 for most highly exposed group, compared to least exposed group. For cumulative TC exposure = 4.9 mg-yr/m ³ : RR = 1.16 to 2.70 depending on statistical model.

[†]Statistically significant at a 95-percent confidence level.

Although MSHA places less weight on the studies by Burns and Swanson and by Lerchen than on the other three, it is significant that the five best available studies involving miners all support an increased risk of lung cancer attributable to dpm exposure.

(2) Meta-Analyses

MSHA recognizes that simply tabulating epidemiologic studies as positive or negative can sometimes be misleading. There are generally a variety of outcomes that could render a study positive or negative, some studies contain different analyses of related data sets, some studies involve multiple comparisons of various subgroups, and the studies differ widely in the reliability of their results. Therefore, MSHA is not limiting its assessment of the epidemiologic evidence to such a tabulation or relying only on the sign test described above. MSHA has also considered the results of two statistical meta-analyses covering most of the available studies (Lipsett and Campleman, 1999; Bhatia *et al.*, 1998). These meta-analyses weighted and pooled independent results from those studies meeting certain inclusion requirements to form overall estimates of relative risk for exposed workers based on the combined body of data. In addition to forming pooled estimates of the effect of diesel exposure, both meta-analyses analyzed sources of heterogeneity in the individual results and investigated but rejected publication bias as an explanation for the generally positive results reported. Both meta-analyses derived a statistically significant increase of 30 to 40 percent in the risk of lung cancer, attributable to occupational dpm exposure.

Lipsett and Campleman (1999) systematically analyzed and combined results from most of the studies summarized in Tables III-4 and III-5. Forty-seven studies published between 1957 and 1995 were identified for initial consideration. Some studies were excluded from the pooled analysis because they did not allow for a period of at least 10 years for the development of clinically detectable lung cancer. Others were excluded because of bias resulting from incomplete ascertainment of lung cancer cases in cohort studies or because they examined the same cohort population as another study. One study was excluded because standard errors could not be calculated from the data presented. The remaining 30 studies, contributing a total of 39 separate estimates of exposure effect (for distinct occupational groups within studies),

were analyzed using a random-effects analysis of variance (ANOVA) model.

Potential effects of publication bias (*i.e.*, the likelihood that papers with positive results may be more likely to be published than those with negative results) were investigated by plotting the logarithm of relative risk estimated from each study against its estimated precision, as expressed by the inverse of its standard error. According to the authors, the resulting "funnel plot" was generally consistent with the absence of significant publication bias, although there were relatively few small-scale, statistically insignificant studies. The investigators performed a further check of potential publication bias by comparing results of the included studies with the only relevant unpublished report that became available to them during the course of their analysis. Smoking-adjusted relative risks for several diesel-exposed occupations in the unpublished study were, according to the investigators, consistent with those found in the studies included in the meta-analysis.

Each of the 39 separate estimates of exposure effect was weighted by a factor proportional to its estimated precision. Sources of heterogeneity in results were investigated by subset analysis—using categorical variables to characterize each study's design, target population (general or industry-specific), occupational group, source of control or reference population, latency, duration of exposure, method of ascertaining occupation, location (North America or Europe), covariate adjustments (age, smoking, and/or asbestos exposure), and absence or presence of a clear healthy worker effect (as manifested by lower than expected all-cause mortality in the occupational population under study).

Sensitivity analyses were conducted to evaluate the sensitivity of results to inclusion criteria and to various assumptions used in the analysis. This included (1) substitution of excluded "redundant" studies of the same cohort population for the included studies and (2) exclusion of studies involving questionable exposure to dpm. An influence analysis was also conducted to examine the effect of dropping one study at a time, to determine if any individual study had a disproportionate effect on results of the ANOVA.

The pooled relative risk from all 39 exposure effects (estimated from 30 studies) was RR = 1.33, with a 95-percent confidence interval (CI) extending from 1.21 to 1.46. For the subgroup of 13 smoking-adjusted exposure effects (nine studies) from populations "most likely to have had substantial exposure" to dpm, the

pooled effect was RR = 1.47, with a CI from 1.29 to 1.67. Based on all of the various analyses they conducted, the authors concluded:

Although substantial heterogeneity existed in the initial pooled analysis, stratification on several factors substantially reduced heterogeneity, producing subsets of studies with increased relative risk estimates that persisted through various influence and sensitivity analyses. * * *

In studies that adjusted for confounding by cigarette smoking, not only did the positive association between diesel exhaust exposure and lung cancer persist but the pooled risk estimate showed a modest increase, with little evidence of heterogeneity.

* * * [T]his meta-analysis provides quantitative evidence consistent with several prior reviews, which have concluded that the epidemiologic evidence supports a causal relationship between occupational exposure to diesel exhaust and lung cancer. [Lipsett and Campleman, 1999]

The other meta-analysis was conducted by Bhatia *et al.* (1998) on epidemiologic studies published in peer-reviewed journals between 1957 and 1993. In this analysis, studies were excluded if actual work with diesel equipment "could not be confirmed or reliably inferred" or if an inadequate latency period was allowed for cancer to develop, as indicated by less than 10 years from time of first exposure to end of follow-up. Studies of miners were also excluded, because of potential exposure to radon and silica. Likewise, studies were excluded if they exhibited selection bias or examined the same cohort population as a study published later. A total of 29 independent results on exposure effects from 23 published studies were identified as meeting the inclusion criteria.

To address potential publication bias, the investigators identified several unpublished studies on truck drivers and noted that elevated risks for exposed workers observed in these studies were similar to those in the published studies utilized. Based on this and a "funnel plot" for the included studies, the authors concluded that there was no indication of publication bias.

After assigning each of the 29 separate estimates of exposure effect a weight proportional to its estimated precision, Bhatia *et al.* (1998) used a fixed-effects ANOVA model to calculate pooled relative risks based on the following groupings: all 29 results; all case-control studies; all cohort studies; cohort studies using internal reference populations; cohort studies making external comparisons; studies adjusted for smoking; studies not adjusted for smoking; and studies grouped by occupation (railroad workers,

equipment operators, truck drivers, and bus workers). Elevated risks of lung cancer were shown for exposed workers overall and within every individual group of studies analyzed. A positive duration-response relationship was observed in those studies presenting results according to employment duration. The weighted, pooled estimates of relative risk were identical for case-control and cohort studies and nearly identical for studies with or without smoking adjustments.

The pooled relative risk from all 29 exposure effects (estimated from 23 studies) was RR = 1.33, with a 95-percent confidence interval (CI), adjusted for heterogeneity, extending from 1.24 to 1.44. For just the smoking-adjusted studies, it was 1.35 (CI: 1.20 to 1.52); and for cohort studies making internal comparisons, it was 1.43 (CI: 1.29 to 1.58). Based on their evaluation of the all the analyses on various subgroups, Bhatia *et al.* (1998) concluded that the elevated risk of lung cancer observed among exposed workers was unlikely to be due to chance, that confounding from smoking was unlikely to explain all of the excess risk, and that "this meta-analysis supports a causal association between increased risks for lung cancer and exposure to diesel exhaust."

The pooled relative risks estimated in both meta-analyses equal 1.33 and exceed 1.4 for studies making internal comparisons, or comparisons to similar groups of workers. Both meta-analyses found these results to be statistically significant, meaning that they cannot be explained merely by random or unexplained variability in the risk of lung cancer that occurs among both exposed and unexposed workers. Although both meta-analyses relied, by necessity, on an overlapping selection of studies, the inclusion criteria were different and some studies included in one meta-analysis were excluded from the other. They used different statistical models for deriving a pooled estimate of relative risk, as well as different means of analyzing heterogeneity of effects. Nevertheless, they derived the same estimate of the overall exposure effect and found similar sources of heterogeneity in the results from individual studies.⁶⁸ One commenter observed that—

⁶⁸ Several commenters suggested that because the two meta-analyses both received direct or indirect funding from the same governmental agency, they were not independently conducted. These commenters speculated that Dr. Allan Smith, a co-author of Cal-EPA (1998) and Bhatia *et al.* (1998), contributed to both meta-analyses. Although an earlier version of Lipsett and Campleman (1999) appeared as an appendix to Cal-EPA (1998),

Lung cancer relative risks for occupational "control groups" vary over a range from 0.4 to 2.7 * * *. Therefore, the level of relative risks being reported in the dpm epidemiology fall within this level of natural variation. [IMC Global]

This argument is refuted by the statistical significance of the elevation in risk detected in both meta-analyses in combination with the analyses accounting for heterogeneity of exposure effects.

The EMA objected that MSHA's focus on these two meta-analyses "presents an incomplete picture because the counter-arguments of Silverman (1998) were not discussed in the same detail." IMC global also faulted MSHA for dismissing Dr. Silverman's views without adequate explanation.

In her review,⁶⁹ Dr. Silverman characterized Bhatia *et al.* (1998) as a "careful meta-analysis" and acknowledged that it "add[s] to the credibility that diesel exhaust is carcinogenic * * *." She also explicitly endorsed several of its most important conclusions. For example, Dr. Silverman stated that "[t]he authors convincingly show that potential confounding by cigarette smoking is likely to have little impact on the estimated RRs for diesel exhaust and lung cancer." She suggested, however, that Bhatia *et al.* (1998) "ultimately do not resolve the question of causality." (Silverman, 1998)

Dr. Silverman imposed an extremely high standard for what is needed to ultimately resolve the question of causality. The precise question she posed, along with her answer, was as follows:

Has science proven causality *beyond any reasonable doubt?* Probably not. [Silverman, 1998, emphasis added.]

Neither the Mine Act nor applicable case law requires MSHA to prove causality "beyond any reasonable doubt." The burden of proof that Dr. Silverman would require to close the case and terminate research is not the same burden of proof that the Mine Act requires to warrant protection of miners subjected to far higher levels of a probable carcinogen than any other occupational group. In this risk assessment, MSHA is evaluating the collective weight of the best available

commenters provided no evidence that Dr. Smith contributed anything to that appendix. Dr. Smith is not listed as a co-author of Lipsett and Campleman (1999).

⁶⁹ Silverman (1998) reviewed Bhatia *et al.* (1998) but not Lipsett and Campleman (1999) or the earlier version of that meta-analysis (Lipsett and Alexeeff, 1998) cited in MSHA's proposed preamble.

evidence—not seeking proof "beyond any reasonable doubt."⁷⁰

The EMA objected to MSHA's reliance on the two meta-analyses because of " * * * serious deficiencies in each" but did not, in MSHA's opinion, identify any such deficiencies. The EMA pointed out that "most of the original studies in each were the same, and the few that were not common to each were not of significance to the outcome of either meta-analysis." MSHA does not regard this as a deficiency. Since the object of both meta-analyses was to analyze the available epidemiologic evidence linking dpm exposure with lung cancer, using defensible inclusion criteria, it is quite understandable that they would rely on overlapping information. The principal differences were in the types and methods of statistical analysis used, rather than in the data subjected to analysis; and MSHA considers it informative that different approaches yielded very similar results and conclusions. It is noteworthy, moreover, that both of the meta-analyses explicitly addressed the EMA's concern by performing analyses on various different sub-groupings of the available studies. The sensitivity of results to the inclusion criteria was also explicitly investigated and considered. MSHA believes that the conclusions of these meta-analyses did not depend on unreasonable inclusion or exclusion criteria.

The EMA also argued that—

[a] meta-analysis cannot compensate for basic deficiencies in the studies used to create the meta-analysis, and this fact is not clearly stated by MSHA. Instead, MSHA follows the tack of the meta-analysis authors, who claim that the meta-analysis somehow overcomes deficiencies of the individual studies selected and presents a stronger case. This is simply not true. [EMA]

MSHA agrees that a meta-analysis cannot correct for all deficiencies that may be present in individual studies. It

⁷⁰ It is noteworthy that, in describing research underway that might resolve the issue of causality, Dr. Silverman stressed the need for studies with quantitative exposure measurements and stated that "underground miners may, in fact, be the most attractive group for study because their exposure to diesel exhaust is at least five times greater than that of previously studied occupational groups." (Silverman, 1998) She then mentioned a study on underground miners in Germany that had recently been initiated. The study of German underground potash miners (Säverin *et al.*, 1999), published after Dr. Silverman's article, utilizes quantitative exposure measurements and is included in MSHA's selection of best available epidemiologic evidence (see Section 3.a.iii(1)(a) of this risk assessment). MSHA also includes in that selection another underground miner study utilizing quantitative exposure measurements (Johnston *et al.*, 1997). The 1997 study was available prior to Dr. Silverman's article but is not listed among her references.

can, however, correct for certain types of deficiencies. For example, individual studies may lack statistical power because of small study populations. By pooling results from several such studies, a meta-analysis may achieve a level of statistical significance not attainable by the individual studies. Furthermore, both of the meta-analyses used well-defined inclusion criteria to screen out those studies with the most severe deficiencies. In addition, they both found that it was the more rigorous and technically more valid studies that reported the strongest associations between excess lung cancer and dpm exposure. They also performed separate analyses that ruled out inflationary effects of such "deficiencies" as lack of a smoking adjustment. For example, Lipsett and Campleman (1999) reported a pooled RR = 1.43 for 20 smoking-adjusted results, as compared to a pooled RR = 1.25 for 19 results with no smoking adjustment.

IMC Global and MARG submitted five specific criticisms of the meta-analyses, to which MSHA will respond in turn.

(1) Publication Bias

* * * both studies * * * rely only on published studies. * * * the authors rely on statistical analysis in an attempt to uncover possible publication bias. * * * the only safeguard to protect against possible publication bias is to seek out unpublished results * * *. [IMC Global]

Both meta-analyses compared the results of published and unpublished studies and found them to be similar. Bhatia *et al.* (1998) found several unpublished studies of lung cancer among truck drivers that " * * * were not included in our analysis; however the risk ratios of these studies are similar to the [sic] those in published studies among truck drivers." (Bhatia *et al.*, p. 90) Lipsett and Campleman (1999) checked "[s]moking-adjusted relative risks for several diesel-exposed occupations" in an unpublished report on U.S. veterans and found them " * * * consistent with those reported here." They remarked that "although publication bias cannot be completely ruled out, it is an unlikely explanation for our findings." (Lipsett and Campleman, p. 1015) In addition to comparing results directly against unpublished studies, both meta-analyses used the statistical method of "funnel plots" as an indirect means of checking for the existence of significant publication bias. It should also be noted that MSHA did not exclude unpublished studies from this risk assessment.

(2) Selection Bias

* * * [the] meta-analyses have to provide a much more convincing rationale as to why all miners were excluded even when the confounders that are mentioned are not likely or important, for example in studies conducted in potash and salt mines. * * * IMC Global sees no reason why the older studies of potash workers [Waxweiler *et al.*, 1973] and more recent studies on New South Wales coal miners [Christie *et al.*, 1995] should not be included * * *. [IMC Global]

Studies were selectively included or excluded, without good or sufficient explanation. [MARG]

Contrary to the commenters' characterization, both meta-analyses listed each study excluded from the analysis of pooled relative risk and gave a good reason for its exclusion. For example, both meta-analyses excluded studies that failed to allow for a minimum 10-year latency period for lung cancer to develop after first exposure. With respect to the exclusion of all studies on miners, Bhatia *et al.* (1998) pointed out that "[s]ince studies of miners often indicate higher relative risks for lung cancer than those considered in this meta-analysis, this was a conservative exclusion." Even if studies on miners had been considered, Waxweiler *et al.* (1973) and Christie *et al.* (1995) would have been excluded from both meta-analyses because of their failure to meet the 10-year minimum latency requirement.

(3) Lack of Actual Exposure Data

* * * [N]ondifferential exposure or disease misclassification can sometimes produce bias away from the null * * * Thus, tests for heterogeneity performed in both these meta-analyses won't detect or correct this problem. [IMC Global]

Lipsett and Campleman acknowledged that "[e]xposure misclassification is a problem common to all studies of cancer and diesel emissions. In no case were there direct measurements of historical diesel exhaust exposures of the subjects." However, as Dr. Silverman pointed out in her review, " * * * this bias is most likely to be nondifferential, and the effect would probably have been to bias point estimates toward the null value. Thus the summary RR of 1.33 may be an underestimate of the true lung cancer effect associated with diesel exposure." (Silverman, 1998)

(4) Smoking as a Confounder

* * * The use of data manipulation and modeling adjustments in both these meta-analyses cannot rectify the flaws in the initial studies. [IMC Global]

* * * misclassification of this exposure [cigarette smoking] could result in residual confounding of individual studies and,

consequently, meta-analyses, of those studies. [MARG]

Contrary to the commenter's suggestion, neither of the meta-analyses made any attempt to manipulate or adjust the data in order to rectify what the commenter regards as "flaws" in the way smoking or other potential confounders were treated in the initial studies. Both meta-analyses, however, compared the pooled RR for studies with a smoking adjustment to the pooled RR for studies without any such adjustment. Both meta-analysis calculated a pooled RR for the smoking-adjusted studies greater than or equal to that for the unadjusted studies. In addition, Bhatia *et al.* (1998) analyzed the impact of the smoking adjustment for the subgroup of studies reporting results both with and without such an adjustment and found that the "small reduction in the pooled RR estimates would not be consistent with a major effect from residual confounding." Dr. Silverman concluded that "[t]he authors convincingly show that potential confounding by cigarette smoking is likely to have little impact on the estimated RRs for diesel exhaust and lung cancer." (Silverman, 1998)

(5) Inadequate Control in the Underlying Studies for Diet

As noted by Lipsett and Campleman, "Diet may also confound the diesel-lung cancer association." The researchers also caution that this risk factor was not controlled for in the nearly 50 diesel studies they examined. [MARG]

Since inhalation is the primary route of dpm exposure, and the lung is the primary target organ, MSHA considers potential dietary confounding to be of minor importance in the diesel-lung cancer association. Lipsett and Campleman acknowledged that diet might be a relevant consideration for long-haul truck drivers, but stated that "diet would probably not be an important confounder in studies of other occupations, particularly those using internal or other occupationally active reference populations." Studies making internal comparisons, or comparisons to similar groups of workers, are unlikely to be seriously confounded by dietary differences, because the groups of workers being compared are likely to have very similar dietary habits, on average. The pooled relative risk for cohort studies making comparisons internally or to other active workers was 1.48 (95% CI = 1.28 to 1.70). (Lipsett and Campleman, 1999, Table 3) This was considerably higher than the pooled RRs for studies making comparisons against regional or national populations, where dietary differences

(and also differences with respect to other potential confounders) would be more important.

(3) Potential Systematic Biases

Citing failure to account for dietary differences as an example, some commenters argued that the meta-analyses may simply propagate weaknesses shared by the individual studies. These commenters contended that many of the studies MSHA considered in this risk assessment share methodological similarities and that, therefore, a "deficiency" causing bias in one study would probably also bias many other studies in the same direction. According to these commenters, no matter how great a majority of studies report a 30- to 40-percent increase in the risk of lung cancer for exposed workers, the possibility of systematic bias prevents the collective evidence from being strong or sufficient.

Although this point has some theoretical foundation, it has no basis in fact for the particular body of epidemiologic evidence relating lung cancer to diesel exposure. The studies considered were carried out by many different researchers, in different countries, using different methods, and involving a variety of different occupations. Elevated risk was found in cohort as well as case-control studies, and in studies explicitly adjusting for potential confounders as well as studies relying on internal comparisons within homogeneous populations. The possibility that systematic bias explains these results is also rendered less plausible by results from studies of a radically different type: the elevated risk of lung cancer associated with chronic environmental exposures to PM_{2.5} (Dockery *et al.* 1993; Pope *et al.*, 1995).

Furthermore, the commenters advancing this argument presented no evidence that the studies shared any deficiencies of a type that would systematically shift results in the direction of showing a spurious association. As explained in Subsection 2.c.i(2)(a), exposure misclassification, healthy worker effect, and low power due to insufficient latency generally have the opposite effect—systematically diluting and masking results. Although many studies may share a similar susceptibility to bias by dietary differences or residual smoking effects,⁷¹ there is no reason to expect that such effects will consistently bias

results in the same direction, across all occupations and geographic regions.

Associations between dpm exposure and excess lung cancer are evident in a wide variety of occupational and geographical contexts, and it is unlikely that all (or most) would be biased in the same direction by lifestyle effects. There is no reason to suppose that, in nearly all of these studies, exposed subjects were more likely than unexposed subjects to have lifestyles (apart from their occupations) that increased their risk of lung cancer. On the other hand, exposures to other occupational carcinogens, such as asbestos dust, radon progeny, and silica, could systematically cause studies in which they are not taken into account to exhibit spurious associations between lung cancer and occupational diesel exhaust exposures. Silica dust and radon progeny are frequently present in mining environments (though not usually in potash mines), and this was the reason that studies on miners were excluded from the two meta-analyses.

IMC Global argued that because of the possibility of being misled by systematic biases, epidemiologic evidence can be used to identify only those hazards that, at a minimum, double the risk of disease (i.e., RR \geq 2.0). IMC Global explained this viewpoint by quoting an epidemiologist as follows:

* * * [E]pidemiologic methods can only yield valid documentation of large relative risks. Relative risks of low magnitude (say, less than 2) are virtually beyond the resolving power of the epidemiologic microscope. We can seldom demonstrably eliminate all sources of bias, and we can never exclude the possibility of unidentified and uncontrolled confounding. If many studies—preferably based on different methods—are nevertheless congruent in producing markedly elevated relative risks, we can set our misgivings aside. If however, many studies produce only modest increases, those increases may well be due to the same biases in all the studies. [Dr. Samuel Shapiro, quoted by IMC Global]

It is important to note that, unlike IMC Global, Dr. Shapiro did not suggest that results of RR < 2.0 be counted as "negative." He contended only that low RRs do not completely rule out the possibility of a spurious association due to unidentified or uncontrolled confounding. More importantly, however, this restriction would allow workers to be exposed to significant risks and is, therefore, unacceptable for regulatory purposes. For purposes of protecting miners from lung cancer, certainty is not required; and an increase in the relative risk of less than 100 percent can increase the absolute risk of lung cancer by a clearly unacceptable amount. For example, if

the baseline risk of lung cancer is six per thousand, then increasing it by 33 percent amounts to an increase of two per thousand for exposed workers.

IMC Global went on to argue that—

* * * only a few of these studies have relative risks that exceed 2.0, and some of the studies that do exceed 2.0 exhibit biases that make them unsuitable for rulemaking purposes in our opinion. * * * Thus, in IMC Global's opinion, the epidemiologic evidence demonstrates an artificial association that can be explained through common biases probably due to smoking habits and lifestyle factors. [IMC Global]

This line of reasoning leaps from the *possibility* that systematic biases might account for observed results to a conclusion that they actually do so. Furthermore, after proposing to allow for possible biases by requiring that only relative risks in excess of 2.0 be counted as positive evidence, IMC Global has ignored its own criterion and discounted results greater than 2.0 for the same reason. Contrary to IMC Global's claim that "only a few of the studies have relative risks that exceed 2.0," Tables III-4 and III-5 show 23 separate results greater than 2.0, applying to independent categories of workers in 18 different studies.

According to Stöber and Abel (1996), the potential confounding effects of smoking are so strong that "residual smoking effects" could explain even statistically significant results observed in studies where smoking was explicitly taken into account. MSHA agrees that variable exposures to non-diesel lung carcinogens, including relatively small errors in smoking classification, could bias individual studies. However, the potential confounding effect of tobacco smoke and other carcinogens can cut in either direction. Spurious positive associations of dpm exposure with lung cancer would arise only if the group exposed to dpm had a greater exposure to these confounders than the unexposed control group used for comparison. If, on the contrary, the control group happened to be more exposed to confounders, then this would tend to make the association between dpm exposure and lung cancer appear negative. Therefore, although smoking effects could potentially distort the results of any single study, this effect could reasonably be expected to make only about half the studies that were explicitly adjusted for smoking come out positive. Smoking is unlikely to have been responsible for finding an excess prevalence of lung cancer in 17 out of 18 studies in which a smoking adjustment was applied. Based on a 2-tailed sign test, this possibility can be

⁷¹The term "residual smoking effects" refers to the potentially confounding effects of smoking that may remain after a smoking adjustment has been made.

rejected at a confidence level greater than 99.9 percent.

Even in the 29 studies for which no smoking adjustment was made, tobacco smoke and other carcinogens were important confounders only to the extent that the populations exposed and unexposed to diesel exhaust differed systematically with respect to these other exposures. Twenty-four of these studies, however, reported some degree of excess lung cancer risk for the diesel-exposed workers. This result could be attributed to other occupational carcinogens only in the unlikely event that, in nearly all of these studies, diesel-exposed workers happened to be more highly exposed to these other carcinogens than the control groups of workers unexposed to diesel.

Like IMC Global, Stöber and Abel (1996) do not, in MSHA's opinion, adequately distinguish between a *possible* bias and an *actual* one. Potential biases due to extraneous risk factors are unlikely to account for a significant part of the excess risk in all studies showing an association. Excess rates of lung cancer were associated with dpm exposure in all epidemiologic studies of sufficient size and scope to detect such an excess. Although it is possible, in any individual study, that the potentially confounding effects of differential exposure to tobacco smoke or other carcinogens could account for the observed elevation in risk otherwise attributable to diesel exposure, it is unlikely that such effects would give rise to positive associations in 41 out of 47 studies. As stated by Cohen and Higgins (1995):

* * * elevations [of lung cancer] do not appear to be fully explicable by confounding due to cigarette smoking or other sources of bias. Therefore, at present, exposure to diesel exhaust provides the most reasonable explanation for these elevations. The association is most apparent in studies of occupational cohorts, in which assessment of exposure is better and more detailed analyses have been performed. The largest relative risks are often seen in the categories of most probable, most intense, or longest duration of exposure. In general population studies, in which exposure prevalence is low and misclassification of exposure poses a particularly serious potential bias in the direction of observing no effect of exposure, most studies indicate increased risk, albeit with considerable imprecision. [Cohen and Higgins (1995), p. 269].

Several commenters identified publication bias as another possible explanation for the heavy preponderance of studies showing an elevated risk of lung cancer for exposed workers. As described earlier, both of the available meta-analyses investigated and rejected the hypothesis of

significant publication bias affecting the overall results. This was based on both a statistical technique using "funnel plots" and a direct comparison between results of published and unpublished studies. Commenters presented no evidence that publication bias actually exists in this case. After the 1988 NIOSH and 1989 IARC determinations that diesel exhaust was a "potential" or "probable" human carcinogen, negative results would have been of considerable interest, and, in the absence of any evidence specifically applying to dpm studies, there is no reason to assume they would not have been published.

(4) Causality

MSHA must draw its conclusions based on the weight of evidence. In the absence of any statistical evidence for differential confounding or significant publication bias, the weight of epidemiologic evidence strongly favors a causal connection. On the one side, it is evident that virtually all of the studies that adjusted for smoking and other known confounders, or controlled for them by comparing against similar groups of workers, showed positive associations (i.e., relative risk or odds ratio > 1.0). Also on this side of the balance are all eight of the studies MSHA identified as comprising the best available human evidence. These include three studies reporting positive exposure-response relationships based on quantitative dpm exposure assessments: two recent studies specifically on underground miners (one coal and one potash) and one on trucking industry workers.⁷² On the other side of the balance is the possibility that publication bias or other systematic biases may have been responsible for some unknown portion of the overall 30- to 40-percent elevation in lung cancer risk observed—a possibility that, while conceivable, is based on speculation. After considering other viewpoints (addressed here and in the next subsection), MSHA has accepted what in its view is the far more likely alternative: that the vast majority of epidemiologic studies showed an elevated risk in association with occupational exposures to diesel exhaust because such exposures cause the risk of lung cancer to increase. The toxicity experiments discussed in Subsection 2.d.iv of this risk assessment support the causal interpretation that MSHA has placed on the associations observed in epidemiologic studies.

⁷² These studies (respectively: Johnston et al., 1997; Säverin et al., 1999; Steenland et al., 1998) are discussed in detail in Subsection 2.c.i(2)(a) of this risk assessment.

In this risk assessment, MSHA is basing its conclusions primarily on epidemiologic studies. However, the results obtained from animal studies confirm that diesel exhaust can increase the risk of lung cancer in some species and help show that dpm (rather than the gaseous fraction of diesel exhaust) is the causal agent. The fact that dpm has been proven to cause lung cancer in laboratory rats only under conditions of lung overload does not make the rat studies irrelevant to miners. The very high dpm concentrations currently observed in some mines could impair or even overwhelm lung clearance for miners already burdened by respirable mineral dusts, thereby inducing lung cancer by a mechanism similar to what occurs in rats (Nauss et al., 1995). It must also be noted, however, that most of the human studies show an increased risk of lung cancer at dpm levels lower than what might be expected to cause overload. Therefore, the human studies suggest that overload is not a necessary condition for dpm to induce or promote lung cancer among humans. Salvi et al. (1999) reported marked inflammatory responses in the airways of healthy human volunteers after just one hour of exposure to dpm at a concentration of 300 µg/m³. Animal studies provide evidence that inhalation of dpm has related effects, such as induction of free oxygen radicals, that could promote the development of human lung cancers by mechanisms not requiring lung overload. (See Sec. III.2.d.iv(2).)

Similarly, the weight of genotoxicity evidence helps support a causal interpretation of the associations observed in the epidemiologic studies. This evidence shows that dpm dispersed by alveolar surfactant can have mutagenic effects, thereby providing a genotoxic route to carcinogenesis that is independent of overloading the lung with particles. After a comprehensive review of the evidence, IPCS (1996) concluded that both the particle core and the associated organic materials have biological activity. The biological availability of carcinogens present in the organic portion of dpm may, however, differ significantly in different species. Chemical byproducts of phagocytosis, which occurs even when the lung is not overloaded, may provide another genotoxic route. Inhalation of diesel emissions has been shown to cause DNA adduct formation in peripheral lung cells of rats and monkeys, and increased levels of human DNA adducts have been found in association with occupational exposures. (See Sec. III.2.d.iv(1)) None of this evidence

suggests that a lung cancer threshold exists for humans exposed to dpm, despite its importance in the rat model. Nor does this evidence suggest that lung overload is necessary for dpm to induce lung cancer in humans. Indeed, lung overload may be only one of many mechanisms through which lung cancer is produced in humans.

Results from the epidemiologic studies, the animal studies, and the genotoxicity studies are coherent and mutually supportive. After considering all these results, MSHA has concluded that the epidemiologic studies, supported by the experimental data establishing the plausibility of a causal connection, provide strong evidence that chronic occupational dpm exposure increases the risk of lung cancer in humans.

In a review, submitted by MARG, of MSHA's proposed risk assessment, Dr. Jonathan Borak asserted that MSHA's determination that results from the epidemiologic and toxicity studies were "coherent and mutually reinforcing" involved circular reasoning. He supported this assertion by incorrectly attributing to MSHA the view that "most of the individual [epidemiologic] studies are not very good" and that their suggestion of an association between dpm and lung cancer is "made credible in light of the animal data." To complete his argument that MSHA relied on circular reasoning, Dr. Borak then suggested that the epidemiologic data provided MSHA's sole basis for considering the animal data relevant to humans. In a similar vein, Kennecott Minerals claimed there was an "absence of toxicological support for epidemiologic findings that are themselves inconclusive."

Contrary to Dr. Borak's assertion, MSHA has not characterized most of the epidemiologic studies as "not very good." Nor has MSHA suggested that the epidemiologic evidence would not be credible or plausible in the absence of supporting animal data. As Dr. Borak correctly noted, MSHA acknowledged that "none of the existing human studies is perfect" and that "no single one of the existing epidemiological studies, viewed in isolation, provides conclusive evidence of a causal connection * * *." That a study is not "perfect," however, does not imply that it is "not very good." MSHA's position has consistently been that, as demonstrated by the two available meta-analyses, the collective epidemiologic evidence is not merely credible but statistically significant and indicative of a causal association. Although MSHA views the toxicity data as supporting and reinforcing the epidemiologic

evidence, MSHA believes that the collective epidemiologic evidence is highly credible in its own right.

Furthermore, MSHA does not consider the animal data relevant to humans simply because of the positive epidemiologic evidence. The animal evidence is also credible in its own right. As MSHA has repeatedly pointed out, dust concentrations in some mines have been measured at levels of the same order of magnitude as those found to have caused lung cancer in rats. Such high exposures, especially when combined with occupational exposures to respirable mineral dusts and exposures to particles in tobacco smoke, could overload the human lung and promote lung cancer by a mechanism similar to that hypothesized for rats. (Hattis and Silver, 1992, Figures 9, 10, 11). Also, many of the animal experiments have elucidated genotoxic effects that, while apparently not responsible for the excess lung cancers observed for rats, may be responsible for some or all of the excess risk reported for humans.

MSHA has not relied on circular reasoning. If either the animal data or the toxicity data had failed to show any link between dpm and effects implicated in the induction or promotion of lung cancer, then MSHA's conclusion would have been weakened. The existence of experimental evidence confirming that there is such a link is not imaginary and is logically independent of the epidemiologic evidence. Therefore, contrary to Dr. Borak's characterization, the "coherency and reinforcement" arising from the epidemiologic, animal, and genotoxicity data are not the product of circular reasoning. A more apt description is that the three sources of evidence, like three legs of a tripod, support the same conclusion.

Many commenters argued that a causal connection between dpm exposure and an increased human risk of lung cancer should not be inferred unless there is epidemiologic evidence showing a positive exposure-response relationship based on quantitative measures of cumulative dpm exposure. MSHA does not agree that a quantitative exposure-response relationship is essential in establishing causality. Such a relationship is only one of several factors, such as consistency and biological plausibility, that epidemiologists examine to provide evidence of causality. As mentioned earlier, however, there are three studies providing quantitative exposure-response relationships. One of these studies (Steenland et al., 1998) controlled for age, race, smoking, diet,

and asbestos exposure, but relied on "broad assumptions" to estimate historical exposure levels from later measurements. Two of the studies, however, (Johnston et al., 1997, and Säverin et al., 1999) utilized measurements that were either contemporaneous with the exposures (Johnston) or that were made under conditions very similar to those under which the exposures took place (Säverin). Both of these studies were conducted on underground miners. The Säverin study used exposure measurements of total carbon (TC). All three of the studies combined exposure measurements for each job with detailed occupational histories to form estimates of cumulative dpm exposure; and all three reported evidence of increasing lung cancer risk with increasing cumulative exposure.

Several commenters, expressing and endorsing the views of Dr. Peter Valberg, incorrectly asserted that the epidemiologic results obtained across different occupational categories were inconsistent with a biologically plausible exposure-response relationship. For example, MARG argued that—

It is biologically implausible that, if dpm were (causally) increasing lung cancer risk by 50% for a low exposure (say, truck drivers), then the lung cancer risk produced by dpm exposure in more heavily exposed worker populations (railroad shop workers) would fall in this same range of added risk. The added lung-cancer risk for bus garage workers is half that of either railroad workers or truck drivers, but dpm concentrations are considerably higher. [MARG]

Earlier, MARG had argued to the contrary that, due to their lack of concurrent exposure measurements, these studies could not reliably be used for hazard identification. MARG then attempted to use them to perform the rather more difficult task of making quantitative comparisons of relative risk. If cumulative exposures are unknown, as MARG argued elsewhere, then there is little basis for comparing responses at different cumulative exposures.

In an analysis submitted by the West Virginia Coal Association, Dr. Valberg extended this argument to miners as follows:

* * * If dpm concentrations for truck drivers is in the range of 5–50 $\mu\text{g}/\text{m}^3$, then we can assign the 0.49 excess risk (Bhatia's meta-analysis result) to the 5–50 $\mu\text{g}/\text{m}^3$ exposure. Hence, dpm concentrations for miners in the range of 100–2,000 $\mu\text{g}/\text{m}^3$ should have yielded excess risks forty times larger, meaning that the RR for exposed miners would be expected to be about 21 (i.e., 1 + 19.6), whereas reported risk estimates are less than 3 (range from 0.74

2.67). Such an utter lack of concordance argues against a causal role for dpm in the reported epidemiologic associations.

Based on a similar line of reasoning, IMC Global asserted that “* * * the assumptions that MSHA used to develop [Figure III-4] * * * do not do make sense in the context of a dose-response relationship between lung cancer and dpm exposure.” This was one of the reasons IMC Global gave for objecting to MSHA’s comparison (in Section III.1.d) of exposure levels measured for miners to those reported for different occupations. IMC Global proposed that, as a consequence of this argument, MSHA should delete this comparison from its risk assessment.

MSHA sees three major flaws in Dr. Valberg’s argument and rejects it for the following reasons:

(1) The argument glosses over the important distinction between exposure concentrations (intensity) and cumulative exposure (dose). Total cumulative exposure is the product of intensity and duration of exposure. Depending on duration, high intensity exposure may result in similar (or even lower) cumulative exposure than low intensity exposure. Furthermore, different industries, in different nations, introduced diesel equipment at different times. The studies being considered were carried out in a variety of different countries and covered a variety of different historical periods. Therefore, the same number of years in different studies can correspond to very different durations of occupational exposure.

Many of the miners in the studies Dr. Valberg considered may have been occupationally exposed to dpm for relatively short periods of time or even not at all. Various forms of exposure misclassification would tend to obscure any exposure-response relationship across industries. Such obscuring would result from both exposure misclassification within individual studies and also variability in the degree of exposure misclassification in different industries.

Furthermore, the exposure levels or intensities assigned to the various occupations would not necessarily be proportional to cumulative exposures, even if the average number of years of exposure were the same. Different job conditions, such as longer-than-average work hours, could have major, variable impacts on cumulative exposures. For example, lower dpm concentrations have been measured for truck drivers than for other occupationally-exposed workers. But as a group, the truck drivers who were studied, due to their work conditions, may have been in their trucks for longer than the standard 40-

hour work week and therefore have larger cumulative dpm exposures. These truck drivers commonly congregated in parking areas and slept in their trucks with the engines idling, thereby disproportionately increasing their cumulative dpm exposures compared to miners and other types of workers.

(2) The commenters advancing this argument assumed that an exposure-response relationship spanning occupations at different levels of exposure intensity would take the form of a straight line. This assumption is unwarranted, since carcinogens do not necessarily follow such a simple pattern across a broad range of exposure levels. There is little basis for assuming that the relationship between cumulative dpm exposures and the relative risk of lung cancer would appear as a straight line when plotted against exposure levels that may differ by a factor of 100. Steenland et al. (1998) reported a better statistical “fit” to the data using a model based on the logarithm of cumulative exposure as compared to simple cumulative exposure. Even across the relatively limited range of exposures within the trucking industry, the logarithmic exposure model exhibits pronounced curvature towards the horizontal at the higher cumulative exposures (Steenland et al., 1998, Fig. 5). If this model is extrapolated out to the much higher exposures currently found in underground mining, then (as shown in Subsection 3.b.ii(3)(b) of this risk assessment) it diverges even more from a straight-line model.

Toxicological evidence of curvature in the dose-response relationship has also been reported (Ichinose et al., 1997b, p. 190).

Furthermore, the exposure-response pattern may depend on other aspects of exposure, besides how much is accumulated. For example, the National Research Council (NRC) has adopted a risk model for radon-induced lung cancer in which the relative risk (RR) at any age depends on both accumulated exposure and the rate (reflecting the intensity of exposure) at which total exposure was accumulated. In this model, which was derived empirically from the epidemiologic data, exposures accumulated over long time periods at relatively low rates result in a greater risk of lung cancer than the same total exposures accumulated over shorter time periods at relatively higher rates (NRC, 1999). A similar effect for dpm could cause apparent anomalies in the pattern of relative risks observed for occupations ranked simply with respect to the intensity of their average exposures.

(3) Mean exposures and relative risks reported for miners involved in the available studies were mischaracterized. Although dpm levels as high as 2000 $\mu\text{g}/\text{m}^3$ have been measured in some mines, the levels at most mines surveyed by MSHA were substantially lower (see Figures III-1 and III-2). The average levels MSHA measured at underground mines were 808 $\mu\text{g}/\text{m}^3$ and 644 $\mu\text{g}/\text{m}^3$ for M/NM and coal mines using diesel equipment for face haulage, respectively (Table III-1). However, these were not necessarily the levels experienced by miners involved in the available studies. The mean TC exposure concentration reported by Säverin et al. (1999), for work locations having the highest mean concentration, was 390 $\mu\text{g}/\text{m}^3$ —corresponding to a mean dpm concentration of about 490 $\mu\text{g}/\text{m}^3$. In the only other study involving miners for which exposure measurements were available, Johnston et al. (1997) reported dpm concentrations for the most highly exposed category of workers (locomotive drivers), ranging from 44 $\mu\text{g}/\text{m}^3$ to 370 $\mu\text{g}/\text{m}^3$. Therefore, the mean dpm concentration experienced by the most highly exposed miners involved in these two studies was not “forty times larger” than the level imputed to truck drivers, but closer to seven times larger.⁷³ Applying Dr. Valberg’s procedure, this yields an “expected” relative risk of about 4.4 for the underground miners who happened to work at mines included in these particular studies ($1 + 7 \times (0.49)$). Miners exposed at higher levels would, of course, face a greater risk.

Dr. Valberg asserted that the highest relative risk reported for miners was 2.67 (from Boffetta et al., 1988). Dr. Valberg failed to note, however, that the upper 95-percent confidence limit for miners’ relative risk in this study was 4.37, so that this result hardly qualifies as an “utter lack of concordance” with the 4.4 “expected” value for miners. Furthermore, even higher relative risks for miners have been reported in other studies. Burns and Swanson (1991) reported 5.0 for operators of mining machinery, with an upper 95-percent confidence limit of 16.9. The relative risk estimated for the most highly exposed miners in the study by Johnston et al. (1997) was either 5.5 or 11.0, depending on the statistical model used. These results appear to be quite consistent with the data for truck drivers.

⁷³ The estimate of seven times larger dpm exposure in miners is the result of averaging data from Säverin et al. (1999) with data from Johnston et al. (1997) and comparing the combined average miner dpm exposure to the average truck driver dpm exposure.

(5) Other Interpretations of the Evidence

After reviewing the same body of scientific evidence as MSHA, Dr. Peter Valberg came to a very different conclusion with respect to the likelihood of causality:

Flawed methodology (lack of adequate control for smoking); values for relative risks ("RR") that are low and often not statistically elevated above 1.0; inadequate treatment of sources of variability; reliance on multiple comparisons; and inadequate control over how authors choose to define dpm exposure surrogates (that is, job category within a profession, cumulative years of work, age at time of exposure, etc.), all undermine the assignment of causality to dpm exposure.

On the other hand, many scientific organizations and governmental agencies have reviewed the available epidemiologic and toxicological evidence for carcinogenicity and, in accordance with MSHA's conclusion, identified dpm as a probable human carcinogen—at levels far lower than those measured in some mines—or placed it in a comparable category. These include:

YEAR

2000 National Toxicology Program (NTP);
1999 (tentative) U.S. Environmental Protection Agency (EPA)

1998 (tentative) (American Conference of Governmental Industrial Hygienists (ACGIH); Currently on Y2K NIC list. Probable vote in 10/2000.

1998 California Environmental Protection Agency (Cal-EPA);

1998 Federal Republic of Germany;

1996 International Programme on Chemical Safety (IPCS), a joint venture of the World Health Organization, the International Labour Organization, and the United Nations Environment Programme;

1989 International Agency for Research on Cancer (IARC);

1988 National Institute for Occupational Safety and Health (NIOSH).

Nevertheless, several commenters strongly objected to MSHA's conclusion, claiming that the evidence was obviously inadequate and citing scientific authorities who, they claimed, rejected MSHA's inference of a causal connection. In some cases, views were inaccurately attributed to these authorities, and misleading quotations were presented out of context. For example, the Nevada Mining Association stated that its own review of the scientific literature led to—

* * * the only reasonable conclusion possible: there is no scientific consensus that there is a causal link between dpm exposure and lung cancer. The HEI [1999 Expert Panel] report concludes that the causal link between diesel exhaust and lung cancer remains unproven, and that further study and analysis are clearly required. [Nevada Mining Assoc.]

Although HEI (1999) recommended further study and analysis for purposes of quantitative risk assessment, the report contains no findings or conclusions about the "causal link." To the contrary, the report explicitly states that the panel "* * * was not charged to evaluate either the broad toxicologic or epidemiologic literature concerning exposure to diesel exhaust and lung cancer for hazard identification purposes, which has been done by others." (HEI, 1999, p. 1) Furthermore, the HEI panel "* * * recognize[d] 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. 20)

MARG, along with the Nevada Mining Association and several other commenters, mischaracterized the Expert Panel's findings as extending beyond the subject matter of the report. This report was limited to evaluating the suitability of the data compiled by Garshick et al. (1987, 1988) and Steenland et al. (1990, 1992, 1998) for quantitative risk assessment. Contrary to the characterization by these commenters, HEI's Expert Panel explicitly stated:

[The Panel] was not charged to evaluate the broad toxicologic or epidemiologic literature for hazard identification purposes, which has been done by others. State, national, and international agencies have all reviewed the broader animal and human evidence for carcinogenicity and, in either their draft or final reports, have all identified diesel exhaust as [a] probable human carcinogen or placed it in a comparable category." [HEI, 1999, p. 1]

The Panel then identified most of the organizations and governmental institutions listed above (HEI, 1999, p. 8).

One commenter (MARG) also grossly misrepresented HEI (1999) as having stated that "the available epidemiologic work has 'study design flaws, including uncontrolled, confounding and lack of exposure measures, leading to a lack of convincing evidence.'" (MARG post-hearing comments) The opinion falsely attributed to HEI was taken from a sentence in which HEI's Diesel Epidemiology Expert Panel was describing opinions expressed in "[s]ome reviews critical of these data." (HEI, 1999, p. 10) The Panel did not suggest that these opinions were shared by HEI or by any members of the Panel. In fact, the cited passage came at the end of a paragraph in which the Panel cited a larger number of other review articles that had "discusse[d] this literature in depth" and had expressed no such opinions. In the same paragraph, the Panel confirmed that

"[t]he epidemiologic studies generally show higher risks of lung cancer among persons occupationally exposed to diesel exhaust than among persons who have not been exposed, or who have been exposed to lower levels or for shorter periods of time." (HEI, 1999, p. 10)

Several commenters noted that the U.S. EPA's Clean Air Scientific Advisory Committee (CASAC) issued a report (CASAC, 1998) critical of the EPA's 1998 draft Health Assessment Document for Diesel Emissions (EPA, 1998) and rejecting some of its conclusions. After the HEI (1999) Expert Panel report was published, the EPA distributed a revised draft of its Health Assessment Document (EPA, 1999). In the 1999 draft, the EPA characterized human exposures to diesel exhaust as "highly likely" to be carcinogenic to humans at ambient (i.e., environmental) exposure levels. After reviewing this draft, CASAC endorsed a conclusion that, at ambient levels, diesel exhaust is likely to be carcinogenic to humans. Although CASAC voted to recommend that the designation in the EPA document be changed from "highly likely" to "likely," this change was recommended specifically for ambient rather than occupational exposures. The CASAC report states that "[a]lthough there was mixed opinion regarding the characterization of diesel emissions as 'highly likely' to be a human carcinogen, the majority of the Panel did not agree that there was sufficient confidence (i.e., evidence) to use the descriptor 'highly' in regard to environmental exposures." (CASAC, 2000, emphasis added)

MSHA recognizes that not everyone who has reviewed the literature on lung cancer and diesel exposure agrees about the collective weight of the evidence it presents or about its implications for regulatory decisions. IMC Global, for example, stated:

After independently reviewing most [of the] * * * epidemiologic studies, the literature reviews and the two meta-analyses, IMC Global believes * * * MSHA has misrepresented the epidemiologic evidence in the Proposed Rule. The best conclusion that we can reach based on our review of this information is that different reputable studies reach conflicting conclusions * * *. [IMC Global]

IMC Global continued by expressing concern that MSHA had "dismissed" opposing arguments critical of the positive studies, especially "regarding lack of statistical significance; small magnitudes of relative risk * * *; and the impact of confounding factors, especially smoking * * *." [IMC Global]

MSHA has addressed these three issues, as they relate to the evaluation of individual studies, in Section 2.c.i(2)(a) of this preamble. The argument that confounding factors such as smoking may have been systematically responsible for the positive results was discussed above, under the heading of "Potential Systematic Biases." Statistical significance of the collective evidence is not the same thing as statistical significance of individual studies. Application of the sign test, as described Subsection 3.a.iii(1) above, is one way that MSHA has addressed statistical significance of the collective evidence. Another approach was also described above, under the heading of "Meta-Analyses."

IMC Global quoted Morgan et al. (1997) as concluding that "[a]lthough there have been a number of papers suggesting that diesel fumes may act as a carcinogen, the weight of the evidence is against this hypothesis." This conclusion was based largely on the authors' contention, shared by IMC Global, that the epidemiologic results were inconsistent and of insufficient strength (i.e., $RR < 2.0$) to rule out spurious associations due to potential confounders. MSHA, on the other hand, interprets the epidemiologic studies as remarkably consistent, given their various limitations, and has argued that the strength of evidence from individual studies is less important than the strength of evidence from all studies combined. Dr. Debra Silverman has referred to the "striking consistency" of this evidence. (Silverman, 1998)

Ironically, Morgan et al. point out many of the very limitations in individual studies that may actually explain why the studies do not yield entirely equivalent results. The 1997 Morgan article was written before the meta-analyses became available and resolved many, if not all, of the apparent inconsistencies in the epidemiologic results. Since none of the existing human studies is perfect and many contain important limitations, it is not surprising that reported results differ in magnitude and statistical significance. The meta-analyses described earlier showed that the more powerful and carefully designed studies tended to show greater degrees of association. MSHA has addressed the joint issues of consistency and strength of association above, under the heading of "Consistency of Epidemiologic Evidence."

The Engine Manufacturers Association (EMA) quoted Cox (1997) as concluding: "* * * there is no demonstrated biological basis for

expecting increased risk at low to moderate levels of [diesel] exposure." (Cox, 1997, as quoted by EMA) The EMA, however, prematurely terminated this quotation. The quoted sentence continues: "* * * low to moderate levels of exposure (those that do not lead to lasting soot deposits, chronic irritation, and perhaps GSH enzyme depletion in the lung)." MSHA does not regard concentrations of dpm exceeding $200 \mu\text{g}/\text{m}^3$ as "low to moderate," and the EMA presented no evidence that the effects Dr. Cox listed do not occur at the high exposure levels observed at some mines. Salvi et al. (1999) reported marked inflammatory responses in the airways of healthy human volunteers after just one hour of exposure to dpm at a concentration of $300 \mu\text{g}/\text{m}^3$. The deleted caveat ending the quotation is especially important in a mining context, since mine atmospheres generally contain respirable mineral dusts that may diminish clearance rates and contribute to meeting thresholds for chronic irritation and inflammation leading to oxidative damage. Based on miners' testimony at the public hearings and workshops, there is, in fact, reason to believe that exposed miners experience lasting soot deposits and chronic irritation as a result of their exposures.

With respect to the epidemiologic evidence, the EMA quoted Dr. Cox as concluding: "* * * among studies that demonstrate an increased relative risk, it appears plausible that uncontrolled biases in study design and data analysis methods can explain the statistical increases in relative risk without there being a true causal increase." (Cox, 1997, quoted by EMA) Dr. Cox refers to non-causal explanations for positive epidemiologic results as "threats to causal inference." In considering Dr. Cox's discussion of the evidence, it is important to bear in mind that his purpose was "* * * not to establish that any (or all) of these threats do explain away the apparent positive associations between [dpm] and lung cancer risk * * * but only to point out that they plausibly could * * *." (Cox, 1997, p. 813) Dr. Cox's stated intent was to identify non-causal characteristics of positive studies that could potentially "explain away" the positive results. This is a relatively simple exercise that could misleadingly be applied to even the strongest of epidemiologic studies. As stated earlier, no epidemiologic study is perfect, and it is always possible that unknown or uncontrolled risk factors may have given rise to a spurious association. Neither the EMA nor Dr. Cox pointed out however, that

there are characteristics common to the negative studies that plausibly explain why they came out negative: insufficient latency allowance, nondifferential exposure misclassification, inappropriate comparison groups (including healthy worker effect, negative confounding by smoking or other variables). A similar approach could also be used to explain why many of the positive studies did not exhibit stronger associations. As observed by Dr. Silverman, "an unidentified negative confounder may have produced bias across studies, systematically diluting RRs."

b. Significance of the Risk of Material Impairment to Miners

The fact that there is substantial and persuasive evidence that dpm exposure can materially impair miner health in several ways does not imply that miners will necessarily suffer such impairments at a significant rate. This section will consider the significance of the risk faced by miners exposed to dpm.

i. Meaning of Significant Risk

(1) Legal Requirements

The benzene case, cited earlier in this risk assessment, provides the starting point for MSHA's analysis of this issue. Soon after its enactment in 1970, OSHA adopted a "consensus" standard for exposure to benzene, as authorized by the OSH Act. The standard set an average exposure limit of 10 parts per million over an 8-hour workday. The consensus standard had been established over time to deal with concerns about poisoning from this substance (448 U.S. 607, 617). Several years later, NIOSH recommended that OSHA alter the standard to take into account evidence suggesting that benzene was also a carcinogen. (*Id.* at 619 et seq.). Although the "evidence in the administrative record of adverse effects of benzene exposure at 10 ppm is sketchy at best," OSHA was operating under a policy that there was no safe exposure level to a carcinogen. (*Id.*, at 631). Once the evidence was adequate to reach a conclusion that a substance was a carcinogen, the policy required the agency to set the limit at the lowest level feasible for the industry. (*Id.* at 613). Accordingly, the Agency proposed lowering the permissible exposure limit to 1 ppm.

The Supreme Court rejected this approach. Noting that the OSH Act requires "safe or healthful employment," the court stated that—

* * * 'safe' is not the equivalent of 'risk-free' * * * a workplace can hardly be considered "unsafe" unless it threatens the

workers with a significant risk of harm. Therefore, before he can promulgate any permanent health or safety standard, the Secretary is required to make a threshold finding that a place of employment is unsafe—in the sense that significant risks are present and can be eliminated or lessened by a change in practices. [*Id.*, at 642, italics in original].

The court went on to explain that it is the Agency that determines how to make such a threshold finding:

First, the requirement that a 'significant' risk be identified is not a mathematical straitjacket. It is the Agency's responsibility to determine, in the first instance, what it considered to be a 'significant' risk. Some risks are plainly acceptable and others are plainly unacceptable. If, for example, the odds are one in a billion that a person will die from cancer by taking a drink of chlorinated water, the risk clearly could not be considered significant. On the other hand, if the odds are one in a thousand that regular inhalation of gasoline vapors that are 2% benzene will be fatal, a reasonable person might well consider the risk significant and take appropriate steps to decrease or eliminate it. Although the Agency has no duty to calculate the exact probability of harm, it does have an obligation to find that a significant risk is present before it can characterize a place of employment as "unsafe." [*Id.*, at 655].

The court noted that the Agency's " * * * determination that a particular level of risk is 'significant' will be based largely on policy considerations." (*Id.*, note 62).

Some commenters contended that the concept of significant risk, as enunciated by the Supreme Court in the Benzene case, requires support by a quantitative dose-response relationship. For example, one commenter argued as follows:

* * * OSHA had contended in * * * [the benzene] case that "because of the lack of data concerning the linkage between low-level exposures and blood abnormalities, it was impossible to construct a dose-response curve at this time". 448 U.S. at 632-633. The court rejected the Agency's attempt to support a standard based upon speculation that "the benefits to be derived from lowering" the permissible exposure level from 10 to 1 ppm were 'likely' to be 'appreciable'." 448 U.S. at 654.

One year after the Benzene case, the Court in *American Textile Mfr's Inst. v. Donovan*, 452 U.S. 490 (1981), upheld OSHA's "cotton dust" standard for which a dose-response curve had been established by the Agency. The Court relied upon the existence of such data to find that OSHA had complied with the Benzene mandate, stating: "In making its assessment of significant risk, OSHA relied on dose-response curve data * * * It is difficult to imagine what else the agency could do to comply with this Court's decision in the Benzene case." *Id.* at 505, n. 25. See also *Public Citizen Research Group v. Tyson*, 796 F. 2d 1479, 1496, 1499 (D.C.

Cir. 1986) (where a dose response curve was constructed for the ethylene oxide standard and the agency [had] gone to great lengths to calculate, within the bounds of available scientific data, the significance of the risk); *United Steelworkers of America v. Marshall*, 647 F. 2d 1189, 1248 (D.C. Cir. 1980), cert. denied, 453 U.S. 913 (1981) (where in promulgating a new lead standard "OSHA amassed voluminous evidence of the specific harmful effects of lead at particular blood levels and correlated these blood lead levels with air lead levels"). [NMA]

A dose-response relationship has been established between exposure to PM_{2.5} (of which dpm is a major constituent) and the risk of death from cardiovascular, cardiopulmonary, or respiratory causes (Schwartz et al., 1996; EPA, 1996). Furthermore, three different epidemiologic studies, including two carried out specifically on mine workers, have reported evidence of a quantitative relationship between dpm exposure and the risk of lung cancer (Johnston et al., 1997, Steenland et al., 1998, Säverin et al., 1999). However, the Secretary has carefully reviewed the legal references provided by the commenters and finds there is no requirement in the law that the determination of significant risk be based on such a relationship. The cited court rulings appear to describe sufficient means of establishing a significant risk, rather than necessary ones. Indeed, as stated earlier in this section, the Benzene court explained that:

* * * the requirement that a "significant" risk be identified is not a mathematical straitjacket. It is the Agency's responsibility to determine, in the first instance, what it considered to be a "significant" risk. * * * the Agency has no duty to calculate the exact probability of harm * * *.

The Agency has set forth the evidence and rationale behind its decision to propose a rule restricting miner exposure to dpm, obtained an independent peer review of its assessment of that evidence, published the evidence and tentative conclusions for public comment, held hearings, kept the record open for further comments for months after the hearings, and reopened the record so that stakeholders could comment on the most recent evidence available. Throughout these proceedings, the Agency has carefully considered all public comments concerning the evidence of adverse health effects resulting from occupational dpm exposures. Based on that extensive record, and the considerations noted in this section, the Agency is authorized under the statute and relevant precedents to act on this matter—despite the fact that a more

conclusive or definitively established exposure-response relationship might help address remaining doubts among some members of the mining community.

As the Supreme Court pointed out in the benzene case, the appropriate definition of significance also depends on policy considerations of the Agency involved. In the case of MSHA, those policy considerations include special attention to the history of extraordinary occupational risks leading to the Mine Act. That history is intertwined with the toll to the mining community of silicosis and coal workers' pneumoconiosis (CWP or "black lung"), along with billions of dollars in Federal expenditures.

(2) Standards and Guidelines for Risk Assessment

Several commenters suggested that this risk assessment, as originally proposed, deviated from established risk assessment guidelines, because it did not provide a sufficiently quantitative basis for evaluating the significance of miners's risks due to their dpm exposures. One of these commenters (Dr. Jonathan Borak) maintained that a determination of significant risk based on a "qualitative" assessment "has no statistical meaning."

MSHA recognizes that a risk assessment should strive to provide as high a degree of quantification and certainty as is possible, given the best available scientific evidence. However, in order to best protect miners' health, it is not prudent to insist on a "perfect" risk assessment. Nor is it prudent to delay assessing potentially grave risks simply because the available data may be insufficient for an ideal risk assessment. The need for regulatory agencies to act in the face of uncertainty was recognized by the HEI's Diesel Epidemiology Expert Panel as follows: "The Panel recognizes 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) When there is good, qualitative evidence—such as the sight and smell of heavy smoke—that one's house is on fire, an inference of significant risk may be statistically meaningful even without quantitative measurements of the smoke's density and composition.

Moreover, as will be demonstrated below, the question of whether a quantitative assessment is or is not essential is, in this case, moot: this risk assessment does, in fact, provide a quantitative evaluation of how significant the risk is for miners occupationally exposed to dpm.

ii. Significance of Risk for Underground Miners Exposed to dpm

An important measure of the significance of a risk is the likelihood that an adverse effect actually will occur. A key factor in the significance of risks that dpm presents to miners is the very high dpm concentrations to which a number of those miners are currently exposed—compared to ambient atmospheric levels in even the most polluted urban environments, and to workers in diesel-related occupations for which positive epidemiologic results have been reported. Figure III-4 compared the range of median dpm exposure levels measured for mine workers at various mines to the range of medians estimated for other occupations, as well as to ambient environmental levels. Figure III-7 presents a similar comparison, based on

the highest mean dpm level observed at any individual mine, the highest mean level reported for any occupational group other than mining, and the highest monthly mean concentration of dpm estimated for ambient air at any site in the Los Angeles basin.⁷⁴ As shown in Figure III-7, underground miners are currently exposed at mean levels up to 10 times higher than the highest mean exposure reported for other occupations, and up to 100 times higher than the highest mean environmental level even after adjusting

⁷⁴ For comparability with occupational lifetime exposure levels, the environmental ambient air concentration has been multiplied by a factor of approximately 4.7. This factor reflects a 45-year occupational lifetime with 240 working days per year, as opposed to a 70-year environmental lifetime with 365-days per year, and assumes that air inhaled during a work shift comprises half the total air inhaled during a 24-hour day.

the environmental level upwards to reflect an equivalent occupational exposure.

Given the significant increases in mortality and other acute health effects associated with increments of 25 $\mu\text{g}/\text{m}^3$ in fine particulate concentration (see Table III-3), the relative risk of acute effects for some miners (especially those already suffering respiratory problems) appears to be extremely high. Acute responses to dpm exposures have been detected in studies of stevedores, whose exposures were likely to have been less than one tenth the exposure of some miners on the job. Likewise, the risk of lung cancer due to dpm exposure would appear to be far greater for those underground miners who are exposed at such high levels than for other workers or general urban populations.

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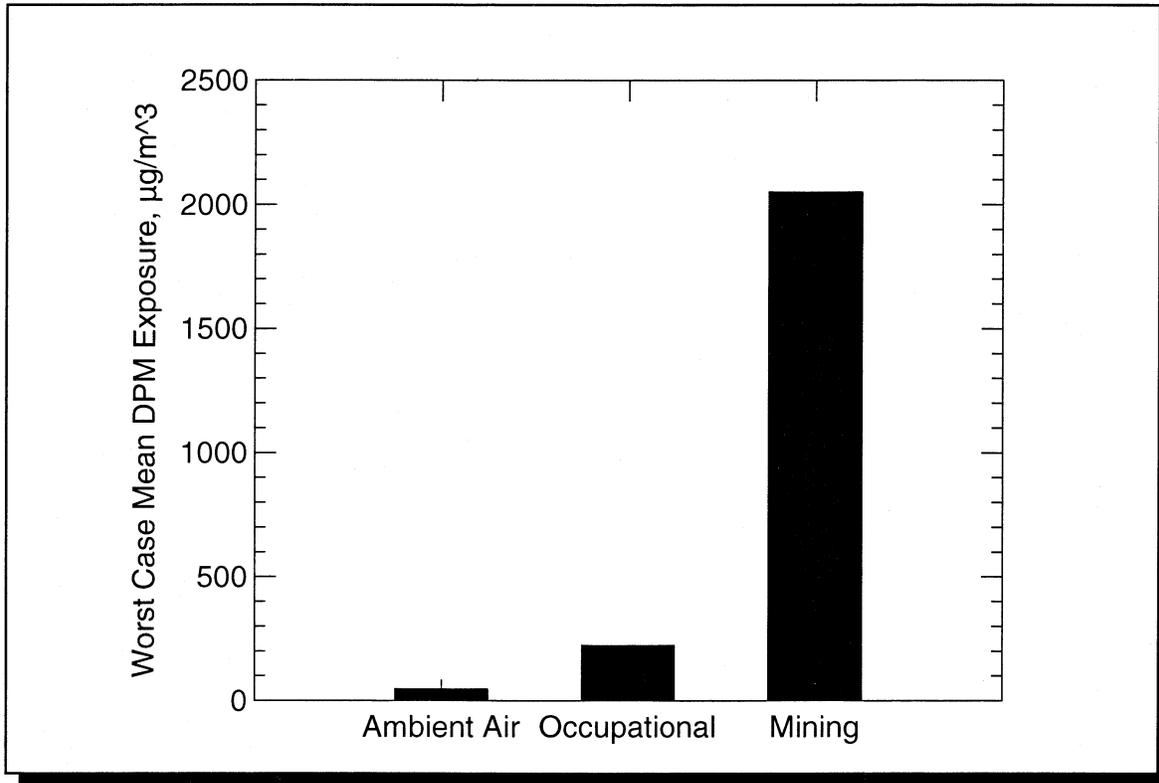


Figure III-7. — Worst case observed or reported mean diesel particulate exposure concentrations for urban ambient air, occupations other than mining, and mining. Worst case for mining is mean dpm measured within an underground mine. Worst case for occupations other than mining is mean respirable particulate matter, other than cigarette smoke, reported for railroad workers classified as hostlers (Woskie et al., 1988). Worst case for ambient air is mean estimated for peak months at most heavily polluted site in Los Angeles area (Cass and Gray, 1995), multiplied by 4.7 to adjust for comparability with occupational lifetime exposure levels. For additional information on means and ranges see Section III.1.d.

Several commenters asserted that current dpm exposures in underground mines are lower than they were when MSHA conducted its field surveys and that MSHA had not taken this into account when assessing the significance of dpm risk to miners. A related comment was that MSHA had not designed its sampling studies to provide a statistically representative cross section of the entire industry but had nevertheless used the results in concluding that the risk to underground miners was significant.

In accordance with § 101.(a)(6) of the Mine Act, MSHA is basing this risk assessment on the best available evidence. None of the commenters provided evidence that dpm levels in

underground metal/nonmetal mines had declined significantly since MSHA's field studies, or provided quantitative estimates of any purported decline in average dpm concentrations, or submitted data that would better represent the range of dpm concentrations to which underground miners are typically exposed at the present time. Although MSHA's field studies were not designed to be statistically representative in a way that can be readily quantified, they were performed at locations selected, according to MSHA's best engineering judgement, to be typical of the type of diesel equipment used. Furthermore, as will be shown below, MSHA's evaluation of the significance of risks

presented to underground metal/nonmetal miners by their dpm exposures does not rely on the highest levels, or even the average levels, that MSHA has measured. As documented in Section 1.d of this risk assessment, some of the highest of MSHA's measurements were made as recently as 1996–1997. It is important to note, as is shown below, the cancer risks of dpm exposure are clearly significant even at a concentration of 300 $\mu\text{g}/\text{m}^3$ —less than half of the average level that MSHA observed in its field studies. Therefore, MSHA believes that a reduction in exposure of more than 50 percent in the last couple of years is highly implausible.

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A number of other governmental and nongovernmental bodies have concluded that, even at the far lower levels evident in other occupational environments or in ambient air, the health risks of dpm exposure are of sufficient significance that exposure should be limited:

- (1) In 1988, after a thorough review of the scientific literature, the National Institute for Occupational Safety and Health (NIOSH) recommended that diesel exhaust be controlled to the *lowest feasible exposure level*. The document did not contain a recommended exposure limit.
- (2) In 1996, the Federal Republic of Germany classified dpm as "probably carcinogenic for humans" and established legally binding technical limits on dpm concentrations in occupational environments. The classification requires that the "best available technology" be used for emission reduction. The technical concentration limits, applying to all workplaces except coal mines, are the lowest limits thought to be feasible in Germany with current technology. Expressed as limits on elemental carbon (EC), they are: 300 $\mu\text{g}/\text{m}^3$ for tunneling and non-coal mining; 100 $\mu\text{g}/\text{m}^3$ for all other workplaces (except coal mines).
- (3) An ad hoc committee of the Canada Centre for Mineral and Energy Technology (CANMET) has recommended that a limit of 500 $\mu\text{g}/\text{m}^3$ RCD be adopted as a goal for underground mining environments.
- (4) The International Programme on Chemical Safety (IPCS), which is a joint venture of the World Health Organization, the International Labour Organisation, and the United Nations Environment Programme, performed a comprehensive evaluation of the scientific evidence linking diesel exhaust with adverse health effects (IPCS, 1996). IPCS concluded that inhalation of diesel exhaust is of concern with respect to both neoplastic and non-neoplastic diseases and that the particulate phase appears to have the greatest effect on health. As a result of this evaluation, the IPCS recommended that "in the occupational environment, good work practices should be encouraged, and adequate ventilation must be provided to prevent excessive exposure."
- (5) In light of the significant health risks associated with environmental exposures to fine particulates ($\text{PM}_{2.5}$), in 1997 the U.S. Environmental Protection Agency revised national air quality standards regulating PM to include $\text{PM}_{2.5}$ in the ambient air. Diesel particulate matter was a major constituent of $\text{PM}_{2.5}$ in many of the areas forming the basis of the EPA's health risk assessment. (EPA, 1996)
- (6) In 1998, the California Environmental Protection Agency identified dpm as a toxic air contaminant, as defined in their Health and Safety Code, Section 39655. According to that section, a toxic air contaminant is an air pollutant which may cause or contribute to an increase in mortality or in serious illness, or which may pose a present or potential hazard to human health. This conclusion, unanimously adopted by the California Air Resources Board and its Scientific Review Panel on Toxic Air Contaminants, initiates a process of evaluating strategies for reducing dpm concentrations in California's ambient air.
- (7) In 1999, the American Conference of Governmental Industrial Hygienists (ACGIH) proposed a Threshold Limit Value of 50 $\mu\text{g}/\text{m}^3$ for the dpm component of diesel exhaust and placed dpm on its Notice of Intended Changes. This ACGIH proposal was based on a determination that occupational exposure levels exceeding 50 $\mu\text{g}/\text{m}^3$ would present a significant "incremental" or excess risk of lung cancer.

Earlier in this risk assessment, MSHA identified three types of material impairment that can result from occupational exposures to dpm. The next three subsections present the Agency's evaluation of how much of a risk there is that miners occupationally exposed to dpm will actually incur such consequences. Each part addresses the risk of incurring one of the three types of material impairment identified earlier.

(1) Sensory Irritations and Respiratory Symptoms (Including Allergenic Responses)

It is evident from the direct testimony of numerous miners working near diesel equipment that their exposures pose a significant risk of severe sensory irritations and respiratory symptoms. This was underscored during the workshops and public hearings by several miners who noted that such effects occurred immediately and consistently after episodes of intense exposure (Section 2.b.i). There is also persuasive experimental evidence that exposure at levels found in underground mines frequently cause eye and nose irritation (Rudell et al., 1996) and pulmonary inflammation (Salvi et al., 1999). Section 2.a.ii and 3.a.i of this risk assessment explain why these effects constitute "material impairments" under the Mine Act and why they threaten miners' safety as well as health. Therefore, it is clear that even short-term exposures to excessive concentrations of dpm pose significant risks.

MSHA's quantitative evaluation of how significant the risks of sensory irritations and respiratory symptoms are for miners is limited, by the quantitative evidence available, to acute respiratory symptoms linked to fine particulate exposures ($PM_{2.5}$) in ambient air pollution studies. MSHA recognizes that, for miners exposed to dpm, this type of risk cannot be quantified with great confidence or precision based on the available evidence. This is because $PM_{2.5}$ is not solely comprised of dpm and also because miners, as a group, have different demographic and health characteristics from the general populations involved in the relevant studies. However, MSHA believes that the quantitative evidence suffices to establish a lower bound on the significance of this type of risk to miners exposed to dpm. Even at this lower bound, which is likely to substantially underestimate the degree of risk, the probability that a miner's occupational exposure to dpm will cause adverse respiratory effects is clearly significant.

As shown in Table III-3, the risk of acute lower respiratory tract symptoms has been reported to increase, at a 95-percent confidence level, by 15 to 82 percent (RR = 1.15 to 1.82) for each incremental increase of $20 \mu\text{g}/\text{m}^3$ in the concentration of $PM_{2.5}$ in the ambient air. This means that the relative risk estimated for a given $PM_{2.5}$ concentration ranges between $(1.15)^k$ and $(1.82)^k$, where k = the concentration of $PM_{2.5}$ divided by $20 \mu\text{g}/\text{m}^3$. For example, for a $PM_{2.5}$ concentration of $40 \mu\text{g}/\text{m}^3$, the RR is estimated to be between $(1.15)^2$ and $(1.82)^2$, or 1.32 to 3.31. MSHA believes that part of the reason why the range is so wide is that the composition of $PM_{2.5}$ varied in the data from which the estimates were derived.

MSHA acknowledges that there are substantial uncertainties involved in converting 24-hour environmental exposures to 8-hour occupational exposures. However, since mining often involves vigorous physical activity (thereby increasing breathing depth and frequency) and sleep is characterized by reduced respiration, it is highly likely that miners would inhale at least one-third of their total 24-hour intake of air during a standard 8-hour work shift. If it is assumed that the acute respiratory effects of inhaling dpm at a concentration of $60 \mu\text{g}/\text{m}^3$ over an 8-hour workshift are at least as great as those at a concentration of $20 \mu\text{g}/\text{m}^3$ over a 24-hour period, then it is possible to estimate a lower bound on the relative risk of such effects.

Based solely on the fact that dpm consists almost entirely of particles much smaller than 2.5 micrometers in diameter, the dpm would be expected to penetrate the lower respiratory tract at least as effectively as $PM_{2.5}$. Also, given the complex chemical composition of dpm, and its generation within a confined space, there is no reason to suspect that dpm in an underground mining environment is less potent than ambient $PM_{2.5}$ in inducing respiratory symptoms. Under these assumptions, a short-term environmental exposure to $PM_{2.5}$ at a concentration of $20 \mu\text{g}/\text{m}^3$ would correspond to a short-term occupational exposure to dpm at a concentration of $60 \mu\text{g}/\text{m}^3$. Consequently, the RR at an occupational exposure level of $Y \mu\text{g}/\text{m}^3$ would equal the RR calculated for an ambient exposure level of $20 \times (Y/60) \mu\text{g}/\text{m}^3$. For example, the relative risk (RR) of acute lower respiratory symptoms at an occupational exposure level of $300 \mu\text{g}/\text{m}^3$ dpm would, at a minimum, correspond to the RR at an ambient exposure level equal to $5 \times 20 \mu\text{g}/\text{m}^3$ $PM_{2.5}$. (See Table III-3) A dpm

concentration of $300 \mu\text{g}/\text{m}^3$ happens to be the level at which Salvi et al. (1999) found a marked pulmonary inflammatory response in healthy human volunteers after just one hour of exposure.

Under these assumptions, the risk of lower respiratory tract symptoms for a miner exposed to dpm for a full shift at a concentration of $300 \mu\text{g}/\text{m}^3$ or more, would be at least twice the risk of ambient exposure (i.e., $RR = (1.15)^5 = 2.01$). This would imply that for miners exposed to dpm at or above this level, the risk of acute lower respiratory symptoms would double, at a minimum. The Secretary considers such an increase in risk to be clearly significant.

(2) Premature Death From Cardiovascular, Cardiopulmonary, or Respiratory Causes

As in the case of respiratory symptoms, the nature of the best available evidence limits MSHA's quantitative evaluation of how large an excess risk of premature death, due to causes other than lung cancer, there is for miners exposed to dpm. As before, this evidence consists of acute effects linked to fine particulate exposures ($PM_{2.5}$) in ambient air pollution studies. Therefore, the analysis is subject to similar uncertainties. However, also as before, MSHA believes that the quantitative evidence suffices to place a lower bound on the increase in risk of premature mortality for miners occupationally exposed to dpm. As will be shown below, even this lower bound, which is likely to substantially underestimate the degree of increase, indicates that a miner's occupational exposure to dpm has a clearly significant impact on the likelihood of premature death.

Schwartz et al. (1996) found an average increase of 1.5 percent in daily mortality associated with each increment of $10 \mu\text{g}/\text{m}^3$ in the daily concentration of fine particulates. Higher increases were estimated specifically for ischemic heart disease (IHD: 2.1 percent), chronic obstructive pulmonary disease (COPD: 3.3 percent), and pneumonia (4.0 percent). The corresponding 95-percent confidence intervals for the three specific estimates were, respectively, 1.4% to 2.8%, 1.0% to 5.7%, and 1.8% to 6.2%, per increment of $10 \mu\text{g}/\text{m}^3$ in daily $PM_{2.5}$ exposure. Within the range of dust concentrations studied, the response appeared to be linear, with no threshold. The investigators checked for but did not find any consistent or statistically stable relationship between increased mortality and the atmospheric concentration of "course" respirable

particles—i.e., those with aerodynamic diameter greater than 2.5 micrometers but less than 10 micrometers.

As explained earlier, it is highly likely that miners would inhale at least one-third of their total 24-hour intake of air during a standard 8-hour work shift. Therefore, under the same assumptions made in the previous subsection, the 24-hour average concentrations of PM_{2.5} measured by Schwartz et al. are no more potent, in their impact on mortality risk, than eight-hour average concentrations that are three times as high. As discussed in Section 2.a.iii of this risk assessment, underground miners may be less, equally, or more susceptible than the general population to the acute mortality effects of fine particulates such as dpm. However, miners who smoke tobacco and/or suffer various respiratory ailments fall into groups identified as likely to be especially sensitive (EPA, 1996). Consequently, for such miners occupationally exposed to dpm, the relative risk of each type of premature mortality would be at least equal to the corresponding lower 95-percent confidence limit specified above.

Therefore, MSHA estimates that, on average, each increment of 30 µg/m³ in the dpm concentration to which miners are exposed increases the risk of premature death due to IHD, COPD, and pneumonia by a factor of at least 1.4 percent, 1.0 percent, and 1.8 percent, respectively. As noted earlier, these estimates are based on the evidence of acute effects linked to fine particulate exposures (PM_{2.5}) in ambient air pollution studies. A lower bound on the increased risk expected at an occupational dpm concentration greater than 30 µg/m³, is obtained by raising the relative risks equivalent to these factors (i.e., 1.014, 1.01, and 1.018) to a power, k, equal to the ratio of the concentration to 30 µg/m³. For a concentration of 300 µg/m³, k = 10; so MSHA estimates the lower bounds on relative risk to be: (1.014)¹⁰ = 1.149 for IHD; (1.01)¹⁰ = 1.105 for COPD; and (1.018)¹⁰ = 1.195 for pneumonia. This means that for miners exposed to dpm at or above this level, MSHA expects the risks to increase by at least 14.9 percent for IHD, 10.5 percent for COPD, and 19.5 percent for pneumonia. The Secretary considers increases of this magnitude to be clearly significant, since the causes of death to which they apply are not rare among miners.

(3) Lung Cancer

In contrast to the two types of risk discussed above, the available epidemiologic data can be used to relate the risk of lung cancer directly to dpm

exposures. Therefore, the significance of the lung cancer risk can be evaluated without having to make assumptions about the relative potency of dpm compared to the remaining constituents of PM_{2.5}. This removes an important source of uncertainty present in the other two evaluations.

There are two different ways in which the significance of the lung cancer risk may be evaluated. The first way is based on the relative risk of lung cancer observed in the best available epidemiologic studies involving miners (identified as such in Subsections 3.a.iii(1) (b) and (d) of this risk assessment). As will be explained below, this approach leads to an estimated tripling of lung cancer risk for miners exposed to dpm, compared to a baseline risk for unexposed miners. The second way is to calculate the lung cancer risk expected at exposure levels MSHA has observed in underground mines, assuming a specified occupational lifetime and using the exposure-response relationships estimated for underground miners by Johnston et al. (1997) and Säverin et al. (1999). As will be explained further below, this second approach yields a wide range of estimates, depending on which exposure-response relationship and statistical model is used. All of the estimates, however, show at least a doubling of baseline lung cancer risk, assuming dpm exposure for a 45-year occupational lifetime at the average concentration MSHA has observed. Most of the estimates are much higher than this. If the exposure-response relationship estimated for workers in the trucking industry by Steenland et al. (1998) is extrapolated to the much higher exposure levels for miners, the resulting estimates fall within the range established by the two mine-specific studies, thereby providing a degree of corroboration. Since lung cancer is not a rare disease, the Secretary considers even the very lowest estimate—a doubling of baseline risk—to represent a clearly significant risk.

Both of these methods provide quantitative estimates of the degree by which miners' risk of lung cancer is increased by their occupational dpm exposures. The estimate based on exposure-response relationships is more refined, in that it ties the increased risk of lung cancer to specific levels of cumulative dpm exposure. However, this added refinement comes at the price of an additional source of uncertainty: the accuracy of the exposure-response relationship used to calculate the estimate. This additional uncertainty is reflected, in MSHA's evaluation, by a broad range of relative

risk estimates, corresponding to the range of exposure-response relationships derived using different statistical models and epidemiologic data. The next two subsections present the details of MSHA's two approaches to analyzing lung cancer risk for miners exposed to dpm, along with MSHA's responses to the relevant public comments.

(a) Risk Assessment Based on Studies Involving Miners

As one commenter pointed out, the epidemiologic evidence showing an elevated risk of lung cancer for exposed workers is mostly based on occupations estimated to experience far lower exposure levels, on average, than those observed in many underground mines:

* * * [U]nderground coal, metal and non-metal miners face a significant risk of lung cancer from occupational exposure to diesel particulate. Numerous epidemiologic studies of workers exposed to levels far below those experienced by coal, metal and non-metal miners have found the risk for exposed workers to be 30–50% greater than for unexposed workers. [Washington State Dept. of Labor and Industries]

Indeed, although MSHA recognizes that results from animal studies should be extrapolated to humans with caution, it is noteworthy that dpm exposure levels recorded in some underground mines (see Figures III–1 and III–2) have been well within the exposure range that produced tumors in rats (Nauss et al., 1995).

Both existing meta-analyses of the human studies relating dpm exposure and lung cancer excluded studies on miners but presented evidence showing that, averaged across all other occupations, dpm exposure is responsible for an increase of about 40 percent in lung cancer risk (See Section 3.a.iii(2) of this risk assessment). Even a 40-percent increase in the risk of lung cancer would clearly be significant, since this would amount to more than two cases of lung cancer per year per thousand miners at risk, and to an even greater risk for smoking miners. The best available evidence, however, indicates (1) that exposure levels in underground mines generally exceed exposures for occupations included in the meta-analyses and (2) that lung cancer risks for exposed miners are elevated to a greater extent than for other occupations.

As Dr. Valberg and other commenters pointed out, the epidemiologic studies used in the meta-analyses involved much lower exposure levels than those depicted for mines in Figures III–1 and III–2. The studies supporting a 40-percent excess risk of lung cancer were

conducted on populations whose average exposure is estimated to be less than 200 µg/m³—less than one tenth the average concentration MSHA observed in some underground mines. More specifically, average exposure levels in the two most extensively studied industries—trucking (including loading dock workers) and railroads—have been reported to be far below the levels observed in underground mining environments. For workers at docks employing diesel forklifts—the occupational group estimated to be most highly exposed within the trucking industry—the highest average dpm concentration reported was about 55 µg/m³ EC at an individual dock (NIOSH, 1990). As explained in Subsection 1.d of this risk assessment, this corresponds to less than 150 µg/m³ of dpm, on average. Published dpm measurements for railworkers have generally also been less than 150 µg/m³ (measured as respirable particulate matter other than cigarette smoke). The reported mean of 224 µg/m³ for hostlers displayed in Figure III–7 represents only the worst-case occupational subgroup (Woskie et al., 1988). In contrast, in the study on underground potash miners by Säverin et al. (1999), the mean TC concentration measured for production areas was 390 µg/m³—corresponding to a mean dpm concentration of about 490 µg/m³. As shown in Table III–1, the mean dpm exposure level MSHA observed in underground production areas and haulageways was 644 µg/m³ for coal mines and 808 µg/m³ for M/NM.

In accordance with the higher exposure levels for underground miners, the five studies identified in Section III.3.a.iii(1)(d) as comprising the best available epidemiologic evidence on miners all show that the risk of lung cancer increased for occupationally exposed miners by substantially more than 40 percent. The following table presents the relative risk (RR) of lung cancer for miners in these studies, along with the geometric mean based on all five studies:

Study	Relative risk of lung cancer
Boffetta et al., 1988	2.67
Burns & Swanson, 1991	5.03
Johnston et al., 1997 (mine-adjusted model applied at highest cumulative exposure)	5.50
Lerchen et al., 1987	2.1
Säverin et al., 1999 (highest vs least exposed)	2.17
geometric mean	3.2

As shown in this table, the estimated RR based on these five studies is 3.2 for miners exposed to dpm. In other words, the risk of lung cancer for the highly exposed miners is estimated to be 3.2 times that of a comparable group of occupationally unexposed workers. The geometric mean RR remains 3.2 if the two studies on which MSHA places less weight (by Burns & Swanson and by Lerchen) are excluded from the calculation. This represents a 220-percent increase in the risk of lung cancer for exposed miners, in contrast to the 40-percent increase estimated, on average, for other occupationally exposed workers. The Secretary believes that a 40-percent increase in the risk of lung cancer already exceeds, by a wide margin, the threshold for a clearly significant risk. However, a 220-percent increase to more than three times the baseline rate is obviously of even greater concern.

Some commenters questioned whether increased lung cancer risks of this magnitude were plausible, since they were not aware of any unusually high lung cancer rates among workers at mines with which they were familiar and which used diesel equipment. There are several reasons why an elevated risk of lung cancer might not currently be conspicuous among U.S. miners exposed to dpm. Lung cancer not only may require a latency period of 30 or more years to develop, but it may also not develop until beyond the normal retirement age of 65 years. Cases of lung cancer developing after retirement may not all be known to members of the mining community. Also, in a population that includes many tobacco smokers, it may be difficult to discern cases of lung cancer specifically attributable to dpm exposure when they first begin to become prevalent. Two commenters expressed some of the relevant considerations as follows. Although they were referring to coal miners, the same points apply to M/NM miners.

Because the latency period for lung cancer is so long, and diesel-powered equipment has only been used extensively in U.S. coal mines for about 25 years, the epidemic may well be progressing unnoticed. [UMWA]

If dpm exposure will cause cancer, there is a huge population of miners here in the West that have already been exposed. Considering the latency periods indicated by MSHA, these miners should be beginning to develop cancers. [Canyon Fuels]

(b) Risk Assessment Based on Miners' Cumulative Exposure

Although it is evident that underground miners currently face a significant risk of lung cancer due to

their occupational exposure to dpm, there are certain advantages in utilizing an exposure-response relationship to quantify the degree of risk at specific levels of cumulative exposure. As some commenters pointed out, for example, dpm exposure levels may change over time due to changes in diesel fuel and engine design. The extent and patterns of diesel equipment usage within mines also has changed significantly during the past 25 years, and this has affected dpm exposure levels as well. Furthermore, exposure levels at the mines involved in epidemiologic studies were not necessarily typical or representative of exposure levels at mines in general. A quantitative exposure-response relationship provides an estimate of the risk at any specified level of cumulative exposure. Therefore, using such a relationship to assess risk under current or anticipated conditions factors in whatever differences in exposure levels may be relevant, including those due to historical changes.

(i) Exposure-Response Relationships from Studies Outside Mining

Stayner et al. (1998) summarized quantitative risk assessments based on exposure-response relationships for dpm published through 1998. These assessments were broadly divided into those based on human studies and those based on animal studies. Depending on the particular studies, assumptions, statistical models, and methods of assessment used, estimates of the exact degree of risk varied widely even within each broad category. However, as presented in Tables III and IV of Stayner et al. (1998), all of the very different approaches and methods published through 1998 produced results indicating that levels of dpm exposure measured at some underground mines present an unacceptably high risk of lung cancer for miners—a risk significantly greater than the risk they would experience without the dpm exposure.⁷⁵

⁷⁵ In comments submitted by MARG, Dr. Jonathan Borak asserted that MSHA had “misrepresented the findings of a critical study” by stating that all methods showed an “unacceptably high risk” at exposure levels found at some mines. Dr. Borak claimed that Stayner et al. (1998) had described an analysis by Crump et al. “that reached an opposite conclusion.” Dr. Borak failed to distinguish between a finding of high risk and a finding of changes in that risk corresponding to changes in estimated exposures. The findings to which Dr. Borak referred pertained only to the exposure-response relationship within the group of exposed workers. Garshick (1981), Crump (1999), and HEI (1999) all noted that the risk of lung cancer was nevertheless elevated among the exposed workers, compared to unexposed workers in the same cohort.

Continued

Quantitative risk estimates based on the human studies were generally higher than those based on analyses of the rat inhalation studies. As indicated by Tables 3 and 4 of Stayner et al. (1998), a working lifetime of exposure to dpm at 500 $\mu\text{g}/\text{m}^3$ yielded estimates of excess lung cancer risk ranging from about 1 to 200 excess cases of lung cancer per thousand workers based on the rat inhalation studies and from about 50 to 800 per thousand based on the epidemiologic assessments. Stayner et al. (1998) concluded their report by stating:

The risk estimates derived from these different models vary by approximately three orders of magnitude, and there are substantial uncertainties surrounding each of these approaches. Nonetheless, the results from applying these methods are consistent in predicting relatively large risks of lung cancer for miners who have long-term exposures to high concentrations of DEP [i.e., dpm]. This is not surprising given the fact that miners may be exposed to DEP [dpm] concentrations that are similar to those that induced lung cancer in rats and mice, and substantially higher than the exposure concentrations in the positive epidemiologic studies of other worker populations.

Restricting attention to the exposure-response relationships derived from human data, Table IV of Stayner et al. (1998) presented estimates of excess lung cancer risk based on exposure-response relationships derived from four different studies: Waller (1981) as analyzed by Harris (1983); Garshick et al. (1987) as analyzed by Smith and Stayner (1991); Garshick et al. (1988) as analyzed by California EPA (1998); and Steenland et al. (1998). Harris (1983) represented upper bounds on risk; and all of the other estimates represented the most likely value for risk, given the particular data and statistical modeling assumptions on which the estimate was based. Three different ranges of estimates were presented from the California EPA analysis, corresponding to various statistical models and assumptions about historical changes in dpm exposure among the railroad workers involved. As mentioned above and in the proposed version of this risk assessment, the low end of the range of estimates was 50 lung cancers per 1000 workers occupationally exposed at 500 $\mu\text{g}/\text{m}^3$ for a 45-year working lifetime. This estimate was one of those based on railroad worker data from Garshick et al. (1988).

Several commenters objected to MSHA's reliance on any of the

and they all identified reasons why the data used in this study might fail to detect a positive exposure-response relationship among the exposed workers.

exposure-response relationships derived from the data compiled by Garshick et al. (1987) or Garshick et al. (1988). These objections were based on re-analyses of these data by Crump (1999) and HEI (1999), using different statistical methods and assumptions from those used by Cal-EPA (1998). For example, the NMA quoted HEI (1999) as concluding:

At present, the railroad worker cohort study * * * has very limited utility for QRA [quantitative risk assessment] of lifetime lung cancer risk from exposure to ambient levels of diesel exhaust * * * [NMA, quoting HEI (1999)]

From this, the NMA argued as follows:

What then is the relevance of this data to the proceedings at issue? Simply put, there is no relevance. The leading epidemiologist [sic], including Dr. Garshick himself, now agree that the data are inappropriate for conducting risk assessment. [NMA]

MSHA notes that the HEI (1999) conclusion cited by the NMA referred to quantitative risk assessments at ambient, not occupational, exposure levels. Also, HEI (1999) did not apply its approach (i.e., investigating the correlation between exposure and relative risk within separate job categories) to the Armitage-Doll model employed by Cal-EPA in some of its analyses. (Results using this model were among those summarized in Table IV of Stayner et al., 1998). Therefore, the statistical findings on which HEI (1999) based its conclusion do not apply to exposure-response relationships estimated using the Armitage-Doll model. Furthermore, although HEI concluded that the railroad worker data have "very limited utility for QRA * * * at ambient levels" [emphasis added], this does not mean, even if true, that these data have "no relevance" to this risk assessment, as the NMA asserted. Even if they do not reliably establish an exposure-response relationship suitable for use in a quantitative risk assessment, these data still show that the risk of lung cancer was significantly elevated among exposed workers. This is the only way in which MSHA is now using these data in this risk assessment.

In the proposed risk assessment, MSHA did not rely directly on the railroad worker data but did refer to the lowest published quantitative estimate of risk, which happened, as of 1998, to be based on those data. MSHA's reasoning was that, even based on the lowest published estimate, the excess risk of lung cancer attributable to dpm exposure was clearly sufficient to warrant regulation. If risk assessments

derived from the railroad worker data are eliminated from consideration, the lowest estimate remaining in Table IV of Stayner et al. (1998) is obviously even higher than the one that MSHA used to make this determination in the proposed risk assessment. This estimate (based on one of the analyses performed by Steenland et al., 1998) is 89 excess cases of lung cancer per year per thousand workers exposed at 500 $\mu\text{g}/\text{m}^3$ for a 45-year working lifetime.

HEI (1999) also evaluated the use of the Steenland data for quantitative risk assessment, but did not perform any independent statistical analysis of the data compiled in that study. Some commenters pointed out HEI's reiteration of the cautionary remark by Steenland et al. (1998) that their exposure assessment depended on "broad assumptions." The HEI report did not rule out the use of these data for quantitative risk assessment but suggested that additional statistical analyses and evaluations were desirable, along with further development of exposure estimates using alternative assumptions. MSHA has addressed comments on various aspects of the analysis by Steenland et al., including the exposure assumptions, in Section 2.c.i(2)(a) of this risk assessment.

One commenter noted that Steenland et al. (1998) had recognized the limitations of their analysis and had, therefore, advised that the results "should be viewed as exploratory." The commenter then asserted that MSHA had nevertheless used these results as "the basis for a major regulatory standard" and that "[t]his alone is sufficient to demonstrate that MSHA's proposal lacks the necessary scientific support." [Kennecott Minerals]

The Secretary does not accept the premise that MSHA should exclude "exploratory" results from its risk assessment, even if it is granted that those results depend on broad assumptions possibly requiring further research and validation before they are widely accepted by the scientific community. Steenland et al. (1998) estimated risks associated with specific cumulative exposures, based on estimates of historical exposure patterns combined with data originally described by Steenland et al., 1990 and 1992. Regardless of whether the cumulative exposure estimates used by Steenland et al. (1998) are sufficiently reliable to permit pinpointing the risk of lung cancer at any given exposure level, the quantitative analysis indicates that as cumulative exposure increases, so does the risk. Therefore, the 1998 analysis adds significantly to the weight of evidence supporting a causal

relationship. However, MSHA did not use or propose to use exposure-response estimates derived by Steenland et al. (1998) as the sole basis for any regulatory standard.

The exposure-response relationships presented by Steenland et al. were derived from exposures estimated to be far below those found in underground mines. As Stayner et al. (1998) point out, questions are introduced by extrapolating an exposure-response relationship beyond the exposures used to determine the relationship. The uncertainties implicit in such extrapolation are demonstrated by comparing results from two statistical models based on five-year lagged exposures—one using simple cumulative exposure and the other using the natural logarithm of cumulative exposure (Steenland et al., 1998, Table II).

Assuming that, on average, EC comprises 40 percent of total dpm,⁷⁶ the formula for calculating a relative risk (RR) using Steenland's simple cumulative exposure model is $RR = \exp(0.4 \times 0.389 \times \text{CumExp})$, where CumExp is occupationally accumulated dpm exposure (expressed in mg-yr/m³), ignoring the most recent five years. Again assuming $EC = 0.4 \times \text{dpm}$, the corresponding formula using Steenland's Log(CumExp) model is: $RR = \exp(0.1803 \times (\text{Log}(0.4 \times 1000 \times \text{CumExp} + \text{BG}) - \text{Log}(\text{BG})))$, still ignoring occupational dpm exposure in the most recent five years.⁷⁷

The risk estimates from these two models are similar at the cumulative exposure levels estimated for workers involved in the study, but the projected risks diverge markedly at the higher exposures projected for underground miners exposed to dpm for a 45-year occupational lifetime. For example, a cumulative dpm exposure of 2.5 mg-yr/m³ (i.e., 45 years of occupational exposure at an average dpm concentration of about 55.6 µg/m³) is within the range of cumulative exposures from which these exposure-response relationships were estimated. At this level of cumulative exposure, the models (both lagged five years) yield relative risk estimates of 1.48 (based on simple cumulative exposure) and 1.64 (based on the logarithm of cumulative

exposure, with $BG = 70 \mu\text{g}\cdot\text{yr}/\text{m}^3$). On the other hand, 45 years of occupational exposure at an average dpm concentration of 808 µg/m³ amounts to a cumulative dpm exposure of 36,360 µg-yr/m³, or about 36.4 mg-yr/m³. At this level, which lies well beyond the range of data used by Steenland et al. (1998), the simple and logarithmic exposure models produce relative risk estimates of about 300 and 2.6, respectively.

Despite the divergence of these two models at high levels of cumulative exposure, they can provide a useful check of excess lung cancer risks estimated using exposure-response relationships developed from other studies. For highly exposed miners, the Steenland models both produce estimates of lung cancer risk within the range established by the two miner studies discussed below. This corroborates the upper and lower limits on such risk as estimated by the various statistical models used in those two studies.

(ii) Exposure-Response Relationships from Studies on Miners

As described in Section 2.c.i(2)(a) of this risk assessment, two epidemiologic studies, both conducted on underground miners, provide exposure-response relationships based on fully quantitative dpm exposure assessments. Johnston et al. (1997) conducted their study on a cohort of 18,166 underground coal miners, and Säverin et al. (1999) conducted theirs on a cohort of 5,536 underground potash miners. Each of these studies developed a number of possible exposure-response relationships, depending on the statistical model used for analysis and, in the case of Säverin et al. (1999), inclusion criteria for the cohort analyzed. For purposes of this risk assessment, MSHA has converted the units of cumulative exposure in all of these exposure-response relationships to mg-yr/m³.

Two exposure-response relationships derived by Johnston et al. (1997) are used in this risk assessment, based on a "mine-adjusted" and a "mine-unadjusted" statistical model. In both of these models, cumulative dpm exposure is lagged by 15 years.⁷⁸ This reflects the

long latency period required for development of lung cancer and means that the most recent 15 years of exposure are ignored when the relative risk of lung cancer is estimated. The exposure-response relationships, as reported by the investigators, were expressed in terms of g-hr/m³ of cumulative dpm exposure. MSHA has converted the exposure units to mg-yr/m³ by assuming 1920 work hours per year.

Two different methods of statistical analysis were applied by Säverin et al. (1999) to both the full cohort and to a subcohort of 3,258 miners who had worked underground, in relatively stable jobs, for at least ten years. Thus, the investigators developed a total of four possible exposure-response relationships from this study. Since they were based on measurements of total carbon (TC), these exposure-response relationships were expressed in terms of mg-yr/m³ of cumulative TC exposure. MSHA has converted the exposure units to mg-yr/m³ of cumulative dpm exposure by assuming that, on average, TC comprises 80 percent of total dpm.

The following table summarizes the exposure-response relationships obtained from these two studies. Each of the quantitative relationships is specified by the unit relative risk (RR) per mg-yr/m³ of cumulative dpm exposure. To calculate the relative risk estimated for a given cumulative dpm exposure (CE), it is necessary to raise the unit RR to a power equal to CE. For example, if the unit RR is 1.11 and CE = 20, then the estimated relative risk is $(1.11)^{20} = 8.1$. Therefore, the estimated relative risk of lung cancer increases as CE increases. For the two Johnston models, CE does not include exposure accumulated during the 15 years immediately prior to the time in a miner's life at which the relative risk is calculated.

allocates a significant number of the lung cancers otherwise attributable to dpm exposure to the "norm" for specific mines. Therefore, if the differences in lung cancer prevalence between mines is actually due to corresponding differences in mean dpm exposure, then this model will mask a significant portion of the risk due to dpm exposure. After adjusting for miners' age and smoking habits, the mine-unadjusted model attributes differences in the prevalence of lung cancer between mines to corresponding differences in mean dpm exposure. However, the mine-adjusted model has the advantage of taking into account differences between mines with respect to potentially confounding factors, such as radon progeny and silica levels.

⁷⁶ The assumption is that, on average, $EC = \text{TC} / 2$ and $\text{TC} = 0.8 \times \text{dpm}$.

⁷⁷ BG, expressed in µg-yr/m³, accounts for an assumed background (i.e., non-occupational) EC exposure level of 1.0 µg/m³. At age 70, after a 45-year worklife and an additional 5-year lag after retirement, BG is assumed to equal 70 µg-yr/m³. "Log" refers to the natural logarithm, and "exp" refers to the antilogarithm of the subsequent quantity.

⁷⁸ The 15-year lagged mine-unadjusted and mine-adjusted models are respectively denoted by M/03 and M/06 in Table 11.2 of Johnston et al. (1997). As explained earlier, the individual mines considered in this study differed significantly with respect to both dpm exposures and lung cancer experience. The investigators could not determine exactly how much, if any, of the increased lung cancer risk associated with dpm exposure depends on other, unknown factors differentiating the individual mines. The mine-adjusted model

EXPOSURE-RESPONSE RELATIONSHIPS
OBTAINED FROM TWO STUDIES ON
UNDERGROUND MINERS.

Study and statistical model	Unit RR per mg-yr/m ³ dpm
Säverin et al. (1999) ¹ :	
Poisson, full cohort	1.024
Cox, full cohort	1.089
Poisson, subcohort	1.110
Cox, subcohort	1.176
Johnston et al. (1997) ² :	
15-year lag, mine-adjusted ...	1.321
15-year lag, mine-unadjusted	1.479

¹ Unit RR calculated from Tables III and IV, assuming TC = 0.8×dpm.

² Unit RR calculated from Table 11.2, assuming 1920 work hours per year.

For example, suppose a miner is occupationally exposed to dpm at an average level of 500 µg/m³. Then each year of occupational exposure would contribute 0.5 mg-yr/m³ to the miner's cumulative dpm exposure. Suppose also that this miner's occupational exposure begins at age 45 and continues for 20 years until retirement at age 65. Consequently, at or above age 65, this hypothetical miner would have accumulated a total of 10 mg-yr/m³ of occupational dpm exposure. According to the Säverin-Cox-subcohort model, the relative risk estimated for this miner after retirement is $RR = (1.176)^{10} = 5.1$. This means that, at or above age 65, the retired miner's risk of lung cancer is estimated (by this model) to be about five times that of another retired miner having the same age and smoking history but no occupational dpm exposure.

Since the two Johnston models exclude exposure within the last 15 years, it is instructive to calculate the relative risk using these models for the same hypothetical retiree at age 75. Since this miner retired at age 65, immediately after 20 years of occupational exposure, the cumulative exposure used in applying the Johnston models must be reduced by the 2.5 mg-yr/m³ accumulated from age 60 to age 65. Therefore, according to the Johnston mine-adjusted model, the relative risk

estimated for this retired miner at age 75 is $RR = (1.321)^{7.5} = 8.1$. At age 80 or above, however, this model predicts that the relative risk would increase to $RR = (1.321)^{10} = 16.2$.

The six exposure-response relationships obtained from these two studies establish a range of quantitative risk estimates corresponding to a given level of cumulative dpm exposure. This range provides lower and upper limits on the risk of lung cancer for workers exposed at the given level, relative to similar workers who were not occupationally exposed. The lower limit of this range is established by Säverin's full cohort Poisson model. Therefore, the lowest estimate of relative risk after 45 years of occupational dpm exposure is $RR = (1.024)^{45 \times 0.644} = 2.0$ at a mean concentration of 644 µg/m³ or $RR = (1.024)^{45 \times 0.808} = 2.4$ at mean concentration of 808 µg/m³. These exposure levels correspond to the averages presented in Table III-1 for underground coal and underground M/NM mines, respectively.

A relative risk of 2.0 amounts to a doubling of the baseline lung cancer risk, and all of the models project relative risks of at least 2.0 after 45 years of exposure at these levels. Therefore, MSHA expects that underground miners exposed to dpm at these levels for a full 45-year occupational lifetime would, at a minimum, experience lung cancer at a rate twice that of unexposed but otherwise similar miners. Five of the six statistical models, however, predict a relative risk much greater than 2.0 after 45 years at a mean dpm concentration of 644 µg/m³. The second-lowest estimate of relative risk, for example, is $RR = (1.089)^{45 \times 0.644} = 11.8$, predicted by Säverin's full cohort Cox model.⁷⁹

⁷⁹ Some commenters contended that MSHA cannot establish a reliable exposure-response relationship because of potential interferences in MSHA's dpm concentration measurements. More specifically, some of these commenters claimed that MSHA's dpm measurements in underground coal mines were significantly inflated by submicrometer coal dust.

As explained in Subsection 1.a of this risk assessment, the sampling device MSHA used to measure dpm in underground coal mines was designed specifically to allow for the

In the next subsection of this risk assessment, relative risks will be combined with baseline lung cancer and mortality data to estimate the lifetime probability of dying from lung cancer due to occupational dpm exposure.

(iii) *Excess Risk at Specific dpm Exposure Levels.* The "excess risk" discussed in this subsection refers to the lifetime probability of dying from lung cancer resulting from occupational exposure to dpm for 45 years. This probability is expressed as the expected excess number of lung cancer deaths per thousand miners occupationally exposed to dpm at a specified level. The excess is calculated relative to baseline, age-specific lung cancer mortality rates taken from standard mortality tables. In order to properly estimate this excess, it is necessary to calculate, at each year of life after occupational exposure begins, the expected number of persons surviving to that age with and without dpm exposure at the specified level. At each age, standard actuarial adjustments must be made in the number of survivors to account for the risk of dying from causes other than lung cancer.

Table III-7 shows the excess risk of death from lung cancer estimated across the range of exposure-response relationships obtained from Säverin et al. (1999) and Johnston et al. (1997). Estimates based on the 5-year lagged models from Steenland et al. (1998) fall within this range and are included for comparison. Based on each of the eight statistical models, the excess risk was estimated at four levels of dpm exposure: 200 µg/m³, 500 µg/m³, 644 µg/m³ (the mean dpm concentration observed by MSHA at underground coal mines, as shown in Table III-1), and 808 µg/m³ (the mean dpm concentration observed by MSHA at underground M/NM mines, as shown in Table III-1).

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submicrometer fraction of coal dust. Both the size-selective and RCD methods are reasonably accurate when dpm concentrations exceed 300 µg/m³. Moreover, neither of these methods was used to establish the exposure-response relationships presented by Säverin et al. (1999) or Johnston et al. (1997).

Table III-7. — Lifetime excess risk of lung cancer mortality at specific dpm exposure levels.

Study and Statistical Model	Excess Lung Cancer Deaths per 1000 Occupationally Exposed Workers [†]			
	200 $\mu\text{g}/\text{m}^3$	500 $\mu\text{g}/\text{m}^3$	644 $\mu\text{g}/\text{m}^3$	808 $\mu\text{g}/\text{m}^3$
Säverin et al. (1999)				
Poisson, full cohort	15	44	61	83
Cox, full cohort	70	280	422	577
Poisson, subcohort	93	391	563	693
Cox, subcohort	182	677	761	802
Steenland et al. (1998)				
5-year lag, log of cumulative exposure	67	89	95	101
5-year lag, simple cumulative exposure	159	620	721	771
Johnston et al. (1997)				
15-year lag, mine-adjusted	313	724	770	800
15-year lag, mine-unadjusted	513	783	811	830

[†] Assumes 45-year occupational exposure at 1920 hours per year from age 20 to retirement at age 65. Lifetime risk of lung cancer adjusted for competing risk of death from other causes and calculated through age 85. Baseline lung cancer and overall mortality rates from NCHS (1996).

All of the estimates in Table III-7 assume that occupational exposure begins at age 20 and continues until retirement at age 65. Excess risks were calculated through age 85 as in Table IV of Stayner et al. (1998). Table III-7 differs from Table IV of Stayner et al. in that results from Johnston et al. and Säverin et al. are substituted for results based on the two studies by Garshick et al. Nevertheless, at 500 µg/m³, the range of excess risks shown in Table III-7 is nearly identical to the range (50 to 810 µg/m³) presented in Table IV of Stayner et al. (1998).

MSHA considers the exposure levels shown in Table III-1 to be typical of current conditions in underground coal mines using diesel face equipment. At the mean dpm concentration observed by MSHA at underground M/NM mines (808 µg/m³), the eight estimates range from 83 to 830 excess lung cancer deaths per 1000 affected miners. At the mean dpm concentration observed by MSHA at underground coal mines (644 µg/m³), the estimates range from 61 to 811 excess lung cancer deaths per 1000 affected miners. MSHA recognizes that these risk estimates involved extrapolation beyond the exposure experience of the miner cohorts in Säverin et al. (1999) and Johnston et al. (1997). However, the degree of extrapolation was less for those two studies than the extrapolation that was necessary for the diesel-exposed truck drivers in Steenland et al. The lowest excess lung cancer risk in dpm exposed miners found in Table III-7 is 61/1000 per 45-year working lifetime. Based on the quantitative rule of thumb established in the benzene case, this estimate indicates a clearly significant risk of lung cancer attributable to dpm exposure at current levels. [*Industrial Union vs. American Petroleum*; 448 U.S. 607, 100 S.Ct. 2844 (1980)].

c. The Rule's Expected Impact on Risk

MSHA strongly disagrees with the views of some commenters who asserted that the proposed rules would provide no known or quantifiable health benefit to mine workers. On the contrary, MSHA's assessment of the best available evidence indicates that reducing the very high exposures currently existing in underground mines will significantly reduce the risk of three different kinds of material impairment to miners: (1) Acute sensory irritations and respiratory symptoms (including allergenic responses); (2) premature death from cardiovascular, cardiopulmonary, or respiratory causes; and (3) lung cancer. Furthermore, as will be shown below, the reduction in lung cancer risk expected as a result of the rule can

readily be quantified based on the estimates of excess risk at exposure levels given in Table III-7.

Using exposure-response relationships and assumptions described in Subsections 3.b.ii(1) and 3.b.ii(2) of this risk assessment, MSHA estimated lower bounds on the significance of risks faced by miners occupationally exposed to dpm with respect to (1) acute sensory irritations and respiratory symptoms or (2) premature death from cardiovascular, cardiopulmonary, or respiratory causes. MSHA expects the rules to significantly and substantially reduce all three kinds of risk. However, MSHA is unable, based on currently available data, to quantify with confidence the reductions expected for the first two kinds. A 24-hour exposure at 20 µg/m³ may not have the same short-term effects as an 8-hour exposure at 60 µg/m³. Furthermore, this concentration is only 30 percent of the maximum dpm concentration that MSHA expects once the rules are fully implemented and represents an even smaller fraction of average dpm concentrations many underground miners currently experience. It is unclear whether the same incremental effects on acute respiratory symptoms and premature mortality would apply at the much higher exposure levels found in underground mines. Additionally, as MSHA suggested in the proposed preamble and several commenters repeated, the toxicity of dpm and PM_{2.5} may differ because of differences in composition. Finally, underground miners as a group may differ significantly from the populations for which the PM_{2.5} exposure-response relationships were derived.

Therefore, MSHA's quantitative assessment of the rule's impact on risk is restricted to its expected impact on the third kind of risk—the risk of lung cancer. The rule will limit dpm concentrations to which miners in underground M/NM mines are exposed. The rule will limit these dpm concentrations to approximately 200 µg/m³ by limiting the measured concentration of total carbon to 160 µg/m³. Assuming that, in the absence of this rule, underground M/NM miners would be occupationally exposed to dpm for 45 years at a mean level of 808 µg/m³, the following table contains the estimated reductions in lifetime risk expected to result from full implementation of the rule, based on the various exposure-response relationships obtained from Säverin et al. (1999) and Johnston et al. (1997). These estimates were obtained by calculating the difference between the corresponding estimates of excess lung cancer

mortality, at 808 µg/m³ and 200 µg/m³, shown in Table III-7. The Regulatory Impact Analysis (RIA), presented later in this preamble, contains further quantitative discussion of the benefits anticipated from this rule.

REDUCTION IN LIFETIME RISK OF LUNG CANCER MORTALITY EXPECTED AS RESULT OF REDUCING EXPOSURE LEVEL FROM 808 µG/M³ TO 200 µG/M³.

Study and statistical model	Expected reduction in lung cancer deaths per 1000 affected miners ¹
Säverin et al. (1999):	
Poisson, full cohort	68
Cox, full cohort	507
Poisson, subcohort	600
Cox, subcohort	620
Johnston et al. (1997):	
15-year lag, mine-adjusted ...	487
15-year lag, mine-unadjusted	317

¹ Calculated from Table III-7.

Although the Agency expects that health risks will be substantially reduced by this rule, the best available evidence indicates that a significant risk of adverse health effects due to dpm exposures will remain even after the rule is fully implemented. As explained in Part V of this preamble, however, MSHA has concluded that, due to monetary costs and technological limitations, the underground M/NM mining sector as a whole cannot feasibly reduce dpm concentrations further at this time.

4. Conclusions

MSHA has carefully considered all of the evidence and public comment submitted during these proceedings to determine whether dpm exposures, at levels observed in some mines, present miners with significant health risks. This information was evaluated in light of the legal requirements governing regulatory action under the Mine Act. Particular attention was paid to issues and questions raised by the mining community in response to the Agency's ANPRM and NPRM and during workshops on dpm held in 1995. Based on its review of the record as a whole, the agency has determined that the best available evidence warrants the following conclusions:

1. Exposure to dpm can materially impair miner health or functional capacity. These material impairments include acute sensory irritations and respiratory symptoms (including allergenic responses); premature death

from cardiovascular, cardiopulmonary, or respiratory causes; and lung cancer.

2. At dpm levels currently observed in underground mines, many miners are presently at significant risk of incurring these material impairments due to their occupational exposures to dpm over a working lifetime.

3. By reducing dpm concentrations in underground mines, the rule will substantially reduce the risks of material impairment faced by underground miners exposed to dpm at current levels.

In its response to MSHA's proposals, the NMA endorsed these conclusions to a certain extent, as follows:

The members of NMA have come to recognize that it would be prudent to limit miners' exposure to the constituents of diesel exhaust in the underground environment. [NMA]

A number of commenters, however, urged MSHA to defer rulemaking for either the coal or M/NM sector, or both, until results were available from the NCI/NIOSH study currently underway. For example, referring to the M/NM proposal, one commenter stated:

Vulcan agrees with MSHA that underground miner dpm exposure needs to be addressed by mine operators. Vulcan agrees with MSHA that a permissible exposure level (PEL) should be established, but disagrees that adequate information is currently available to set a PEL. [Vulcan Materials]

MSHA believes that expeditious rulemaking, in both underground mining sectors, is necessary for the following reasons:

(1) The NCI/NIOSH study currently in progress will eventually provide additional information on lung cancer mortality. Non-cancer health effects, such as sensory irritations, respiratory symptoms, or premature death from cardiovascular, cardiopulmonary, or respiratory causes will not be addressed. MSHA believes that these non-cancer effects constitute material impairments.

(2) NIOSH itself has recommended that, " * * * given the length of time to complete this study and the current state of knowledge regarding dpm exposures and health effects in miners," MSHA should "proceed with rulemaking based on the evidence currently available as presented in this FR notice." [NIOSH testimony by Paul Schulte, dated 5/27/99]

(3) Given the very high exposure levels measured at some underground mines, miners should not be required to serve as human guinea pigs in order to remove all doubts about the excess risks of dpm exposures in underground mines. While additional studies are in

progress, miners should be protected by reducing dpm concentrations to a level more nearly commensurate with exposures in other industries.

Referring to some commenters' position that further scientific study was necessary before regulatory action could be justified, a miner at one of the dpm workshops held in 1995 said:

* * * if I understand the Mine Act, it requires MSHA to set the rules based on the best set of available evidence, not possible evidence * * * Is it going to take us 10 more years before we kill out, or are we going to do something now * * *? (dpm Workshop; Beckley, WV, 1995).

Similar concern with the risk of waiting for additional scientific evidence was expressed by another miner, who testified:

* * * I got the indication that the diesel studies in rats could no way be compared to humans because their lungs are not the same * * * But * * * if we don't set the limits, if you remember probably last year when these reports come out how the government used human guinea pigs for radiation, shots, and all this, and aren't we doing the same thing by using coal miners as guinea pigs to set the value? (dpm Workshop; Beckley, WV, 1995).

MSHA shares these sentiments. That is why MSHA considers it imperative to protect miners based on the weight of existing evidence, rather than to wait for the results of additional studies.

IV. Section by Section Discussion of Final Rule

This part of the preamble describes the provisions of the final rule on a section-by-section basis. As appropriate, this part references discussions in other parts of this preamble: in particular, the background discussions on measurement methods and controls in part II, and the feasibility discussions in part V.

The final rule would add nine new sections to 30 CFR Part 57 immediately following § 57.5015. It would not amend any existing sections of that part.

Many provisions of the final rule are identical to the proposed rule, but some provisions have been changed. The following table provides a quick overview of the key changes:

Section	Final rule (changes from proposal)
57.5060	When specified conditions have been met and various precautions have been taken (including use of proper PPE), miners performing certain inspection, maintenance and repair activities may be granted permission from MSHA to work in certain areas where miners normally work and travel, but where the dpm concentration limit is exceeded (not authorized in proposed rule)
57.5061	Compliance sampling must always be done with sub-micrometer impactor (unspecified in proposed rule)
57.5067	Engines meeting the applicable EPA requirements as per a table provided in the rule may be introduced underground after rule's effective date (under proposal, only MSHA approved engines were so allowed)

Section 57.5060 Limit on Concentration of Diesel Particulate Matter

Summary. This section of the final rule limits the concentration of dpm in underground metal and nonmetal mines. It has six subsections.

Subsection (a) provides that 18 months after the date of promulgation, dpm concentrations would be limited by restricting total carbon to 400 micrograms per cubic meter of air (400_{TC}µg/m³). The reason why the concentration limit for dpm is expressed in terms of total carbon is explained below. A total carbon limit of 400_{TC}µg/m³ is the equivalent of about 500 micrograms per cubic meter of air of dpm (500_{DPM}µg/m³). This limit would apply only for a period of 42 months; accordingly, it is sometimes referred to in this preamble as the "interim" concentration limit. The final rule is the same as the proposed rule in this regard.

Subsection (b) provides that five years after the date of promulgation, the concentration limit would be reduced, restricting total carbon to 160 micrograms per cubic meter of air (160_{TC}µg/m³, or about 200_{DPM}µg/m³). This is sometimes referred to in this preamble as the "final" concentration limit. The final rule is the same as the proposed rule in this regard.

Subsection (c) provides for a special extension of up to two additional years in order for a mine to comply with the final concentration limit. This special extension is only available when the mine operator can establish that the final concentration limit cannot be met